Challenges of the current medicine

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Tell me, and I forget.
Teach me, and I remember.
Involve me, and I learn.
Benjamin Franklin

Dear Colleagues

A report, created in cooperation with Prof. Tomasz Sobierajski's Sociomedical Research Center, was presented during FOP 2024. The survey asked about concerns about disease and health attitudes.

It shows that the greatest sources of concern for Polish women are cancer, strokes, and Alzheimer's disease. Next, we are afraid of depression and obesity and definitely the least afraid of infectious diseases, such as HIV, flu, and COVID-19. Due to the disease, respondents are most afraid of disability, loss of income, and dependence on others. Due to the disease, we are also afraid of death and loneliness.

As a result of the analysis, it was observed that there is a very diverse level of fear related to diseases recognized by WHO as current threats to global health, and at the same time, taking into account demographic factors such as gender, age, place of residence, income, and education, an insufficient number of preventive actions taken that can protect against these diseases. This paradoxical research result suggests that despite relatively high fears of diseases, Polish women have difficulties in translating fear into specific, health-promoting decisions and behaviors.

Cancer is the greatest source of concern for Polish women and men participating in the study; nearly two-thirds (62%) of respondents reported fears related to this disease. This group of diseases was clearly indicated by the vast majority of people as the first in the ranking of health concerns. Regardless of age, place of residence, or gender, cancer causes the greatest concern.

Next on the list of diseases that respondents are most afraid of are strokes (51%)—every second person taking part in the study indicated that they fear contracting this disease. The next most feared diseases among Polish women and men surveyed were Alzheimer's disease, which 47% of respondents fear, and chronic rare diseases, which 45% of respondents fear.

A similar percentage of respondents are afraid of developing coronary heart disease (37%) and depression (36%). Slightly fewer (35%) are afraid of developing diabetes. It is worth noting the significant differences in the level of concern among Polish women regarding diseases such as liver cirrhosis (30%), obesity (25%), or HIV/AIDS (24%), which are also objects of noticeable social concern, although at a much lower level than the previously mentioned diseases. Declaratively, the respondents were least afraid of influenza (20%) and COVID-19 (20%).

The monograph periodical "*Challenges of Current Medicine—13 Edition" is* a collection of works written by authors from many different medical centers.

Prof. Elżbieta Krajewska-Kułak
Prof. Jolanta Lewko
Prof. Wojciech Kułak
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CONTENS

Contens

HEALTH BEHAVIORS AND HEALTH PROMOTION

THE EFFECT OF DIET ON IMPROVING COGNITIVE FUNCTION IN THE ELDERLY

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INTRODUCTION

The increasing life expectancy results in a major population of elderly who are prone to dementia and Alzheimer's disease because aging is an important risk factor for most neurodegenerative diseases [1]. These conditions impact thinking, memory, and behavior, affecting approximately 55 million people globally, with estimations suggesting this will double by 2050 [2]. Currently, over 14 million people in Europe are affected [3].

Age-related cognitive impairment significantly impacts the quality of life for these individuals and places a substantial burden on the healthcare system. Promoting cognitive health among the elderly is crucial. Cognitive decline is described as a progressive process with stages such as memory impairment, mild cognitive impairment, and dementia [4].

Research increasingly indicates that improved nutritional conditions can enhance neurological functions in older people. The relationship between dietary nutrition and cognitive function is complex, and the molecular mechanisms require thorough research to fully understand.

OMEGA-3 AND OMEGA-6 POLYUNSATURATED FATTY ACIDS

Polyunsaturated fatty acids (PUFAs) have attracted great attention for their health-enhancing effects as well as specific vitamins for their strong antioxidant abilities [5]. PUFAs such as omega-3 and omega-6 fatty acids are fatty acids with two or more double bonds in their carbon chain backbone. Omega-6 fatty acids include linoleic acid (LA), γ-linolenic acid (GLA), and arachidonic acid (AA). Omega-3 fatty acids include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). However, these fatty acids should be consumed from the

diet or through supplementation since their synthesis is limited in humans [6].

The potential benefits of PUFAs, especially EPA and DHA, in preventing cognitive decline have been of clinical interest due to their neuroprotective properties, such as increasing the neuroplasticity of nerve membranes, promoting synaptogenesis, modulating signal transduction pathways in neuronal cells, and attenuating inflammation [7].

Over a period of 6 months, a randomised, double-blind, placebo-controlled study examined the effects of high-dose omega-3 and omega-6 fatty acid supplementation combined with antioxidant vitamins on cognitive function and functional performance in older adults with mild cognitive impairment (MCI). The results of the study, conducted on forty-six individuals, showed that high doses of omega-3 and omega-6 fatty acids, along with antioxidant vitamin supplementation, improved cognitive function and functional performance in individuals with MCI. Additionally, participants receiving this dietary supplement demonstrated beneficial improvements in fatigue, the physical component of quality of life, and daytime sleepiness [8].

Supplementation with omega fatty acids under appropriate formulations and dosage in older adults with MCI might improve cognitive function. Bo et al. demonstrated that six months of supplementation with 480 mg DHA and 720 mg EPA per day could improve perceptual speed, space imagery efficiency, and working memory in older adults with MCI, whereas Sinn et al. showed that sic months' supplementation with fish oils rich in DHA (1.55 g DHA and 0.40 g EPA per day) improved fluid thinking ability [9,10].

SOURCES OF OMEGA-3 AND OMEGA-6

Fatty fish such as salmon, mackerel, sardines, herring, and tuna are rich in eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [11]. Flaxseed oil, chia seed oil, walnut oil, and canola oil contain alpha-linolenic acid (ALA), which is a precursor to EPA and DHA [12].

Soybean oil, corn oil, walnuts, and Brazil nuts are rich in linoleic acid (LA) [13]. Omega-6 sources also include poultry, eggs, milk, and canola oil [14].

ANTIOXIDANTS

Prominent antioxidants include specific vitamins, namely vitamins A, C, and E, minerals such as selenium, chromium, and zinc, as well as carotenoids, flavonoids, polyphenols and lignans. These components protect against free radicals and help maintain

healthy functioning of cognitive processes, such as memory, cognition, and concentration [15]

Research has shown that daily supplementation of 75 mg of resveratrol led to a significant improvement in overall cognitive function among middle-aged women [16]. It also demonstrated promising positive effects on memory, quality of life, and levels of selective oxidative indices in patients with mild to moderate Alzheimer's disease (AD) who received 5 cc of fenugreek seed extract (equivalent to 500 mg of dry extract) for 4 months [17].

The supplementation of 1000 mg/day of vitamin C [18], carotenoids: lutein and zeaxanthin (13 mg, or 27 mg/day) supplementation [19], as well as 1.6 g/day of alpha-lipoic acid resulted in significant improvement compared to the control group in terms of attention, memory, and other observed cognitive tests [20].

One of the most potent carotenoids is natural astaxanthin (AST), which has been shown to have the greatest oxygen radical absorbance capability, surpassing other antioxidants like vitamin E [21]. Astaxanthin has been shown to benefit different facets of cognitive function in humans, primarily subdivisions of episodic memory, response time, and working memory [22]. Notable key natural sources of astaxanthin include red yeast, Phaffia rhodozyma, shrimp, salmon, crustacean by-products, and some forms of green algae [23].

VITAMIN B

Vitamins contribute significantly to neurological health by supporting various processes critical for nerve function, protection, and overall brain health. Sufficient intake of vitamins B6, B9, and B12 has been strongly linked to improved cognitive function among seniors [24]. Additionally, vitamin B1 is vital in the field of neuropathology. Research has shown that vitamin B1 is linked to various neurological disorders, primarily because it is essential for the synthesis of acetylcholine, a neurotransmitter vital for proper nervous system function. Its deficiency is associated with cognitive impairment, especially in the older adult population [25].

The study revealed that a 24-month regimen of folic acid supplementation (400 μg/day) significantly improved cognitive function and reduced blood biomarker levels of amyloid β protein (Aβ) in mild cognitive impairment [26]. The combination of folic acid and vitamin B12 was significantly superior to either folic acid or vitamin B12 alone. The combination of oral folic acid plus vitamin B12 in MCI elderly for six months can

significantly improve cognitive performance and reduce the levels of inflammatory cytokines in human peripheral blood [27].

Vitamin B6 is widely distributed in foods of plant and animal origin. It is found in meats and eggs and in plant foods such as beans, cereals, and brown rice [28].

Humans depend on their dietary intake of vitamin B12. The best sources are ruminant meat and milk due to the natural bacterial populations that synthesize vitamin B12 in these animals' rumens [29].

VITAMIN D

Vitamin D deficiency or insufficiency is common - so much so it can be called a pandemic, approximately 1 billion individuals worldwide [30]. The recognition of the role of vitamin D in brain health and function is increasing.

Many studies have shown an independent link between vitamin D deficiency and a greater risk of mild cognitive impairment and dementia in the future [31,32]. The reason behind this might be the neuroprotection of the hippocampus by upregulating protein expression in the Nrf2/HO-1 pathway, which has been demonstrated both in vitro and in vivo in aging mice [33]. Vitamin D also plays a role in the downregulation of NF-kB, TNF-α, and IL-1β protein expression while stopping the amyloidogenic pathway in amyloid beta production [34].

A low serum level of 25(OH)D can independently predict a decline in cognitive functions and dementia [35,36]. Studies show inadequate serum 25-hydroxyvitamin D (25(OH)D) levels in individuals with vascular dementia and Alzheimer's disease compared to healthy controls [37]. It can potentially be viewed as a biomarker for Alzheimer's disease [38].

Reviews found that low vitamin D concentration worsens executive, visuospatial, and memory processing functions, while supplementation may alleviate the symptoms and enhance decision-making, planning, attention, learning, and cognitive flexibility, mainly among insufficient patients [39,40,41]. Furthermore, Young-Onset Dementia is proven to be associated with vitamin D deficiency [42].

SOURCES OF VITAMIN D

Ultraviolet radiation on the skin is needed to convert provitamin D3 into a previtamin and finally into its final form - a vitamin. The skin is the primary source of vitamin D in

in humans, but there are some dietary sources: oily fish, egg yolks, and supplements [43].

FLAVONOIDS

This group of dietary polyphenolic compounds is found in various fruits, such as apples, citrus, and berries, vegetables, such as parsley, celery, leeks, onions, and soybeans; herbs, such as oregano; olive oil, dark chocolate, and beverages, such as green tea and wine [44]. The Mediterranean diet is rich in flavonoids [45]. They play a significant role in cognitive abilities and improve memory, executive function, and attention.

Studies indicate that flavonoids reduce oxidative stress, which damages brain cells, protecting neurons from injury and death [46,47]. Moreover, they stimulate the growth of new neurons and improve synaptic plasticity in the hippocampus, which is crucial for learning and memory [48].

Flavonoids can enhance cognitive function and protect against neurodegenerative diseases by attenuating neuroinflammation associated with cognitive decline. They achieve that effect by down-regulating proinflammatory cytokine expression and regulating macrophage activity [49, 50].

Additionally, recent studies suggest a diet high in flavonoids is proven to lower cytokine production in the gut, promoting beneficial bacteria growth [51].

ALCOHOL CONSUMPTION

The relationship between alcohol consumption and cognitive functions in the elderly is complex and has been the subject of different studies, yielding mixed results.

Many studies found the nonlinear, U-shaped effect of alcohol - both abstinent and heavy drinkers (characterised by intake greater than 14 standard drinks per week, or 3 per day) had a higher risk of cognitive decline and dementia in older adults, while low and moderate drinkers had the best results. This neuroprotective effect might be linked to the potential of alcohol to enhance cardiovascular health, which in turn benefits brain function [52, 53, 54]. The smallest risk of dementia is linked to consuming 6 grams of alcohol per day, with wine specifically noted for its protective effects [55].

Moderate alcohol consumption has been reported to have protective effects on cognitive functions; nonetheless, several studies suggest that this impact may be influenced by other factors, i.e., abstainer bias, and vary based on individual health, lifestyle, and genetic factors. For instance, factors like gender, existing health conditions, and overall lifestyle can

influence how alcohol affects cognitive functions in the elderly [56, 57].

However, other studies caution against the potential negative effects of moderate alcohol consumption on cognitive functions. A longitudinal cohort study found that even moderate alcohol consumption could be associated with adverse brain outcomes and cognitive decline over time. The study highlighted that moderate drinkers showed a greater decline in certain memory tests compared to non-drinkers [58,59].

On the other hand, drinking among the elderly is a pressing concern. Guidelines recommend no more than one standard drink per day or seven per week. One study reported that among women aged 60 and above, 12% exceed said alcohol consumption, they can be particularly vulnerable to alcohol-related cognitive issues [60].

Alcohol intake, besides smoking and stress, is one of the most important modifiable risk factors for cognitive decline and other health problems.

WASABI

Wasabi, *Eutrema japonicum* is a traditional Japanese spice. Because of its bioactive compound 6-Methylsulfinyl Hexyl Isothiocyanate (6-MSITC), it has been studied for its potential benefits on cognitive function.

The recent randomized controlled trial demonstrated that consuming 0.8 mg of the 6-MSITC supplement daily for 12 weeks led to significant improvements in memory performance, both episodic and working memory, in healthy elderly. This can be understood through several mechanisms. 6-MSITC has demonstrated strong anti-inflammatory and antioxidant properties, which can help reduce oxidative damage in brain cells and lower inflammation, potentially preserving cognitive function and enhancing neuroplasticity in the hippocampus [61].

GINKGO BILOBA

Ginkgo biloba is a herbal supplement containing flavonoids, organic acids and terpenoids, and has been widely studied for its potential benefits on cognitive function. It helps to enhance blood flow to the brain, reduce oxidative stress and inflammation. Ginkgo biloba can regulate neurotransmitters and thus enhance synaptic plasticity [62].

Some studies suggest that Ginkgo biloba may slow the progression of Alzheimer's disease [63], mild cognitive impairment and other forms of dementia [64,65] by improving cognitive function and reducing behavioural symptoms, but it is still controversial [66].

One should be aware that supplements may have interactions with drugs, particularly considering that the elderly tend to use multiple medications – polypharmacy [67].

CONCLUSIONS

A diet rich in essential fatty acids, antioxidants, vitamins, and other bioactive compounds can significantly improve and maintain cognitive health in the elderly. As our understanding of the relationship between diet and cognitive function deepens, dietary interventions can be more effectively tailored to promote healthy aging and mitigate cognitive decline and neurodegenerative diseases.

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THE INFLUENCE OF NUTRITION, DIETARY HABITS, AND DIETARY SUPPLEMENTS ON LIBIDO-2

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INTRODUCTION

The topic of enhancing libido has existed for a long time with the usage of various natural products, alone or combined. The influence of nutrition, dietary habits, and dietary supplements on libido has been widely discussed. In our review, we tend to sum up the newest medical knowledge on that topic. Now, there are unlimited options for various supplements on the market, but not all have been studied that deeply. Most of the ingredients are known to "enhance sex drive" only by empirical method (and let's not forget about the placebo effect), and the pathway of such effects is not understood. However, a few key ingredients or even simple groceries have been systematically studied. Apart from all the substances that people can take in to boost their sexual behavior, there is also the influence of the general consummatory nature, rhythmic patterns, and the psychosocial aspects of sexual wellness that are extremely important to understand this issue as a whole. The aphrodisiac foods, which elicit sexual instinct and desire and enhance sexual performance, supplements, and substances found in everyday meals are a topic of particular interest. In this article, we explored the world of foods that can boost libido and evaluated which ones are recommended and which are suspicious.

NUTRITIONAL COMPONENTS RELEVANT TO LIBIDO

The substances used to enhance sexual health can be categorized into trace minerals, vitamins, plant derivatives, and amino acids. They mainly impact libido through hormonal mechanisms (such as testosterone and estrogen production and endocrine balance) and vascular mechanisms (including relaxation of smooth muscles, increased blood flow, and support of endothelial function). Based on a review article by Clemesha et al. [1], about 30 different substances are included in supplements aiming to increase sexual health and libido. In a different study by Cui et al. [2], various nutraceuticals commonly found in men's health

supplements have been reviewed with practicing urologists in mind to understand better the mechanisms through which these substances may affect sexual health.

For this paper, a consensus on which substances are used commonly enough and their effect has been documented, and an objective has to be reached.

Zinc is essential in various physiological processes, including immune function, wound healing, and DNA synthesis. It is involved in the production and regulation of hormones, especially testosterone, which can influence libido in both men and (possibly) women [3]. Research on zinc supplementation for female libido is limited compared to that in men. However, zinc deficiency has been associated with decreased libido and sexual dysfunction in both sexes. That is due to the conversion of testosterone into its active form, dihydrotestosterone, via 5-alpha reductase, which depends on zinc for its activity.

Studies [3, 4] have shown that the main reason testosterone levels decrease in zinc deficiency is the change in testosterone's enzymatic conversion. What is worth noting is that the pro-androgenous effect is dose-dependent, with higher doses hindering sexual desire rather than supporting it.

Animal studies [3, 5] show increased libido in animals supplemented with various zinc chemical compounds. In human studies, the consensus is that zinc intake can increase libido, especially in a priori zinc-deficient individuals [5, 6, 7].

Magnesium is an essential electrolyte for all living organisms and is the fourth most abundant ion in human bodies, especially in the intracellular space, teeth, and bones. It supports muscle and nerve function, energy metabolism, bone health, and sleep patterns. While its direct impact on libido in both males and females is not extensively studied, there is evidence to suggest that magnesium may influence sexual health and desire by way of regulating one’s hormonal balance [8, 9]. It is worth emphasizing its directly proportional influence on serotonergic signaling in the brain, which can negatively influence libido (serotonin is known to be an inhibitory modulator of desire, decreasing the ability of excitatory systems to be activated by sexual cues) [10].

Magnesium is also linked to managing stress response (which hinders sexual drive) and muscle relaxation (supporting blood flow to various tissues increases sensitivity), thus reinforcing physiological processes of experiencing and acting on one’s sexual desire. [8, 11].

Boron, a trace mineral in various fruits and vegetables, is essential for adequately functioning processes including wound healing, bone regeneration, and the calcification and synthesis of sex steroid hormones [12, 13].

Daily supplementation of 3 mg of boron in postmenopausal women (who had been on a low-boron diet before that) markedly increased (doubled, in fact) serum levels of both estradiol (E2) and testosterone. What is more, urinary magnesium and calcium loss have been ameliorated, especially in magnesium-deficient women. All the changes mentioned above happened in 8 days following the beginning of boron supplementation.

Naghii et al. [14] also observed that male subjects' free testosterone (FT) levels rose markedly after only one week of boron supplementation. Furthermore, estradiol plasma concentration decreased from 42.33 pg/mL to 25.81 pg/mL, possibly due to an increased conversion of total testosterone into free testosterone. The ratio between FT and E2 changed from 0.31 to 0.67 ng/mL, which leads to the conclusion that boron has pro-androgenous effects in men. A study carried out on rabbits showed a prolonged reaction time (authors use it as a marker of libido, which in this instance means decreased sexual drive) in the treated group, with their sperm quality having improved significantly. A similar study should be conducted in human subject groups to ascertain a similar correlation [15].

Vitamin D is a secosteroid hormone, presenting pleiotropic effects ranging from bone health, calcium, and phosphorus homeostasis through sex hormones synthesis (namely, testosterone), and regulation (estrogen, AMH, DHEA) [16, 17, 18, 19]. Vitamin D receptors (VDRs) found in testes bind with retinoid X receptors, forming VDR-RXR complexes. This causes an up-regulation of androgen-related genes, thus increasing the concentration of testosterone produced in vivo. [16]. Evidence of the positive influence of vitamin D on both semen quality via calcium levels and testosterone production is well documented [20].

Contrary to the abovementioned studies, Zhao et al. [21] conducted an extensive study in which 3017 men and 2929 women of various ethnicities participated. Findings were that lower 25-(OH)-D concentrations were positively associated with SHBG (sex hormone binding globulin) levels, resulting in higher free testosterone levels in both sexes. In women, lower concentrations of E2 and higher DHEA levels have been observed. A relatively novel finding of how vitamin D deficiency can be linked to anti-Mullerian hormone levels and lowered ovarian reserve in women aged >40 years. The anti-inflammatory effects of vitamin D may help modulate immune function and reduce inflammation. Chronic inflammation has been associated with hormonal imbalances and may negatively affect sex hormone levels. By reducing inflammation, vitamin D may help support optimal hormone levels and overall sexual health.

Vitamin A is known for its antioxidative properties while also playing a role in ovarian

functioning and steroidogenesis (via retinoic acid receptors (RARs)). A correlation between serum levels of retinol and higher levels of estradiol and testosterone has been documented in a BioCycle study.[22] Damdimopoulou et al. [23] state that retinoic acid signaling impacts gonadotropin receptor expression. At the administration of isotretinoin acid, estradiol synthesis in vivo went up. However, there is no proven correlation between retinoic acid supplementation and libido per se. All possibly achievable effects are due to its antioxidant properties and impact on steroid hormones.

Alpha-tocopherol (vitamin E) is a fat-soluble vitamin whose vasodilatory and antioxidant properties aid hormonal homeostasis and, thus, one's sexual response [22, 24, 25, 26, 27].

Ascorbic acid has potent antioxidant properties while supporting the regeneration and efficacy of other ROS (reactive oxygen forms) scavengers (such as glutathione and vitamin E). Reactions depend on vitamin C to synthesize collagen (a structural component of the vasculature, including genital organs), L-carnitine (a substrate for NO synthesis and thus erectile function), norepinephrine, and epinephrine.

Among **vitamins from the B group**, all of which are enzyme cofactors, a few can, according to some studies, support sexual health.

Decreased vitamin levels in this particular group are associated with increased incidence of hyperlipidemia, hyperhomocysteinemia, and degenerative neuropathy. Ameliorating the abovementioned metabolic dysfunctions may indeed help restore sexual functions to their optimum.

In a study by Gianfrilli et al. [28], it was noted that vitamin B3 plays a role in endothelial function support due to minimizing levels of free radical production and fat metabolism, thus enhancing blood flow. According to Ghanbari-Homaie et al. [17], niacin supplementation of 1500 mg daily (a supraphysiological dose) for 12 weeks had a significant effect on augmenting erectile function in males. Vitamin B6 is needed for estrogen, testosterone, and neurotransmitters [27]. It acts as a cofactor for regulating the metabolism of glucose, lipids, and amino acids. The synergistic effect of B6, B9, and B12 vitamins aids in homocysteine level regulation. Homocysteine is known for decreasing levels of NO and, thus, decreased blood flow. Vitamin B12 also participates in DNA synthesis, energy metabolism (along with vitamin B1), and optimal nervous system function.

As far as **amino acids** are concerned, namely L-arginine, L-citrulline, and L-carnitine, used for treating erectile dysfunction in men [28, 29, 30], there is no proven direct impact on male libido. It should be emphasised, though, that improved tumescence and performance can

lead to lowered levels of performance anxiety, which in turn can support prevalence of heightened sexual desire. Additionally, a study carried out on menopausal women who chose to participate due to lack of sexual desire after four weeks of using ArginMax® (L-arginine, ginkgo, ginseng, damiana, multivitamins, and minerals) showed notable improvements in sexual desire, reduction of vaginal dryness, frequency of sexual intercourse and orgasm, and clitoral sensation. [31] In another instance, a systematic review of potential treatment of Hypoactive Sexual Desire Disorder (HSDD) with L-arginine showed it to be effective for women of all ages. [32]

DIETARY SUPPLEMENTS IN ENHANCING LIBIDO - NOT-SO-URBAN MYTH OR REAL CLINICAL KNOWLEDGE?

The FDA definition of an aphrodisiac drug product is "any product that bears labeling claims that it will arouse or increase sexual desire, or that it will improve sexual performance." As of today, there aren't any approved and clinically proven medications for the lowered desire for women, which results in high demand for "natural" medications - such as herbs, specific products, supplements, and many more [27].

Different plant parts, such as the roots of plants such as Pausinystalia johimbe, Lepidium meyenii, Panax ginseng, and others discussed in this article, are used, roots being the most common. Less than half of the plants often used as sexual performance enhancers have been evaluated scientifically, and those that have usually shown mixed results regarding their usefulness [33]. In this chapter we will reveal the information found in clinical studies about commonly used dietary supplements used separately, such as Ashwagandha (*Withania somnifera*), Red Ginseng (*Panax Ginseng*), *Tribulus terrestris, Epimedium koreanum, Lepidium meyenii* (Maca), *Trigonella foenum-graecum* (Fenugreek), APO (apomorphine), Yohimbine, *Turnera diffusa, Ambra grisea, Ginkgo biloba,* other spices and groceries and/or combined in the multicompound products.

Ashwagandha (*Withania somnifera*)

Ashwagandha (*Withania somnifera*) has been known in traditional Indian Ayurvedic medicine as a treatment for men's sexual dysfunction and infertility. In the study by Ambiye et al. (2013) [34], treatment with a high-concentration, full-spectrum root extract was used, resulting in improved semen quality and hormone levels in previously oligospermic males. The most important criteria for fertilizing ability - sperm motility has also been normalized compared to the test results before the treatment, as well as testosterone levels, serum LH,

follicle-stimulating hormone, and progesterone [35]. Additionally, the artificial form of testosterone, contained in many pharmaceutical products, was shown to be much less safe than its plant analogy.

Findings by Lopresti et al. (2019) [35] suggest that ashwagandha's stress-relieving qualities are reasoned by it moderating the hypothalamus-pituitary-adrenal axis. It is grown in dry regions of South Asia, Central Asia, and Africa and contains over 50 chemical substances known as withanolides, which include steroidal alkaloids and lactones. Its effects on the organism have been additionally found to be anti-inflammatory, antioxidant, anticancer, anxiolytic, and immunomodulatory, influencing neurological, endocrine, and cardiovascular activity. Moreover, significant emotional improvements over time and greater reductions in morning cortisol and DHEA-S were noticed. In the study by Lopresti et al. (2019) [35], good tolerability of ashwagandha intake was reported, with no significant adverse events reported by participants. Pre- and post hematological tests and lipid profiles showed no statistically significant differences over time.

Red Ginseng (*Panax Ginseng*)

Red Ginseng (Panax Ginseng or Korean Ginseng) extract is one of the most common ingredients in top-selling supplements promoting sexual health. Its mechanism relies on increasing NO production, which increases blood flow into the corpora cavernosa. [2]

Such KRG extracts are used to treat anxiety, stamina, cognitive function, depression, male fertility, migraines, immunostimulants, symptoms of menopause, and impotence. Its intake was also correlated with maintaining the suppleness, moisture, and overall health of the vaginal walls, thus minimising dryness, tearing, and pain [36].

In the study by Oh et al. [39], oral administration of KRG extracts had positive effects on such conditions as anaemia, chronic fatigue, diabetes mellitus, HIV-1 infection, decreased libido, and erectile dysfunction, as well as improved sexual arousal in menopausal women.

Contraditionally, West and Krychman [27] suggest little evidence to recommend KRG extracts as an effective aphrodisiac.

An additional study combined KRG and vitamin E, improving erectile function. Another study found an improvement in Intercourse Satisfaction only. Major active isolates are unique to ginseng species, specifically *Panax ginseng* - ginsenosides, steroid-like saponins. In animal studies, those isolates were shown to induce NO synthesis in the endothelium, vasodilation of the corpus cavernosum and subsequent erection, increase testosterone concentrations, improve erection, and increase copulatory behavior. *Panax ginseng* is

considered safe within the dosage range of 0.5–3 g/day, with no significant herb-drug interactions reported. However, more research is needed to explore ginseng's potential mechanisms and active components in improving erectile dysfunction [36].

Tribulus terrestris

Tribulus terrestris is a medicinal annual plant of the family *Zygophyllaceae.* [40] It has a long history of usage in India and China in the Ayurvedic, Unani, Siddha, and Chinese Traditional Medicine systems. Animal studies conducted by Leisegang & Finelli [41] indicate its pro-erectile effect on the corpus cavernosum mediated through increased NO in the endothelium and nitrergic nerve endings, which leads to vasodilation, increased testosterone levels, and a dose-dependent increase in sexual behavior. Such effects are likely seen as the result of its secondary metabolites: steroidal saponins spirostanol and furostanol, flavonoids, and alkaloids.

Epimedium koreanum

Epimedium koreanum is also a herb used in traditional Chinese and Korean herbal medicine to enhance erectile function. The main active component, Icariin, improves general cardiovascular function, regulates hormones, modulates immunological processes, and even shows anti-tumor activity. In the study by Makarova et al. [35], dry extract of Epimedium koreanum was suspended in wheat germ oil, lecithin, and bee wax for oral administration, positively affecting androgenic status and copulative function.

Lepidium meyenii (Maca)

Lepidium meyenii (more commonly known as Maca or Peruvian bark) is a native plant to the Central Andes Mountains of Peru at altitudes of 4000–4500 m. There are mixed results regarding Maca's effects on sexual function. In animal studies, there was little evidence that it could increase serum or testicular testosterone; however, an increase in the intracavernosal pressure to mean arterial pressure ratio was noted, which could lead to improving ED [36]. In another study of *Lepidium meyenii* (maca), *Rhodiola rosea* (Rhodiola), Chlorophytum borivilianum (muscle), *and Garcinia cambogia (garcinia), testosterone concentrations did not statistically significantly increase after 12 weeks of supplementation with* these substances [33].

In human studies, though, no significant effect on sexual function in males and females was noted. Still, it was underlined that it might cause psychological adverse events such as anxiety, mood swings, hallucinations, and addictive behavior [36].

Trigonella foenum-graecum (Fenugreek)

In the study of *Trigonella foenum-graecum* Seed Extract (Libifem), a significant increase in free testosterone and E2 in the active group, as well as sexual desire and arousal compared with the placebo group, was shown. Such results of tests conducted by Rao et al. [42] indicate that it may be used as a treatment for lowered sexual desire in women, although it still needs to be certified in clinical trials. Fenugreek (*Trigonella foenumgraecum*) is also used to increase prolactin levels, leading to enlarging the fullness and breast size in women and easing PMS and menopausal symptoms. It is considered safe, but it's worth mentioning that high doses may cause mild stomach upset [18].

APO (apomorphine)

Another double-blind, randomized placebo control study conducted by Bechara et al. [43] compared the objective and subjective changes in female sexual response by using sublingual apomorphine (APO). As a result, APO seemed to produce more subjective and objective changes in the sexual arousal phase of women with orgasmic sexual dysfunction than placebo, which suggests conducting more research on this medication.

Yohimbine and *Turnera diffusa*

Yohimbine and *Turnera diffusa* are sequent substances that were shown to significantly increase the percentage of males achieving one ejaculatory series and resuming a second one by Estrada-Reyes et al. [44]. Not only that, but *Turnera diffusa* also noticeably reduced the post-ejaculatory interval. In this study, the HPLC–ESI-MS analysis showed caffeine, arbutine, and flavonoids in the active extract. Susset et al. [45] claim that the maximum effect takes 2 to 3 weeks, with only a few benign side effects recorded.

Ambra grisea

Ambra grisea is a natural remedy used in Arab countries for the treatment of headaches, rheumatism, and improvement of sexual performance. This substance is found in the gut of sperm whales and has only been examined in animal studies, where its usage led to increased serum testosterone and LH levels [43].

Ginkgo biloba

Effects of *Ginkgo biloba* studied by Kumar Maurya [36] in perimenopausal and menopausal women were seen as boosted sex drive, balanced hormones, boosted menopausal estrogen levels, activated Leydig cells, and boosted NO.

Multicompound products

Among available products, some contain multiple substances listed above. One example is Libicare®, an oral food supplement. It contains dry extracts of *Trigonella foenum graecum*, *Turnera diffusa*, *Tribulus terrestris*, and *Ginkgo biloba* and is manufactured by Procare

Health (Barcelona, Spain). The results of tests performed by Palacios et al. [46] suggest that it may have a double effect. With an increase in free testosterone, sexual desire was improved. Additionally, a vaginal vasodilating effect was noticed, which led to improving arousal. Those effects are known to be seen in studies on the separate components. Pygnogenol® is an extraction of the powdered *Pinus pinaster*, which contains huge amounts of procyanidins with significant antioxidant qualities. Except for them, the extraction was also found to possess immune regulating properties, increase vascular NO synthesis, and, consequently, vasodilation, which improves erection. Prelox is another multi-substance product containing the previously mentioned Pygnogenol®, L-arginine, L-citrulline, and roburins. Prelox reportedly improved testosterone levels and erectile function, although the role of L-arginine in these effects is still questionable [36].

It's important to remember that with some yet properly unstudied substances, the risk could outweigh the benefit—as shown in the research by West and Krychman [27] regarding yohimbine, Spanish fly, mad honey, and Bufo toad.

Spices and groceries

Spices commonly used in cooking are also known for having a libido-boosting effect - take at least Cayenne pepper (Capsicum annum L), cinnamon (Cinnamomum zeylanicum), and ginger (*Zingiber officinale*) as examples. They produce heat within the body and promote circulation in the lower abdominal and pelvic regions. Promoted circulation increases vaginal moisture and, thus, sensitivity, intensifying sexual arousal [36]. A similar mechanism is demonstrated in various products shown in Tab.1.

Table 1. Effects of various products and nutrients on sexual and overall health

Product name	Effect	Reference
Garlic (*Allium sativum*)	Promotes circulation to genital organs	[36]
Saffron (*C. sativus flower spice*)	Improves sexual dysfunction caused by antidepressant drugs	[36]
Cardamon	Due to the high concentration of antioxidants improves circulation in the penis	[36]
Pumpkin seeds (*Cucurbita moschata*)	Improves the functioning of the prostate gland and male sexual hormones	[36]
Bananas (*Musa acuminata*)	Improves libido; assists in the creation of testosterone (due to potassium and riboflavin); improves impotence desire to have sexual encounters in males (due to bromelain)	[36]

Walnuts (*Juglans spp.*)	Increases libido and dopamine levels; improves the quality and intensity of orgasms; stimulates the production of nitric oxide; relaxes blood vessels; boosts circulation.	[36]
Avocado (*Asparagus officinalis*)	Increases energy levels in men; promotes healthy circulation; naturally protects the arteries; lowers the risk of metabolic syndrome (a risk factor for ED)	[36]
Asparagus (*A. officinalis)*	Enhances libido; helps in the production of sex hormones; improves orgasms and sexual health by increasing overall excitement	[36]
Basil (*Ocimum basilicum*)	Boosts female fertility and men's desire to have sexual encounters; enhances blood circulation.	[36]
Honey	Enhances stamina due to the high sugar levels; acts as a vasodilator.	[36]
Watermelon (*Citrullus lanatus*)	Promotes NO production, thus normalising blood circulation	[36]
Nutmeg (*Myristica fragrans*)	Increases libido (its extract has been proven to have the same effect on mating behaviour as Viagra does in animal studies)	[36]
Broccoli (*Brassica oleracea*)	Lowers estrogen levels in men with the opposite effect in women	[36]
Sauerkraut	Enhances testosterone production	[36]
Celery	Increases the male aphrodisiac pheromone and androsterone; acts as a vasodilator; improves sex drive; enhances climax.	[36]
Flaxseeds (*Linum usitatissimum*)	Enhances testosterone, libido and fertility; increases sperm counts; improves blood flow to the sexual organs; prolongs erections.	[36]
Bee pollen	Increases energy levels; has a high concentration of enzymes, amino acids, vitamins, and minerals. As a result increases sexual stamina, frequency of erections, and the volume of ejaculate produced.	[36]
Black cohosh (*Actaea racemose*)	A plant-based estrogen contained in it helps to regulate hormones, decrease menopause symptoms.	[36]
Yam (*Dioscorea alata*)	Used for maintaining healthy hormone levels, particularly progesterone; treating depression, low libido, irritability, and anger.	[36]

Caffeine

A study by Guarraci and Benson (2005) [37] showed that caffeine, specifically moderate doses, has altered paced mating behavior in OVX (ovariectomized) rats primed with estrogen and progesterone and shortened the latency to return to the male following an ejaculation during paced mating behavior. However, the result didn't repeat itself with a higher dose of caffeine.

Chocolate

There is even a study showing that women who consumed chocolate had higher FSFI scores than women who didn't, so it seemed to have either a psychological or a biological positive impact on women's sexuality [38]. Although the Journal of Sexual Medicine reported more active sex lives in women who ate dark chocolate every day than those who did not. That fact may be associated with phenylethylamine found in dark chocolate, which boosts well-being and general mood. [36]

DIETARY SUPPLEMENTS ARE NOT BE USED UNCONTROLLABLY

It's not possible to discuss the topic of herbal sex remedies without mentioning pharmacovigilance, possible side effects, and the lack of sufficient clinical trials conducted on most products. It's important to notice that such practice may place consumers at risk for side effects, from abnormal vision, headaches, myalgia, dizziness, flushing, dyspepsia, and many more. As an example, most studies on Yohimbine, Ginseng, and Maca show that these substances can cause serious adverse effects, which include gastric upset, headache, insomnia, constipation, and rhinitis, even mentioning the risk of cancer. [47]

At present, regulating sexually enhancing supplements on the pharmacological market is burdened with laws regarding it, which assume that all supplements are safe until dozens of deaths are reported due to adverse events. There is even a sort of "guideline" for clinicians to advise patients that, at the moment, two types of products are available: (1) those that might be safe but do not work and (2) those that might work but are not safe. [47]

DIETARY HABITS

Sexual behavior and dietary habits have long been subjects of scientific inquiry owing to their shared consummatory nature and rhythmic patterns. Aphrodisiac foods, which elicit sexual instinct and desire and enhance sexual performance and pleasure, are a topic of particular interest.

Aphrodisiac foods can be classified into three groups (i) improving libido, (ii) enhancing power, (iii) heightening sexual pleasure. In a study conducted by Younis et al., it was revealed that seafood emerged as the most common food associated with improved sexual behavior, followed closely by chocolate. Additionally, mushrooms were noted for their libido-stimulating properties. Foods rich in protein, such as meat, are believed to boost organism vitality and increase sexual energy. Notably, the consumption of seafood, as a direct aphrodisiac, also improves sexual activity because it often involves shared meals, potentially influencing the frequency of sexual intercourse among couples [48]. Among beverages, tea is suggested to possess potent aphrodisiac qualities. Furthermore, coffee and caffeine intake, prevalent among 85% of adults in the US, have been linked to a decreased risk of erectile dysfunction (ED). However, the beneficial effects are contingent upon moderate consumption, with a recommended limit of up to 375 mg/day (approximately 2/3 cups per day). Caffeine has also been observed to decrease ED risk among men with obesity, hypertension, and no diabetes [49].

The misconception regarding alcohol as a sexual facilitator is prevalent, with some mistakenly viewing it as an aphrodisiac. While low-dose alcohol may induce euphoria and openness in some individuals, higher doses have the opposite effect, depressing the nervous system and attenuating sexual response. This can manifest as erectile dysfunction in men and reduced vaginal lubrication in women. Women seeking treatment for alcohol dependence commonly report lower sexual desire and difficulty reaching orgasm [50].

The correlation between a satisfying sex life and overall health is undeniable, exerting a significant influence on the lifestyle choices of both partners. The research underscores the adverse impact of an unhealthy lifestyle characterized by substance abuse (e.g., drugs, alcohol, smoking) and obesity on male and female sexual function. Obesity, in particular, stands out as a leading risk factor for sexual dysfunction, exacerbated by the current global epidemic affecting over 500 million adults.

Obesity not only compromises physical and mental well-being but also profoundly impacts sexual health. Its association with cardiovascular disease, diabetes, dyslipidemia, and hypertension underscores the multifaceted nature of its harmful effects on overall health and sexual function.

Research indicates that obesity mainly affects women in terms of sexual dysfunction, particularly arousal, lubrication, satisfaction, and orgasm, as assessed by the Female Sexual Function Index (FSFI). While obesity does not significantly impact pain during intercourse, it notably impairs various aspects of sexual function in women. Moreover, evidence suggests

that weight loss in obese women leads to increased libido, highlighting the potential benefits of weight management in improving sexual health [50].

Furthermore, obesity carries a significant social stigma that can contribute to depression among affected individuals [50]. Overweight or obese women are less likely to engage in sexual intercourse compared to their healthy counterparts, potentially due to subjective evaluations of their sexual appeal and desirability. Partner attitude also play a pivotal role, with instances of sexual abuse and discrimination based on body shape reported among obese women [51].

Socio-psychological factors also exert a profound influence on libido. Fatigue, insecurity, tension, and poor sleep quality can all diminish sexual desire. Low self-esteem and lack of confidence may further contribute to decreased libido levels. Thus, it is essential to consider the holistic interplay of physiological, psychological, and social factors when addressing issues related to libido and sexual function [36].

CONCLUSION

The role of dietary supplements in enhancing libido remains an area of ongoing research and debate.

Some well-designed studies highlight the significance of trace minerals (zinc, magnesium, and boron aid testosterone synthesis, enzymatic conversion, stress management and hormonal balance), vitamins (D, A, E, C and group B exhibit pleiotropic effects on sexual health, influencing hormone synthesis, metabolism, and regulation) and amino acids (L-arginine, L-citrulline, L-carnitine enhance blood flow and testosterone production) in modulating libido and sexual function, while other present inconclusive data.

Various plant-derived substances, such as Ashwagandha, Red Ginseng, *Tribulus terrestris*, *Epimedium koreanum*, and Trigonella foenum-graecum seed extract, have shown potential benefits for sexual health. Others (Yohimbine, Spanish fly, mad honey, and Bufo toad) lack sufficient evidence or may carry risks of severe adverse effects.

There are good-quality supplements whose effects have been tested and proven salient. Libifem® and Prolox® are both worthy of endorsement if sexual health needs to be supported.

The current trend of nutraceutical use demands medical practitioners to be especially curious and knowledgeable about such substances for the sake of their patient's well-being. It is crucial to approach the use of such supplements (especially combined ones) for libido

enhancement with caution and skepticism, seeking guidance from literature of good quality and

However, the psychosocial aspects of sexual wellness cannot be overlooked. Factors such as stress, mental health, and relationship dynamics can profoundly influence sexual desire and satisfaction, highlighting the need for a holistic approach to the topic at hand.

In summary, while nutrition, dietary habits, and dietary supplements can play a role in supporting libido and sexual health, they are just one aspect of a broader picture. Moving forward, well-designed clinical trials and longitudinal studies are needed to elucidate the long-term effects and clinical significance of these substances in improving libido and sexual function. Further research is required in order to understand better the mechanisms underlying the relationship between diet and libido and to identify safe and effective interventions for enhancing sexual function.

Promoting a balanced diet, maintaining healthy lifestyle habits, and fostering open communication about sexual health are essential to overall well-being.

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MAJOR APPLICATIONS OF 3D PRINTING IN MEDICINE

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INTRODUCTION

A few decades ago, 3D printing technology seemed possible only in science fiction movies. Since its inception, 3D printing has developed in multiple directions, offering increasingly diverse possibilities. The first devices using this groundbreaking technology were created in the 1990s [1].

Although the initial prints were imperfect, continuous improvements have significantly enhanced their quality. Today, 3D printing has a wide range of applications across various industries, and in recent years, it has garnered significant attention in the medical field.

In medicine, 3D printing is being researched, implemented, and utilized in numerous areas. Custom prostheses and implants, anatomical models for educational purposes, preoperative planning models, components of medical equipment, and rehabilitation devices are all being produced using 3D printing technology [2].

Additionally, some medications are being manufactured this way. There is ongoing work to create bioprints, which include cells, tissues, and even entire organs. This innovative technology is precious in scenarios where tailor-made components are essential, such as reconstructing bone fragments or creating precise preoperative models.

In the medical sector, 3D printing has shown particular promise and has begun to revolutionize the way medical professionals approach patient care. Custom prosthetic limbs can be tailored to patients' specific anatomy, offering better fit and comfort. Implants, such as joint replacements and cranial implants, can be customized to match a patient's unique anatomy, reducing complications and improving surgical outcomes.

Anatomical models, created from patient-specific imaging data, assist surgeons in planning complex procedures with greater precision and provide invaluable educational tools for medical students and professionals.

PROSTHETICS

This is one of the most rapidly growing branches of medicine that utilizes 3D printing technology. In the United States alone, approximately 1.7 million people are living with limb loss [3].

Traditional prosthetics can be relatively expensive, heavy, or poorly fitted , which unfortunately, may result in reduced availability or patient rejection [4].

However, with development of 3D printing, it has become possible to create prosthetic components or even entire prostheses at a lower cost. The advantages of this technology include the relatively low cost, which is particularly important for children who outgrow their prostheses quickly, and the ability to precisely fit the prosthetic to the patient's body using a computer-generated accurate model.

A 3D-printed arm or forearm can significantly aid individuals in managing daily life activities and improve their mental well-being, enabling them to lead more independent and fulfilling lives. [5].

The customization offered by 3D printing ensures that each prosthesis can be tailored to the user's specific needs, enhancing both functionality and comfort.

Different companies develop 3D-printed prostheses, leading to variations in design and functionality. Recently, scientists, medical professionals, and engineers have focused on creating advanced 3D-printed prosthetics that mimic limb motion and function more accurately.

These sophisticated prostheses can be controlled using signals directly from the brain (EEG signals) or the muscles (EMG signals), providing a more natural and responsive experience for the user.

The growth of 3D printing in prosthetics represents a significant advancement in medical technology. It offers practical benefits in terms of cost and customization and profound improvements in the quality of life for individuals with limb loss.

By leveraging the precise capabilities of 3D printing, medical professionals can create prosthetic devices that are better suited to each patient's unique needs, fostering greater independence and enhancing overall well-being.

As research and development in this area continue to advance, the potential for 3D-

printed prosthetics to revolutionize the field of limb replacement is immense.

Innovations in materials, design, and control mechanisms will likely lead to even more sophisticated and effective prosthetic solutions, further improving the lives of those who rely on these devices.

MEDICAL EDUCATION AND TRAINING

3D printing has also revolutionized medical education by providing detailed and accurate anatomical models for teaching and training purposes. Unlike traditional methods such as cadaver dissection and 2D images, 3D-printed models offer a tangible, precise, and often customizable alternative that enhances the learning experience. Additionally, 3D printing makes medical education more accessible by providing cost-effective models compared to traditional cadaveric specimens, which are expensive and subject to legal and ethical considerations. 3D-printed models can be easily reproduced and distributed, ensuring that students worldwide have access to high-quality educational tools [6].

Medical students benefit from 3D-printed anatomical models because they provide a hands-on, tactile way to explore complex structures. These models can be printed in various materials and colors to highlight different tissues, organs, and systems, making it easier to understand spatial relationships and intricacies that might be missed in textbook images or 2D digital representations [7].

A study found that students using 3D-printed models had several advantages over those in the conventional group, such as higher accuracy and faster response times. The 3D printing group performed at least as well as the conventional group regarding anatomical knowledge. Additionally, their post-training test scores were higher than those of the cadaver or 2D group. Furthermore, more students in the 3D printing group reported higher satisfaction with their learning experience compared to the conventional group [7].

3D-printed models are also used in simulation training, allowing medical students and professionals to practice procedures without patient risk. For instance, models of bones, organs, or entire body parts can be printed to practice surgical techniques, suturing, and other procedures. In general, 3D-printed models are anatomically accurate, provided that high-quality CT scan data are available. However, in most cases, 3D-printed models are inflexible, which makes application difficult in cases involving soft tissue, such as the brain or lungs [8].

In neurosurgery, a solution to this problem was proposed by Ploch et al., who used a surrogate gelatin-type material that closely mimics the mechanical properties of the human

brain. While the model is not entirely accurate, it was deemed very useful in planning and training for medical procedures [9].

The future of 3D printing in medical education is promising, with technological advancements likely to produce even more detailed and functional models. Innovations such as multi-material and bio-printed models that mimic natural tissue properties could further enhance training and educational outcomes [10].

ORGAN PRINTING

Organ printing, or bioprinting, is an emerging field within 3D printing technology that aims to fabricate biological tissues and organs using living cells and biomaterials. A 3D-printed organ replicates bodily tissue crafted using a 3D bioprinter. The artificial organ or tissue is printed using bioink, developed to support cells in building the function and structure of the natural organ it mimics. These 3D-printed organs hold promise for various applications, including transplantation, disease modeling, drug testing, and personalized medicine. However, challenges remain in achieving full functionality, vascularization, and addressing the regulatory landscape for clinical implementation [11].

The process of organ printing consists of several steps and can be divided into three groups. The first step, bioprinting, involves forming a model for the printer and selecting materials for the process. It begins with extracting a tissue biopsy to create a biological model for 3D bioprinting. CT or MRI scans are used to obtain tomographically reconstructed 2D images. Necessary cells are then selected and multiplied, with the resulting cell mass mixed with oxygen and nutrients to keep them viable [12].

The second step in the bioprinting process involves using bioink, a mixture of cells, nutrients, and matrix placed in the printer to create a 3D structure. This bioink is deposited layer by layer onto a scaffold, forming a 3D tissue based on the digital model. The process is complex, requiring the creation of different cell types according to the specific tissues and organs being formed. A patient's cells are harvested and used to minimize the risk of organ rejection. These cells are grown and mixed with bioink tailored to print the desired tissue [11,12].

The final step in the bioprinting process is post-bioprinting, which ensures the stability of the printed structure. This step involves applying physical and chemical stimulations to maintain the structure and function of the biological matter. These stimulations signal the cells to reorganize and sustain tissue growth. Without post-bioprinting, the mechanical integrity and functionality of the material could be compromised [12].

Bioprinting can revolutionize organ transplantation by creating tissues and organs tailored to the patient's specific genetic and immunological profile, thereby reducing the risk of rejection. While fully functional printed organs for transplantation are still experimental, significant progress has been made in printing simpler tissues such as skin, cartilage, and vascular grafts [13].

3D-printed models, when based on high-quality CT or MRI data, are anatomically accurate, allowing for precise replication of tissues and organs. Surgeons can create personalized medical solutions, such as dental implants, prosthetics, and specific organ tissues, tailored to individual patients' needs. Bioink design and synthesis advances have led to materials that support cell growth and mechanical stability, accommodating various bioprinting techniques. Methods like extrusion in granular support baths enable the creation of intricate 3D structures, overcoming previous limitations with low-viscosity bioinks. Successful examples include tracheal grafts, cartilage engineering, bone defect treatments, and vascularized bone constructs, demonstrating the potential for practical medical applications. Bioprinting also provides in-vitro models for drug screening, disease modeling, and personalized medicine, enhancing research and treatment development. Furthermore, 3D bioprinting can generate complex tissues and organs, potentially addressing organ shortages and improving transplantation outcomes [14].

Despite its promise, 3D organ printing faces several challenges. A limited number of bio-inks are both bioprintable and accurately represent the required tissue architecture, posing a challenge for restoring organ function post-printing [14].

The bioprinting process involves shear stress that can damage cells and alter gene expression, especially affecting sensitive stem cells like iPSCs, which often do not survive printing [14].

Stem cell research has predominantly been conducted in 2D environments, leaving many unknowns in the context of 3D stem cell culture and its implications. Proper nutrient exchange and integrated printed vasculature with host vasculature post-implantation remain significant obstacles [14].

Without proper post-bioprinting procedures, bio-printed tissues' mechanical structure and functionality can be compromised. Additionally, the technology and processes involved in 3D bioprinting are complex and can be expensive, limiting widespread adoption and application in clinical settings. The development and use of 3D-printed organs involve regulatory and ethical considerations that must be addressed to ensure safe and equitable access [14].

DRUG DELIVERY

3D printing can be crucial in the drug delivery system. Since the 2015 approval of the first 3D-printed drug product, the number of publications on this topic has multiplied [15]. The progress of 3D printing and scanning can result in creating personalized treatment plans and moving away from mass manufacture toward small-batch personalized medicines [8,16].

This technology enables us to create personalized tablets, capsules, or microneedles, but we must not forget about the system itself. 3D printing allows us to adjust the treatment path. In recent years, thanks to this technology, doctors and engineers have created numerous 3D-printed devices designed to deliver drugs into patients' systems in ways previously unknown. One of the devices created by a 3D printer is an Intrauterine Device (IUD) [15].

This device is a form of birth control that a healthcare provider inserts into the uterus. Once inserted, an IUD can prevent pregnancy for up to 10 years or more, depending on the specific type. The provider can remove the IUD at any time if a woman decides to become pregnant. This method has a 99% success rate, is very cost-effective, and eliminates the concern of missing a birth control pill or forgetting to get a birth control shot, etc. [17].

Another device created using this technology is the Vaginal Ring, which is not only a contraceptive device but also a way to prevent bacterial vaginosis[15].

Research shows that in patients using the vaginal ring, the mean Nugent score (a scale evaluating vaginal microbiota) decreased significantly, indicating improvement in treating and preventing bacterial vaginosis [18,19].

3D printing has a bright future ahead. It allows manufacturers to create personalized drug delivery systems and makes them cost-effective and perfectly suited for each patient, but we cannot forget its limitations [15].

For now, 3D printing cannot compete with the speed of traditional methods, and it is also limited by the availability of materials used for printing [15].

3D printing is a promising step toward applying more technology in medicine, but it will be fully reliable and appreciated only if it overcomes its limitations.

SURGERY PLANNING

Another field of medicine where 3D printing technology can lead to significant progress is surgery planning. It is widely used in many areas of medicine, such as orthopedics, anesthesiology, pediatrics, vascular surgery, and reconstructive surgery. This technology is primarily used to print accurate copies of organs on which surgery is to be performed, persona-

nalized surgical tools, and even implants or prostheses [20].

This technology allows surgeons to familiarize themselves with the anatomical structure of the organ, prepare for the surgery in advance, analyze different approaches, and precisely practice the movements needed before entering the operating room [8].

Thanks to the aforementioned personalized tools, surgeries can be performed safer, more accurately, and ultimately more effectively than traditional approaches. For example, detailed anatomical models printed in 3D technology enable surgeons to better understand the unique anatomical features of the patient, which can lead to more precise and effective operations [21].

Personalized surgical instruments tailored to the specific surgery can also enhance the precision and effectiveness of the procedure [21].

We must not forget about the surgeon. Using this technology, the surgeon can perform the procedure in a shorter time than without it, which allows for a shorter anesthesia duration for the patient. This reduces the risks associated with
prolonged anesthesia and decreases the number of errors caused by surgeon fatigue. Shortening the operation time allows the surgeon to admit, diagnose, and attempt to treat more patients, which is particularly important in high-traffic medical facilities [21].

Thanks to 3D printing, surgery planning has become more efficient and has yielded positive results for both the patient and the surgeon [21].

This technology increases the precision and safety of procedures, reduces the costs associated with lengthy operations, and improves the overall quality of healthcare. Examples of the application of 3D printing in surgery planning include creating anatomical models for educational purposes allowing young surgeons to refine their skills in realistic conditions. However, like everything, it also has its limitations [21].

Attention must be paid to the cost, the time required to print the perfect element, and the availability of materials [21].

The cost of 3D printing can be high, especially if specialized materials are required. The time needed to prepare and print models can also be a challenge, particularly in situations requiring urgent intervention. If these challenges are overcome, surgery planning will reach an even higher level than it is currently at. The development of 3D printing technology has the potential to revolutionize not only surgery planning but the entire approach to surgical treatment, offering more personalized, effective, and safe treatment methods.

CONCLUSIONS

3D printing technology has undeniably transformed various sectors, and its impact on medicine is particularly profound.

Throughout this monograph, we have explored the significant applications of 3D printing in the medical field, highlighting its revolutionary potential and practical benefits.

While the potential of 3D printing in medicine is vast, it is essential to acknowledge the remaining challenges. Issues related to material availability, cost, and the complexity of bioprinting processes need to be addressed to realize this technology's benefits fully.

Nevertheless, the advancements made thus far indicate a promising future where 3D printing continues to revolutionize medical practice, offering innovative solutions and improving patient care across various domains.

In conclusion, 3D printing is a transformative force in medicine, driving progress and innovation. As research and technology continue to evolve, the applications of 3D printing in the medical field will expand, paving the way for more personalized, effective, and accessible healthcare solutions.

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MEDICAL MOBILE APPS AND MEDICAL PROFESSIONALS, THE DUO OF THE CURRENT MEDICINE?

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INTRODUCTION

Nowadays, it's hard to imagine our daily lives without a smartphone waiting in our pockets for our commands. These ubiquitous devices have become integral to our entertainment, work, and many other activities. They are our constant companions, providing instant access to a wealth of information, connecting us with others through calls, texts, and social media, and offering countless apps that cater to our every need and interest. From streaming our favorite shows and playing games to managing our schedules and keeping track of our fitness goals, smartphones are indispensable tools that enhance our productivity and leisure.

In recent years, smartphones have also become a helpful tool for doctors, facilitating many aspects of their work. With the advent of advanced medical applications, these devices now play a crucial role in healthcare settings, assisting physicians in diagnosing illnesses, monitoring patient health, and accessing the latest medical research. In a survey conducted in 2021, nearly half of the respondents believed that more medical apps should be developed to implement them as tools in medical practice [1].

They also pointed out the need to adapt these apps to the realities of medicine so that privacy and patient confidentiality would not suffer.

This concern is paramount, as the sensitive nature of medical information requires robust security measures to protect patient data from unauthorized access and breaches.

Already, however, medical apps are finding several applications in the treatment

process and are becoming an integral part of many doctors' professional lives. These applications range from telemedicine platforms allowing virtual consultations to diagnostic tools utilizing artificial intelligence to interpret medical images. Mobile health (mHealth) apps enable patients to track their health metrics, such as blood pressure, glucose levels, and heart rate, and share this data with their healthcare providers in real-time. This continuous flow of information helps doctors make more informed decisions and gives patients a more active role in managing their health [2].

Furthermore, educational apps are revolutionizing how medical students and professionals continue their education. Interactive learning modules, virtual reality simulations, and up-to-date medical journals at their fingertips ensure that medical practitioners stay current with the latest advancements and techniques. These resources enhance their knowledge and can improve patient outcomes by promoting best practices in clinical settings.

INFORMATION AND TIME MANAGEMENT

In the fast-paced world of healthcare, efficient information and time management are essential for medical professionals. Integrating medical applications has significantly transformed these aspects by providing real-time access to patient data, medical records, and other crucial information. This chapter delves into how mobile apps facilitate information and time management for healthcare professionals (HCPs), leveraging insights from various sources. In the past, particularly around 2014, HCPs relied heavily on mobile devices and applications to manage information efficiently. These devices were instrumental in various tasks such as writing notes, dictating notes, recording audio, taking photographs, and organizing information. These functionalities allow medical professionals to maintain accurate and comprehensive records, which is crucial for patient care [3].

Popular information management apps during that period included Evernote and Notability, which enabled users to write or dictate notes, record audio, store photographs, and organize material into searchable electronic databases [4].

These apps allowed for efficient categorization and retrieval of information, a vital feature in clinical settings where timely access to patient data could significantly impact treatment outcomes. E-book reader apps like GoodReader and iAnnotate provide additional capabilities by allowing users to view, underline, highlight, enlarge, and annotate text in PDF files [5,6]. This was particularly useful for HCPs who needed to review and annotate medical

literature, guidelines, and research papers [3]. Performing these functions on mobile devices enabled healthcare professionals to stay updated with the latest medical knowledge and apply it to their practice.

Cloud-based storage and file-sharing services enhanced information management by providing platforms for storing, updating, and sharing documents or photographs without physical media like flash drives or CDs. Popular cloud services such as Dropbox, Google Drive, SkyDrive, and Box offered varying storage capacity and compatibility with operating systems [4–6]. These services allowed multiple users to access and collaborate on documents in real-time, streamlining communication and information sharing among healthcare teams.

Efficient time management was another critical aspect of healthcare that mobile apps significantly improved. HCPs use mobile device apps to organize and track appointments, meetings, call schedules, and other clinical obligations (Source 2). These tasks could often be handled by native apps pre-installed on mobile devices, eliminating the need for specialized applications.

Apps such as ZocDoc further streamlined the appointment scheduling process by allowing patients to view information about and make appointments with participating doctors directly from their mobile devices [7]. This facilitated appointment booking for patients and helped doctors manage their schedules more effectively by reducing the administrative burden.

Today, while many of these apps are still available on the market, they have been replaced by programs encompassing most of the abovementioned functions. One notable example is Asseco Medical Management Solutions (AMMS), which is widely used in many Polish hospitals.

AMMS represents a system designed to streamline and optimize time and information management within healthcare settings. This integrated platform is crucial in enhancing operational efficiency, improving patient care delivery, and supporting healthcare professionals in daily tasks.

AMMS offers solid capabilities for managing information effectively. It provides a comprehensive Electronic Health Records (EHR) system that digitizes and centralizes patient health information, including medical histories, diagnoses, treatment plans, medications, lab results, and imaging studies.

This ensures that healthcare providers have immediate access to accurate data regardless of location, which enhances clinical decision-making and patient care continuity.

By consolidating patient information into a centralized repository, AMMS eliminates inefficiencies related to paper-based and disparate electronic records. The central repository ensures easy access and updates, minimizing duplication and errors and improving data reliability and security to meet HIPAA regulations.

AMMS supports interoperability with other healthcare systems, facilitating seamless data exchange across departments. Integration with laboratory, imaging, and pharmacy systems allows real-time updates and collaboration, enhancing clinical workflow efficiency.

In time management, AMMS optimizes appointment scheduling with advanced functionalities that streamline booking, manage patient queues, and improve operational efficiency. Automated reminders reduce no-shows, ensuring patients arrive prepared for appointments.

Task management and workflow automation tools enable real-time task prioritization, assignment, and progress tracking. This enhances staff productivity, reduces administrative burdens, and ensures effective resource allocation for patient care.

AMMS also provides robust reporting and analytics capabilities, enabling administrators to monitor KPIs, analyze trends, and make data-driven decisions. Detailed reports on patient outcomes, resource utilization, and financial performance support strategic planning and continuous improvement initiatives within healthcare facilities.

COMMUNICATION AND CONSULTING

In recent years, mobile phones and apps have revolutionized our ability to complete various tasks without leaving our homes. This technological convenience extends to the healthcare sector through the innovative approach known as telemedicine. Telemedicine, also called remote medicine, is a modern medical service delivery method using information and communication technologies.

With telemedicine, patients can access healthcare services without being physically present at a doctor's office. This method leverages technology to bridge the gap between healthcare providers and patients, ensuring that medical care is accessible regardless of geographic location. Telemedicine covers various services, including medical consultations, diagnoses, patient health monitoring, and education [8].

The scope of telemedicine is vast and versatile. It allows for real-time consultations with healthcare professionals through video calls, enabling doctors to diagnose and recommend

treatments remotely. Patients can also use telemedicine platforms to monitor their health status, such as tracking vital signs or managing chronic conditions, with data being shared directly with their healthcare providers. Additionally, telemedicine provides educational resources to patients, helping them understand their health conditions and the necessary steps for management and prevention.

Telemedicine has gained much popularity, especially in the context of the COVID-19 pandemic, which has accelerated its large-scale implementation. The need for social distancing and the reduction of in-person interactions made telemedicine an essential tool for maintaining healthcare services. It brings numerous benefits.

Telemedicine also minimizes the risk of infection, as patients can receive medical advice and treatment from the safety of their homes. This aspect is particularly crucial for individuals with compromised immune systems or those managing contagious diseases [9]. Another advantage of this technology is saving money and time. Patients do not have to spend their transportation resources since they can call the doctor from home and use their time for other activities [10].

Looking ahead, the potential for telemedicine continues to grow. Advances in technology are expected to introduce even more sophisticated tools for remote diagnostics, virtual reality consultations, and seamless integration with electronic health records. These innovations will further refine the delivery of healthcare, making it more efficient and personalized.

PATIENT MANAGEMENT AND DECISION-MAKING

Integrating mobile devices and advanced technologies has revolutionized patient management and clinical decision-making. This evolution is evident in the widespread adoption of telehealth and mobile health applications, which have significantly impacted how (HCPs) manage patient care and make clinical decisions.

Telehealth has become a vital component of patient management, especially in light of the COVID-19 pandemic. Telehealth monitoring allows patients to contact their doctors or medical staff using smart devices via audio or video calls. According to Snoswell et al. (2021), the use of telehealth has exponentially increased over the last decade. Their systematic review, covering 38 meta-analysis articles published between 2010 and 2019 demonstrated the clinical effectiveness of telehealth applications across various medical disciplines, including mental

health support, pain management, blood pressure and glucose control, stroke management, and diagnostic services for dermatological and ophthalmic conditions [11].

Despite its advantages, telehealth also presents challenges. Issues such as overutilization, increased healthcare costs, and disparities between rural and urban populations due to varying access to the internet and technology are significant concerns. Additionally, patient data security remains a critical challenge, as the lack of end-to-end encrypted communication services can jeopardize sensitive health information.

REMOTE PATIENT MONITORING

However, we must not forget about the daily monitoring of patients. Mobile monitoring of vital signs such as heart rate, blood glucose levels, rehabilitation progress, and overall data collection can greatly aid physicians in proposing treatment plans and adjusting strategies if the current plan is ineffective [3]. Continuous remote monitoring can also adjust the timing of follow-up visits based on the patient's needs and help identify the causes of emerging problems [12]. Numerous apps and programs are available for real-time patient monitoring, but we will focus on just a few of them [7].

PREVENTION TASKFORCE APP

The Prevention TaskForce app assists primary care clinicians in selecting appropriate screening, counseling, and preventive medication services for patients. It uses the latest recommendations from the U.S. Preventive Services Task Force (USPSTF) and allows searches based on patient characteristics such as age, gender, and behavioral risk factors. While the app is useful, clinicians should consult specific recommendations to confirm suitability, as it is intended to complement, not replace, clinical judgment and individualized care [13].

MEDIQUATIONS

The Mediquations app, developed by a physician at UTSW (UT Southwestern), offers healthcare workers easy access to over 200 medical formulas and scoring systems. The intuitive user interface includes an alphabetical list of formulas, a category sorting option, and a search bar for quick access. Users can select a formula and input necessary values, and the app calculates the required scores or values. A brief description and references for additional information accompany each formula. The app also allows users to take notes and favorite frequently

used formulas for quick reference, making it a comprehensive tool for medical calculations and scoring [14].

CONCLUSIONS

Smartphones and mobile apps have become a big part of our everyday lives, making things more accessible and connected. This is especially true in healthcare, where these tools are helping doctors and patients in many ways. Apps like the Prevention TaskForce and Medications provide essential medical information and calculations, helping doctors make better decisions.

Telehealth and mobile health apps have made it possible to monitor patients remotely. These apps allow doctors to keep track of vital signs and other health data in real-time, making it easier to adjust treatment plans as needed. Educational apps also help medical students and professionals stay updated with the latest medical knowledge.

However, it is essential to remember that these tools have their limits. Protecting patient privacy and data security is crucial, and these apps cannot replace the need for in-person doctor visits and complete medical exams.

Overall, mobile apps are a valuable addition to healthcare. They help doctors provide better care, keep up with new information, and make healthcare more efficient and effective. However, they should be used alongside traditional methods, not as a complete replacement.

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BLEEDING, HELP! - CURRENT MANAGEMENT OF TRAUMATIC AND NON-TRAUMATIC BLEEDING PATIENTS

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INTRODUCTION

The management of bleeding patients is a very demanding and challenging medical emergency faced by physicians, intensivists, and surgeons almost every day in medical facilities worldwide. Whether due to injury, inherited, or acquired disorders of hemostasis, this phenomenon significantly increases the risk of serious health issues such as hemodynamic instability, shock, or death. As a result, an emergency team must provide fast, decisive, and well-coordinated action to optimize patient outcomes.

Current strategies emphasize a systematic approach to assessment, stabilization, and definitive treatment tailored to the type and severity of hemorrhage. Patients presenting with bleeding in the emergency department often exhibit symptoms such as tachypnea (rapid breathing), decreased urine output, alterations in blood gas analysis, and changes in blood pressure, heart rate, and body temperature [1]. These clinical signs are crucial for identifying the severity of the condition and initiating appropriate treatment.

Recognition and swift identification of these features are essential in managing bleeding. Another critical step is obtaining comprehensive health-related information from the patient or their medical records. This information helps in understanding the underlying condition, whether it be trauma, a congenital bleeding disorder like hemophilia, or an acquired condition such as anticoagulant use or liver disease. A thorough patient history and physical examination allow for a more accurate assessment and tailored treatment plan. Evaluation of hemoglobin levels and coagulation variables, such as prothrombin time (PT), activated partial thromboplastin time (aPTT), and platelet count, must be carried out promptly [2]. These laboratory tests provide vital information on the patient's hemostatic status and guide the

need for interventions such as blood product transfusions. The availability of blood and its products, including packed red blood cells, fresh frozen plasma, platelets, and cryoprecipitate, is crucial. Immediate transfusion may be necessary to restore hemodynamic stability and correct coagulopathy.

In addition to these measures, adjunctive therapies such as tranexamic acid (TXA) to inhibit fibrinolysis and the administration of specific clotting factors for patients with known deficiencies can be lifesaving [3,4]. Based on the bleeding source, advanced interventions, including endoscopic procedures for gastrointestinal bleeding or surgical exploration for uncontrolled hemorrhage, might be required [4].

TRAUMATIC BLEEDING

INTRACRANIAL BLEEDING

Globally, each year, 69 million people have a traumatic brain injury (TBI). The highest incidence rate of TBI is observed in low and middle-income countries. [5].

Intracranial bleeding (IB) often occurs as a serious consequence of TBI. TBI is a type of acquired brain injury with multiple possible causes. Two main trauma mechanisms are falls - 52.6% and traffic accidents - 31.6%. [6].

TBIs can be classified as mild, moderate, or severe. Mild TBIs (mTBI) account for 70-90% of all TBIs, moderate (modTBI) and severe TBIs (sTBI) for 10%, each. The international CRASH trial, consisting of 10 008 patients, demonstrated a rate of any type of IB in 56% of cases, and 27% presented a subarachnoid hemorrhage. [7] A study by Perel et al. comprised 13 962 patients with TBI and Glasgow Coma Scale (GCS) <15. Results showed that 6445 patients (46%) had some type of IB. The most common type of IB was subdural hematoma (SDH), present in 30% of patients. Epidural hematoma (EDH), Intraparenchymal bleeding, and subarachnoid hemorrhage were present in 22% each [8].

A study by Alberts et al. demonstrated an IB rate of 4.8% in patients with mTBI with no neurological deterioration. Need for neurosurgical treatment were only required in selected cases. IB risk was linked with older age and intake of anticoagulants. [9] Recent meta-analysis results, demonstrate that patients with mTBI, taking oral anticoagulants (direct oral results, demonstrate that patients with mTBI, taking oral anticoagulants (direct oral anticoagulants (DOACs), vitamin K antagonists (VKA)) had IB incidence of 8.5% [95%CI 6.6 – 10.9%], and delayed IB incidence of 1.7% [95% CI 1 – 2.8%] [10]. Considering these results, patients taking oral anticoagulants should not be overlooked in case of mild TBI. sTBI pose a significant therapeutic challenge due to its significant brain damage and often large bleeding. Mortality

rate in patients with sTBI ranges about 24 to 30% [11,12]. Proper initial management is crucial in patients with sTBI to achieve favorable outcomes as sTBIs are linked with poor neurological outcomes, high morbidity and health-related quality of life. To increase chances of more favorable outcomes, guidelines of the management of sTBI should be applied. Here we present the most important ones. Assessment of sTBI should be done using GCS, specifically the motor response as well as pupillary size and reactivity [7,13]. Severity of TBI should be assessed by clinical and radiological signs without delay (computed tomography - CT) [13]. It is critical to avoid episodes of hypotension (systolic BP <110 mmHg or mean arterial pressure (MAP) >80 mmHg) to maintain adequate cerebral perfusion pressure (CBP). Initial correction of hypotension should consist of vasopressors like norepinephrine, fluid infusions if needed (in hypovolemic patients), mechanical ventilation to facilitate central venous return. Hypotensive hypnotic agents should be avoided. After decompressive craniectomy or hematoma evacuation, intracranial pressure monitoring should be applied [14]. Additionally, in case of elevated ICP caused by IB or brain edema, external ventricular drainage should be applied to control ICP [15]. Additional initial resuscitation targets contain of preserving SpO_2 >90% and hemoglobin (Hb) concentration >7 g/dL to avoid brain hypoxia, End-tidal CO_2 ($EtCO_2$) 30 – 35 mmHg to preserve CBF, reversal of anticoagulants to limit blood loss and expansion of hemorrhage [16]. Other guidelines are available in this article [13].

For early management of IB, the CRASH-3 trial comes in handy. Tranexamic Acid (TXA) usage in the first 3 hours (TXA should be administered as soon as possible) from brain injury with potential bleeding results in a reduction of head – injury-related death with no evidence of adverse effects. However, this reduction was substantial in mTBI to modTBI and not in sTBI patients [17].

TRAUMATIC ABDOMINAL BLEEDING

In abdominal trauma patients, bleeding management is the primary action. Fast assessment of ongoing intra-abdominal bleeding is a key intervention to undertake proper course of action. The most commonly injured organs are the liver, spleen, or intestines [18]. A quick (requires only several seconds to do) and easy tool to assess abdominal hemorrhage is a focused assessment with sonography for trauma (FAST) examination. In the study by Schwed et al., FAST examination was proven to be a reliable method of intra-abdominal hemorrhage detection. In patients with pelvic fractures and hemorrhage, sensitivity and specificity were

85.4% and 98.8%, respectively. Out of 1219, only 21 (1.1%) had false-positive result [19]. In prehospital setting, there are many strategies to manage abdominal hemorrhage. Previously mentioned use of TXA within the 3h of trauma, prevention of hypothermia, permissive hypotension, avoiding hemodilution with excessive crystalloids infusions and management of acidosis. Target of hypothermia prevention is to maintain satisfactory platelet function and avoid impairment of coagulation [20]. Permissive hypotension is a temporary strategy in resuscitation of patients with traumatic hemorrhage. It helps to maintain sufficient organ perfusion and reduce the risk of multi-organ failure. Permissive hypotension can be achieved with mean MAP of 50 mm Hg or systolic blood pressure of 80-90 mm Hg [21]. However, permissive hypotension can only be applied to patients without brain injury. We explained this topic in previous paragraph. Excessive crystalloids infusions may result in an increase of cardiac output with subsequent elevation of MAP, reduction of peripheral vasoconstriction and more bleeding. Additionally, dilution coagulopathy, hypothermia, edema, organ failure or even degradation of forming clot [22]. Therefore, it is important to remember that even in bleeding patients too much fluids can deteriorate their condition even more. However, these procedures can't lead to delay in patient's transportation to the nearest trauma center.

Emergent trauma laparotomy (ETM) is a procedure performed to trauma patients in critical condition with suspected bleeding. Unfortunately, despite being a live-saving procedure, ETM still has high mortality rates. Harvin et al. demonstrated a 21% (60% deaths due to hemorrhage) mortality rate among the cohort that had undergone ETM in the non-hypotensive group and 46% (65% deaths due to hemorrhage) in a hypotensive group with SBP <90 mm Hg. The most common procedures during ETM were enterectomy (23%), hepatorrhaphy (20%), enterorrhaphy (16%) and splenectomy (16%) [18]. Tolstrup et al. demonstrated similar results of mortality after emergency laparotomy – 21% patients died within first 24h after procedure [23].

Other, interesting technique for management of hemorrhage is Intra-Aortic Ballon Occlusion (IABO). This particular device was developed in 1953 by Edwards et al. Initially, IABO was designed to treat aortic aneurysms. IABO can temporarily limit blood loss from hemorrhage by a balloon inflated in the aorta, blocking blood flow. A retrospective analysis of IABO effectiveness among patients with hemorrhagic shock demonstrated that IABO is an effective method for traumatic hemorrhage shock, as it reduces the need for blood transfusions and total occlusion times [24].

NON-TRAUMATIC BLEEDING

Non-traumatic bleeding, or bleeding not caused by physical injury, encompasses a wide range of medical conditions that can lead to significant morbidity and mortality. These bleedings can occur in various anatomical regions, each presenting unique challenges in diagnosis and management. The common areas affected include the head, gastrointestinal tract, aorta, and sex organs. Understanding the etiology, epidemiology, clinical presentation, potential complications, and appropriate treatment strategies for each type of non-traumatic bleeding is crucial for effective patient care. This chapter will delve into the specific conditions associated with non-traumatic bleeding, highlighting key aspects necessary for proper medical intervention.

INTRACRANIAL BLEEDING

The most common cause of non-traumatic intracranial hemorrhage is hypertension. Chronic high blood pressure can lead to the weakening and rupture of small arteries in the brain, resulting in hemorrhagic stroke. Other significant causes include cerebral amyloid angiopathy, which is more common in the elderly. These two causes are accountable for 85% of non-traumatic hemorrhages [25].

Intracerebral hemorrhage (ICH) is a type of intracranial bleeding. It accounts for approximately 10-20% of all strokes. Intracerebral hemorrhage remains at 29.9 per 100,000 person-years, with a notably higher incidence in Asian populations. The risk of ICH increases with age, particularly beyond 85 years, and is more prevalent in men, primarily affecting the basal ganglia [26].

The clinical presentation of ICH depends on the size, location, and presence of intraventricular extension of the hemorrhage. Headache of variable intensity always occurs and may be. The clinical presentation of ICH depends on the size, location, and presence of intraventricular extension of the hemorrhage. Headache of variable intensity always occurs and may be accompanied by nausea and vomiting, focal signs, and progressive neurologic deficits. The deficits may not follow a typical infarction distribution pattern in patients with large artery strokes. Seizures occur in approximately 10% of all patients with ICH and almost one-half of patients with lobar [27,28]. If not treated, it may lead to permanent neurological deficits or death [29].

Patients eligible for non-surgical treatment include those exhibiting minimal symptoms that do not severely impact neurological function. This category also includes patients with a

large hemorrhage, poor initial neurological condition, advanced age, or a pre-existing bleeding disorder, as they have a minimal chance of a favorable outcome. Additionally, patients with hemorrhages located in areas where surgical intervention does not offer better outcomes than medical management, such as the basal ganglia or thalamus, are also considered for non-surgical treatment [30].

Types of non-surgical treatments include clotting factor administration, blood pressure control, and measuring and controlling intracranial pressure (ICP). For patients on blood thinners, administering clotting factors can counteract the effects of these medications and promote blood clotting to stop the bleeding. Managing blood pressure is crucial to reduce the risk of further bleeding, which involves using medications to maintain blood pressure within a target range. Monitoring and controlling ICP is essential to prevent additional brain damage, including medications, draining cerebrospinal fluid, or other medical interventions to manage the pressure within the brain [30].

Candidates for surgical treatment include younger patients, typically those under 50 years old, who tolerate surgery better and have a higher chance of recovery. Surgical intervention is also considered for patients with hemorrhages in favorable locations for evacuation, such as the lobar region, cerebellum, external capsule, and non-dominant hemisphere. Additionally, surgery may be beneficial for patients where it can reduce the risks associated with re-bleeding, brain edema, and necrosis, although it rarely results in immediate neurological improvement [30].

Types of surgical treatments include craniotomy and stereotactic clot aspiration. A craniotomy involves removing a piece of the skull to expose the brain and remove the clot, which is particularly useful when the clot is near the brain's surface or associated with an underlying brain lesion. This procedure allows direct access to the hemorrhage for effective removal. Stereotactic clot aspiration is a minimally invasive technique used to evacuate clots located deep within the brain. It utilizes neuronavigation technology, which functions similarly to GPS, to accurately guide instruments to the clot, reducing trauma to surrounding brain tissues and being highly effective for deep-seated hemorrhages [30].

GASTROINTESTINAL TRACT BLEEDING

When examining non-traumatic gastrointestinal bleeding, it is essential to differentiate between Lower Gastrointestinal Bleeding (LGIB) and Upper Gastrointestinal Bleeding (UGIB). The most common cause of UGIB is Peptic Ulcer Disease (PUD), followed by

Esophagogastric Varices (EV)[31]. For LGIB, the leading cause is Diverticular Disease [32].

Incidence rates range from 15.0 to 172.0 per 100,000 person-years for UGIB and from 20.5 to 87.0 per 100,000 person-years for LGIB. A 2023 meta-analysis reported an overall decline in UGIB incidence over time, with a slight increase between 2003 and 2005, followed by a decrease noted in five of the thirteen studies [33].

Symptoms of gastrointestinal bleeding may include epigastric pain, dyspepsia, lightheadedness, dizziness, and/or syncope. First-line treatment for peptic ulcer disease involves a combination of medications to reduce gastric acid, protect tissues, and antibiotics if an infection is present. It's crucial to eliminate the ulcer's underlying cause. While medications are sufficient for most peptic ulcers, complications like bleeding or perforation may require additional treatment, such as endoscopy. Medications include antibiotics for H. pylori or other bacterial infections (e.g., doxycycline, metronidazole, clarithromycin, amoxicillin), cytoprotective agents to protect the gastrointestinal lining (e.g., sucralfate, misoprostol, bismuth subsalicylate), H2 blockers to reduce stomach acid (e.g., famotidine, cimetidine, nizatidine), and proton pump inhibitors (PPIs) for acid reduction and mucosal protection (e.g., esomeprazole, dexlansoprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole). Alternatives to NSAIDs, like acetaminophen, may also be recommended. For complicated or bleeding ulcers, minor medical procedures like endoscopy are used to treat bleeding through cauterization or medication injection and to repair perforations with stitches. If an ulcer obstructs the duodenum or pyloric channel, interventions such as stomach suction or surgery may be necessary to reopen the channel [34].

Acute variceal hemorrhage is a critical medical emergency necessitating immediate and intensive intervention. The primary treatment goals are to achieve hemodynamic stability, safeguard the airway from aspiration risks, and effectively manage active bleeding to minimize mortality. Patients with variceal hemorrhage require prompt resuscitation to stabilize hemodynamics. Recent research underscores the efficacy of a restrictive packed red blood cell (pRBC) transfusion strategy (maintaining hemoglobin levels between 7-9 g/dL) over a liberal approach in reducing mortality, particularly beneficial in cirrhotic patients [35]. Vasoactive medications like octreotide are crucial for splanchnic vasoconstriction and reducing portal pressure, with early initiation recommended upon suspicion of variceal hemorrhage. Endoscopic band ligation is the preferred treatment for both bleeding and non-bleeding esophageal varices due to its superior efficacy and lower complication rates compared to sclerotherapy [35].

Mild diverticulitis can be managed at home with antibiotics and paracetamol, followed by a fluid-only diet initially and a gradual reintroduction of solids. Hospital treatment is necessary for severe cases, particularly if pain control, hydration, or antibiotic intake is problematic or if complications are suspected. Previously considered preventive, surgery is now reserved for specific severe cases or emergency perforations. Open or laparoscopic colectomy may be performed, potentially leading to a temporary or permanent stoma [36].

AORTIC BLEEDING

Regarding bleeding from the aorta, the most common cause is the rupture of an aortic aneurysm. An aortic aneurysm most frequently occurs in the abdomen[37]. Abdominal aortic aneurysm (AAA) is more often associated with older age, male sex, and white populations. The annual incidence of new AAA diagnoses is approximately 0.4 to 0.67 percent in Western populations. This equates to 2.5 to 6.5 aneurysms per 1000 person-years. Aneurysmal disease is the cause of death in 0.13 percent of males, compared with 0.07 percent of females [38]. The most common symptoms for AAA are acute onset back and/or abdominal pain accompanied by symptoms of shock. However, half of the patients may not present pain [39].

The rupture of an abdominal aortic aneurysm (AAA) requires urgent treatment or preventive surgical intervention. Current guidelines suggest immediate CT evaluation for symptomatic AAAs to assess rupture. Emergent repair is necessary if rupture is confirmed. Surgery for symptomatic, non-ruptured AAAs can be briefly delayed for medical optimization in an intensive care unit. Elective repair for asymptomatic AAAs typically targets aneurysms larger than 5.5 cm or those growing more than 1 cm per year. Ongoing research aims to improve rupture risk assessment for better elective AAA repair decisions. Surgical interventions include open repair and endovascular aneurysm repair (EVAR). EVAR now dominates elective AAA repairs, comprising over 80% in the US since 2013. Recent studies show comparable mortality rates between EVAR and open repair, though EVAR patients may require more secondary procedures. Both procedures carry risks of complications like ischemic colitis (more common in open repair), abdominal compartment syndrome, and multisystem organ failure. Careful patient selection and ongoing outcome assessment are crucial for optimizing AAA treatment strategies[40].

CONCLUSIONS

The management of bleeding patients is a complex and urgent issue that doctors, intensi-

vists, and surgeons throughout the world deal with daily. Blood loss, whether from trauma or hemostasis issues, significantly raises the risk of serious health problems, including shock, hemodynamic instability, and even death. Emergency teams must respond to this quickly, decisively, and collaboratively to improve patient outcomes. Current strategies focus on a systematic approach to assessment, stabilization, and definitive treatment tailored to the hemorrhage type and severity. In the emergency department, recognizing symptoms like tachypnea, decreased urine output, and changes in blood pressure and heart rate is critical for determining the severity of bleeding and initiating appropriate treatment. Swift identification of these features, alongside obtaining comprehensive patient history and physical examination, facilitates accurate assessment and tailored treatment plans. Prompt laboratory evaluations, including hemoglobin levels and coagulation variables, guide necessary interventions such as blood product transfusions. Adjunctive therapies, including tranexamic acid, specific clotting factors, and advanced interventions like endoscopic procedures or surgical exploration, are often required based on the bleeding source. Continuous monitoring of vital signs and laboratory parameters ensures the effectiveness of interventions and allows for necessary adjustments. A multidisciplinary approach, incorporating specialists from hematology, surgery, anesthesia, and critical care, is vital for providing comprehensive care and improving the chances of a favorable outcome. Managing bleeding patients effectively requires quick evaluation, tailored treatment actions, and teamwork among medical professionals.

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KNOWLEDGE OR IGNORANCE? THE USE OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS) BY HIGH-SCHOOL STUDENTS AND THEIR KNOWLEDGE IN THIS AREA

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INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) constitute a well-known and esteemed group of pharmacotherapeutics. They are among the most frequently purchased drugs in Europe, and their astonishing availability means that in many countries they can be obtained not only in pharmacies but even in kiosks or gas stations [1,2]. Despite their current popularity, drugs from this group have a long and fascinating history dating back to ancient times. For centuries, people have used natural remedies to relieve pain and inflammation, and it was based on one of these – salicin found in the bark of white willow – that synthetic acetylsalicylic acid was created in 1897, revolutionizing the treatment of pain and inflammatory conditions [3]. Since then, many different substances from the NSAID group (including ibuprofen, naproxen, and diclofenac) have been developed, characterized by different action profiles and applications, allowing doctors and patients to choose the most optimal therapy method today.

They are characterized by antipyretic, anti-inflammatory, and analgesic effects achieved by inhibiting an enzyme called cyclooxygenase (COX) that participates in the metabolism of arachidonic acid. As a result, this leads, among other things, to the reduced production of prostaglandins – chemical substances responsible for the occurrence of pain, fever, and inflammation [4]. Although the main mechanism of action of NSAIDs is the inhibition of prostaglandin production, some of these drugs can also indirectly affect the production of other

inflammatory mediators such as leukotrienes or cytokines, through inhibiting cell activation or through interactions with other signaling pathways. It is also worth mentioning that there are two main isoforms of cyclooxygenase – COX 1 and COX 2. The antipyretic, analgesic and anti-inflammatory effects are mainly achieved by inhibiting the COX 2 isoform, whereas a significant part of the side effects of using NSAIDs are associated with inhibiting COX-1 [5]. It is a constitutive form, constantly present in most cells and tissues, playing an important role in protecting the gastric mucosa, regulating renal blood flow, and activating platelets, so its dysfunction can lead to disturbances in many systems of the human body. Due to differences in selectivity towards COX-1 and COX-2, different NSAIDs can have different profiles of action and side effects. For example, acetylsalicylic acid significantly leads to the inhibition of COX-1, while some newer NSAIDs, such as celecoxib, are more selective for COX-2. Nowadays, NSAIDs are eagerly used by many people, primarily to relieve pain caused by both acute and chronic conditions, as well as to reduce inflammation or lower fever. Additionally, the ease of their acquisition and effectiveness means that, for many, they have become the first choice in combating sudden ailments. Unfortunately, despite being considered safe, taking NSAIDs is not without risk. Long-term use or abuse of these drugs can lead to various side effects [6]. The most common include problems with the gastrointestinal mucosa, such as stomach ulcers, which, in extreme cases, can lead to bleeding or even perforation of the gastrointestinal tract, posing a direct threat to life [7,8]. Moreover, there is also a risk of impaired kidney function and cardiac problems.

Recent studies indicate that non-steroidal anti-inflammatory drugs are becoming increasingly popular among the youth [9]. They are often perceived as "safe" and "harmless," mainly due to their wide availability in pharmacies and stores. Many young people reach for these drugs to alleviate symptoms associated with sports injuries, menstrual pains, or even headaches after intense studying. However, such a trivializing approach to NSAIDs can lead to the abuse of these drugs. Long-term or frequent use of NSAIDs, especially without consulting a doctor, can lead to the aforementioned negative health effects. It's also important to emphasize that many side effects may not be immediately noticeable, and their symptoms may only appear after a longer time. This can make it difficult to identify them and, more importantly, to stop NSAID therapy at the right time.

Schools, parents, and guardians should be aware of this issue and take care of educating young people about the proper use of these drugs and warn them of the potential risks associated with NSAID abuse. Organizing workshops, lessons, or meetings with doctors and pharmacists in schools could help increase awareness of this topic among young people.

AIM OF THE STUDY

The aim of the study was to assess the use of non-steroidal anti-inflammatory drugs by high school students and their knowledge of topics related to this group of drugs.

MATERIAL AND METHODS

In the study, 301 (100%) respondents aged 15 to 20 years (M = 17 ± 1.21) participated. The majority of the respondents were women (186; 61.8%). The study utilized a proprietary survey questionnaire consisting of questions about the use of non-steroidal anti-inflammatory drugs, knowledge about their action and potential side effects, and other issues related to the topic. Participation in the study was voluntary, and completing the questionnaire was completely anonymous. Respondents were recruited from among high school students located in the Silesian Voivodeship, after obtaining informed consent from the participants and, in the case of younger students, their guardians. The collected data were entered into a database, and the Statistica 13.1 software was used for their processing and analysis.

RESULTS

General characteristics of the study group

Table 1 presents the general characteristics of the study group, including age, gender, place of residence, and education.

Table 1. Characterisation of the study group

Study group (301; 100%)			
Variable		**Data**	
		n	**%**
Age	15	50	17
	16	46	15
	17	87	29
	18	96	32
	19	16	5
	20	6	2
Sex	Woman	186	62
	Man	115	38
Place of residence	Village	225	75
	City	76	25

Explanation of abbreviations: **n** - number, **%** - percentage.

The majority of the study group were women, and the respondents mainly lived in rural areas. Individuals aged 17-18 years constituted over 50% of all respondents.

Use of Non-Steroidal Anti-Inflammatory Drugs

The characteristics of the study group, including declarations regarding the use of non-steroidal anti-inflammatory drugs are presented in Figure 1.

More than half of the respondents asked about the use of non-steroidal anti-inflammatory drugs stated that they do not take them (152; 51%).

Table 2 presents the characteristics of the study group, including data on the types of non-steroidal anti-inflammatory drugs used.

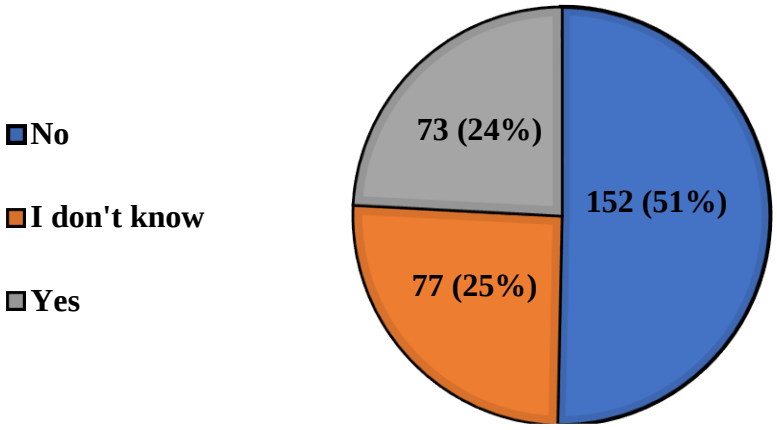

Figure 1. Characteristics of the study group including declarations on the use of non-steroidal anti-inflammatory drugs.

Table 2. Characteristics of the study group including the types of active substances used from the group of non-steroidal anti-inflammatory drugs

What NSAIDs do you use?	n	%
Ibuprofen	158	52%
Acetylsalicylic acid	67	22%
Ketoprofen	46	15%
Naproksen	14	5%
Diclofenac	12	4%

Explanation of abbreviations: **n** - number, **%** - percentage.

The most commonly used drug from the NSAID group by the respondents was Ibuprofen (158; 52%). The characteristics of respondents who denied using non-steroidal anti-inflammatory drugs are presented in Figure 2.

As shown in Figure 2, nearly 40% of respondents who denied using non-steroidal anti-inflammatory drugs were actually using them. Consequently, over two-thirds of the study group used drugs from the NSAID group (209; 69%), and a significant portion was not aware of it.

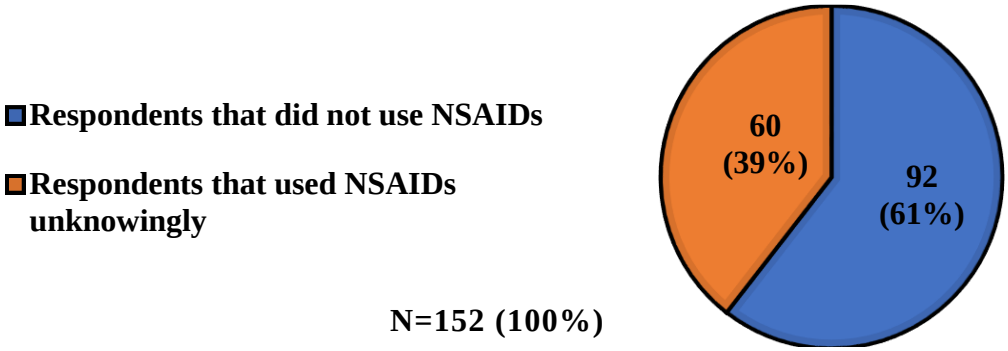

Figure 2. Characteristics of the part of the study group denying the use of non-steroidal anti-inflammatory drugs

The characteristics of the part of the study group that used non-steroidal anti-inflammatory drugs, including information on the frequency of their use, are presented in Table 3.

Table 3. Characteristics of the part of the study group using non-steroidal anti-inflammatory drugs, including the frequency of their use

Respondents using NSAIDs (208; 100%)		
How often do you use NSAIDs?	**n**	**%**
Once a month	61	29%
A different frequency	37	17%
Couple of times a week	27	13%
Once every half a year	26	13%
Everyday	23	11%
Once a week	21	10%
Less often than every half a year	14	7%

Explanation of abbreviations: **n** - number, **%** - percentage.

Among the respondents who used non-steroidal anti-inflammatory drugs, nearly every fourth person used them several times a week (27; 13%) or daily (23; 11%).

The characteristics of the part of the study group that used non-steroidal, anti-inflammatory drugs, including information on the reasons for their use, are presented in Table 4.

Table 4. Characteristics of the part of the study group, including reasons for using non-steroidal anti-inflammatory drugs

Respondents using NSAIDs (208; 100%)		
Reason for using NSAIDs	**n**	**%**
Headaches	122	59%
Menstrual pains	102	49%
Fever	72	35%
Muscle pains	59	28%
Migraine	38	18%
Don't know	32	15%
Joint pains	30	14%
Abdominal pains	27	13%
Cough	25	12%
Neuralgia	25	12%
Common cold	23	11%
Minor injuries and contusions	17	8%

Explanation of abbreviations: **n** - number, **%** - percentage.

The most common reasons for respondents' use of non-steroidal anti-inflammatory drugs were headaches (122; 59%) and menstrual pains (102; 49%).

It is concerning that non-steroidal anti-inflammatory drugs were also used in situations where their use is pointless – such as for cough (25; 12%) and common cold (23; 11%).

The characteristics of the part of the study group that used non-steroidal anti-inflammatory drugs, including the places where they purchased the mentioned drugs, are presented in Figure 3.

The characteristics of the part of the study group that used non-steroidal anti-inflammatory drugs, including information on the occurrence of past adverse effects related to the use of NSAIDs, are presented in Figure 4.

A significant majority of respondents purchased NSAIDs from a pharmacy (163; 78%).

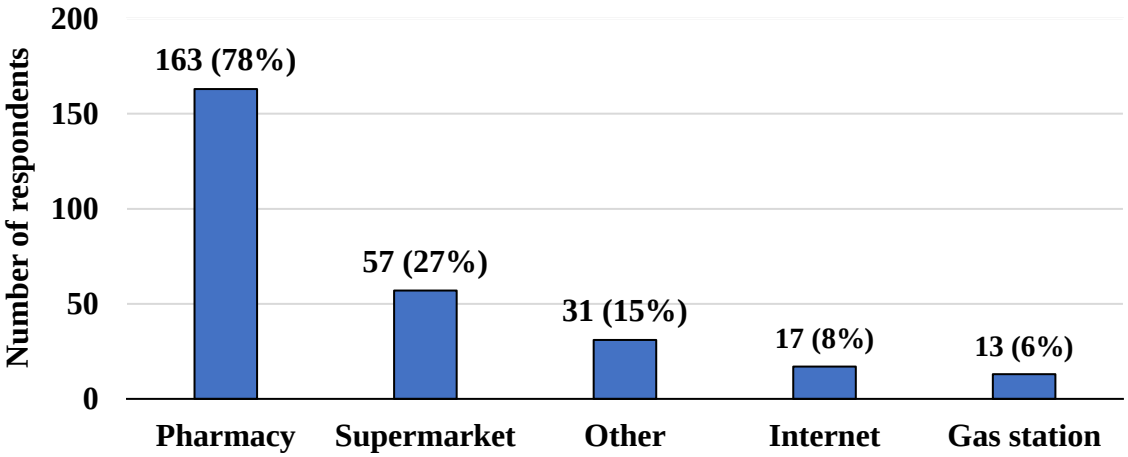

Figure. 3. Characteristics of the part of the study group that used non-steroidal anti-inflammatory drugs, including information regarding the places where they were purchased.

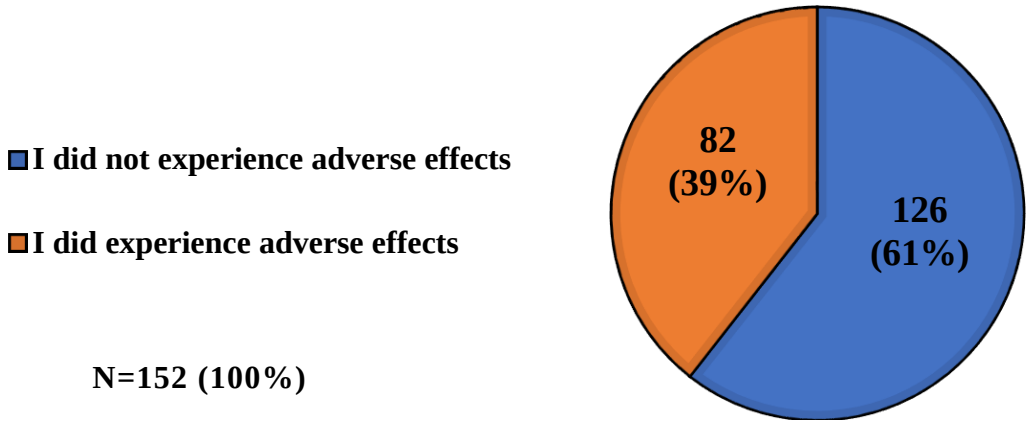

Figure. 4. Characteristics of the part of the study group that used non-steroidal anti-inflammatory drugs, including information regarding past adverse effects of NSAIDs experienced by them.

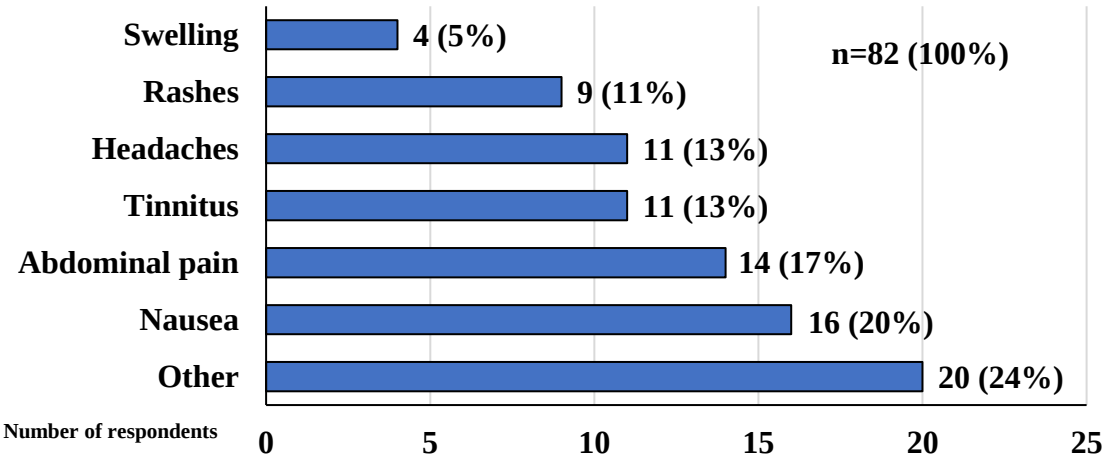

Figure. 5. Characteristics of the part of the study group that reported experiencing adverse effects in terms of specific ailments.

Figure 5, in turn, presents the information declared by the respondents regarding specific adverse effects resulting from the use of NSAIDs.

The most commonly reported adverse effects of using NSAID group drugs by the respondents were nausea (16; 20%) and abdominal pain (14; 17%).

Knowledge about Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Figure 6 presents the characteristics of the respondents, including information on their familiarity with the term "non-steroidal anti-inflammatory drugs" and whether they have encountered it in the past.

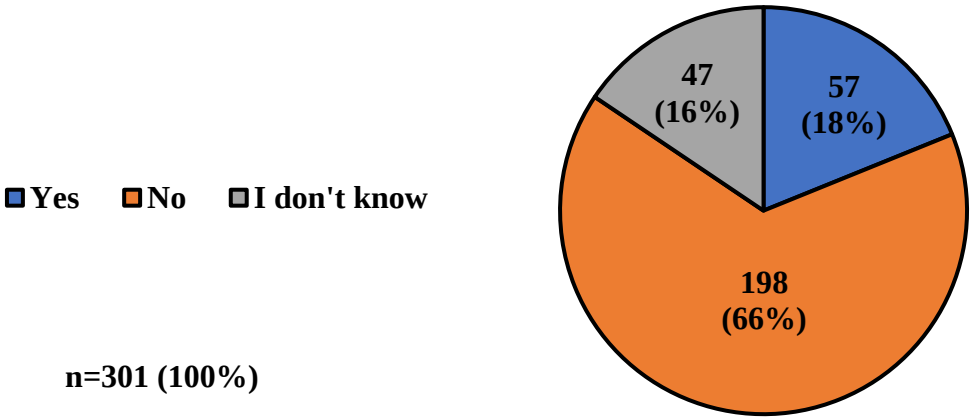

Figure 6 Characteristics of the respondents in terms of familiarity with the term "Non-Steroidal Anti-Inflammatory Drugs".

Over 2/3 of the respondents have never encountered the term "non-steroidal anti-inflammatory drugs" (198; 66%)

Figure 7 presents the characteristics of the study group in terms of the declared level of knowledge about non-steroidal anti-inflammatory drugs.

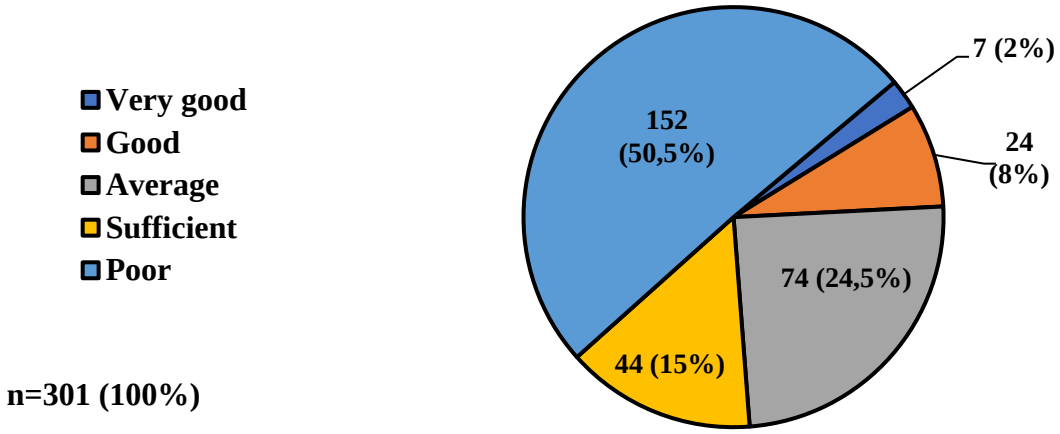

Figure 7. Characteristics of the study group, including information on the self-assessment of their knowledge about non-steroidal anti-inflammatory drugs.

Over half of the respondents rated their knowledge of non-steroidal anti-inflammatory drugs as poor (152; 50.5%). Only about 10 percent of the participants felt satisfied with their level of knowledge in this area (31; 10%).

Figure 8 presents the characteristics of the study group, including responses to a question regarding the scope of actions of non-steroidal anti-inflammatory drugs.

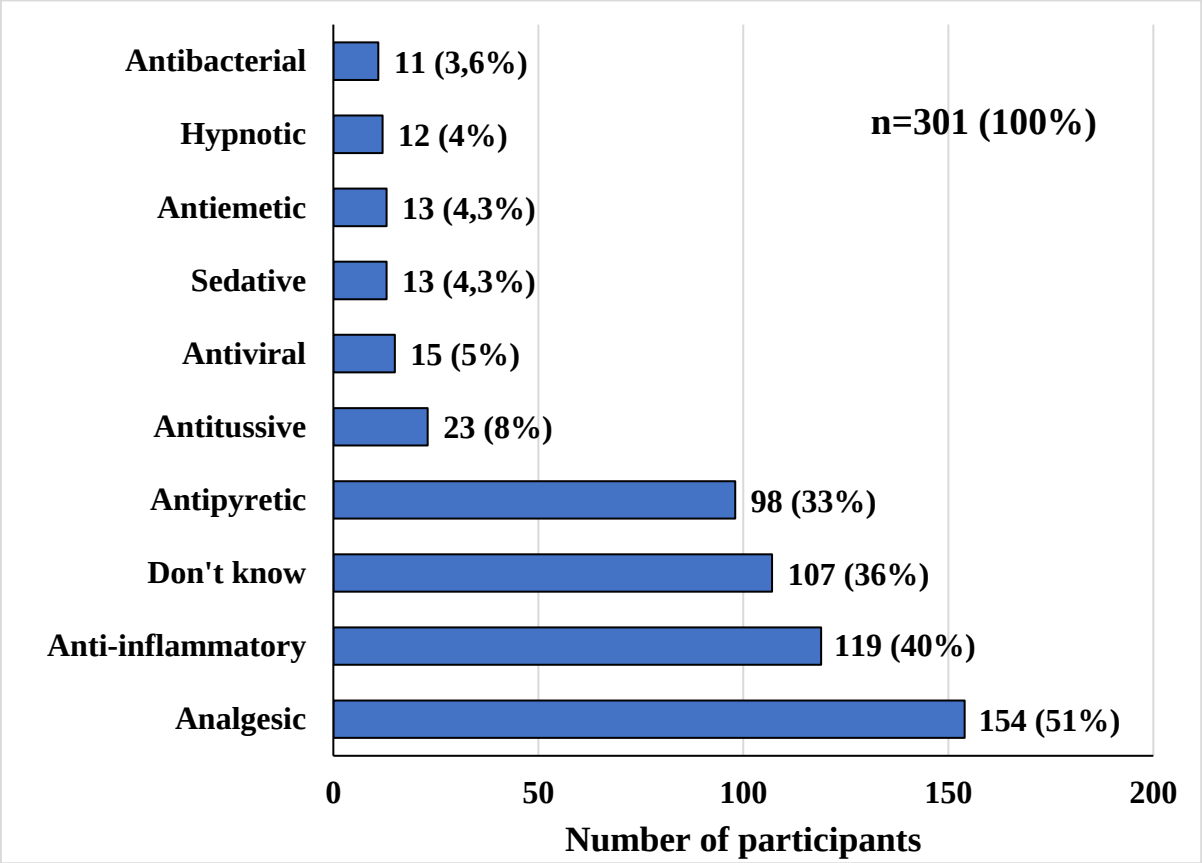

Figure 8. Characteristics of the study group, including responses to the question "What effects do non-steroidal anti-inflammatory drugs have?"

Only half of the respondents attributed analgesic action to the NSAID group drugs (154; 51%) and worse yet – only every third of respondents knew that non-steroidal Anti-inflammatory drugs have anti-inflammatory action (119; 40%). Moreover, in the study group, individuals attributed false actions to these drugs, including antiviral properties (15; 5%) and antitussive effects (23; 8%).

Table 5 presents the characteristics of the study group, including responses to the question "Please indicate the conditions and ailments in which non-steroidal anti-inflammatory drugs are used".

Table 5. Characteristics of the part of the study group, including responses to the question regarding the conditions and ailments in which NSAID group drugs are used

Respondents (301; 100%)		
"Conditions and ailments in which NSAIDs are used"	**n**	**%**
Headaches	145	48%
Fever	111	37%
Muscle pains	100	33%
Don't know	98	33%
Joint pains	77	26%
Abdominal pains	66	22%
Neuralgia	46	15%
Minor injuries and contusions	40	13%
Hangover	36	12%
Common cold	22	7%
Cough	20	7%
Insomnia	10	3%

Explanation of abbreviations: **n** - number, **%** - percentage.

According to nearly half of the respondents, non-steroidal anti-inflammatory drugs are used for headaches (145; 48%) and to reduce fever (111; 37%). Additionally, some participants correctly interpreted NSAIDs as effective for muscle pains (100; 33%) and joint pains (77; 26%).

The characteristics of the respondents, including their knowledge of adverse effects resulting from the use of NSAIDs, are presented in Table 6.

The majority of respondents (183; 61%) were unaware of the side effects that could occur after using drugs from the NSAID group. A small portion of the participants correctly identified, among other things, liver damage (53; 18%) and the possibility of developing stomach ulcers (25; 8%).

Table 7 presents the characteristics of the study group, including the accuracy of statements about drugs from the NSAID group.

Nearly half of the respondents correctly determined that different active substances within the NSAID group have varying strengths of action (141; 47%) and that they are among the most frequently used drugs in Poland (139; 46%). Unfortunately, only about one in four

respondents correctly identified the existing risk of damage to the gastrointestinal mucosa when using drugs from the mentioned group (79; 26%). Additionally, some individuals in the study group claimed that NSAIDs directly act on the cause of a cold (31; 10%).

Table 6. Characteristics of the respondents, including knowledge of potential adverse effects that may occur after using drugs from the NSAID group

Respondents (301; 100%)		
"What side effects may occur with the use of NSAIDs"	**n**	**%**
Don't know	183	61%
Liver damage	53	18%
Abdominal pain	49	16%
Nausea	49	16%
Kidney damage	37	12%
Rashes	28	9%
Hypertension	27	9%
Stomach ulcers	25	8%
Headaches	24	8%
Tinnitus	18	6%
Reduced coagulation	17	6%
Asthma attack	8	3%
Swelling	7	2%

Explanation of abbreviations: **n** - number, **%** - percentage.

Table 7. Characteristics of the study group, including respondents' answers to the issue "Please indicate true statements about drugs from the NSAID group"

Respondents (301; 100%)		
Statements regarding NSAIDs	**n**	**%**
Different NSAIDs have different strengths of action	141	47%
They are among the most frequently used drugs in Poland	139	46%
I do not know which active ingredient I most often take from the NSAID group (I only know its trade name)	86	29%
It is usually not advisable to combine two drugs from the NSAID group	85	28%
Taking them for an extended period can damage the mucous membrane of the gastrointestinal tract	79	26%
In ointment form, they have fewer side effects than those taken orally	50	17%
Their use shortens the duration of a cold	40	13%
Their use increases the risk of bleeding	38	13%
Act on the cause of a cold	31	10%
Some of them are used in the prevention of heart attacks	24	8%
There is a condition known as aspirin-induced asthma	24	8%
When used in children, they can cause disorders on the autism spectrum	20	7%
In ointment form, they show the same effect as in oral form	19	6%
They can be safely taken while consuming alcohol	15	5%

Explanation of abbreviations: **n** - number, **%** - percentage.

DISCUSSION

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly used groups of drugs worldwide, valued for their rapid action, easy availability, and relatively high safety compared to other pharmaceuticals [10]. Their popularity in Polish society, while understandable, raises concerns about potential abuse. NSAIDs, like other drugs, require moderation and conscious consumption to minimize the associated risks [11]. Our study focuses on the practices and awareness concerning NSAIDs among school-aged youth. We believe that young adults, being at the stage of forming their health habits and beliefs, are a key group for building social awareness about responsible medication use. Their openness to new ideas and willingness to engage in discussions, as well as the ability to spread the acquired knowledge in their communities, make them significant health ambassadors. The habits and beliefs they bring into adult life will most likely accompany them until old age, which is why we wanted to investigate how they use pharmaceuticals from this group and what they know about them.

Our research revealed that a significant majority of respondents (209; 69%) use NSAIDs, but alarmingly, more than half of them (136; 65%) are not aware of the type of preparations they are using. These results may cause concern. It might be thought that knowledge of the drug group is not important for people without medical education, but this way of thinking is erroneous, especially in the context of widely available NSAIDs that can be purchased even at gas stations. The ubiquity of non-steroidal anti-inflammatory drugs may further influence their perception in the population. In the study by L. H. M. Alomaim et al, 70% of respondents stated that the general availability and reputation of these drugs as safe unequivocally contributed to their use [12]. There is no doubt that conscious and safe use of drugs requires basic knowledge about them [13]. Furthermore, the role of healthcare workers in patient education cannot be overlooked – in the study conducted by R. I Farah et al, over 60% of the surveyed group consisting of 604 respondents used NSAIDs, and only 29% of them were informed by a doctor or pharmacist about their potential adverse effects [14]. Considering how often self-medication occurs in populations, healthcare workers should seize every opportunity to educate patients in this area [15].

The most commonly used NSAID was Ibuprofen (158; 52%), taken by over half of the respondents. Among those using non-steroidal anti-inflammatory drugs, one in three people used them at least once a week (71; 34%). Ibuprofen is one of the most popular NSAIDs due to its moderate strength and relative safety, and it is also often recommended by healthcare workers [16]. However, the frequency of drug use presented in our own study may raise concerns, especially considering the potential side effects associated with long-term and

excessive use of NSAIDs [17]. Moreover, the misuse of these drugs is not uncommon – in the study conducted by B. Cryer et al, nearly 25% of the respondents from a group of 1750 abused them [18]. This could directly impact the risk of long-term adverse effects of NSAIDs.

In the studied group, the main reported reasons for using NSAIDs were pain-related: headaches (122; 59%), menstrual pains (102; 49%), and muscle pains (59; 28%). Unfortunately, some respondents used NSAIDs in situations where it was not advisable, such as to treat a cough (25; 12%) or a cold (23; 11%). Similar results were obtained by A. I Aboalrob et al. in a study of 206 students, where over 50% of the women in the study group used NSAIDs for menstrual pain [19]. In another study conducted by I. Coskuner et al. among 210 residents of Turkey, the most commonly mentioned reason for using NSAIDs was headaches and musculoskeletal pains [20]. NSAIDs undoubtedly represent a valuable tool in combating transient pain conditions.

As for the respondents' knowledge about NSAIDs, it turned out to be incomplete – more than two-thirds of the study group had never encountered the term "non-steroidal anti-inflammatory drugs" (198; 66%), and more than half of them rated their knowledge in this area as poor (152; 50.5%). Additionally, only one-third of the respondents correctly indicated that NSAIDs have an antipyretic effect (98; 33%), and only about half of the respondents correctly identified their anti-inflammatory (119; 40%) and analgesic (154; 51%) actions. Moreover, myths about NSAIDs persisted in the study group, such as "their use shortens the duration of a cold" (40; 13%) and "they act on the cause of a cold" (31; 10%), or "they can be safely taken while consuming alcohol" (15; 5%). These results are alarming, as they illustrate the actual state of knowledge about non-steroidal anti-inflammatory drugs. Unfortunately, this is not an isolated case of such study outcomes. In the research conducted by R. K. Sinuraya et al, and O. A. Asiri et al, an unsatisfactory level of respondents' knowledge was also observed, showing significant under-information about such a popular group of drugs [21,22].

Respondents correctly identified headaches (111; 37%) and fever (145; 48%) as ailments for which it is worth taking NSAIDs. Unfortunately, the situation was much worse in the context of potential adverse effects – nearly one-third of the respondents were unable to answer the posed question (183; 61%) and correctly indicate any potential consequences of abusing non-steroidal anti-inflammatory drugs. In a study conducted by J. Mullan et al, involving more than 250 individuals, similar knowledge gaps were found: less than 60% of respondents correctly identified abdominal pain and less than half identified kidney damage as potential adverse effects associated with the use of NSAIDs [23]. Similar results were obtained by D. Roshi et al, according to which most of the respondents presented poor knowledge about

the adverse effects of these drugs, and like in our own study – only a small group was aware of the risk of gastrointestinal tract damage [24].

In light of the results of our own study, it is clear that education on NSAIDs among the youth is extremely important. The findings indicate insufficient knowledge in this area, both regarding the types of drugs used and their potential side effects. This clearly points to the need for more effective educational programs focused on informing young people about the safe use of NSAIDs, their effects, possible interactions, and consequences of misuse. It is also crucial to involve all healthcare workers in the education process, so they can efficiently impart knowledge to patients, especially in the context of the popularity of self-medication. Such knowledge could significantly impact public health and the safety of drug use by future generations.

CONCLUSIONS

1. A significant portion of the studied group of students used non-steroidal anti-inflammatory drugs.
2. The respondents' knowledge of non-steroidal anti-inflammatory drugs was found to be insufficient, especially in terms of their potential side effects and the principles of proper use.
3. Widespread educational programs focused on conveying accurate knowledge about the use of non-steroidal anti-inflammatory drugs are needed, which can significantly improve the quality and safety of self-medication with them.

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NEW EPIDEMIC OF NICOTINISM - IMPACT OF E-CIGARETTES ON HUMAN HEALTH

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INTRODUCTION

E-cigarettes (Electronic cigarettes) are gaining popularity around the world every year. The small, colorful devices are filled with liquids in a variety of flavors, from tobacco to various fruits, beverages, and cannabis flavors. They are shown in the media and online advertising as a way to spend time with friends or as a great alternative to traditional cigarette smoking, which has become much less fashionable. Not much is said about the dangers of using these seemingly harmless devices. Our goal is to show what we currently know about the impact of e-cigarettes on human health.

TERMINOLOGY

E-cigarettes, known as electronic cigarettes, consist of a device containing a battery, a charging port, a coil, and a container for liquid [1,2,3]. The battery transfers energy to the coil, which heats the liquid inside the container, resulting in smoke. The most common ingredients are propylene glycol (PG), vegetable glycerin (VG), nicotine, and food flavorings [1,2]. Liquids can be made based on free nicotine or nicotine salts and can differ significantly in its content [1]. The most popular concentrations vary between 3mg/ml and 20 mg/ml. Differences in nicotine concentration, types of devices, coils, and voltages affect the subsequent concentration of nicotine and other harmful substances in the body, which makes it difficult to study the effects of vaping on humans [4].

EPIDEMIOLOGY

E-cigarettes were launched in the United States in 2007 and immediately became very popular among teenagers [1,2]. Between 2011 and 2015, the number of e-cigarette users increased by 900% (from 3% to 27%) [5]. Since 2014, they have become the most frequently chosen form of nicotine dosage by teenagers [5]. According to surveys done in schools there in 2019, as many as 35% of 12th-grade students admitted to having used e-cigarettes at least once in 12 months [1]. Following the announcement of this data, the FDA (U.S. Food and Drug Administration) commissioner declared e-cigarette smoking an "epidemic" among teenagers [1,2].

JUUL and SMOK brand products were the most popular devices [1]. Fruit flavors, mint flavors, and those imitating desserts are the most popular, and those people who used them were more likely to continue smoking later [6].

EVALI

E-cigarette or Vaping-Associated Lung Injury - EVALI has become a very high-profile topic in 2019 in the United States [7-9]. More than 2,500 cases of acute respiratory failure arising under unexplained circumstances have been reported [3]. After deeper analysis, it turned out that the disease was related to vaping but, as we now know, probably not traditional liquids [1]. Analyses of patients' bronchoalveolar fluid samples revealed the presence of vitamin E acetate, used to dilute THC (Tetrahydrocannabinol) -containing liquids sold on illegal markets [1]. A significant minority of patients used liquid without THC and only with nicotine. [9] This substance is not commonly used in traditional liquids, but it is worth considering when testing newly introduced liquids in the future [9]. We still don't fully know if vitamin E acetate is the sole cause of the EVALI (E-Cigarette or Vaping-Associated Lung Injury) epidemic that is sweeping the market since there were more than 8,000 different flavors of liquids on the market in 2014 alone. The number grew by up to 250 monthly [3]. The exact mechanism by which acetate damages the lungs is unknown; however, it is most likely that it damages the pulmonary surfactant [3].

Symptoms most commonly seen in patients were tachycardia, shortness of breath, hemoptysis, and coughing [2,10,11].

Patients had CT (Computed tomography) scans of their lungs, and the most common lesions mentioned were diffuse, multifocal, bilateral vitreous opacities. In addition, lung nodules, thickened interlobular septa, pneumothorax, mediastinitis, and pleural effusions were

observed [3]. Unfortunately, the lesions varied among patients, and no specific pattern of abnormality could be assigned to them [3].

Histological examinations of patients' lungs obtained by biopsy showed evidence of acute or subacute lung damage and incipient inflammation [9,11]. This was the predominant pattern in the study [9]. In addition, congestion from fibroblasts, vitreous membranes, fibrinous exudates, type 2 pneumocyte hyperplasia, and, in some cases, a rare interstitial inflammatory infiltrate were also observed [9].

The EVALI picture is nonspecific, and the symptoms are indicative of acute lung injury. Unfortunately, similar results are seen from other damage caused by drugs, gastric acid aspiration, inhaled agents, and viral infections [3]. Therefore, the diagnosis must be made based on a well-collected patient history enriched with medical tests [3].

IMPACT ON RESPIRATORY SYSTEM

E-cigarette liquids are associated with damage to the respiratory epithelium, lung lining inflammation, and mucociliary clearance damage [1]. Going from the very top of the respiratory system, the results show that propylene glycol, generally considered safe in the food industry, irritates the oral and nasal cavities, causes minimal metaplasia of squamous cells, and has toxic effects on human cells [1,8]. Other adverse effects of glycol, such as chest tightness, wheezing, throat irritation, mucous membranes, and narrowing of the airways, have also been reported [8]. In addition, the thermal decomposition of propylene glycol has been shown to release several carcinogenic compounds, including acrolein, acetaldehyde, and glycidol [3]. Other common side effects of liquids include asthma exacerbations, eosinophilic pneumonia, epiglottitis, bronchitis, and ARDS (Acute Respiratory Distress Syndrome) [2].

Asthma is a chronic inflammatory airway disease characterized by variable airflow limitation secondary to narrowing and thickening of the airway walls, leading to shortness of breath, chest tightness, and coughing [12]. Numerous studies have been conducted attempting to link asthma to electronic cigarette use, but the results have not always been consistent [13]. Xuechao Li and co-authors looked at these studies in which the total number of participants was almost 500,000 [13].

All the participants were students, and their average age was 15-16 [13]. This study showed that both current and previous vaping were related to the incidence of asthma in adolescents, where the OR (Odds ratio) ranged between 1.22 and 1.54 depending on the study groups, which means a 22%-54% greater chance of asthma in smokers than non-smokers [13].

It is unclear why it occurs in some people and not in others, but it is most likely related to other factors such as genetics or environmental [13].

Nicotine is a substance that has been known for years and can cause lung damage when inhaled. [1] It stimulates parasympathetic ganglia, which leads to bronchospasm, increases airway resistance, and disrupts CNS (Central nervous system) control of breathing [1]. Short-term effects of nicotine exposure include tremors, increased heart and respiratory rates, increased blood pressure, and increased levels of alertness [8]. With increasing nicotine use, COPD (Chronic obstructive pulmonary disease) can occur by decreasing elastin in the lungs and increasing alveolar volume [1]. Tests on mice showed that nicotine exposure reduced the FEF50/FVC (Forced expiratory flow at 50%/forced vital capacity) ratio from 23 to 15, suggesting airway obstruction. In addition, emphysema-like changes appeared in the lungs. [1] Human studies, on the other hand, have shown a reduction in FEV1/FVC (Forced expiratory volume at the first second/ Forced vital capacity) [14,15]

It has been shown that liquid can significantly affect the immune system by increasing the number of macrophages and caspase expression, which leads to cell apoptosis [1,2]. Studies in mice have shown many other changes ranging from airway hyperresponsiveness, increased eosinophils, elevated levels of pro-inflammatory cytokines, impaired response to infection, and increased oxidative stress markers [3]. During smoking, disorders are created in the mucociliary apparatus by decreasing the frequency of ciliary beats in lung epithelial cells [9]. In addition, in vitro analyses showed that the genes directing cilia formation were being disrupted, which translated into fewer cilia and impaired function [3].

Considering flavors used in liquids, the situation becomes more difficult because the composition depends on the flavor, and thus, the health effects may also vary [1]. Harmful substances can include diacetyl and acetylpropionyl, which destroy the bronchi and cause inflammation [1,2]. In addition, alpha-diketones can lead to bronchial fibrosis [1]. Other substances often found in e-cigarette flavors include pentanedione, cinnamaldehyde, maltol, ortho-vanillin, and coumarin [1]. The most significant cytotoxic effects characterized Cinnamaldehyde but not significantly different from previously mentioned substances [1]. In addition, the above substances increased the production of IL-8 (Interleukin 8) which has a role in cancer processes [1,9].

Lung cancer is one of the most common and deadliest cancers in the world [16]. It is known that traditional cigarettes are a significant risk factor for lung cancer development; however, we are now looking at how much e-cigarettes contribute [17]. E-cigarettes contain

nicotine derivatives (e.g, nitrosonornicotine, nitrosamine ketone), heavy metals (including organometallic compounds), polycyclic aromatic hydrocarbons, and flavoring agents (aldehydes and complex organic compounds) [17]. Looking at nitrosamine compounds, it was noted that their concentrations were increased in the bronchi and alveoli, which translated into DNA (Deoxyribonucleic acid) damage [17]. It was also found that due to these substances, there is increased oxidative stress, which is one of the factors in cancer transformation [17]. In addition, thermal decomposition produces carcinogenic organic aldehydes such as formaldehyde, acetaldehyde, and acrolein [17]. Recent studies have shown that PG from liquids is metabolized to methylglyoxal (MGO) in the airway epithelium, and recent evidence suggests that MGO plays a role in cancer development and progression [17]. Considering the flavoring agents of liquids due to their transformations, there is an increased inflammatory response with macrophage activation and chemotaxis, vascular damage, dyslipidemia, and increased platelet reactivity [17]. These inflammatory and toxic processes lead to the formation of reactive oxygen species (ROS) and promote damage to lung tissue, thus increasing the chances of lung cancer [17].

GENERAL SYMPTOMS, ORAL AND OCULAR HEALTH

Among general symptoms, headaches, insomnia, weakness and chest pain were the most common in teenagers [2]. Aerosolized propylene glycol and glycerol cause mouth and throat irritation and a dry cough [18]. Contact with glycol mist can also dry mucous membranes and eyes [18].

Since the oral cavity is constantly exposed to aerosol from liquids, it is also courted by pathologies [19]. The first aspect is periodontal disease, which can develop while smoking [19]. It has been proven that plaque rates were significantly elevated in e-cigarette users, and there was gum pain and periodontal inflammation [19]. Another aspect is tooth decay, which can develop due to PG and VG [19]. Due to the deposition of these substances in the mouth and their viscosity, they make it easier for bacteria to adhere, leading to infection and decay [19]. In addition, sugars in flavors can also promote this process [19]. Recent studies have shown increased adhesion of *Streptococcus mutans* to enamel and increased biofilm formation [19]. The next thing to watch out for when smoking is the adverse effects of liquids on teeth and oral tissues, as it has been proven that some people develop cracks or fractures in their teeth, in addition to bleeding gums, sore tongue and cheeks, ulcers and dry mouth [19].

Dry eye has long been associated with traditional smoking and has recently been repor-

ted in electronic cigarette users as well [20]. A clinical study found that vapers experienced "moderate to severe dry eyes" after using electronic cigarettes, as well as impaired tear film stability [20]. Exposure to toxic substances, such as ROS and aldehydes, in liquid or vapor, can cause these disorders because these toxins damage the lipid layer of the tear film [21]. Looking further at another structure of the eye such as the cornea, abnormalities such as those seen with traditional smoking i.e. reduced corneal sensitivity and delayed wound healing were not observed [22]. Going to another structure, it has been shown that nicotine can not only affect the ocular surface but also the vascular system of the eye [21]. During smoking, there can be changes in blood flow in the eye and the thickness of the choroid [21]. The last structure of the eye in which smoking-related changes have been observed is the retina where nicotine-induced dopamine overexpression can interfere with the retina's ability to respond properly to the normal human diurnal cycle [23].

Nicotine is readily absorbed through the respiratory tract, skin, mucous membranes and gastrointestinal tract [18]. Acute exposure to inhaled nicotine can cause dizziness, nausea, or vomiting, but serious poisoning is rare [18]. Its contact with the skin can cause toxic reactions. Nicotine also has been documented to have negative effects on cognitive function and brain development among adolescents [2]. The main problems were memory loss, concentration and focus, and increased impulsivity [2]. In functional MRI studies, it was found that adolescents had a less developed prefrontal cortex of the brain responsible for inhibitory control and more developed reward periphery [2]. It was also found that vapers had a higher risk of developing mental illness later in life [2].

IMPACT ON THE CARDIOVASCULAR SYSTEM

The harmful consequences for the respiratory system were described earlier, but it was not the only system affected by the negative consequences of vaping. Potential cardiovascular side effects of e-cigarettes are generally attributed to nicotine and oxidizing chemicals, particulates, and acrolein [24]. The former activates the sympathetic nervous system and causes vasoconstriction and arrhythmogenesis, while the latter induces inflammation in endothelial cells and activates platelets, increasing the risk of heart attack [25,26]. E-cigarette use is correlated with a 2-3 higher risk of stroke, myocardial infarction, and ischemic heart disease and induces atherosclerotic conditions in healthy individuals with increased CVD (Cardiovascular disease) risk [8,25, 26,27]. Studies also have shown an increase in blood pressure and heart rate in people who vape [2]. In addition, the latest clinical practice guidelines

from the American College of Cardiology/American Heart Association Task Force seem to confirm this and speak to an increased risk of arrhythmias and hypertension, as well as increased oxidative stress and sympathetic stimulation in young, healthy individuals who vape [25,28]. A meta-analysis performed by Georgie Skotsimare and co-workers also showed increased heart rate and systolic and diastolic blood pressure [29]. An interesting finding was a reduction in these parameters in people who switched from traditional cigarettes to e-cigarettes, but this requires further research [29]. In addition, facts about increased risk of myocardial infarction, impaired vascular endothelial function, and increased arterial stiffness were confirmed [26,29,30,31]. Kennedy and colleagues reviewed several experimental and clinical studies on the cardiovascular safety of vaping. They found that it can cause cardiomyocyte mutagenesis, vasculitis, vasospasm, complement deposition, and platelet aggregation, with atherosclerosis and thrombosis risk, in addition to those previously mentioned [31,32].

A study on mice showed that exposure to e-cigarettes reduced heart rates [8]. One study indicated a slight increase in heart weight, but another showed the opposite condition and a decrease in weight [8]. Histological evaluation showed no significant changes in myocardial fibrillation after a short exposure but a slight increase in collagen protein expression [8]. The adverse effects of liquids are believed to be in the context of thrombosis, as exposed mice had a reduced bleeding time compared to control mice [8]. This indicates that platelets are overactive [8]. It turned out that the number of platelets themselves did not change, however, it was their aggregation that increased through greater activation of GPIIb-IIIa (Glycoprotein IIb/IIIa) integrin [8]. Another study on rats showed an increase in total cholesterol, triglycerides and saturated fatty acids with a decrease in polyunsaturated fatty acids [8]. Other changes described in this study described increased vascular angiogenesis in the periphery of the heart [8].

CONCLUSION

E-cigarettes have become a large-scale problem and are slowly replacing traditional cigarettes. Considering the information we have gathered, they cause many health problems related not only to the circulatory and respiratory systems but also to health in general. Further research is needed to study the effects of these new devices on human health; however, we already know that they are not insignificant to the condition of our body. It's hard to see them as a completely healthy alternative to smoking cigarettes.

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SELECTED CLINICAL AND THERAPEUTIC PROBLEMS

IMPLEMENTATION OF PATIENT BLOOD MANAGEMENT STRATEGY FOR THE MANAGEMENT OF ANEMIA

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INTRODUCTION

Anemia is a condition characterized by a reduction in the concentration of hemoglobin in the body, <13 g/dl in men or <12 g/dl in women (<11 g/dl in pregnancy). This can be accompanied by a decrease in the number of red blood cells or other abnormalities of red blood cells, such as variations in cell volume or abnormal hemoglobin concentrations within the cells. It is one of the most common hematological diseases, affecting children, adults, and the elderly. Statistically, anemia is more prevalent in women than in men. This higher incidence in women can be attributed to several factors, including blood loss during menstruation, the increased risk of anemia during pregnancy and lactation, and generally lower body iron stores compared to men [1].

Anemia is a common finding in patients scheduled for surgical intervention or undergoing emergency surgery, with the incidence reaching up to one-third of patients before surgery [2].

Preoperative patients present with anemia at a rate higher than the general population [3].

The prevalence of preoperative anemia varies according to the medical or surgical condition being treated and demographic variables such as age, gender, and geographical region. Perioperative anemia is associated with poorer surgical outcomes, even when the anemia is mild in severity. Anemia can act synergistically with other comorbidities, such as heart and renal failure, contributing to what is known as cardiorenal anemia syndrome, which further worsens patient outcomes [2].

One traditional approach to managing perioperative anemia is through blood transfusion and the restoration of hemoglobin levels. However, transfusions come with several potential complications, including alloimmunization, transfusion-transmitted diseases, and transfusion reactions [4]. Additionally, blood is a limited and costly resource. Consequently, over the past few decades, the focus has shifted from relying primarily on blood transfusions and transfusion thresholds to emphasizing the diagnosis, treatment, and prevention of the underlying causes of anemia.

In the modern healthcare, patient blood management (PBM) in surgical cases is tailored to individual patients, aiming to optimize outcomes. Effective treatment of anemia reduces the need for transfusions, minimizes associated risks, shortens hospital stays, and ultimately lowers healthcare costs [5]. By focusing on personalized anemia management, healthcare providers can improve patient outcomes and enhance the overall efficiency of surgical care.

PREOPERATIVE ANEMIA

Anemia can have various causes. The two main mechanisms responsible for its occurrence are abnormal production (reduced or impaired) of red blood cells and loss of red blood cells.

Hemorrhages

Preoperative anemia often results from acute hemorrhage, frequently observed in urgent surgical scenarios like ruptured abdominal aortic aneurysms or severe traumatic injuries. These situations demand immediate intervention due to the rapid loss of blood. Conversely, chronic blood loss develops gradually over time and may be linked to various gastrointestinal conditions such as ulcers, polyps, or colorectal cancer. Additionally, tumors affecting the kidney or bladder and heavy menstrual bleeding are common culprits of chronic blood loss leading to anemia.

Iron Deficiency

Iron deficiency is the most prevalent cause of anemia globally [6]. Iron is critical for hemoglobin synthesis, ensuring red blood cells' proper structure and function. Iron-deficiency anemia typically arises from inadequate dietary intake, blood loss (e.g., through gastrointestinal bleeding), or impaired iron absorption from food sources. In cases of iron deficiency, the production of red blood cells is hindered, resulting in fewer, smaller cells with reduced hemoglobin content. This progression not only compromises overall health but also manifests in clinical symptoms characteristic of anemia.

Chronic Diseases

Anemia of chronic inflammation, also referred to as anemia of chronic disease, occurs amidst systemic inflammation and the activation of immune mediators. These mediators inhibit the kidneys' erythropoietin (EPO) synthesis and diminish its efficacy in stimulating red blood cell production. Moreover, elevated levels of cytokines induce the production of hepcidin, a hormone that hampers the absorption of dietary iron and promotes its retention within storage sites in reticuloendothelial cells. Consequently, this reduces the availability of iron necessary for erythropoiesis.

Chemotherapy and Radiotherapy

Treatment modalities like chemotherapy and radiotherapy, commonly employed in cancer therapy, exert profound effects on hematopoiesis and frequently result in anemia [7]. Myelosuppressive chemotherapeutic agents impede the bone marrow's ability to produce blood cells. Furthermore, certain cytotoxic drugs can decrease the synthesis of EPO by the kidneys, exacerbating anemia. Similarly, radiation therapy damages the bone marrow, leading to decreased red blood cell production and contributing to the development of anemia.

Vitamin B12 and Folic Acid Deficiencies

Vitamin B12 (cobalamin) and folic acid deficiency are significant causes of anemia due to their essential roles in erythropoiesis [8]. Vitamin B12 deficiency may stem from inadequate dietary intake, impaired absorption (e.g., due to autoimmune conditions affecting intrinsic factor production), or surgical interventions affecting gastrointestinal absorption. Likewise, folic acid deficiency can result from insufficient dietary intake, malabsorption syndromes, or the chronic use of medications such as phenytoin or carbamazepine.

Understanding and effectively addressing the diverse causes of preoperative anemia are critical steps in optimizing patient outcomes. It is a highly important matter because patients who were diagnosed with it were associated with a higher rate of increased in-hospital mortality, increased Intensive Critical Care Unit reception rate, and prolonged length of hospital stay[3].

Patient Blood Management

Implementing Patient Blood Management (PBM) is crucial while treating anemic patients. PBM was adopted by the World Health Organization (WHO) and is supported by many committees. Its three main pillars include detecting and managing anemia and iron deficiency, minimizing blood loss and optimizing coagulation, and leveraging and optimizing the patient-specific physiological tolerance of anemia [9]. PBM rejects allogeneic red blood cell transfusions (ABT) as a primary solution for anemic patients. PBM's main goal is to increase

favorable outcomes in anemic patients or anemic patients undergoing major elective surgery. It is worth mentioning that preoperative anemia is defined as the concentration of hemoglobin (Hb) <13 g/dL in both sexes despite WHO definition. This is dictated by the fact that women lose blood amounts similar to men during surgery and have lower erythrocytic masses [3].

First Pillar of PBM - *detection and management of anemia and iron deficiency*

Detection of anemia should be routinely done by conducting blood tests in hospitalized patients. In anemic patients, it is vital to diagnose the etiology of anemia to implement appropriate treatment. The prevalence of anemia varies depending on the type of patient. Randi et al. found that anemia prevalence in 435 hospitalized patients in the internal medicine ward was 62%. Patients aged 65 or above constituted 78.1% of anemic patients, which suggests that anemia is highly prevalent in the elderly population [10].

According to a large cohort study by Muñoz et al., the highest incidence of anemia was present in patients undergoing gynecological surgery (64%), colorectal cancer surgery (58%) followed by cardiac surgery (40%). Patients scheduled for major elective surgery should undergo a complete blood count with iron parameters tests to rule out preoperative or iron deficiency, which can later be responsible for developing iron deficiency anemia (IDA). We recently published a diagnostic algorithm that can be helpful in IDA diagnosis [11].

The optimization of the erythrocytic mass should be achieved by determining the cause of the anemia. IDA develops when iron intake falls below excretion levels, during increased iron demand, and when absorption disturbances or chronic blood loss are present, resulting in inadequate iron supply for Hb synthesis. In IDA's case, implementing oral or intravenous iron treatment is vital. Treatment of IDA should begin four weeks prior to the surgery. Currently, oral iron supplementation remains essential IDA management [12]. However, this seems to be a suboptimal method of treatment. Current evidence suggests that intravenous iron is a better choice. Besides having less side effects than oral iron (stomach aches, dyspepsia, black stool color, intestinal mucosa irritation, nausea, vomiting), intravenous iron allows quicker elevation of Hb concentration [13–15].

In patients with non-iron deficiency anemia (non-IDA), recombinant human erythropoietin (rHuEPO), epoetin alfa or darbepoetin alfa seems reasonable.[16] In renal anemia, chronic kidney disease (CKD), or renal failure, endogenous erythropoietin (EPO) production falls. Without adequate levels of EPO, proliferation, differentiation, and maturation of red blood cells (RBC) in bone marrow deteriorates, resulting in anemia. However, its vital to remember that in CKD population, hepcidin levels are elevated due to reduced renal clearance and

increased interleukin-6 (IL-6) levels. This phenomenon can decrease iron absorption, sequestration, and EPO resistance [17].

In patients undergoing dialysis, rHuEPO, epoetin alfa or darbepoetin alfa administration is an effective method to normalize or maintain Hb concentration [18].

Additionally, erythropoiesis-stimulating agents (ESA) reduce the risk of ABT [19]. In patients with vitamin B12/folic acid deficiency with megaloblastic anemia, it is vital to restore adequate levels of the aforementioned vitamins to deal with the disease.

Second Pillar of PBM - *minimization of blood loss and optimization of coagulation*

Many strategies can be applied to minimize blood loss in surgical or medical patients. Firstly, a thorough medical history should be taken to assess the patient's risk of bleeding and coagulopathy. It should contain questions about past bleeding after surgery or trauma, anticoagulant and antiplatelet drug use, and a family history of bleeding [20]. Revision of drugs taken by surgical patients to modify or temporarily suspend anticoagulants or antiplatelets use to minimize blood loss during surgery. However, the cardiovascular complications of such intervention must be considered, and risk assessment should be performed for each patient individually [21]. Intraoperative tasks include monitoring coagulation with point-of-care testing and appropriate use of blood products and coagulation factors concentrates according to guidelines [22]. Surgical technique plays a vital role in minimizing blood loss during surgery. The choice of robotic or laparoscopic methods reduces the risk of significant blood loss as they are minimally invasive [23,24].

The type of anesthesia during surgery also has an impact on blood loss. A meta-analysis by Richman et al. demonstrates that neuraxial anesthesia, compared to general anesthesia, was associated with a significant decrease in intraoperative blood loss [25]. This phenomenon is caused by neuraxial anesthesia, which decreases arterial and venous blood pressure.

Decreased blood pressure from deliberate hypotension lowers intraoperative blood loss [26].

Other vital factors to preserve proper coagulation during surgery are avoiding hypothermia (<35°C) – and maintaining satisfactory platelet function. A decrease in body temperature of 1°C increases blood loss by 16% and ABT by 22%. [27] Additionally, correcting hypocalcemia and acidosis plays a vital role in preserving adequate coagulation. The use of antifibrinolytic drugs has its role in the prevention of significant bleeding. CRASH-2 trial demonstrated that in significant hemorrhage, administration of tranexamic acid (TXA) within three hours of injury reduced the risk of death and all-cause mortality from

hemorrhage [28].

Third Pillar - *leveraging and optimizing the patient-specific physiological tolerance of anemia*

In case of surgical patients, it is important to preoperatively estimate intraoperative blood loss and compare it with patient-specific tolerable blood loss. Preoperatively, each patient should undergo cardiac and pulmonary function preparation to maintain appropriate oxygen delivery to tissues during and after the surgery. Increasing oxygen delivery and reducing oxygen demand can compensate for lower hemoglobin concentration due to blood loss and dilution with infusion fluids, e.g., crystalloids and colloids. Vasopressors can optimize cardiovascular function to maintain organ perfusion and improve oxygen delivery. Therefore, individual preparation for surgery is vital to predict possibilities and complications [29].

A restrictive approach to ABT is another key element of the Third Pillar of PBM. There are several thresholds for ABT. For the restrictive approach to ABT, the threshold is Hb concentration ≤7 g/dL. TRICC trial demonstrated that this strategy was as effective as a liberal approach in critically ill patients. Additionally, patients in the restrictive approach group with an Acute Physiology and Chronic Health Evaluation score (APACHE II) <20 and age below 55 years had a significantly reduced 30-day mortality rate [30].

Restrictive ABT strategy is also safe in patients with malignancy, upper gastrointestinal bleeding, cardiovascular diseases, and orthopedic surgery [31–34].

CONCLUSIONS

In conclusion, Patient Blood Management (PBM) remains an essential foundation of contemporary surgical care, particularly for patients suffering from anemia. This holistic approach combines three critical pillars: early diagnosis and management of anemia and iron deficits, intraoperative blood conservation strategies, and optimization of individual physiological tolerance to anemia. PBM aims not only to reduce the reliance on blood transfusions but also to enhance patient outcomes across various surgical settings.

The first pillar concerns early recognition and treatment of anemia, highlighting the importance of routine screening and tailored interventions based on individual needs. Proactively identifying underlying causes contributing to anemia facilitates prompt initiation of appropriate treatments, such as oral or intravenous micronutrient replacement or erythropoiesis-stimulating agents for non-iron-deficient causes.

The second pillar focuses on minimizing surgical bleeding through meticulous surgical techniques, advanced hemostatic strategies, and cautious use of antifibrinolytic medications like

tranexamic acid. Additionally, optimizing anesthesia and perioperative care to maintain stable hemodynamics and adequate tissue oxygenation is crucial in reducing the overall need for blood transfusions.

The third pillar involves leveraging and optimizing individual tolerance to anemia by preoperatively optimizing cardiac and pulmonary function to ensure adequate oxygen delivery despite reduced hemoglobin levels. This approach includes assessing and enhancing cardiovascular reserves, judicious use of vasopressors, and minimal red blood cell transfusion based on specific physiological parameters such as blood pressure dynamics.

By embracing these strategies, healthcare systems align with current trends in personalized medicine and value-based care, ensuring that surgical interventions are tailored to each patient's needs to optimize recovery and enhance quality of life post-surgery. Furthermore, adherence to these principles improves patient outcomes and supports healthcare delivery's economic sustainability.

As ongoing research continues to refine our understanding of anemia management and surgical outcomes, the evolution of PBM promises further innovations in surgical care. Collaboration among healthcare providers, researchers, and policymakers is essential to integrate PBM into standard clinical practice, paving the way for a future where surgical care is safer, more effective, patient-centered, and economically viable.

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COMPARISON OF TRANSCATHETER ABLATION METHODS FOR ATRIAL FIBRILLATION TREATMENT

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INTRODUCTION

Atrial fibrillation (AF) is the most common supraventricular tachyarrhythmia [1]. Its course is progressive and chronic with periods of exacerbation and remission [2]. It occurs due to activity initiated by ectopic foci within the pulmonary veins. It is characterized by rapid (350-700/min) and uncoordinated atrial activity, resulting in reduced systolic efficiency. This phenomenon is accompanied by an irregular ventricular rhythm, which may be felt by the patient as palpitations. In addition, there may be paroxysmal sweats, weakness, dizziness and decreased physical performance [1].

Atrial fibrillation is a huge health problem worldwide, as it affects as many as 30 million people [3]. It occurs much more frequently in older people. Statistics show that in people in the 80-89 age bracket, AF occurs in 8.8% of cases and in those aged 50-59 years in 0.5%. Compared to people with normal sinus rhythm, people with AF have almost twice the mortality rate, which is mainly due to strokes [4]. In addition, AF is associated with other cardiovascular diseases and with diseases of the nervous system such as dementia [3]. Frequent hospital admissions make it a serious and costly problem for the healthcare system [3,5]. It is estimated that AF accounts for up to 2.5% of annual healthcare expenditure, and over the next 20 years, this could rise to 4%. Although AF is rarely acutely life-threatening, it is associated with a significant deterioration in quality of life. For this reason, the best possible treatment is still being sought [2].

The first-line treatment is the use of antiarrhythmic drugs (AADs), although it appears that their use has its limitations. In some cases, the ADDs do not help maintain the sinus rhythm, and some of them are toxic and potentially pro-arrhythmic. Long-term use of amiodarone and sotalol has been associated with increased mortality [2].

Current studies report that catheter ablation is more effective than drug therapy [2,6].

However, it should be noted that most of the studies conducted to date have focused on patients in whom antiarrhythmic drugs have not had an adequate effect [2].

RADIOFREQUENCY ABLATION

Radiofrequency ablation (RFA) is the oldest type of ablation procedure used in patients with persistent AF who are unresponsive or intolerant to AADs [5]. RFA is the most frequently used method of PVI worldwide [6]. It involves the suppression of atrial arrhythmogenic factors by isolating pulmonary veins and damage to the surrounding tissue. The procedure is performed through a trans-septal approach and can be complicated by perforation, tamponade, hematoma, pulmonary vein stenosis, and stroke [4]. Radiofrequency (RF) ablation involves resistive heating of the tissue near the tip of the electrode and on conductive heating of the distal zone using a catheter. For this purpose, the electrode generates an alternating current with a high-frequency range of 100 to 2,000 kHz, which causes permanent tissue damage to the heart muscle at a temperature of approx. 55°C. Excess heat is dissipated via the circulating blood. The amount of damage done depends on several factors of energy delivery and environmental conditions. The variables of energy delivery, such as temperature, power, and duration of the RFA and the method of energy delivery, including the direction, size, and force of the electrode and also environmental conditions, including blood flow or local tissue contact [7]. The effectiveness of the treatment depends both on the permanence of the changes made and on the presence of collateral damage around the targeted area [8]. For this reason, there have been recent advances in the catheters used. At the turn of the 20th/21st century, research focused on pulmonary vein isolation (PVI) using unidirectional, non-irrigated catheters [9]. Currently, irrigated tip and power-adjustable catheters are widely used, which has increased the safety profile. With the new technique, the incidence of thrombus formation has decreased. Typically, a power of 20-40W for 20-60s is used, but it is possible to adjust and adapt the power. Another innovation is the introduction of catheters with a contact force (CF) detection function. This provides an assessment of catheter stability and contact between the catheter and the atrium of the heart [6]. Several clinical studies have shown that low CF levels during the RFA procedure can result in complications [10,11]. Despite the benefits of force sensing, there is no evidence to suggest improved safety when using this method. In addition, it has been speculated that AF ablation with CF-detecting catheters may be associated with a higher incidence of atrioesophageal fistula formation [6].

A major challenge is the recurrence of AF that takes place despite ablation. It is estima-

ted that they may occur in 30% to 50% of patients [3]. We distinguish between early, late, and long-term AF recurrences. Early AF recurrences are those that occur between 48h and 3 months after ablation. They occur in 25% to 65% of people, and an early recurrence may predict a late recurrence of AF, i.e. made between 3 and 12 months after RFA. The timing of early recurrence appears to be an important indicator of the possibility of late AF recurrence [12]. It appears that recurrence taking place between the second and third month after ablation suggests a greater likelihood of late recurrence than early recurrence happening up to one month after the procedure [13].

Yan Luo and colleagues showed that 22.8 % of patients had a late recurrence of AF during one year of follow-up and demonstrated that one of the risk factors for late recurrence of AF is impaired renal function. Recurrence is assumed to occur due to atrial fibrosis as a result of metabolic and hemodynamic disturbances. Therefore, renal disease may be a modifiable risk factor for AF [3].

Other factors indicating a higher likelihood of AF recurrence are inflammation and neurohumoral activation, as reflected in CRP levels and NT-proBNP levels. However, the pathophysiology of the increase in these markers is as yet unknown. Given this, further studies are needed to understand the mechanism of AF recurrence after ablation. This will allow more accurate patient selection and planning of post-ablation management. Other risk factors, such as left atrial enlargement, prolonged AF duration, and the presence of structural heart disease, seem to be less useful due to the lack of accuracy in measuring these parameters[4].

CRYOISOLATION

Cryoisolation (CRYO**)** is another effective approach to the invasive treatment of atrial fibrillation. It is the easiest technique with the shortest learning curve. Cryoisolation is safer than RF ablation in terms of major complications (such as stroke, cardiac tamponade, and atrioesophageal fistula) for pulmonary vein isolation. [14]

The procedure time is predictable and relatively short, and its efficacy is comparable to that of point-by-point radiofrequency ablation. It requires only one transseptal puncture. The ablated area shows low thrombogenicity. All of the above makes this method one of the most frequently used techniques of PVI. However, there are disadvantages to this method. It requires contrast administration and the longest fluoroscopy time, which results in a high dosage of radiation. Also, not every anatomical variation of the left atrium is suitable for the cryoballoon. [15].

Pulmonary vein isolation by cryoablation involves creating a lesion at the junction of the left atrial tissue and the pulmonary vein ostia through convective cooling, in which the cryorefrigerant absorbs heat from the tissue surrounding the catheter. Cryoablation leads to cellular injury caused by a combination of forming extracellular ice crystals, which induces osmotic stress, with simultaneous cell membrane destruction, enzyme inhibition, and microvessel failure. Rewarming of tissue increases the damage by inflammation and hemorrhage caused by hyperemic vascular response. In the following weeks, the lesion area develops a well-circumscribed region of fibrosis in the center. This prevents the arrhythmia from being conducted from pulmonary veins to the left atrium [2].

This method gives good results in electrical isolation of pulmonary veins and prevention of AF recurrence. After one year of follow-up, 85.2% of patients with idiopathic AF and 64,6% of patients with non-idiopathic AF were free from atrial arrhythmia. After three years of follow-up, 70,4% of patients with idiopathic and 39,9% of patients with non-idiopathic AF were free from atrial arrhythmias. Additionally, when focusing solely on patients with paroxysmal AF, the success rates at 1 and 3 years of follow-up were 95.7% and 82% for idiopathic AF and 72.6% and 47% for non-idiopathic AF [16].

The occurrence of adverse effects when using this method has been measured in various studies. The most common complications are arteriovenous fistula or pseudoaneurysm at the access which occurs in approximately 3.5% of patients. Phrenic nerve (PN) injury was reported in 7,5% of patients and phrenic nerve palsy in 1,5% of patients. Other procedural complications such as esophageal injury, tamponade, stroke, or TIA occur in less than 1% of patients [17]. Taking all things into consideration, despite the high safety profile and good effectiveness, this method is not perfect, and some patients may require a repeat procedure in the future due to the recurrence of arrhythmia.

PULSED-FIELD ABLATION

It is a relatively new technique of atrial fibrillation AF interventional treatment. It’s a nonthermal method of ablation that uses ultra-rapid electric fields to form nanoscale pores in the cell membrane of a targeted tissue [18,19].

Electroporation (EP) is a method of increasing the permeability of a plasma cell membrane through the application of an electrical field. Pulsed-field ablation (PFA) uses a direct external current that is applied to cardiomyocytes in rapid pulses [18]. The applied electrical field induces the creation of pores within the lipid bilayer of a cell membrane,

resulting in increased permeability of a plasma cell membrane. Depending on the strength of the electric field across the cell membrane, it may result in transient pore formation, permanent pore formation, or no effect at all. That irreversible change in membrane structure is called "irreversible electroporation" [19]. The irreversible electroporation results in cell death via necrosis, apoptosis, necroptosis or pyroptosis. Although the exact mechanisms of the cell death pathway and its clinical implications may vary in different PFA protocols [20].

An especially advantageous feature of PFA is its selectivity in tissue EP. Following cell tissues have their own, unique sensitivities to specific electric field strengths, with the myocardium having the lower threshold for dielectric cell membrane breakdown (375 V/cm), therefore minimalizing the risk of damage to surrounding non-cardiac tissues such as the esophagus, nerves (3,800 V/cm), and vessels (1,750 V/cm for vascular smooth muscle cells or the endothelium) [18,19,20,21].

Additionally, research showed that damage to the esophagus, caused by electroporation lesions, was limited only to the muscular layer contrary to the RF ablations that compressed the esophageal wall and resulted in the destruction of adventitia, epithelial and muscular layers, preventing the complication in the form of atrioesophageal fistula [21,22].

PFA may provide a solution to pulmonary vein stenosis resulting from thermal ablation of pulmonary veins. A study performed on canines aimed at demonstrating the worst-case scenario for pulmonary vein stenosis compared the effects of PFA and RFA. The study showed progressive stenosis in veins subjected to RFA in subsequent CT scans while demonstrating no significant stenosis in veins subjected to the PFA procedure [19].

Although PFA is a recent technique, studies showed that a significant number of first-pass PVI were successful (98.8%), with 16.7% recurrence during the blanking period (the first three months following ablation), 19.1% of patients underwent repeat ablation [15]. Other research showed 78.1% freedom from atrial arrhythmias in 1-year follow-up [23].

Research also shows the PVI procedures performed with PFA were associated with a lower risk of major adverse events than CRYO, such as cardiac tamponade (1.1%), stroke (0.4%), coronary spasm (0.1%), persistent phrenic nerve injury (0.06%), death (0.06%), esophageal fistula (0%), symptomatic pulmonary vein stenosis (0%) [23,24].

Minor Adverse Events occurred in 4% of patients, including vascular complications (2.6%): hematoma (2.1%), arteriovenous fistula (0.3%), transient PN injury (0.4%), air embolism (0.3%), and pericardial effusion without intervention (0.3%) [23].

CONCLUSIONS

All strategies have a low risk of serious complications, ranging between 0.9% and 1.1%. PFA patients have lower overall complication rates, mainly because of a higher occurrence of minor complications among CRYO and RF ablation patients. Long-term arrhythmia freedom is high (>70% in 1 year) and not significantly different among technologies. However, PFA patients trended towards a lower frequency of AF recurrence, with rates of 20.7%, 25.3%, and 27.6% for PFA, CRYO, and RFA, respectively. PFA has significantly shorter procedural time (52 ± 12 min), compared to CRYO (65 ± 22 min) and RF ablation (85±25 min). The exposure to fluoroscopy varies from 13±7 min for RFA to 18±8 min for CRYO [15].

Out of all of the presented procedures each of them has its advantages and disadvantages. While PFA is characterized by rare adverse events occurrence it is a new method that has not been thoroughly investigated in the long run and has not been widely popularized [23,25]. On the other hand, CRYO is widely used and stands out for its efficacy and the shortest learning curve (although PFA may outrun it in the future), while continuously maintaining a higher complication rate than RFA [25,26]. However, an undeniable advantage of RFA is the lowest exposure to fluoroscopy of all of the above, although it has the lowest AF freedom in 1-year follow-up duration [15].

Nonetheless, today's science has not yet found the perfect treatment method for sustaining AF freedom over the long term in all patients.

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INFLAMMATORY LESIONS IN THE THORACIC SPINE – DIAGNOSTIC AND THERAPEUTIC DIFFICULTIES – REPORTS OF 3 CASES

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INTRODUCTION

Infections of the spine and spinal tissues present a significant clinical problem. Diagnosis may initially be difficult due to uncharacteristic symptoms (local or radicular-like pain) that may suggest degenerative or idiopathic changes as the underlying cause. Fever occurs in only 50-60% of patients; the incidence of neurological deficits manifested as limb paresis is estimated at several percent [1,2,3].

Infection is often spread by the blood-borne route, less often by continuity or by direct introduction of the pathogenic agent as a complication of invasive procedures [5,6,7].

Infections most often affect the lumbosacral region (52.3%). The thoracic spine is the second most common infection location (30%), with the least inflammatory lesions localized in the cervical segment [3,8,9]. There is a distinction between osteomyelitis, discitis, and epidural abscesses based on the anatomical location of the spinal infection [10].

Neuroimaging tests are the basis for diagnosing spinal infections, wherein MRI is considered the best diagnostic method [5,11]. Microbiological diagnostics are necessary when suspecting a spinal infection [1,12]. Laboratory tests in most patients show elevated CRP levels (up to 90% of patients) and ESR, with leukocytosis in the peripheral blood count [2,4,5].

Spinal infection treatment involves intravenous antibiotic therapy – initially empirical, then modified based on microbiological results. A small percentage of patients require surgical treatment [14,15].

CASE REPORT

The paper presents a report of three patient cases: 2 men, aged 34 and 49, and a 61-year-old woman, hospitalized in the Neurology Department due to inflammatory infiltrates in the thoracic segment of the spinal canal.

Case 1 Description.

A 34-year-old male patient with no chronic disease treatment was admitted to the Surgical Department of the Ostrzeszów Poviat Hospital due to abdominal pain and fever that had been increasing for several days. After 3 hours of hospitalization, the patient developed flaccid lower limb paresis. The imaging diagnostics performed - a CT scan of the head and the L-S spine and an angio-CT scan of the abdominal aorta and lower extremities- showed no abnormalities. The patient was transferred to the Neurology Department of the Voivodeship Hospital in Kalisz. Obtaining the patient's medical history was difficult due to the language barrier. The patient was a Pakistani citizen, spoke only Urdu, and was illiterate, which prevented the use of a translator; the function of the translator was performed by the patient's cousin; who spoke English to a beginner's degree. On neurological examination on admission, the patient was conscious, without signs of cranial nerve damage, upper extremity muscle strength was expected, and symmetrical reflexes were symmetrical. Regarding lower extremities, there was bilateral plegia, reduced muscle tension, knee reflexes were bilaterally weakened, ankle reflexes were moderately vivid symmetrical, bilateral positive Babinski sign, and interrupted sensory disturbances on the torso from the Th8 level downwards.

Laboratory tests on admission revealed: leukocytosis (WBC 17.6 10^9/L), and elevated CRP level (12.19 mg/dL with laboratory normal range < 0.5).

A bi-phase MRI scan of the cervical spine showed an intrathecal, epidural abscess from the C6 level downward, with preservation of the spinal canal width; the spinal cord image was normal (Fig. 1).

A thoracic spine bi-phase MRI scan showed radiological signs of transverse myelitis at Th1-Th6 and an extrathecal abscess at the Th1-Th6 level (Fig. 2).

Serological diagnostics for HIV infection, hepatitis B and C, syphilis, and Lyme disease with the Elisa method were carried out – with negative results.

The patient underwent a lumbar puncture and cerebrospinal fluid examination – total cytosis 20.0 with predominance of lymphocytic cells and elevated protein level (684.6 mg/dL).

The patient's blood culture demonstrated *Staphylococcus aureus* MRSA, MLSb(+) strain,

and targeted antibiotic therapy (vancomycin) was continued.

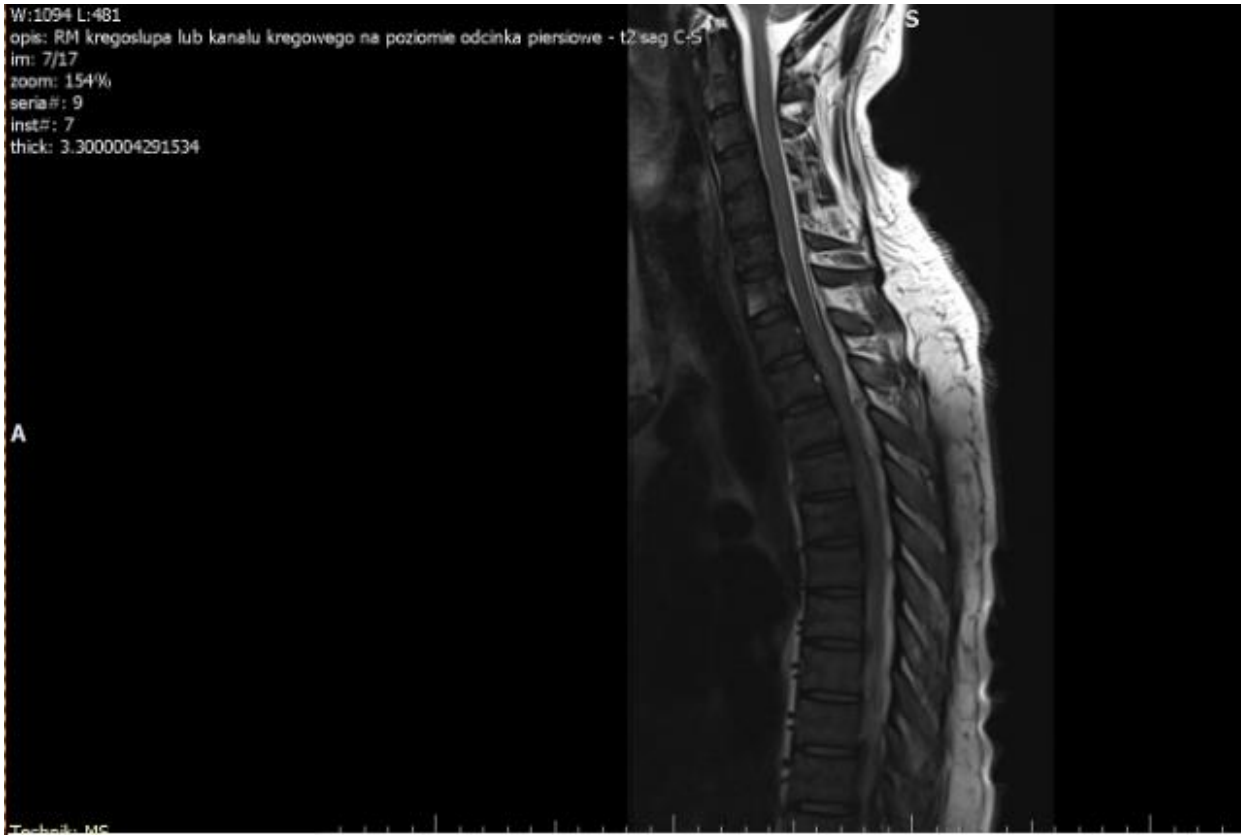

Figure 1. Radiological image of the cervical spine of Patient 1

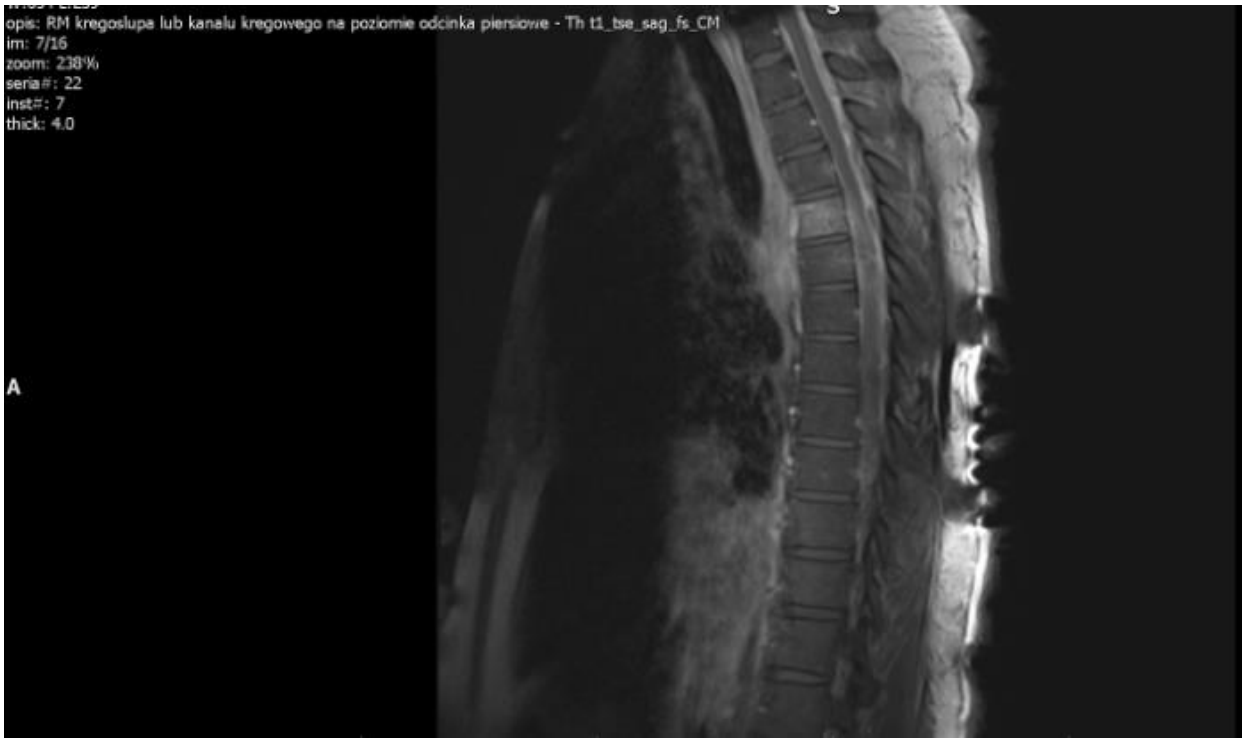

Figure 2. Radiological image of the thoracic spine of Patient 1

On the 3rd day of hospitalization, the patient developed clinical signs of paralytic bowel obstruction, confirmed by an abdominal CT scan.

On the 4th day of hospitalization, the patient developed signs of increasing respiratory failure. The patient was transferred to the Intensive Care Unit and required mechanical ventilation. Due to symptoms of septic shock, the patient was treated with an infusion of pressor amines, and parenteral nutrition was administered at reduced doses due to shock. The patient had a fever above 42 degrees C – antipyretic treatment and physical cooling with a convection blanket were used. After several hours in the ICU, the patient was pronounced dead.

Case 2 Description

A 49-year-old male patient, previously not treated for chronic diseases, was admitted to the Neurology Department of the Voivodeship Hospital in Kalisz due to weakness of muscle strength in the lower extremities with accompanying paresthesias, which had persisted for 24 hours.

On neurological examination on admission, the patient was conscious, logical, without signs of cranial nerve damage, muscle strength was normal in the upper extremities, symmetrical, reflexes were symmetrical, lower extremities: bilateral paresis proximally, 1/5 on the Lovette scale, distally 4/5 on the Lovette scale, knee and ankle reflexes were exaggerated, symmetrical, bilateral positive Babinski sign, interrupted superficial sensory disturbances on the torso, from the Th10 dermatome downward, the patient was lying down.

Laboratory tests on admission: leukocytosis (WBC 24.1 10^9/L), elevated CRP level (8.74 mg/dL with laboratory normal range < 0.5).

MRI scan of the thoracic spine performed on the day of admission showed a widened outline and edema of the intervertebral disc at the Th9/Th10 level, causing spinal canal stenosis, as well as extensive marrow edema of the Th9 and Th10 vertebral bodies and inflammatory infiltration of the vertebral soft tissues at the Th9/10 level, surrounding the descending aorta from the posterior surface (Fig. 3).

The patient's venous blood was drawn for culture, and empirical antibiotic therapy (ceftriaxone and vancomycin) was implemented.

The patient was consulted by a neurosurgeon – and was not qualified for surgery. After blood culture results (*Staphylococcus aureus* strain MSSA, MLSb+) and an antibiogram were obtained, and after consultation with an infectious disease specialist, antibiotic therapy was modified – cloxacillin was included at a dose of 2 g 4 × daily intravenously.

Despite pharmacological treatment and bedside rehabilitation, the patient's condition

deteriorated after a week of hospitalization – the patient developed lower limb plegia.

A bi-phase CT scan of the thorax and abdomen was performed, which showed *spondylodiscitis-type* lesions at the Th9/10 level with inflammatory infiltration of the paraspinal tissues and inflammatory densities in the posterior parts of the inferior lobe of the right lung, spreading through continuity from the paraspinal space. No other purulent foci were visualized on examination. A craniofacial CT scan was performed, ruling out the presence of inflammatory lesions. A bi-phase MRI scan of the head showed small, past vascular lesions without inflammatory foci.

A follow-up MRI scan of the thoracic region performed after two weeks of antibiotic therapy showed persistent inflammatory infiltration of the Th9/Th10 intervertebral disc, spinal vertebrae, and spinal soft tissues, with spinal canal stenosis and spinal edema (Fig. 4).

The patient's neurological condition remained unchanged – plegia of the lower extremities and interrupted superficial sensory disturbances from the Th10-11 level downward persisted. After three weeks of hospitalization, the patient was transferred to the Department of Internal Medicine in Krotoszyn for continued antibiotic therapy. After antibiotic treatment, the patient was referred to the Department of Neurological Rehabilitation in Koźmin Wielkopolski.

Fourteen weeks after the onset of symptoms, the patient was readmitted to the Neurology Department of the WSZ Hospital in Kalisz for follow-up diagnostic imaging.

On admission, he was diagnosed with bilateral lower limb paresis, 1/5 on the Lovette scale, with spastic muscle tone enhancement, bilateral reduction of knee and ankle reflexes, no Babinski sign, and interrupted sensory disturbances from the Th10 dermatome downward.

A follow-up MRI scan of the thoracic spine showed moderate consolidation of the inflammatory infiltrate of Th9/10 *discitis*, with a slight reduction in stenosis (Fig. 5).

The patient was referred to the Neurosurgery Department of the Military Hospital in Kraków, where surgery was performed to decompress the spinal canal at the Th 9-Th 10 level, with the removal of epidural inflammatory lesions. After the surgery, the patient reported pain reduction and slightly improved lower extremity mobility.

Ten weeks after neurosurgical intervention, the patient was readmitted to the Neurology Department of the WSZ Hospital in Kalisz. On admission, neurological examination showed lower limb paresis – on the right side: proximally 3/5, distally 1/5; on the left side: proximally 2/5, distally 1/5 on the Lovette scale, knee reflexes were bilaterally moderately vivid, ankle and sole reflexes were weakened, negative Babinski sign, sensory weakness and paresthesias from the Th10 dermatome level downward. A follow-up MRI of the thoracic spine was performed, which showed

moderate regression of the Th9/Th 10 intervertebral disc inflammatory infiltration, with a slight reduction in spinal canal stenosis. The patient was discharged from the Department with a recommendation for further rehabilitation treatment.

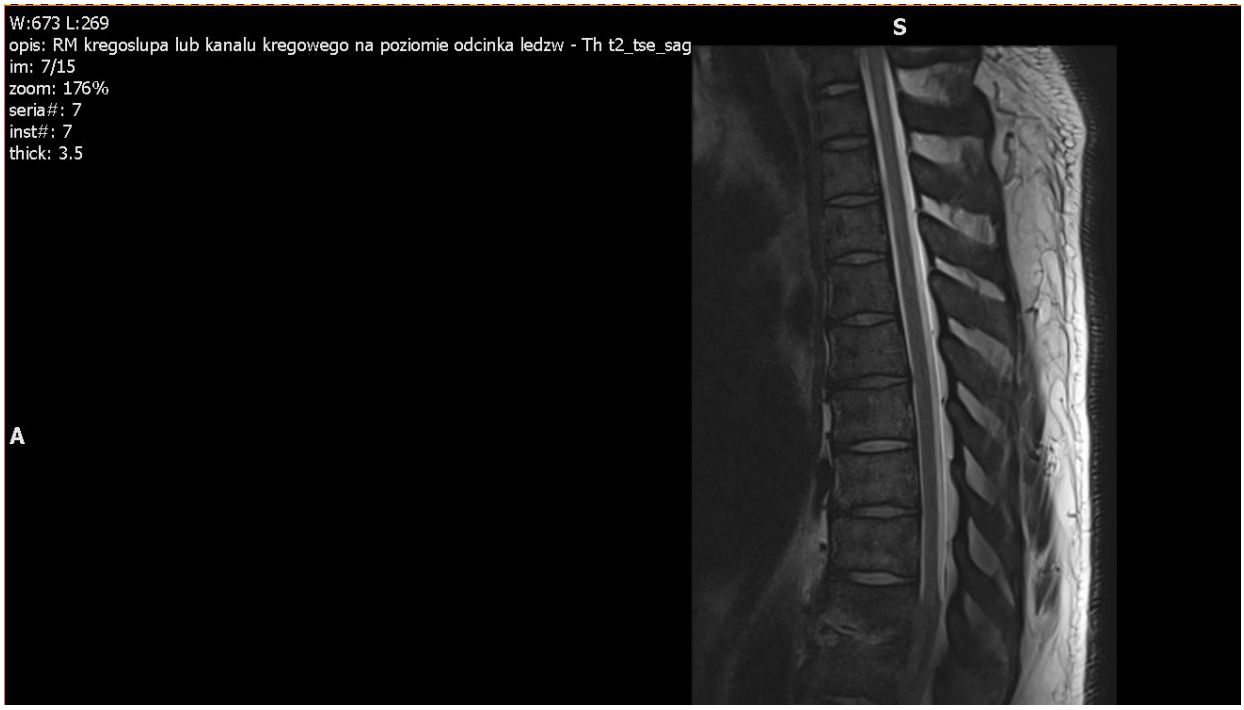

Figure 3. Radiological image of the thoracic spine of patient 2 – examination performed on admission.

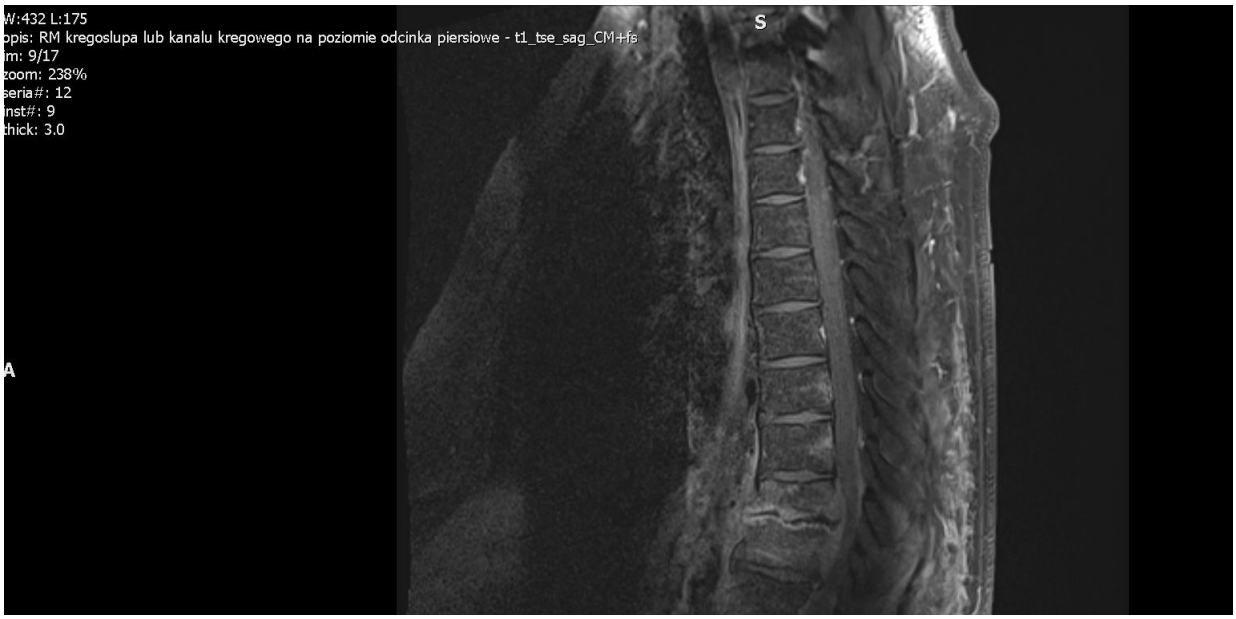

Figure 4. Radiological image of the thoracic spine of patient 2 – follow-up examination performed after 2 weeks of intravenous antibiotic therapy.

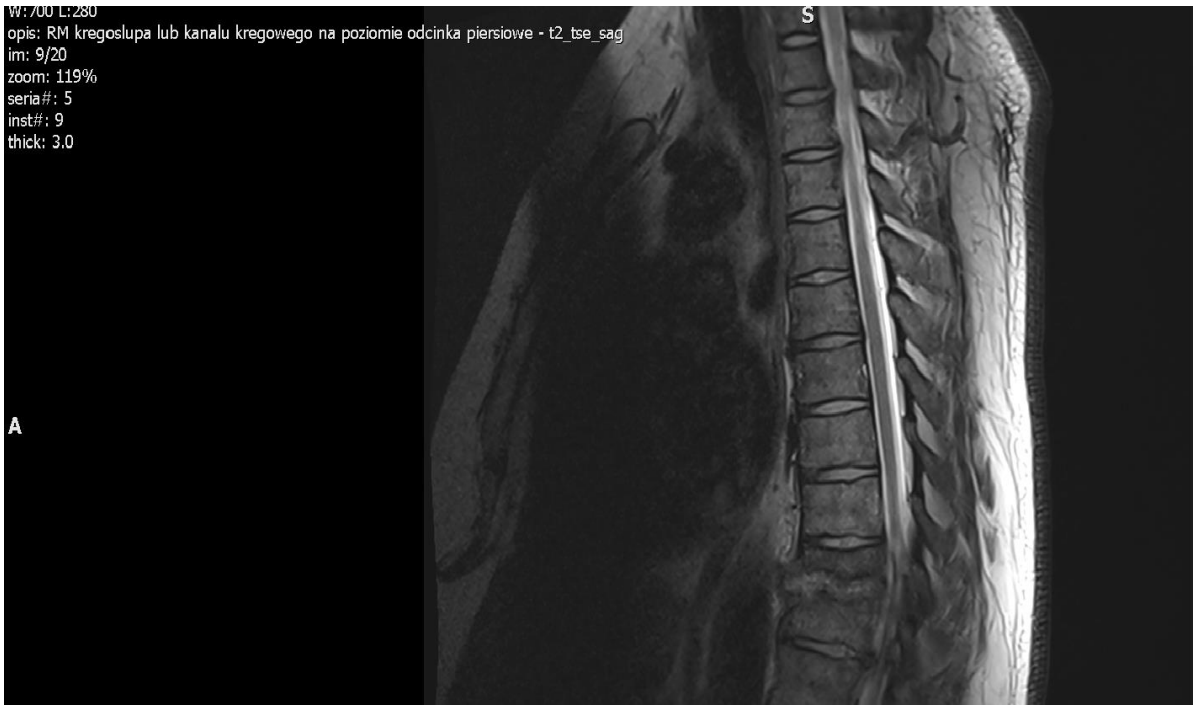

Figure 5. Radiological image of the thoracic spine of patient 2 – follow-up examination performed after 14 weeks of treatment.

Case 3 Description

A 61-year-old female patient was admitted to the Internal Medicine Department of the Jarocin Poviat Hospital due to increasing weakness in both lower extremities and the left upper limb for about a week. In the internal medicine department, a head CT scan (cerebral image was normal), abdominal ultrasound, and thoracic X-ray were performed (with no significant abnormalities). Based on the biochemical tests, acute anterograde renal failure and urinary tract infection were diagnosed, and empirical antibiotic therapy (intravenous ceftriaxone) was implemented without prior culture specimen collection. The patient was previously untreated in terms of internal medicine and was taking chronic escitalopram for depressive disorders. The patient was transferred to the Neurology Department of the WSZ Hospital in Kalisz. On admission to the Neurology Department, the patient was in moderate-severe general condition, with dyspnea, and required passive oxygen therapy due to drops in saturation. On neurological examination, she was conscious, logical, with normal orientation to time, place, and person; cranial nerves showed no signs of damage, nystagmus was absent, there was paresis of the left upper limb 3/5, deep reflexes of the upper limbs were symmetrical, moderately vivid, there was plegia of lower limbs, reduction of deep reflexes of lower limbs, interrupted sensory disturbances from the level of the umbilicus downward, no pathological symptoms, no meningeal signs, the patient was lying down.

On the day of admission to the Neurology Department, the patient had her blood drawn for

culture – the results were negative (the patient was on antibiotic therapy initiated empirically in the internal medicine department).

Laboratory tests on admission: leukocytosis (WBC 10.6 10^9/L), elevated CRP level (13.43 mg/dL with laboratory normal range < 0.5).

A bi-phase MRI scan of the cervical spine was performed, showing signs of C4/C5 intervertebral disc inflammation with paraspinal abscesses and epidural abscesses in the cervical spine, causing moderate spinal canal stenosis, and a bi-phase MRI scan of The Th spine showed extensive intrathecal purulent infiltration at the Th5-Th11 levels, with epidural abscesses causing significant spinal canal stenosis, with spinal cord edema, and extensive infiltration of the paraspinal soft tissues, and abscess in the erector spinae muscle on the left side (Fig. 6, Fig. 7). A bi-phase MRI scan of the L/S spine showed extensive infiltration in the dorsal subcutaneous tissue, with no purulent lesions in the spinal canal. An MRI scan of the head ruled out the presence of abscesses.

The patient was consulted by a neurosurgeon from the Neurosurgical Department of the WSZ Hospital in Kalisz and the Department of Neurosurgery and Neurotraumatology of the Poznań University of Medical Sciences – conservative treatment was recommended. An attempt was made to obtain specimens for microbiological tests. Under ultrasound guidance, a purulent reservoir was punctured within the erector spinae muscle on the left side, and the specimen provided a sterile culture result. The patient was consulted by an infectious disease specialist – empirical antibiotic therapy was modified – metronidazole at 500 mg 3 × day and vancomycin at 1.0 g 2 × day were added to the ceftriaxone used in the Internal Medicine Department.

Since inserting an intravenous line at the patient's periphery in the operating theater was impossible, a central line was inserted into the right superior vena cava.

A follow-up MRI scan of the thoracic spine performed after three weeks of antibiotic therapy showed a partial reduction in intrathecal and spinal infiltration. In addition, the scan showed an ischemic lesion in the spinal cord at the Th8/9 disc level (Fig. 8).

Bedside rehabilitation was provided during hospitalization. After the applied treatment, the neurological condition improved – on the day of discharge, the patient was conscious, in full logical contact, with normal orientation to time, place and person, speech without disturbances, meningeal signs were absent, cranial nerves showed no signs of damage, upper limbs showed no paresis, deep reflexes in upper limbs were symmetrical, moderately vivid, there was flaccid paresis of the lower limbs, with trace of movement proximally, knee joint: right lower extremity 1/5, left lower extremity 1/5, distally right lower extremity 2-/5, left lower extremity 1/5, deep reflexes in lower extremities were bilaterally reduced, no pathological symptoms, interrupted sensory disturbances

from the level of the inguinal region downwards, the patient was lying down.

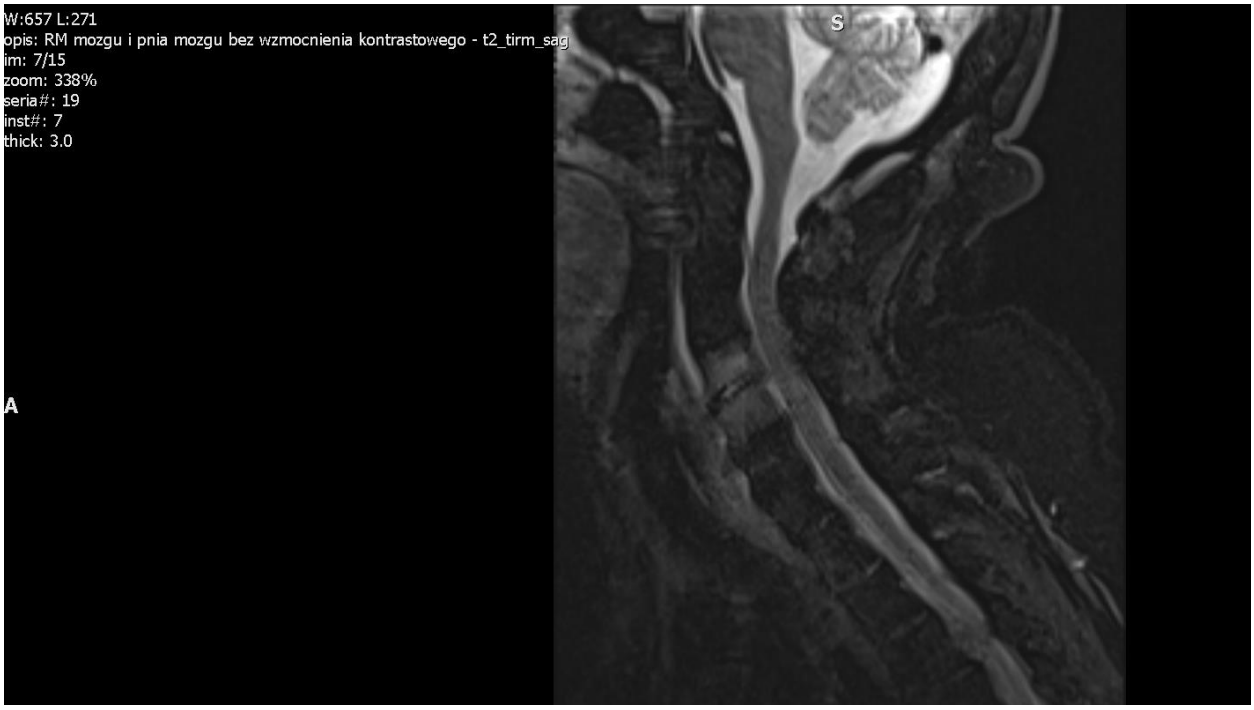

Figure 6. Radiological image of the cervical spine of patient 3 – examination performed on admission

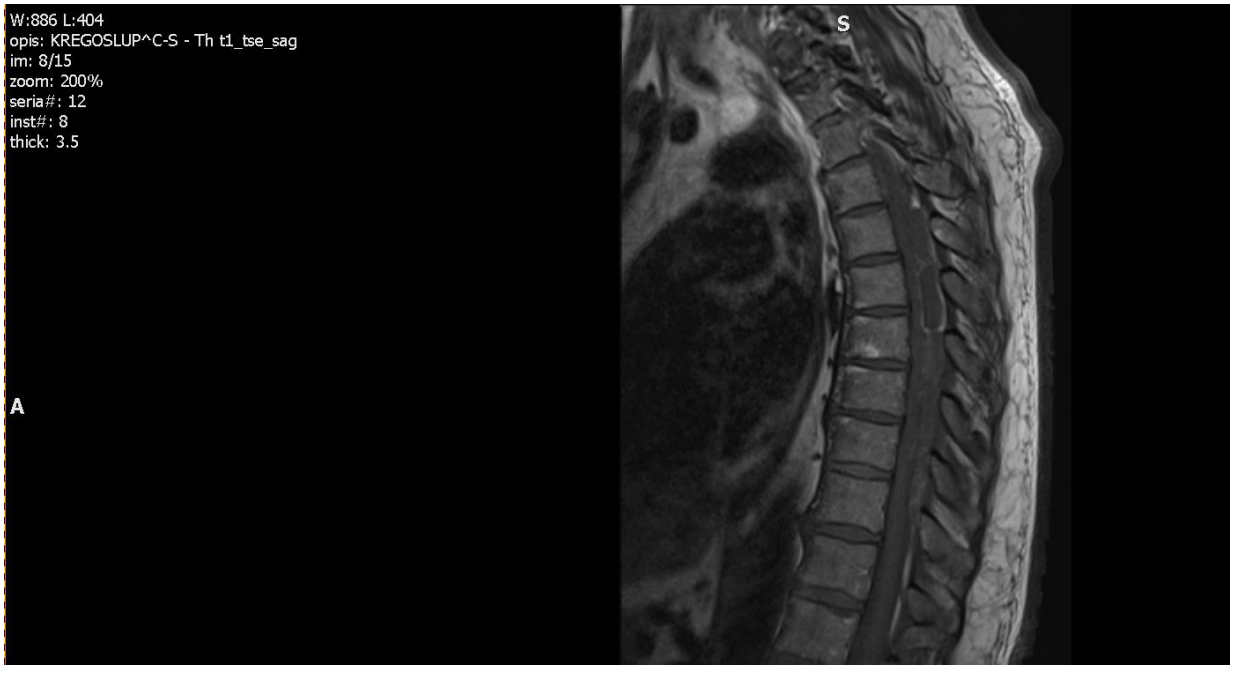

Figure 7. Radiological image of the thoracic spine of patient 3 – examination performed on admission

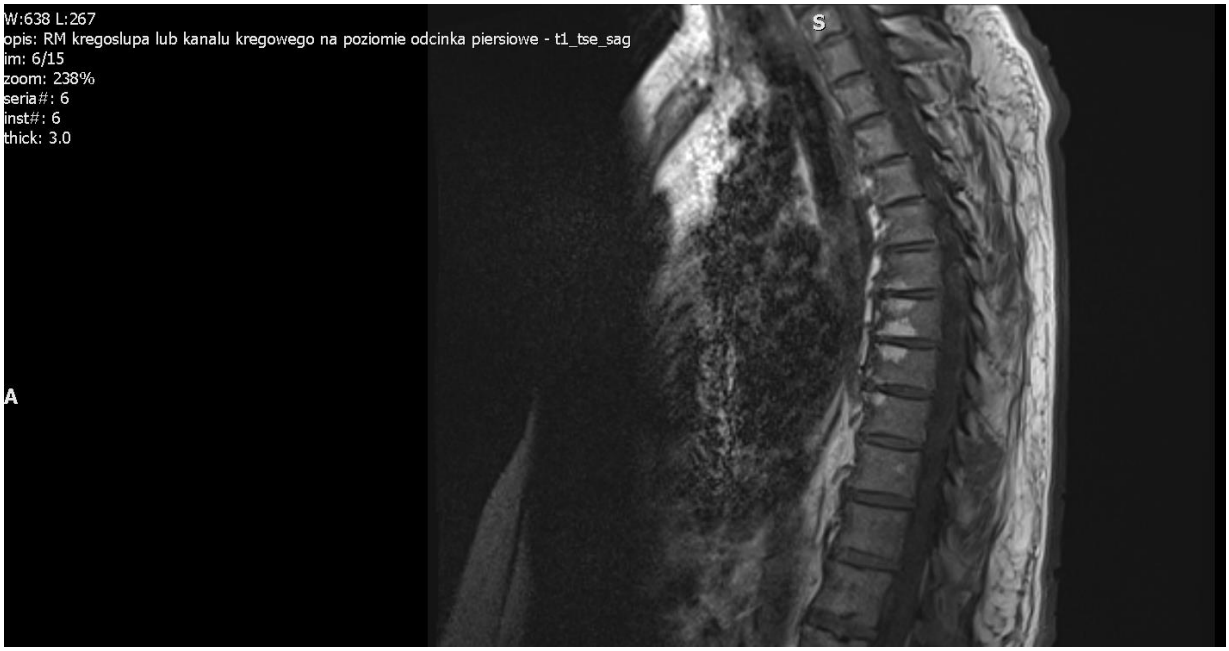

Figure 8. Radiological image of the thoracic spine of patient 3 – examination performed after 21 days of antibiotic therapy

The patient was transferred to the Internal Medicine Department of Jarocin Hospital for continued intravenous antibiotic therapy. Eight weeks after the onset of the disease, the patient was readmitted to the Neurology Department of the WSZ Hospital in Kalisz for follow-up diagnostic imaging of the spine. MRI examination of the cervical spine showed partial regression of the inflammatory changes in C4/C5 *spondylodiscitis* (Fig. 9).

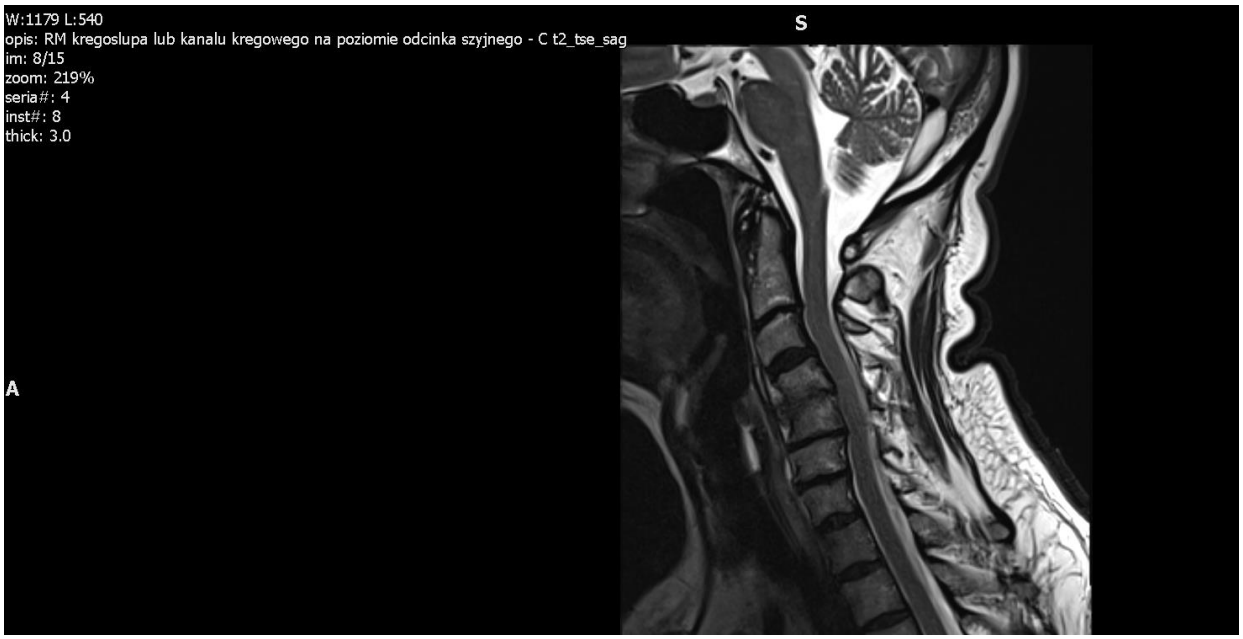

Figure 9. Radiological image of the cervical spine of patient 3 – examination performed after 8 weeks of treatment

A follow-up MRI scan of the thoracic spine showed further regression of the intrathecal and prevertebral inflammatory infiltrate and a spinal ischemic lesion at the Th8/Th9 level with signs of edema at the Th9 and Th10 vertebral bodies (Fig. 10).

The patient was referred to the Department of Neurological Rehabilitation in Koźmin Wielkopolski.

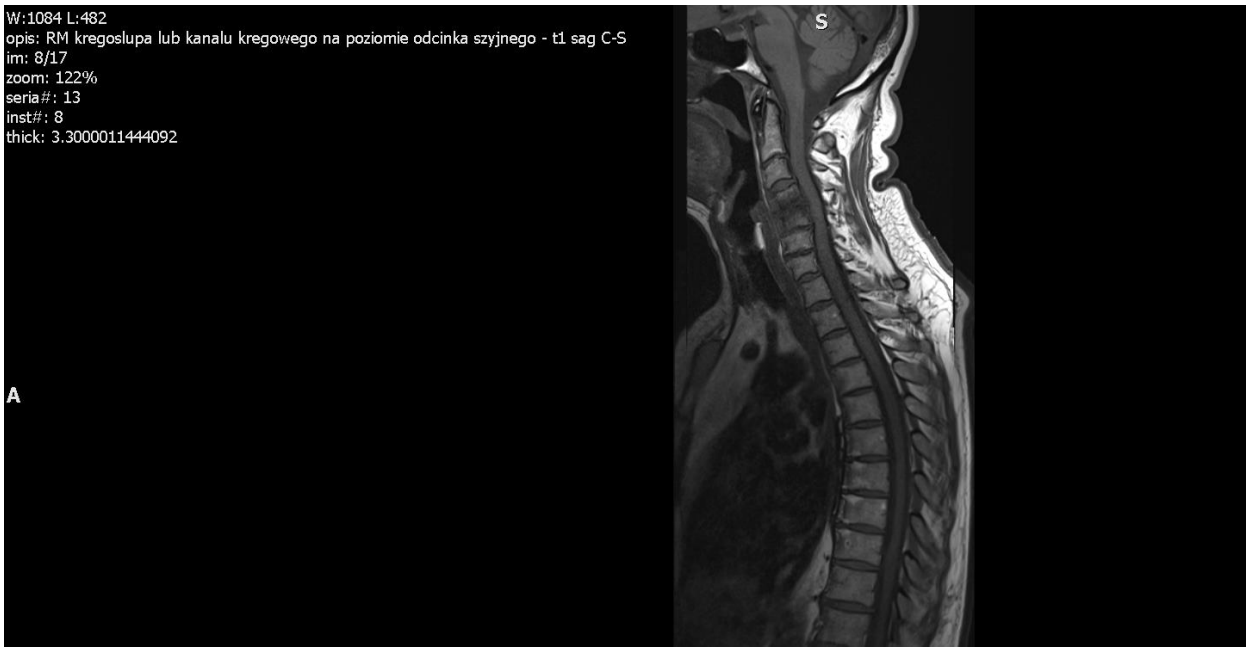

Figure 10. Radiological image of the thoracic spine of patient 3 – examination performed after 8 weeks of treatment

DISCUSSION

Over the past several years, there has been a steady increase in the incidence of spinal infections. The increasing incidence of the diagnoses may be due to demographic changes (progressive population aging), frequent use of immunosuppressive drugs, and improvements in the quality and availability of diagnostic imaging. Furthermore, diabetes, alcoholism, intravenous drug use, HIV/AIDS infection, degenerative spine disease, and a history of spinal trauma are cited as risk factors [2,4,5]. The patients described in the paper had no known risk factors.

Microbiological diagnostics are necessary for targeted antibiotic therapy in patients with spinal infections. According to literature data, positive blood cultures exist in 67-76% of patients [1,12]. In the two cases described, *Staphylococcus aureus* was cultured from blood cultures – in the MRSA MLSb(+) strain in Patient 1 and the MSSA MLSb(+) strain in Patient 2.

These results are consistent with literature data. According to the world literature, staphylococci are the most common etiological agent*(S. aureus* is responsible for 60% of cases,

including MRSA strains being responsible for 40%). Gram-negative bacterial infections (most commonly *E. coli*, *P. aeruginosa* and *Klebsiella spp*.) are the second most common cause. Tuberculous, fungal, and parasitic infections are far less common [12,13].

In Patient 3, despite blood cultures and specimens obtained from the puncture of a pus reservoir in the erector spinae muscle, the etiological agent could not be determined (sterile cultures) - the patient was admitted to the Neurology Department on day 3 of empirical antibiotic therapy (intravenous ceftriaxone). According to literature data, negative blood cultures are considered a negative prognostic factor [13,14].

Eligibility criteria for surgical treatment and the effectiveness of neurosurgical interventions in patients with inflammatory infiltrates in the spinal canal are still under discussion [2,17,19]. No surgical treatment was performed in two of the described patients (Patient 3 was not qualified for intervention by the consulting neurosurgeons, and Patient 1, due to increasing cardiorespiratory failure, was not eligible for surgery under general anesthesia for aesthetic reasons). Patient 2 was initially not qualified for surgery at the WSZ Hospital in Kalisz. A spinal canal decompression performed three months after developing the disorder resulted in a slight neurological condition improvement.

According to the literature, the risk of death from spinal infection ranges from 5% to as high as 11-20%. About 23.5-30% of patients have persistent neurological deficits, such as limb paresis or sphincter dysfunction [2,5,12,16,17]. In the reported cases, there were no satisfactory therapeutic results despite intensive drug treatment – death in the case of the 34-year-old man and permanent significant disability in the case of the 49-year-old man and the 61-year-old woman.

CONCLUSION

Discitis poses diagnostic and therapeutic challenges and is a potentially life-threatening disorder with a high risk of permanent disability.

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LIQUID BIOPSY AND GENETIC BIOMARKERS IN THE TREATMENT OF GASTRIC CANCER WITH HER2 EXPRESSION

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INTRODUCTION

Stomach cancer is a heterogeneous tumor with a diverse genetic and molecular signature. According to the World Health Organization (WHO), it is the fifth most frequently diagnosed form of cancer and the third most common cause of cancer-related deaths. The peak incidence of disease is observed in people over 50. Morphological Classification Laurena divides gastric cancer into two main types: intestinal type cancer and diffuse type cancer. Diffuse cancer is characterized by scattered tumor cells infiltrating the stomach wall, forming a dense mass of tumor cells. An aggressive course characterizes it, often occurs in younger patients, and is unrelated to environmental factors. Histologically, diffuse type carcinoma is characterized by the presence of signet ring cells. In turn, intestinal-type cancer is characterized by well-organized glandular structures resembling the intestinal type of epithelial cells. It is more common in men and is related to environmental factors such as diet or infection of *Helicobacter pylori*. Intestinal-type cancer often develops based on chronic gastritis, and intestinal metaplasia overexpression of the oncoprotein HER2 (human epidermal growth factor receptor 2) is observed in approximately 20% of cases. Its presence is essential in predicting the course of the disease and selecting targeted therapy, which allows for a more personalized approach to treatment [1, 2].

The study aims to present the role of liquid biopsy and genetic biomarkers in the personalized treatment of gastric cancer with HER2 expression. It will also discuss current diagnostic methods, mechanisms of treatment resistance, and future prospects.

PREDICTION OF DISEASE COURSE AND RESPONSE TO TREATMENT

Despite the implementation of treatment with trastuzumab and pembrolizumab and promising results, not all patients benefit equally. Most develop resistance to therapy, indicating

the need for greater individualization and optimization of therapy. It is essential to understand the mechanisms of resistance to therapy and identify biomarkers predictive of treatment response. To predict the course of the disease, it is important to properly determine the expression of the HER2 receptor (immunohistochemical assessment) and to assess the copy number of the ERBB2 gene (fluorescence in situ hybridization). Biomarker studies, tumor and plasma genomics, and molecular imaging features provide additional opportunities in predicting treatment response. Analysis of liquid biopsies and HER2-PET studies allows the identification of patients who are most likely to benefit from HER2-directed therapy [3].

Liquid biopsy

Liquid biopsy analyzes biomarkers in the patient's blood, such as circulating tumor cells (CTCs), tumor DNA (cDNA), RNA, proteins, and microRNA. Techniques used in liquid biopsy include next-generation sectioning (NGS), PCR, and other molecular methods. Liquid biopsy is widely used in diagnosis, monitoring disease progression, and assessing the response to treatment of gastric cancer. An example is clinical trials that show that ctDNA analysis can help identify patients most likely to benefit from targeted therapies such astrastuzumab. The advantages of liquid biopsy include minimal invasiveness, the possibility of multiple repetitions, and better monitoring of dynamic changes in the tumor. However, challenges include issues related to sensitivity and specificity, as well as costs and technical aspects [4].

Personalized treatment for gastric cancer

Currently available targeted therapies for patients with gastric cancer and HER2 expression includetrastuzumab, pertuzumab, lapatiniband new drugs such as trastuzumab deruxtecan.

Clinical trials, such as KEYNOTE-859 and DESTINY-Gastric, provide data upporting the effectiveness of these therapies and indicate the need for further individualization of treatment based on genetic biomarkers [5,6,7] .

KEYNOTE-859 TRIAL RESULTS

The phase III KEYNOTE-859 (2023) trial enrolled 1,579 patients with advanced HER2-negative gastric cancer or GE adenocarcinoma. Patients were randomly assigned (1:1) to receive pembrolizumab (200 mg) or placebo, with combination chemotherapy selected by the investigator (cisplatin80 mg/m2 plus 5-FU 800 mg/m2/day for five days (FP) or oxaliplatin 130 mg/day m2 on day one plus capecitabine 1000 mg/m2 twice daily for 14 days (CAPOX) each 21-day cycle. After a median follow-up period (28.4 months), an increase in progression-

free survival (PFS) was demonstrated compared to placebo and standard therapy in all patients and patients with PD-L1 expression ≥1. Objective response rate (ORR) also improved compared with placebo and standard therapy (73% vs. 60%), with disease control rates of (92% vs. 87%), respectively. The median duration of response was 11.3 months vs. 9.5 months for [8].

PHASE II TRIAL RESULTS CLIN CANCER RES

Gene amplification ERBB2 is associated with increased free survival. From progression (PFS), mutations in MYC and CDKN2A are associated with shortened PFS. In addition, intratumoral genomic heterogeneity found before treatment is associated with PES shortening (heterogeneity of HE expression). In turn, the addition of anti-PD-1 drugs to chemotherapy and trastuzumab improves patient survival, and lasting treatment benefits can be predicted by assessing the decrease and clearance of ctDNA and high uptake glucose in PET before treatment. The presence of lesions on Zr-trastuzumab PET results in a decrease in cDNA tumor-matched by three weeks, and clearance ctDNA tumor-matched after 9 weeks may represent minimally invasive biomarkers of durable PFS. Single-cell sequencing identified MT1H, MT1E, MT2A, and MSMB as transcription-regulatory resistances that may serve as future therapeutic targets [8].

PHASE II DESTINY TRIAL RESULTS -GASTRIC (2024)

Patients with higher levels of HER2-related biomarkers had numerically higher objective response rates (ORR). In patients with HER2, amplification in plasma, DNA ORR was 61% compared with 34% in patients without amplification. Trastuzumab deruxtecan (TDXd) also shows activity in patients with cancers with low HER2 levels. Alterations in the MET, EGFR, FGFR2, or PIK3 GoF genes overlap with amplification com HER2. Patients with changes in signal transduction genes had numerically lower ORR: MET (25%), EGFR (32.1%), and FGFR2 (0%). High concordance was observed between HER2 amplification in plasma inctDNA and tissue HER2 expression. The positive predictive agreement (PPA) between tumor HER2 status and plasma amplification in*ctDNA* was 64%, and the negative predictive agreement (NPA) was 86% [9].

CONCLUSIONS

Liquid biopsy and genetic biomarkers play crucial roles in the personalized treatment of

HER2-expressing gastric cancer. Thanks to them, it is possible to diagnose more precisely, monitor the course of the disease, and select appropriate therapies. HER2 as a biomarker is particularly important because its overexpression enables the use of effective targeted therapies, such as trastuzumab, which significantly improve treatment outcomes.

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ADAPTATION OF LUNG ADENOCARCINOMA CELLS TO TREATMENT WITH KRAS INHIBITORS

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INTRODUCTION

Lung adenocarcinoma is one of the most common forms of non-small cell lung cancer (NSCLC), accounting for 25-29% of all cases of this cancer. Globally, it is responsible for approximately 7% of cancer-related deaths. According to the WHO classification, lung adenocarcinoma includes various stages and forms, ranging from atypical hyperplasia of the adenocarcinoma precursor (AAH) through pre-invasive change-adenocarcinoma in situ (AIS) to the invasive form with a lepidic pattern. The Noguchi classification also distinguishes types A–F, allowing for more detailed morphological differentiation of this tumor. Mutations in the KRAS gene are often responsible for lung adenocarcinoma development. The KRAS gene plays a key role in cancer initiation and progression, and the presence of these mutations is associated with worse prognosis for patients. Understanding the molecular mechanisms of adaptation of lung adenocarcinoma cells to treatment with KRAS inhibitors is crucial for developing effective therapeutic strategies and preventing disease recurrence [1].

SIGNALING PATHWAYS IN LUNG ADENOCARCINOMA

The EGFR-RAS-RAF-MEK (MAP2K)-ERK (MAPK1) pathway is a key regulator of cell growth, proliferation, and survival and plays a vital role in cancer initiation and progression. Activation of this pathway, especially through mutations in the KRAS gene, leads to uncontrolled signal transduction, which results in uncontrolled cell proliferation and increased cell survival. In lung adenocarcinoma, KRAS mutations are common and cause persistent activation of the KRAS protein, which results in uncontrolled transmission of pro-growth and pro-survival signals, contributing to the development and progression of the tumor [2].

DESCRIPTION OF THE PROBLEM

Despite the introduction of selective KRAS inhibitors (sotorasib and adagrasib) in lung cancer therapy, the effectiveness of the treatment remains limited, and disease relapses occur. Research results suggest that some cancer cells that adapt to KRAS inhibition may be responsible, and this adaptation allows them to survive KRAS inhibitor therapy. Therefore, it was hypothesized that these cells should become targets for therapy regardless of KRAS inhibitor treatment.

TUMOR CELL ADAPTATION IN LUNG ADENOCARCINOMA

Studies using genetically modified mouse models, xenografts, and patient samples have shown that inhibition of the KRAS pathway leads to tumor cell differentiation toward alveolar type 1 (AT1) cells in lung adenocarcinoma tumors (LUAD). Moreover, inhibition of the KRAS pathway induces the differentiation of AT2 cells towards AT1 cells after lung injury. AT1-like LUAD cells have high growth and differentiation potential after treatment, which may pose a challenge in the context of tumor recurrence. However, ablation of these cells significantly improves the response to KRAS inhibitor therapy, indicating the possibility of more effective treatment by targeting specific tumor cell populations [3].

THE IMPACT OF KRAS MUTATIONS ON THE DEVELOPMENT OF LUNG ADENOCARCINOMA

It has been shown that KRAS mutations are observed more often in pre-invasive lesions than in invasive titers, as confirmed by experiments in mice in which continuous expression of the KRAS mutant resulted in the formation of benign, non-invasive alveolar tumors of the lung, resembling atypical hyperplasia of adenocarcinoma precursor (AAH). These tumors developed into invasive adenocarcinomas through TP53 inactivation, and KRAS mutant expression mainly affected type II alveolar pneumocytes rather than club cells (Clara). Moreover, benign-appearing bronchoalveolar tumors with KRAS mutations had different biological features from invasive adenocarcinomas, exhibiting oncogenic senescence, as confirmed by the expression of β-galactosidase and heterochromatin foci [4,5,6].

CONCLUSIONS

Genetic mutations in genes such as EGFR, KRAS, and BRAF are crucial for the initiation and progression of lung adenocarcinoma. Residual LUAD after KRAS-targeted therapy consists of AT1-like tumor cells that can resume tumor growth. Therefore, targeting

these specific cells may represent an important therapeutic strategy to overcome treatment resistance and prevent the recurrence of lung adenocarcinoma [7].

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ENDOMETRIOSIS RELATED INFERTILITY - PATHOGENESIS AND POSSIBLE TREATMENTS

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INTRODUCTION

Since the 1960s, the human population growth rate has decreased [1]. As total fertility rates are successively dropping all around the world, infertility (IF) is a rising problem that affects about 15% of couples worldwide [1,2,3,4].

Clinically, infertility is a disease characterized by failure to achieve pregnancy after 12 months of regular, unprotected sexual intercourse or due to an impairment of a person's capacity to reproduce, either as an individual or with their partner [3,5,6].

Reports showed an increase in lifetime infertility prevalence from 3.5% to 17.8% in high-income countries and from 6.9% to 16.5% in low- and middle-income countries since the 1990s [3,7].

15% of all infertility cases had no identifiable cause, about 20% were due to male factors alone, 35% were due to female factors, and the remaining instances resulted from combined male and female factors [2,6,8,9].

Three major causes of female IF are defective ovulation, transport, and implantation [10,11,12].

The conditions that may result in the abovementioned are endocrine disorders, physical disorders (such as obesity), polycystic ovarian disease, and pelvic inflammatory disease, and one of them is endometriosis (EM) [10,13].

Endometriosis affects around 50% of infertile women compared with only 5% of fertile patients, creating a clear association between the two [14,15,16].

ENDOMETRIOSIS

Endometriosis is a benign, chronic, inflammatory gynecological condition characterized by the presence of active endometrial glands and stroma or endometrial tissue outside the uterus cavity, including the muscular layer of the uterus, fallopian tubes, ovaries, bladder, ureters,

intestines, and surrounding tissues. Ectopic tissue may rarely localize in organs outside the pelvic cavity [17,18,19]. EM is the second most common gynecological disease, affecting around 5–10% of reproductive-age women and 35–50% of patients with chronic pelvic pain. The peak of the disease falls in the time frame between 25 and 45 years of age. Diagnosis usually takes up to 8-10 years from the appearance of the first symptom [15,17,18,20,21,22,23].

Despite its commonality, the origin of EM remains a mystery. So far, several theories have been proposed, including retrograde menstruation, coelomic metaplasia, hematogenous/lymphatic spread, Stem cell recruitment, and embryogenetic theory [24].

Retrograde menstruation is the oldest theory explaining the etiology of endometriosis. It identifies the cause of endometriosis as a retrograde flow of menstrual blood and the endometrial cells via the fallopian tubes into the pelvic cavity during menstruation. Then, endometrial cells adhere to the peritoneal mesothelial cells, establish a blood supply, increase, and create endometrial lesions. However, retrograde menstruation occurs in 76%–90% of women with patent fallopian tubes, and endometriosis affects only 1 in 10 of these patients [19,25,26,27,28].

On the other hand, the coelomic metaplasia theory assumes that the coelomic epithelial cells, which are the origin of Müllerian ducts, undergo metaplasia due to hormonal and immunological factors, Eventually creating endometrial stroma and glands. This theory could explain the presence of EM in pre-pubertal girls [19,26,29].

Another theory is the hematogenous and lymphatic spread. It suggests that endometrial cells disseminate by lymphatic or uterine vasculature to distant locations during menstruation, This theory assumes that menstrual endometrium can pass through hemal and lymphatic flow without disruption and implant itself into the muscular layer of organs beyond the pelvic region [24,25,28].

Stem cell recruitment theory contains two main alternatives based on the tissue origin of the stem cells. Endometrial stem cells are responsible for remodeling, regeneration, and homeostasis of the endometrium. The theory suggests the migration of those stem cells with menstrual blood during organogenesis or via angiolymphatic circulation during menstruation. The other alternative includes bone marrow stem cells that can incorporate themselves into the endometrium and regenerate it. This concept proposes that the blood-circulating stem cells can settle in soft tissue instead of endometrium and, as a result, decrease the number of cells recruited to eutopic endometrium [19,24,25,26].

The embryogenetic theory states that residual embryonic cells of the Wolffian or

Müllerian duct may differentiate into endometriotic lesions in response to estrogen. In this concept, anomalous differation or relocation of the Müllerian ducts during embryogenesis can spread primordial endometrial cells. Those cells remain inactive until puberty. Then estrogen stimulates their proliferation and the formation of endometriotic lesions [19,24,26].

Endometriosis is associated with a range of symptoms that can affect women's overall physical, mental, and social well-being. In 66% of patients affected with endometriosis, the first symptoms appear before the age of 20. Whereas the disease is heterogeneous, 20–25% of patients are asymptomatic[30]. The most common symptoms are dysmenorrhea (60–80%), chronic pelvic pain (40–50%), dyspareunia (40–50%), infertility (30–50%), severe menstrual pain, irregular flow or premenstrual spotting (10–20%). Moreover, painful defecation (dyschezia) and urination (dysuria), painful ovulation, blood in the stool, diarrhea or constipation, fatigue, and symptoms of depression may also occur in EM. However, the severity of the disease does not always correlate with its classification and laparoscopic appearance [17,18,22,30,31].

There are several classifications of EM. One of the most commonly used is the revised American Society for Reproductive Medicine (rASRM) classification. It uses the cumulative score to assign a patient to the following categories: minimal, mild, moderate, and severe, with the score classified as 1 to 5, 6 to 15, 16 to 40, and more than 40, respectively. It assesses the number of endometrial lesions, their depth, and size [24,32,33]. However, this classification poorly correlates with the severity of symptoms or prognosis on the reproductive aspect [15,21]. The Endometriosis Fertility Index (EFI) is the newer classification, developed in 2010. The purpose of the system is to predict the pregnancy rate of patients with surgically documented endometriosis who attempt non-IVF (in vitro fertilisation) conceptions. It reflects on various factors such as age, duration of infertility, and previous pregnancies. It considers the rASRM total score and rASRM endometriosis lesion score, and also the functional score determined by the surgeon for each of the tube, fimbria, and ovary and then ranges them from 0 to 4 points as follows:

- absent or nonfunctional (0),
- severe dysfunction (1),
- moderate dysfunction (2),
- mild dysfunction (3),
- normal (4).

The score is calculated by summing the historical and surgical scores and ranges from 0 to 10 points, where 0 represents poor prognosis and 10 indicates the best [24,32,33]. While the rASRM classification has no use in predicting pregnancy, studies showed a significant correlation between EFI score and pregnancy rate that reached 8.3%, 41.2%, and 60.9% for scores of 0 to 3, 4 to 7, and 8 to 10, respectively [24].

THE IMPACT OF ENDOMETRIOSIS ON FERTILITY

Because the etiopathogenesis of endometriosis is not fully understood, it is difficult to identify a specific cause of increased infertility in women struggling with this disease. For this reason, the issue is studied using animal models. However, research is limited due to high costs and ethical issues [25].

So far, researchers have identified several possible causes of infertility associated with endometriosis, which are undoubtedly interconnected.

In the case of endometrioma, there is a decrease in ovarian reserve due to replacing physiological ovarian tissue with fibrous tissue. As a result of this process, a reduced density of follicles has been observed compared to healthy ovaries ($6.3 \pm 4.1/mm^3$ compared to $25.1 \pm 15.0/mm^3$). The probable cause is the presence of reactive oxygen species, proteolytic substances, and adhesive substances derived from the fluid of the endometriotic cyst. These compounds damage DNA and cell membranes, causing irregular development of oocytes [15]. It has been shown that the cyst's fluid contains a high concentration of free iron, which can generate reactive oxygen species. These factors can migrate from the inside of the cyst to the healthy ovarian cortex [25]. In addition to the loss of ovarian follicles, there is damage to intraovarian vessels, resulting in impaired regeneration [34]. Furthermore, mechanical damage to the ovary occurs due to the compression of healthy tissue, mechanical stretching, and impaired blood flow. These phenomena are independent of the size of the endometrioma [35].

Another type of endometriosis is adenomyosis, which is the presence of endometrial epithelial cells and stroma within the uterine muscle [36]. The formation of adenomyosis results in platelet aggregation and hypoxia. This causes the production of pro-inflammatory cytokines and prostaglandins, leading to inflammation within the uterus. Additionally, local estrogen synthesis increases. As a result, uterine hyperperistalsis and fibrosis occur, hindering the transport of gametes and embryo implantation [34].

Another undeniable cause of reducing the chances of having offspring is limited sexual intercourse. For women, this is often due to pain during sexual intercourse caused by

endometriosis [37]. In addition to dyspareunia, chronic pelvic pain associated with endometriosis can adversely affect the frequency of sexual intercourse. This will undoubtedly hurt emotional well-being and quality of life, which is why a holistic approach to the patient is essential [25].

In cases where endometriosis is very advanced, adhesions form within the pelvis. This leads to the obstruction of the fallopian tubes, causing impaired sperm passage and often preventing fertilization [38]. Additionally, anatomical distortions impair the release of oocytes from the ovary and their transport to the fallopian tube [25].

An important issue is also the phenomenon of hormonal changes in women with endometriosis. It turns out that women with endometriosis have increased prolactin levels, which prevent luteinizing hormone pulsatility. This phenomenon leads to the blocking of estrogen receptors and the absence of ovulation [39]. Another cause of ineffective ovulation is luteinized unruptured follicle syndrome, which involves the failure of the dominant follicle to rupture despite luteinization [40]. Kulkarni and colleagues showed that women with laparoscopically confirmed endometriosis go through menopause earlier than women without this condition. This phenomenon results in a shorter fertility window for women with endometriosis [41].

As demonstrated, there are many causes of infertility associated with endometriosis. Therefore, when treating infertility in a patient with endometriosis, it is important to consider the complexity of this disease and the possible pathomechanisms of infertility.

TREATMENT

Infertility associated with endometriosis can be treated with four main types of therapies: medical treatment, surgery, intrauterine insemination (IUI), and in vitro fertilization (IVF) [25].

SURGICAL TREATMENT

Reproductive surgery aims to remove visible endometriosis lesions and restore normal pelvic anatomy [15]. In stage I/II endometriosis, laparoscopic ablation of endometrial implants results in a small but significant increase in live birth rates (29% in the laparoscopic surgery group vs 17% in the untreated group) [42]. In stages III-IV, the situation becomes more complex. Evidence supporting the link between deep infiltrating endometriosis other than deep infiltrating endometriosis (DIE) - induced alteration of pelvic anatomy and adhesions is weak.

There is not enough evidence and high-quality data to conclude the effects of surgery [25]. Moreover, surgical resection of endometrioma is associated with the risk of losing healthy ovarian tissue. In 54% of cases of endometrioma resection, the ovarian tissue was removed which is a higher frequency than observed for other types of ovarian cysts (6%) [16]. Therefore surgical treatment for deep endometriosis is indicated in endometriosis-associated pain, and in symptomatic patients wishing to conceive. Surgery is usually not advised solely to improve fertility in a patient who has no other symptoms [43].

MEDICAL TREATMENT

Hormonal medications such as combined oral contraceptives, progestins, danazol, and gonadotropin-releasing hormone agonists or antagonists are used in endometriosis-related infertility therapy. It was thought that despite benefits in treating pain, these drugs show no benefits in treating endometriosis-associated infertility [28]. In 2020, Hodgson et al. published a network meta-analysis that shows that GnRH agonists alone and laparoscopic surgery alone significantly increased the clinical pregnancy rate to a similar extent (odds ratio [OR] 1.68, 95% confidence interval [CI] 1.07-2.46 and OR 1.63, 95% CI 1.13-2.35, respectively) [44]. Xuemei Qing et al. showed in their systematic review that women undergoing post-surgery GnRH experienced a marginally elevated pregnancy rate (RR = 1.20, 95% CI = 1.02-1.41; P = 0.03) and a reduced mean time to conceive (RR = -1.17, 95% CI = -1.70- -0.64; P < 0.0001) [45].

INTRAUTERINE FERTILIZATION

The first paper on intrauterine insemination was published by Cohen in 1962. Since then, IUI has gained various advancements, including integration with ovarian stimulation techniques involving clomiphene citrate or gonadotropins. Although IUI is not categorized as an assisted reproductive technology (ART), it is commonly utilized, often on an empirical basis, to address a wide array of fertility issues [46].

IUI is a simpler, cheaper, and less invasive procedure compared to IVF [47]. Controlled ovarian stimulation (with clomiphene citrate or gonadotropins) and IUI may be a reasonable treatment alternative to IUI alone, IVF, or further surgical therapy.

The success of this method depends on factors such as duration of infertility, female age, timing, and type of ovarian stimulation [48]. The effectiveness of IUI with controlled ovarian stimulation is higher than IUI with natural ovulation alone [49]. This treatment is beneficial in patients under and above 35 years old; however, in advanced stages of endometriosis (III-IV), laparoscopic surgery is recommended. It should also be mentioned that

in women over 35 with severe endometriosis and a failed attempt of IUI treatment, IVF is an alternative strategy for treating infertility [42].

IN VITRO FERTILIZATION

IVF is another treatment that can be beneficial for patients with endometriosis-related infertility. Although IVF is one of the commonly used methods of treating infertility related to endometriosis, there are no randomized clinical trials that compare this method to no treatment in women with endometriosis [25]. Results of IVF treatment in women with endometriosis compared to women without endometriosis were compared in several meta-analyses. Barnhart K. et al. concluded that the chance of achieving pregnancy was significantly lower for endometriosis patients. Women with endometriosis had a 35% lower chance of pregnancy than women without endometriosis [46]. The fertilization rates, oocyte yield, and implantation rates are significantly decreased. Moreover, the possibility of achieving pregnancy, as defined by a positive serum βHCG after embryo transfer, was considerably lower than in patients without endometriosis [23]. Due to the lack of sufficient data on the effectiveness of this treatment in patients with endometriosis compared to other treatments, further research is crucial for therapeutic strategy development.

CONCLUSIONS

Undoubtedly, scientific research confirms the existence of a link between endometriosis and infertility. However, the cause-and-effect relationship is debatable and still being examined [15]. It is believed that infertility associated with endometriosis is a multifactorial problem related to altered immunity and genetics, which affects the endometrium, fallopian tubes, and gamete transport [28]. Given the declining human population growth, particular attention should be paid to aspects of endometriosis treatment and its potential complications. There is currently no gold standard for treating infertility in women with endometriosis. The mainstay of treatment in all patients remains surgery and assisted reproductive techniques. It is considered that IVF has the best results in the treatment of patients with moderate and severe endometriosis (stages III-IV). Still, further randomized clinical trials are required to compare the effectiveness of therapeutic strategies. Endometriosis-related infertility requires an individual approach based on the patient's expectations, endometriosis subtype, and stage. Treatment choice should also depend on the additional medical conditions, possible complications, and the patient’s comorbidities.

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MONOCLONAL ANTIBODIES IN ASTHMA TREATMENT

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INTRODUCTION AND PURPOSE

Asthma belongs to the group of chronic respiratory diseases, and its main complaints include shortness of breath, coughing, a feeling of pressure in the chest, and wheezing. The aforementioned symptoms are related to the bronchial hyperresponsiveness that occurs during the disease, leading to a reduction in airflow [1,2,3].

The American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines are used to assess the severity of this condition. Asthma can be defined as severe when high doses of inhaled corticosteroids and an additional controller drug are required to control symptoms. The main goal of treatment is to nullify the frequency of exacerbations, using minimal amounts of corticosteroids. New therapeutic options using monoclonal antibodies as an alternative to current treatment with steroids are currently under intensive investigation. Introducing biological therapy is expected to reduce hospitalizations and improve patients' quality of life [4,5].

STATE OF KNOWLEDGE

Asthma affects about 340 million people worldwide and is the most common chronic inflammatory disease of the respiratory system. Unfortunately, underdiagnosis of it remains a significant problem, which can consequently be associated with ineffective treatment and excess mortality. The correct diagnostic process is based on observing the main complaints, such as chest tightness, a feeling of shortness of breath, and wheezing, but also on specific clinical tests. One such test is spirometry, which is the basis for the evaluation of disorders affecting the respiratory system. It allows observation of the reversibility of obstruction. An increase in FEV1 greater than 12% and 200 ml indicates asthma, and a result greater than 400 ml practically confirms its diagnosis. Another parameter for diagnosis is peak expiratory flow rate (PEFR). Its result can indicate the variability of daily bronchial obstruction and disease

control [6,7]. Measurement of exhaled NO fraction (FeNO) also plays an important role in the diagnosis of asthma. It makes it possible to determine the degree of inflammation within the airways and facilitates the evaluation of the effectiveness of treatment of patients [8].

PATHOGENESIS

Asthma is a heterogeneous disease with a complex pathophysiological picture. Its main subtypes are eosinophilic asthma and non-eosinophilic asthma [9].

A vital role in the pathogenesis is played by Th type 2 lymphocytes, whose main task is the synthesis of interleukins IL-4, IL-5, and IL-13. This process results in the activation and recruitment of eosinophils, B lymphocytes, and mast cells, leading to inflammation [4,10]. Accumulation of these cells causes overproduction of mucus and Ig-E synthesis. Other important factors involved in developing type 2 inflammation are the cytokines IL-23, IL-33, and thymic stromal lymphopoietin (TSLP). An asthma attack is triggered by airway constriction, which is led by inflammation-induced edema, excessive mucus production by mucus cells, and bronchial muscle contraction [10,11].

The mechanism of non-inflammatory type 2 asthma, or non-eosinophilic asthma, is not fully understood. Several cell types and cytokines are thought to be involved, mainly neutrophils and Th1, Th17, IL-6, and IL-17 lymphocytes [12].

RISK FACTORS

There is currently an upward trend in the incidence of asthma despite the development of new and improved therapeutic options. This is largely due to risk factors that favor the onset of asthma. These include:

1) genetic predisposition,
2) exposure to indoor allergens,
3) exposure to tobacco smoke,
4) air pollution,
5) exposure to stress,
6) obesity,
7) occupational exposure to irritants,
8) sex hormones,
9) diet and medications used,
10) respiratory infections [13,14].

PRIMARY TREATMENT

1. **Inhaled corticosteroids (ICS)**

   Inhaled corticosteroids are usually the first-line therapy for asthma. They can be used in exacerbations of the disease, but one should be wary of long-term steroid use because of possible side effects. Their mechanism is to reduce inflammation in the airways and decrease swelling and mucus secretion [15]. Commonly used inhaled corticosteroid drugs are not always able to provide adequate control of the severity of asthma symptoms [16].

2. **Short-acting beta-agonists (SABA)**

   SABAs are used to rapidly relieve asthma symptoms by causing airway dilation. They provide immediate control of an exacerbation but do not affect the pathological process underlying the condition's onset [17].

3. **Long-acting beta-receptor agonists (LABA)**

   LABAs stimulate beta-adrenergic receptors and lead to airway smooth muscle relaxation. They are used in patients with asthma in which exacerbations occur frequently and in combination with corticosteroids. No clear evidence has been shown for the effectiveness of treating asthma with LABAs in monotherapy [15, 18].

4. **Long-acting muscarinic drugs (LAMA)**

   LAMAs block muscarinic receptors, leading to smooth bronchial muscle relaxation. They are adjunctive treatments in patients taking LABAs and inhaled corticosteroids [15].

BIOLOGICAL DRUGS

In recent years, research on the pathophysiological processes of asthma has led to the development of new treatment options for the disease using monoclonal antibodies. Biologic drug therapies target specific pathways in the pathogenesis of asthma and have been shown to have positive effects on lung function, reduce the frequency of exacerbations, and thereby improve patients' quality of life [5][5].

1. **Dupilumab**

   Dupilumab belongs to the human monoclonal antibodies directed against the α interleukin-4 receptor. Its action is based on blocking IL-4 and IL-13 signaling [19]. Castro et al. and Corren et al, in their randomized clinical trials, showed that patients who took dupilumab achieved significantly lower rates of severe asthma exacerbations and improved lung function and disease control compared to those receiving placebo

[20,21]. Wenzel et al. noted that dupilumab treatment of asthmatic patients with elevated eosinophil counts led to calming inflammation after discontinuing previously used inhaled corticosteroids and LABAs [22]. For severe asthma, dupilumab makes it possible to reduce the dose of oral corticosteroids (OCS) to control the disease, as demonstrated in their study by Sher et al. [23]. In the study by Akenyore et al. among patients with eosinophil counts of 150 cells/μL or more and IgE levels of 30-700 kU/L, dupilumab showed the most significant improvement in exacerbations and FEV1 values compared to omalizumab and mepolizumab [24].

2. Tezepelumab

Tezepelumab is a specific human monoclonal antibody directed against the epithelial cytokine thymic stromal lymphopoietin (TSLP). Patients treated with chronic long-acting beta-agonists and moderate to high doses of inhaled glucocorticoids after taking tezepelumab showed a lower risk of asthma exacerbation, according to a study by Corren et al. [25]. Lin et al. noted that tezepelumab has a positive effect on FEV1 and on reducing the number of asthma symptoms and exacerbations. According to this study, however, during treatment with this antibody, attention should be paid to possible side effects of the drug, such as headaches, upper respiratory tract infections, nasopharyngitis, and bronchitis [26]. In patients with uncontrolled severe asthma, tezepelumab reduces airflow limitation, as confirmed in a clinical trial by Menzies-Gow et al. [27]. Tezepelumab showed an impact on reducing airway hyperresponsiveness after mannitol administration, indicating that TSLP blockade may also have additional benefits in asthma beyond reducing inflammation, as demonstrated by Diver et al. in a clinical trial [28].

3. Benralizumab

Benralizumab is a monoclonal antibody that targets the alpha subunit of the IL-5 receptor found on the surface of eosinophils, resulting in reduced receptor production [29]. It significantly reduces the frequency of exacerbations with concomitant good tolerance in patients with severe asthma, as demonstrated in their study by FitzGerald et al. [30]. Bleecker et al. and Nair et al. in their clinical trials confirmed the efficacy of benralizumab in the treatment of asthma not controllable with high-dose ICS and LABAs [31,32]. Treatment with benralizumab reduced the doses of inhaled corticosteroids needed to control asthma, as observed in clinical trials by Jackson et al. [33].

4. Omalizumab

Omalizumab is one of the first biologic drugs used to control asthma therapy. It is a humanized monoclonal antibody that selectively binds to free IgE, thus inhibiting the IgE-dependent cascade - reducing its concentration in serum and inhibiting binding to effector cells - mast cells, basophils, dendritic cells, and eosinophils [34,35]. By inhibiting IgE receptors, Omalizumab shows positive effects on airway remodeling, particularly on bronchial epithelial cells and smooth muscle cells. Thanks to its high safety profile, it may fulfill an important therapeutic option as an additional biologic drug in severe asthma [36]. A clinical trial by Hanania et al. confirmed omalizumab's effectiveness in controlling this disease's exacerbations [37]. Use of the drug also contributed to a reduction in the frequency of hospitalizations, as confirmed in their clinical study by Casale et al. [38].

5. Mepolizumab

Mepolizumab belongs to the humanized monoclonal antibodies directed against IL-5 [39]. Therapy with this antibody leads to improved lung function and a reduced risk of exacerbations. It makes it possible to reduce the doses of glucocorticosteroids required to control asthma, as observed by Gibson et al. in a clinical trial [40]. Chapman et al. and Liu et al, in their study, observed that mepolizumab showed greater efficacy in disease control than another biologic drug, omalizumab [41,42]. Supplementing therapy with mepolizumab by adding OCS did not improve treatment outcomes, according to Yang et al. [43].

6. Reslizumab

Reslizumab is a humanized monoclonal antibody that exhibits antagonistic activity against IL-5, thus contributing to the reduction of eosinophil activity [44,45]. Reslizumab proved effective in patients treated with oral corticosteroids and allowed lower doses of these drugs for asthma control. It also improved lung function and had a positive effect on the control of disease exacerbations [46]. An index called lung age is calculated as the difference between the actual age of the lungs and the patient's chronological age. Treatment with resulizumab reduced it by an average of 5 years and correlated with improved quality of life, according to a study by Carr et al. [47].

7. Astegolimab

Astegolimab is a human monoclonal antibody that selectively blocks the ST2 receptor. Its action is based on inhibiting IL-33, an alarmin derived from the airway epithelium.

The use of astegolimab makes it possible to reduce the annual frequency of asthma exacerbations. It is also a safe drug and well tolerated by the body [48,49].

8. **Itepekimab**

Itepekimab is a new monoclonal antibody directed against the IL-33 pathway involved in the inflammatory process in bronchial asthma. In the study, Wechsler et al. noted that itepekimab therapy reduced the frequency of asthma exacerbations compared to placebo and improved lung function in patients [50,51].

CONCLUSION

Asthma is a chronic inflammatory disease of the airways common throughout the world. Its characteristic feature is the occurrence of symptoms in variable frequency and severity. An asthma attack is associated with a restriction of airflow through the airways, and this is related to smooth muscle contraction, mucosal swelling, and excessive secretion production, eventually leading to remodeling of the bronchial wall. The pathogenesis of the disease is complex, and a wide variety of factors can promote the development of asthma. The overriding role in the pathomechanism of asthma is played by helper lymphocytes that produce specific cytokines that induce the appearance of the inflammatory process. Primary treatment includes taking inhaled corticosteroids and SABA, LAMA, and LABA drugs. In recent years, biological therapy using monoclonal antibodies targeting specific pathways in asthma pathogenesis has gained popularity. These include dupilumab, tezepelumab, benralizumab, omalizumab, mepolizumab, reslizumab, astegolimab and itepekimab. The aforementioned drugs improve lung function, allow for reduced doses of glucocorticosteroids, all of which lead to improved quality of life for patients and better control of disease symptoms.

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UNCONVENTIONAL METHODS OF TREATING KIDNEY STONES

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INTRODUCTION

Kidney stones are a significant medical issue due to their prevalence and potential for severe pain and complications. Advances in medical technology have led to various effective treatments for kidney stones. This paper reviews the most common methods:

- Percutaneous Nephrolithotomy (PCNL),
- Extracorporeal Shock Wave Lithotripsy (ESWL),
- Retrograde Intrarenal Surgery (RIRS),
- Ureterorenoscopy (URS).

PCNL is the standard for large renal stones, involving a minimally invasive approach with endoscopes. ESWL uses shock waves to break stones into smaller pieces for natural passage. RIRS utilizes flexible ureteroscopy for kidney stones, offering high success rates with low complications. URS is used for ureteral stones, providing direct visualization and removal or fragmentation.

Additionally, the paper discusses chemolytic treatments, which dissolve stones using chemical solutions, and Medical Expulsive Therapy (MET), which uses medications to help pass stones. Though less common, open surgery is still used in specific cases where other treatments fail.

This review aims to summarize the current best practices, indications, contraindications, and complications associated with each treatment method, guiding healthcare professionals in managing kidney stones effectively.

Summary of the currently most common treatment methods for kidney stones (PCNL, ESWL, SWL, RIRS, URS).

The current treatments for kidney stones include, among others Percutaneous Nephrolitho-

tomy (PCNL), Extracorporeal Shock Wave Lithotripsy (ESWL), Retrograde Intrarenal Surgery (RIRS), and Ureterorenoscopy (URS).

PCNL is the standard treatment for large renal calculi using rigid and flexible endoscopes. It involves posterolateral access tracts, with standard tracts being 24-30 F and mini-PCNL tracts being less than 18 F. Contraindications for PCNL include anticoagulant therapy, untreated urinary tract infections (UTIs), tumors in the access tract area, potential malignant kidney tumors, and pregnancy. Best practices involve intracorporeal lithotripsy methods such as ultrasonic, pneumatic, combined systems, and lasers for miniaturized and flexible instruments. Preoperative imaging using ultrasound (US) or computed tomography (CT) is crucial to assess interposed organs. Patient positioning can be either prone or supine, with supine positioning potentially reducing operative time. Ultrasound guidance can reduce radiation exposure and complications [1, 2]. Tract dilation methods vary, with single-step dilation possibly reducing operative time and complications [3–5]. Postoperative drainage depends on the presence of residual stones, bleeding, urine extravasation, ureteral obstruction, and infection risk and may involve a nephrostomy tube or a double J stent [6–11]. Common complications include fever, transfusion, thoracic complications, sepsis, organ injury, embolization, urinoma, and death. Increased pressures during mini-PCNL may contribute to febrile complications [12–14], and bleeding can be managed by clamping the nephrostomy tube or using embolic occlusion. Tranexamic acid can reduce bleeding complications and transfusion rates [15–17]. Multiple tracts increase the risks of pleural damage, infections, and the need for transfusion.

ESWL's efficacy depends on the stone's size, location, composition [18–21], and the patient's body habitus. When dealing with stones > 10 mm in diameter, impacted stones, calcium oxalate monohydrate or cystine stones, or stones located in unfavorable anatomical locations e.g., ureter, ESWL is less likely to be successful [22]. Proper acoustic coupling [23, 24] and stepwise power ramping [25–30] improve outcomes and reduce renal injury. Best practices include avoiding the routine use of internal stents unless to prevent steinstrasse [18–21], using a lower shock wave frequency to increase stone-free rates [25, 31–43], and ensuring pain control [44–46], imaging control, and proper coupling during the procedure. Antibiotic prophylaxis is recommended in cases of internal stent placement, infected stones, or bacteriuria [47, 48]. Medical expulsion therapy, post-treatment mechanical percussion, and diuretics can expedite stone passage. Complications from ESWL include steinstrasse [49–51], macroscopic hematuria, pain, regrowth of fragments [52,

53], bacteriuria [52–55], sepsis, renal hematoma, dysrhythmia [52, 54], and rare cases of bowel perforation and hematomas in the liver or spleen [56–59].

RIRS involves using flexible ureteroscopy to treat stones located within the kidney. The stones can be seen through the scope, manipulated or crushed by an ultrasound probe, evaporated by a laser probe (holmium: yttrium-aluminum-garnet Ho: YAG laser), or grabbed by small forceps. Due to significant technological advances, it has become a preferred method for treating renal stones, particularly those larger than 2 cm [58, 59]. Indications for RIRS include treating renal stones larger than 2 cm [58, 59] and cases where access to the kidney is difficult due to the stone's location or the patient's anatomy. Currently achieved technological improvements include the miniaturization of endoscopes, improved deflection mechanisms, enhanced optical quality, and the introduction of disposable instruments. RIRS boasts high stone-free rates (SFR) of about 91% [58, 59], with an average of 1.45 procedures per patient [58, 59]. Complications are relatively low, with about 4.5% of patients experiencing complications greater than the Clavien score grade 3 [58, 59]. Best practices for RIRS generally involve performing procedures under general anesthesia, although local or spinal anesthesia can be used in some instances. Using smaller caliber ureteroscopes is associated with higher SFR, lower ureteric injury rates, and shorter hospital stays. Digital scopes offer shorter operation times due to better image quality. Fluoroscopic equipment should be available during the procedure [60–64], and placement of a safety wire is recommended, though RIRS can be performed without it [60–64]. The use of ureteral access sheaths can facilitate multiple entries to the upper urinary tract (UUT) and improve vision by maintaining a continuous outflow and reducing intrarenal pressure [65, 66]. Postoperative management includes medical expulsion therapy following Ho: YAG laser lithotripsy to increase SFRs and reduce colic episodes. Routine stenting after uncomplicated RIRS is not necessary and may be associated with higher postoperative morbidity and costs. Using smaller diameter ureteric stents and shorter indwelling times can reduce urinary symptoms and patient-reported pain. The overall complication rate for RIRS is 4-25% [67, 68], with most complications being minor and not requiring intervention [67, 68]. The risk of postoperative urosepsis is up to 5% [69, 70]. Ureteral avulsion and strictures are rare, with significant risk factors including previous perforations, preoperative positive urine cultures, comorbidities, and longer operation times [71–73].

URS is used to treat stones in the ureter and involves both rigid and flexible ureteroscopes. It is a standard procedure for ureteral stones and can also be used for renal stones. Antegrade URS

is suitable for treating stones located anywhere in the ureter and is used for larger >15mm, impacted, proximal ureteral calculi in a dilated renal collecting system [74, 75]. Currently achieved technological improvements include the availability of digital and smaller-diameter scopes and the introduction of disposable ureteroscopes, which provide similar safety and effectiveness to reusable scopes [60–63]. URS boasts high success rates, especially with smaller caliber scopes, and has relatively low complication rates, with most minor complications [67, 68]. Best practices for URS include performing procedures under general anesthesia, though local or spinal anesthesia can be used. Hydrophilic-coated ureteral access sheaths improve procedural ease and outcomes [65, 66]. Proper pain management and careful control of intraoperative conditions are crucial. Fluoroscopic equipment should be available in the operating room [60–64], and safety wires, dilators, and access sheaths are recommended as needed [60–64]. Proper training and operator experience are critical for successful outcomes. Postoperative management for URS includes the understanding that routine stenting is unnecessary after uncomplicated URS. Medical expulsion therapy can improve stone-free rates and reduce colic episodes [76, 77], and alpha-blockers can reduce the morbidity associated with ureteral stents. The overall complication rate for URS is 4-25% [67, 68], with most minor complications [67, 68]. There is a risk of postoperative urosepsis [69, 70], as well as rare complications like ureteral avulsion and strictures [67, 68]. Measures to reduce intrarenal pressure and proper antibiotic prophylaxis can minimize complications.

CHEMOLYSIS

The chemolytic treatment of renal calculi is grounded on the chemical properties of the salts that comprise the stones. The use of specific chemicals enables the transformation of hard-to-dissolve minerals in the stone into soluble compounds, which can then be removed by irrigation. There are three ways in which a chemolytic solution may be administered [64].

The oldest uses a traditional catheter to pour solutions into the renal pelvis. It was Crowell who initially achieved success with this treatment approach [65]. He dissolved a cystine stone in the pelvis via retrograde irrigation, utilizing a mildly alkaline solution (mercurochrome) concurrently with oral administration of sodium bicarbonate to alkalinize the urine [64].

A more detailed exploration can be found in the foundational research by Abeshouse [66] and Suby [67], where we see the emergence of citric acid, which would later become a component

of renacidin, as well as ethylene diamine tetraacetic acid (EDTA), used later as an ingredient of Timmermann's P-solution [64, 68].

In the years immediately preceding 1971, the technique was refined regarding instrumentation and solvent selection, making achieving a relatively safe and successful clinical outcome possible. It was found that renacidin and the derivatives of EDTA proved to be the most suitable. Nevertheless, this method required significant effort from patients and physicians, involving great patience and time commitment.

Several approaches have emerged when it comes to retrograde irrigation instruments.

Timmermann suggests continuous irrigation with a 2-eyed plastic catheter [69, 70]. In order to make the insertion easier, it was submerged in water at a temperature of about 80-90°C. It caused the catheter to be more flexible. It became rigid once more when it reached body temperature after insertion, so the urethral peristalsis could not force it out.

Mulvaney advocated employing two catheters - one functioning as the inlet and the other as the outlet [71]. However, this approach can be technically challenging. If blockages occur in either catheter, a backup outflow route remains available through the ureter adjacent to them.

Suby recommended intermittent irrigation through a ureteral catheter, ensuring the solution remained in contact with the stone for a specific duration. In contrast, continuous irrigation carried the risk of the solution flowing directly from the inlet to the outlet without interacting with the stone at all [64, 67].

A drawback of retrograde chemolysis is the extended treatment period required. Timmermann says this can range from approximately 48 to 1,000 hours (or around 10-100 days), with irrigation sessions lasting 8-10 hours daily [69]. Notably, recurrent calculi that have developed within a relatively short timeframe of less than six months are most susceptible to dissolution [64].

Moreover, a catheter left indwelling in the ureter for a long time always produces an increasing risk of an infection. Irrigation may activate chronic pyelonephritis already present. As a preventive measure, the irrigating fluid should contain an antibiotic.

In 1982, some claimed that retrograde infusion chemolysis had been found obsolete due to concomitant complications, advocating for local chemolysis via percutaneous nephrostomy [72].

However, the said study limited the use of chemolysis to treating uric acid, struvite-appatite and cystine stones, due to acceptable time demands. When local chemolysis is found worthwhile,

it advocates for employing two nephrostomy tubes - one for inflow and the other for outflow - which are inserted into the collecting system to prevent a major complication associated with chemolysis: obstruction, that may lead to acute pyelonephritis if left untreated.

In this method chemolytic solution flow takes place only in daytime, with infusion rate at 100-120 mL per hour. Under such circumstances, it takes from 10 to 30 or more days to completely mitigate the condition. Therefore it's the procedure of choice in case of struvite or uric acid calculi, utter removal of which via mechanical ways is impossible. This way is also preferable in cases of cystine stones, which are infamous for their tendency to recur. This calls for the least invasive approach, as such.

In 2000 the role of chemolysis became even more minor. Prior that year a giant leap in terms of knowledge about local chemolysis took place. Many new ways of administering chemolitic solutions emerged, along with very sophisticated ones, such as using computer-controlled, pressure-monitoring intermittent pump, devised by Kuwuahara et al [73, 74].

Moreover, the notion of relation between calculus composition and proper chemical agents broadened considerably. Despite these advances, due to its low cost-effectiveness local chemolysis became perceived only as a way to clear the urinary system of residual stones after a more modern treatment. The study calls for limiting the usage of such approach to cases, when surgical procedures are accompanied by high risk [74].

As for the year 2017, in times of modern techniques, oral chemolysis in treatment of uric acid calculi, becomes one of the last outposts of chemolytic methods of treating urolithiasis. Such stones make up about 10% of all calculi. Though, it shouldn't be used for sodium or ammonium urate stones. During the treatment it is important to perform regular checkups and ultrasonography plays a major role in such monitoring. If renal backpressure is observed, the oral chemolysis is still viable, but after a decompression. The approach is based on alkalization of the urine by the means of citrate or sodium bicarbonate oral intake [75].

The higher the urine pH, the more effective the therapy is, but the value is set to the range of 7.0-7.2. If these values are exceeded, there is a risk of calcium phosphate calculi development. Patients undergoing oral chemolysis therapy should have serum electrolyte levels, blood urea nitrogen and creatinine monitored. If such an approach fails, it calls for endoscopic, lithotripsy of surgical procedures [76].

MEDICAL EXPULSIVE THERAPY

Medical Expulsive Therapy is a treatment for urolithiasis that involves the patient taking medications that relax the smooth muscle of the ureter, thus facilitating their passage through the ureter [77].

Besides ureteral spasm, edema is an important factor in arresting ureteral stone passage. MET is a non-invasive method that can replace conventional methods but only in the case of smaller stones 5-10 mm, located in the lower part of the ureter because those with a high chance of being expelled from the body on their own.

Table 1. Comparison of probability of stone passage with and without MET therapy

	MET	**no MET**
lower ureter	61%	53%
middle ureter	47%	40%
upper ureter	32%	26%

Data based on the MIMIC Calculator for Predicting Spontaneous Stone Passage determining the probability of expelling a 5-7 mm stone from the lower, middle, and upper parts of the ureter in a male patient without hydroureter and hydronephrosis using MET and not using MET. Results show the effectiveness of using MET [78].

The European (EAU) and American Urological Associations (AUA) outline the role of alpha-antagonists as a viable option in a select patient population who are comfortable with the approach and where there is no role for immediate surgical stone removal [79, 80].

The European Association of Urology (EAU) guidelines continue to suggest using MET for all ureteral stones. In contrast, the American Urological Association (AUA) guidelines recommend MET only for patients with distal ureteral stones ≤10 mm.

ALPHA-ANTAGONISTS

In Medical Expulsive Therapy (MET), the most commonly used drug is tamsulosin, which belongs to the alpha-antagonists. In the ureter, α1-receptor antagonists inhibit basal tone and also decrease peristaltic frequency and amplitude. Consequently, intraureteral pressure decreases, and

fluid transport increases. These receptors appear ideal targets for pharmacotherapy as they represent the most significant impediment to stone passage [81].

The 2018 Cochrane review by Campschroer assessed the effectiveness of alpha-blockers as medical expulsive therapy (MET) for ureteral stones in adult patients. This review included 67 studies with 10,509 participants, 15 placebo-controlled trials involving 5,787 participants.

The findings indicate that alpha-blockers likely increase the stone clearance rate compared to placebo, though the effect is more pronounced in patients with larger stones (greater than 5 mm) than smaller stones (5 mm or smaller). Additionally, alpha-blockers were associated with shorter stone expulsion times, reduced use of pain medication like diclofenac, and fewer hospitalizations [82].

The 2016 double-blind, placebo-controlled trial on tamsulosin for ureteral stones conducted in Australia included 403 patients. The study included patients with stones sized 1 to 10 mm. The primary focus was to assess the efficacy of tamsulosin in facilitating the passage of these stones compared to a placebo. Participants received either 0.4 mg of tamsulosin or a placebo daily for 28 days. The results showed that tamsulosin did not significantly increase the stone expulsion rate compared to placebo. Specifically, stone passage rates were 87% for the tamsulosin group versus 81% for the placebo group, indicating no statistically significant difference between the two groups [83].

Another randomized trial comparing tamsulosin with placebo for 4—to 7-mm distal ureteral stones in more than 3,200 patients showed results similar to those of the Australian trial: no difference for stones 5 mm or less and an increase in stone passage in the group with 5.1—to 7-mm stones (87% versus 75%), with a small overall benefit when all sizes were considered (4 to 7 mm; 86% versus 79%) [84].

Both trials showed no advantage of MET over placebo in large cohorts of patients with ureteral stones.

The research results are unclear, but the European Association of Urology 2024 guidelines include MET in treating stone disease. Medical expulsive therapy should only be used in informed patients if active stone removal is not indicated. Treatment should be discontinued if complications develop (infection, refractory pain, deterioration of renal function). In the case of known uric acid stones in the distal ureter, a combination of alkalinisation with tamsulosin can increase the frequency of spontaneous passage.

CORTICOSTEROIDS

A prospective study by Porpiglia and colleagues examined the effects of corticosteroids alone and in conjunction with alpha-antagonists in expulsing distal ureteral stones [85].

Corticosteroids have anti-inflammatory properties, so they may reduce the swelling caused by the deposit's irritation of the ureteral wall, which could facilitate its expulsion.

Studies have shown that corticosteroids are comparable to placebo in terms of effectiveness; moreover, the use of corticosteroids carries the risk of side effects such as immunosuppression or components of Cushing's syndrome.

Although corticosteroids alone do not provide much benefit to the patient, it has been shown that adding deflazacort (corticosteroid) to tamsulosin compared to tamsulosin alone increases its effectiveness. The EAU guidelines do not recommend the use of corticosteroids in MET.

CONCLUSION

Although studies have shown a similar effect of tamsulosin compared to patients using a placebo, Medical Expulsive Therapy is a frequently used treatment method. It can help avoid invasive surgical procedures, thereby reducing the risk of complications and shortening recovery time, so MET is often the first treatment for small urinary stones.

OPEN SURGERY

The "classic" surgical approach to ureteral stone treatment is currently one of the rarely used procedures, usually named as a secondary or even tertiary therapy. It is more of a historical method and shows that total open surgery is currently used in approximately 1-5,4% of cases presented with kidney stones [86]. With the popularity of minimally invasive methods, the number of papers on open surgeries has significantly decreased over the decades. There are some exceptional cases in which the said approach presents superiority over now commonly used methods: unusual anatomy of the calyceal-pelvic system, difficulties in reaching the calculi, recurring UTIs or large deposits, which prove to be difficult to crush [79, 87, 88].

The paper published in The Journal of Urology's pages on February 1st, 2005, compares open surgery to percutaneous nephrolithotomy (later called PCNL) in treating complete staghorn stones [89]. The patients included in the study had renal calculi that took over 80% of the entire

collecting system, among whom 43 were treated by PCNL and 45 by open surgery. Researchers considered preoperative evaluations, operative techniques, and evaluations at follow-up. In both groups, the results were primarily similar - though open surgery showed an increased stone-free rate, PCNL is still considered a superior option with better follow-up results, showing lower morbidity, shorter operative time, and easier return to day-to-day life.

Another paper shows that open surgeries are more efficacious [86]. Laparoscopic surgery is considered to be a reliable option when extracorporeal shock-wave lithotripsy (ESWL) has failed in patients with large and chronically recurring kidney stones. Moreover, laparoscopy allows the surgeon to perform various methods, such as dismembered or non-dismembered pyeloplasty, ablation of calyceal diverticula, partial nephrectomy, heminephrectomy, and nephrectomy. Though endoscopy seems to be a reliable option, there is a barrier in the developing African and Asian countries, where financial problems prevent their common usage. There is a big difference where in the US, open surgeries were 1,5% (in the 2000s), and in Pakistan, they reached even 30%.

Currently, the EUA Guidelines still have an open surgery as a possibility of urolithiasis treatment, though they firmly state, "Offer laparoscopic or open surgical stone removal in rare cases in which shock wave lithotripsy, retrograde or antegrade ureteroscopy, and percutaneous nephrolithotomy fail, or are unlikely to be successful." As we can see, surgical treatment is not a primary method, and the guidelines say that current studies on laparoscopic treatment should be considered with caution due to a lack of reliable sources [79].

CONCLUSIONS

The treatment of kidney stones has evolved significantly, offering multiple effective options tailored to the size, location, and composition of the stones, as well as patient-specific factors. Percutaneous Nephrolithotomy (PCNL) remains the gold standard for large renal calculi due to its high success rates and precision. Extracorporeal Shock Wave Lithotripsy (ESWL) is effective for smaller stones but is influenced by stone characteristics and patient anatomy. Retrograde Intrarenal Surgery (RIRS) and Ureterorenoscopy (URS) provide minimally invasive alternatives with high stone-free rates and low complication risks, thanks to advancements in endoscopic technology.

Chemolytic treatments and Medical Expulsive Therapy (MET) offer non-invasive options, particularly for specific and smaller stone compositions, respectively. While open surgery is now

rare, it remains a crucial option in cases where other treatments are ineffective.

In summary, the diverse array of treatment modalities for kidney stones allows for personalized patient care, optimizing outcomes while minimizing risks. Ongoing advancements and research in this field continue to enhance the efficacy and safety of these treatments, ensuring better management of kidney stones in clinical practice.

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ORTHOKERATOLOGY IN MODERN OPHTHALMOLOGY - A REVIEW

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INTRODUCTION

In recent years, the world of ophthalmology has faced a rapid, global increase in myopia prevalence. In 2020, the World Health Organization estimated that 2,6 billion people around the world suffer from it, and 399 million of them may be classified under high myopia. According to the same report, by 2030, these numbers may rise to 3,361 billion and 516 million, respectively [1]. These numbers pose a significant problem, not just in purely medical terms but also in the context of societal impact. Myopia is known to negatively influence the quality of life of those affected and create a substantial economic burden both on the affected individual and, in turn, on broader communities. Although various methods of visual acuity correction can improve a patient's quality of life, they do not seem to cause it to return to the baseline (corresponding to an emmetropic individual). Therefore, methods that may halt or decrease myopia's progression are a worthwhile investment both economically and socially [2].

There are several methods used to improve a patient's vision. Those include behavioral and pharmacological interventions, spectacle lenses, contact lenses, well as surgical procedures such as LASIK, PRK, or LASEK [3,4,5].

Several types of contact lenses can be distinguished, such as soft, hard, or rigid gas-permeable contact lenses [6].

Orthokeratology (OK) treatment, discussed in this work, requires patients to apply rigid gas-permeable lenses every night. Temporarily reshaping the cornea allows them to function the

next day without the need for additional vision correction methods [7]. It is mostly applied in Asia, which is believed to be more effective than in other continents [8].

APPLICATION

Orthokeratology effectively alters the geometry of the cornea, allowing for the successful treatment and management of several vision defects. Physicians usually use orthokeratology to treat myopia. However, it can also be used to treat other conditions based on correcting refractive errors of the eye, like hyperopia, myopia combined with astigmatism, and presbyopia in elderly patients [9].

MYOPIA

Myopia is a globally common refractive error, and its prevalence is rapidly increasing worldwide. Myopia is an impaired patient's ability to see distant objects [10]. This condition, especially high myopia, is one of the major causes of blindness and severe visual impairment [11,12]. Blinding complications include myopic choroidal neovascularization, myopic macular degeneration, glaucoma, and cataracts [13,14,15]. Multiple studies prove that orthokeratology lenses are effective and improve the quality of vision by correcting refractive errors in juvenile and older patients with myopia, allowing for near-normal vision during the day [16,17,18].

Administering orthokeratology for patients with myopia can drastically slow down the progression of this disorder. In this case, OK significantly reduces axial elongation associated with myopia development and improves choroidal blood perfusion, preventing scleral hypoxia [19]. One of the structural defects of the eyeball in the course of myopia is the thinning of choroid tissue, which may lead to scleral hypoxia in the posterior of the eye, the other hand, leading to scleral extracellular matrix remodeling, causing the development of myopia by the further acceleration of axial elongation [11,13,20,21,22,23]. Research conducted by Jang Hun Lee et al. indicates that in young myopic adults, choroidal thickness increases after three months of OK treatment. Even more beneficial from this study is that after six months of treatment, choroidal thickness recovered almost to baseline, which shows that OK can prevent myopic complications related to thinning of choroid tissue in myopia. On the other hand, currently available literature lacks evidence of changes in choroidal thickness after a follow-up period longer than two years [24,25,26]. Applying orthokeratology to children with myopia from age 8-13 is the most beneficial, as axial elongation

is usually the most rapid in this age range and slows down with age. It is important to note that OK is superior to spectacles when it comes to slowing down axial elongation in the treatment of myopia in children, according to a meta-analysis carried out by Meng Guan et al., in which data from 13 articles was analyzed [27]. Orthokeratology lenses can also benefit young adults who perform intense close visual work because there is an existing onset of myopia in this age group, which, similarly to the development of myopia in children, has an origin associated with axial elongation. From multiple cross-sectional studies summarized by Bullimore et al. in their paper, the proportion of participants who experienced adult-onset myopia varied from 15 to 80% across groups in a given study, and proportions from 30 to 50% were recorded most frequently [28,29].

Orthokeratology can also reduce myopic progression by reducing axial elongation in patients with anisometropia [30]. In particular, those who cannot tolerate the lens effect. Its definition is seeing images significantly different in size while wearing spectacles to correct vision [31,32,33]. In the first part of the study by Jing Xu et al., all the subjects examined suffered from monocular myopia. Each of their eyes was assigned to one of two groups. The increase in the axial length in the OK group, which contained myopic eyes of these patients, was 0.21 ± 0.09 mm after 24 months of treatment, and in the non-OK group, with eyes without OK correction, it was 0.70 ± 0.17 mm. These results show the effectiveness of OK on axial elongation in anisometropes [34]. An interesting analysis was performed by Kirti Singh in India, demonstrating that OK is also a convenient method for treating patients in semi-tropical and underdeveloped countries [35]. However, the literature available in this case is scarce, which indicates a potential area for further investigation.

One currently used method for slowing down myopia progression is eye drops with low-dose atropine, typically in the concentration of 0.01%. However, many studies do not support the effectiveness of low-dose atropine in slowing myopia progression and axial elongation, which raises concerns about its application to myopic patients [36,37]. Combining orthokeratology with atropine provided better results than atropine alone and atropine with spectacles in slowing axial elongation, improving choroidal thickness, and giving patients better control of myopia progression [38]. Furthermore, OK with atropine maintains proper intraocular pressure and visual acuity in patients undergoing this therapy [39,40]. Additionally, orthokeratology combined with atropine gives better results in slowing down myopia progression than OK treatment alone, so atropine has the potential to enhance slowing myopia progression with OK [41,42,43,44,45,46,47].

MYOPIA WITH ASTIGMATISM

Orthokeratology can also be used effectively in treating patients affected by myopia with astigmatism.

In cases of low astigmatism, typical orthokeratology treatment with spherical overnight lenses is applicable. However, moderate to high astigmatism (1.50 D or greater) requires the usage of toric lenses because of possible lens decentration and further induction of astigmatism caused by spherical lenses in those cases [48,49]. These toric lenses have been proven to be effective in correcting low to moderate myopia paired with moderate to high astigmatism with effective control of axial length elongation after 1-year period [50].

HYPEROPIA AND PRESBYOPIA

Orthokeratology treatment in hyperopic and presbyopic patients works similarly to the treatment of myopic patients. Changes in the cornea happen quickly and are reversible. Lenses used in hyperopic and presbyopic orthokeratology cause steepening of the central cornea and flattening of the corneal mid-periphery [7]. This adjustment increases refractive power in the central part of the cornea and effectively corrects refractive error in hyperopia and presbyopia, improving patients' vision [51]. Hyperopia and presbyopia are uncommon targets for orthokeratology. Therefore, the literature available in this case is scarce, and more research about its proper application is needed. Mainly because more knowledge in the field could prevent suboptimal outcomes in treating hyperopia. One example is described in the study by Sánchez-García et al. about applying the new Penta-curve Alexa H contact lens, highlighting essential knowledge deficiencies leading to patient dissatisfaction [52].

When it comes to treating emmetropic presbyopia with the hyperopic OK monovision approach, the study by Paul Gifford and Helen A. Swarbrick provided results that indicate that OK can induce enough increase of refractive power to give patients effective correction of near vision without changing visual acuity in binocular distance vision [25].

THEORY ON ORTHOKERATOLOGY

Orthokeratology (OK) temporarily reduces certain vision defects by altering the shape of the anterior cornea. In the treatment process, the patient is fitted with special lenses that, worn while asleep, temporarily change the geometry and refractive properties of the anterior cornea.

Therefore, normal, uncorrected vision can be achieved during the day [7,53]. What is more, prolonged use of OK has the potential to stunt myopia progression, which is a highly desirable effect nowadays [54].

THE LENS

Lenses used in modern OK are created with a reverse geometry design. They mostly consist of three to five curves. By the number of curves, they can be divided into two major types: CRT lenses with three curves and VST lenses with four or more curves. These two designs produce different results in multiple aspects, including, but not limited to, slowing myopia progression, with VST lenses proving to be more efficient and safe. In contrast, CRT lenses tend to cause fewer adverse effects [7,55,56].

Overnight wear of lenses produces many challenges caused by the unique anatomy and physiology of an eye, which need to be considered when designing the lens. One of the most important limitations that must be addressed is gas permeability. While the material has to be rigid to produce adequate geometry changes, its oxygen transmissibility should be high enough to minimize the possibility of corneal edema and hypoxic stress [54,57]. Until the 1980s, when the first gas-permeable materials were introduced into lens manufacturing, safe overnight lens wear was impossible. Modern lenses have high gas permeability, allowing prolonged closed-eye use [57]. Furthermore, regarding oxygen availability, a potentially significant difference may exist between orthokeratology and regular contact lenses. In OK treatment, lenses are only worn at night, which may result in less time spent with lenses covering the surface of the eye than regular contact lenses [58].

MECHANISM

The exact mechanism in which OK works is not fully known, yet numerous hypotheses exist that try to explain it. One of the oldest theories assumes that the main force reshaping the cornea is the pressure the lens exerts on the apex of the eyeball. Such an assumption creates a lens flatter than the curve of the eyeball to emphasize the pressure on the apex [53]. Yet another old theory suggests that the main driving force bending the cornea is hydraulic pressure caused by the tear film behind the lens. At present, it is proposed that the effects of orthokeratology mainly stem from hydraulic forces in the tear film, which cause an effect that is better described as a change in

the thickness of some regions of the cornea (accompanied by changes in topography) than simple bending [7,53,54].

Another layer of complexity is added to the mechanism when considering the corrective application of OK and its preventive impact on myopia progression. The understanding of myopia progression control is also not perfectly understood. Still, theories exist that try to explain it, e.g, retinal peripheral defocus theory, accommodation theory, and the aberration theory [59,60,61,62,63,64,65].

The first one, retinal peripheral defocus theory, is based on studies showing that peripheral hyperopic defocus can cause axial myopia (the reverse is also true about myopic defocus) [66].

There is substantial evidence that treatments that reduce peripheral hyperopic defocus (which tends to be increased in those suffering from myopia), in turn, reduce myopia progression. One of those methods is OK, which achieves the effect through mid-peripheral steepening of the cornea [60,67]. The second one, the accommodation theory, focuses on the accommodation response and its impact on the changes in the eye [64].

One of the most important measures within it is the accommodative lag. It is the difference between the accommodation appropriate for the stimulus and the accommodation that happens within the accommodation apparatus. Whenever the accommodative lag appears, the eye is focused further than necessary [68].

What is important from the perspective of OK, there seems to be a relationship between the accommodative lag and myopia progression. Some argue that the increased accommodative lag in myopic patients may be a cause of peripheral hyperopic defocus, which, as stated before, may induce axial growth, which, in turn, results in myopia progression [64]. OK is documented to decrease accommodative lag, which could potentially be the source of its potency in controlling myopia [64,65]. The aberration theory states that the cornea's asymmetric shape inhibits axial elongation [61, 62, 63]. Coma-like aberrations are the most influential in axial growth regulation [61].

CHANGES TO THE EYE

In myopic patients, orthokeratological therapy aims to create central corneal flattening, followed by mid-peripheral steepening, as caused by epithelial redistribution [7,69]. Such apical flattening decreases refractive power, which results in improved vision quality.

In hyperopic patients, orthokeratological therapy aims to cause central corneal steepening accompanied by a mid-peripheral flattening of the cornea. In turn, the steepened central region has greater refractive power, allowing correct accommodation and improved vision quality [7,25].

In presbyopic patients, there exist two routes to explore. It is possible to either apply a multifocal correction or a monovision approach. In the monovision approach, each eye is treated differently. The dominant one is corrected for good quality distance vision, while the other is optimized for close range. On the other hand, the multifocal correction treats both eyes the same, allowing each eye to have good vision at all distances. It is possible to reduce the size of the central treatment zone and surround it with a ring-like area with changes opposite the center. Therefore, the center will be steepened and surrounded by a flattened area in a hyperopic eye. The opposite will be valid for treating myopic eyes [7,25,51].

FITTING THE LENS

Proper lens fitment is obligatory for achieving adequate treatment results. Fortunately, advancements in diagnostics have been proven to help eye care practitioners greatly. While the lenses can be fitted more traditionally, utilizing diagnostic lenses and sodium fluorescein, modern corneal topography can allow for a more accurate result [7,70,71].

During assessment after a following overnight trial, different topographical patterns can be observed on the cornea's surface. The appropriate one during therapy for myopia would be a “bulls-eye” pattern, which appears whenever proper centering has been achieved and maintained throughout the night. Whenever the position of the lens is disturbed, a different pattern shall form, allowing for the identification and correcting of the inadequacy in the lens. The patterns that may arise are: decentred “bulls-eye”– caused by a lateral or medial shift, “smiley-face”– caused by a superior shift, and inverted “smiley-face”– caused by an inferior shift. There is another pattern that may occur, yet is not directly connected with a shift in the position of the lens. It is called a central “island” pattern, and a central zone of unaffected tissue characterizes it. It may be caused by a lens with too steep curves [7,72].

CONTRAINDICATIONS AND COMPLICATIONS

Despite orthokeratology's proven effectiveness, there are concerns about using this method to treat vision defects. These concerns mainly involve the complications associated with this

procedure. Accordingly, many scientific articles address the complications after OK.

CONTRAINDICATIONS

There are not many significant contraindications that prevent one from undertaking orthokeratology treatment. Those that do exist, however, are set on two grounds - anatomical and physiological. In the OK process, developing a correct topographic map of the eye is essential. Therefore, any disorders in the structure of the eye preventing this are considered contraindications to the process. These factors include deep-set eyeballs, loose eyelids, or an overly low upper eyelid. In addition, these conditions are potential causes of lens decentration, making it impossible to treat the patient [58] properly. It is important to note that a patient who is to undergo an OK treatment must not have keratoconus, corneal degeneration, or any other active eye pathologies, especially in the anterior eye [73]. A popular contraindication for traditional contact lenses (CL) is dry eye syndrome, which is one of the major reasons for abandoning therapy [74]. Both very advanced dry eye and overactive Meibom's gland are contraindications for orthokeratology treatment. In a patient with advanced dry eye, it will be impossible to correctly create a topographic map of the eye - erroneous values will appear in areas of increased dryness. For the measurements to be correct, it is necessary to ensure adequate moistening of the cornea [58].

Importantly, OK contraindications can also arise during the therapy and become a direct trigger for withdrawing the treatment. Such contraindications include the appearance of a disease in the anterior eye, such as blepharitis, chalazion, or long-term corneal discoloration. Another possible reason for discontinuation of the therapy may be improper lens hygiene, as such behaviour significantly contributes to the appearance of possible complications in the future [75].

COMPLICATIONS

Orthokeratology procedures, like other medical procedures, may result in possible complications. They can be very mild, not adversely affecting the patient's well-being, but they can also be very dangerous, disruptive, and even lead to vision loss.

MICROBIAL KERATITIS

Microbial keratitis (MK) is a condition that can be caused by different types of pathogens, i.e, bacteria, protists, or fungi. Such variation in the infectious agent results in various symptoms

that may be found. Characteristics of MK include redness, tearing, pain, or evolving inflammation [76]. In the course of MK, corneal ulcers can develop. Initially, the inflammation attacks the epithelial and lining cells, leading to swelling in the inflamed area, followed by cell necrosis, hence tissue breakdown. There are cases in which deep stromal abscesses can develop under the ulcer. An important note is that the prevailing inflammation in the organ can spread to other surrounding corneal structures, such as the anterior chamber of the eye, causing hypopyon [77]. Concerns about the link between MK and OK are being examined in detail because of potentially dangerous complications of the condition, the most serious of which is a partial or total loss of vision [78]. Furthermore, it is believed that hypoxia may be one of the factors that promote the development of MK [79]. Ka Wai Kam et al. analyzed studies published in the PubMed database on OK-related keratitis. After discarding studies unsuitable for analysis, they obtained data from 29 scientific articles reflecting 173 eyes. Microbiological cultures were positive in 69.4% of cases, and the microorganisms that most often caused this inflammation were *Pseudomonas aeruginosa* and *Acanthamoeba*. 6% of MK cases were observed with the simultaneous presence of two microorganisms. The mean age of those who developed keratitis was 15.4 ± 6.2 years, with a higher incidence of symptoms in women (1.7 times higher frequency in women). Importantly to highlight, the average duration of the disease was 96.7 ± 67.8 days, with the longest case lasting 223 days. On the other hand, the patients' antibiotic therapy lasted an average of 4.5 ± 5.4 months. A significant proportion of keratitis cases led to corneal scarring [80]. These data indicate that the problem is highly intractable, related to the long duration of the disease. In addition, it is important to emphasize that keratitis can lead to serious health consequences like glaucoma or cataracts, which can lead to partial or total vision loss [81,82]. Importantly, there are cases where OK health complications can be linked to poor lens hygiene, such as washing or storing them in tap water [81,83]. Therefore, it is extremely important to educate medical personnel, patients, and parents of patients in the case of children undergoing the therapy. The problem is important because, as shown in a study on the Chinese population, the full compliance rate examined among patients with an average age of 13.1±3.9 was only 14.1%, with a noticeable increase in the rate with decreasing age, which may indicate greater parental involvement in the treatment process, especially in looking after the lenses [84]. Another questionnaire study found that young patients who rinsed their lenses independently were likelier to use tap water than when the child's parent was responsible for lens cleaning. In addition, the quality of lens care declined among patients as the treatment process

lengthened [85]. Patients' most common mistakes include exposure of lenses to non-sterile surroundings, elimination of residues inconsistent with recommendations, and improper hand hygiene [84]. Despite this, a study by Bullimore et al. found that the risk of MK among patients undergoing the process of OK procedures is no different from the risk for other nocturnal corneal interference. The same study showed no statistically significant difference between the incidence of MK in children and adults [86]. In conclusion, given the serious health consequences of MK as a complication of OK, this issue should be given special attention, and risk factors should be studied in greater detail. In addition, educating patients on proper lens care is essential, as this is undoubtedly a serious problem among lens wearers [87,88].

INFLUENCE ON MEIBOMIAN GLAND AND TEAR FILM

Many studies focus on the impact of OK lenses on the meibomian gland and, hence, tear film. Certain studies show that wearing OK lenses does not influence the tear film or the meibomian gland of treated patients [89]. However, it is not a widely prevailing opinion. Many studies emphasize that when using orthokeratology (OK) lenses, there are disturbances in the tear film [90,91,92]. Some also believe that this negative influence on tear film can mostly affect children, so children should approach these lenses with particular caution. Regarding the features of the tear film, it was examined that the Tear Breakup Time (TBUT) decreased among patients during OK treatment about the time before the therapy. However, basic tear secretion was unaffected [91,93]. Furthermore, a rise in meiboscore, the barometer of meibomian gland functionality, was noted in the lower meibomian gland, indicating a tendency towards dry eye syndrome. Therefore, it is thought that OK therapy can influence the lower eyelid meibomian gland, leading to its decline. No disruptions in the upper meibomian gland were spotted [94]. Another study revealed a disruption in the volume of the upper eyelid gland. Moreover, it showed that inflammation can occur in OK users due to increased levels of specific cytokines such as IL-6, IL-17A, and PGE2 in patients' tears [95].

CORNEAL STAINING AND LENS BINDING

Corneal staining is the most popular consequence of orthokeratology treatment [96]. However, usually, the staining is relatively moderate, and the need for serious medical intervention is not required [97]. Nevertheless, it is advised to temporarily withdraw the therapy if corneal

staining persists for a longer period and maintain Grade 2 according to the Efron scale. The failure to take such actions might result in serious consequences, such as corneal ulcers [98]. Research shows that staining most commonly occurs in the central part of the cornea, and the greatest likelihood of its presence is at the beginning of the treatment [7]. It is believed that this state has its risk factors, such as more advanced myopia, greater anterior corneal eccentricity, smaller anterior horizontal radius, presence of cytokines IL-2, TNF-α in tears as well as disruptions of meibomian glands and residues occurring on lens surface [96]. Additionally, it was observed that corneal staining occurred more frequently in adult patients and among patients with prolonged therapy [96]. It is also believed to be correlated with corneal hypoxia, mechanical irritation due to accumulation of sediments, wrong lens fitting, or hypersensitivity to CL solution [99]. Moreover, it was observed that lens binding is often associated with corneal staining [7].

FIBRILLARY LINES / IRON DEPOSITION

Another common consequence of orthokeratology treatment is the appearance of iron deposits located on the corneal epithelium. These changes have a brownish hue and blur their boundaries [100]. It is important because it does not influence clearness of vision, and the changes are reversible [100,101]. It is suggested that the formation of rings is caused by tears between the lens's back surface and the cornea's surface [102,103]. Another observed alteration is the emergence of white lesions on the cornea, which suggests a rise in stress forces affecting the cornea. It is also assumed that orthokeratology via conversion of epithelial migratory patterns stimulates fiber rearrangements, hence centrally located white alterations. It was also examined that the presence of those lesions positively correlates with the length of the treatment and is likely to expand over time [104].

MICROCYSTS

Microcysts, if present, appear as small spots on the corneal epithelium. Significantly, they do not affect vision nor are painful for the patient [105,106]. The appearance of microcysts associated with hypoxia prevailing in the lens environment was noted in certain OK-wearers. It is thought that the deterioration of eye hygiene was the main contributor to this state [107]. Furthermore, prolonged wearing of an OK lens may result in microcyst formation. Biyue Guo et

al. observed grade 4 microcysts and corneal haze in both eyes of their patient, which also had decentralized OK lens, but it is not known if that was involved in microcyst creation [108].

OTHER

Case reports encompass complications that do not frequently appear in the literature. One of them describes central corneal epitheliopathy (CCE). It concerned a 12-year-old girl which had a “dellen-like” lesion in the area of the central cornea, inferior to the pupil in the right eye. The healing process involved ceasing wearing OK lens and pharmacological treatment. After recovery and reapplication of a new lens, the change reappeared after 1.5 months [109]. There is also a case report concerning the development of strabismus associated with lens wear [110].

CONCLUSION

Ultimately, this study presents enough evidence to conclude that orthokeratology is a safe and effective treatment option for correcting multiple refractive disorders of the eye. Unlike other traditional methods such as spectacles, OK cannot only correct the visual acuity but also significantly slow down myopia's progression, making its application particularly useful during major onsets in the lives of those affected by this disease. This advantage of OK treatment can reduce the chance of critical complications of myopia occurring in late adulthood. It is also important to note that OK has a risk for complications development. However, those complications are avoidable by providing professional care and guidance for the patient, which includes maintaining good hygiene and, in some cases, ordering a break in the therapy before these complications become severe.

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PSYCHOLOGICAL AND PSYCHIATRIC PROBLEMS

THE IMPACT OF BREAST CANCER ON WOMEN'S MENTAL HEALTH

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INTRODUCTION

Breast cancer is the most prevalent cancer among women, with an annual diagnosis rate of approximately 2.3 million cases worldwide, signifying that 1 in 8 women will receive this diagnosis during their lifetime [1]. Projections indicate a 31% increase in breast cancer cases by 2040, which means that nearly 3 million new diagnoses of breast cancer will be made each year [2]. The World Health Organization (WHO) reports that breast cancer has one of the highest mortality rates among cancers, with 13.5 deaths per 100,000 women, heightening the gravity of the diagnosis [3].

A breast cancer diagnosis can be a life-altering event for women, leaving a deep emotional scar. There are plenty of psychological issues associated with this disease, particularly anxiety and depression, which are prevalent among breast cancer patients, significantly affecting their overall well-being and quality of life.

In literature, depression is defined as a complex psychological state characterized by low mood, loss of interest and pleasure, disturbances in appetite and sleep, fatigue, difficulty concentrating, low self-esteem, and sometimes thoughts of death or suicide. It can range from mild to moderate to severe and significantly impact daily functioning [4, 5]. The intensity and manifestation of depressive symptoms can vary across different stages of cancer. The anxiety is mostly connected with the fact that the breast is a symbol of womanhood – women are not only scared of the course and the outcomes of the treatment but also its impact on their self-image [6]. Other critical factors influencing the well-being of breast cancer patients include social support, coping mechanisms, or family situation, but also more connected to the disease as treatment side effects, body image changes, and ongoing fear of cancer recurrence [6].

Worrying about cancer and its undeniable impact on women’s future lives often disturbs sleep, leading to significant sleep problems that further exacerbate mental health issues

[7]. Poor sleep quality is associated with increased bodily pain, reduced energy levels, and diminished social functioning, detracting from the overall quality of life [7].

Physical activity plays a crucial role in mitigating the symptoms of anxiety and depression among breast cancer patients. Regular exercise has been shown to alleviate these symptoms, emphasizing the importance of incorporating physical activity into the treatment and recovery process [8].

Breast cancer diagnosis brings a multitude of emotional challenges. Understanding the prevalence and impact of anxiety and depression among patients is crucial to providing effective psychological support.

THE PSYCHOLOGICAL IMPACT OF BREAST CANCER - ANXIETY AND DEPRESSION IN PATIENTS

Breast cancer is a profoundly traumatic diagnosis for any woman, causing significant anxiety and fear [1]. Upon hearing the diagnosis, many women experience intense uncertainty about their future, including questions about their survival and recovery [9]. While some women respond with determination and strength, ready to fight the disease, others feel unmotivated and overwhelmed by the diagnosis.

Ng et al. conducted a study using the Hospital Anxiety and Depression Scale and the distress thermometer to assess anxiety levels at different stages of breast cancer. It was found that 50.2% of women felt a high level of anxiety at the beginning of the study, 51.6% six months after hearing the diagnosis, and as much as 40.3% a year after becoming aware of breast cancer [10]. This data showed a decrease in perceived anxiety and worry after 12 months of lasting illness [10]. Another study conducted in a public hospital in Greece found that 38.2% of breast cancer patients struggled with depression, and 32.2% felt anxiety related to the disease [1]. Breast cancer significantly affects mental health, often leading to a lower quality of life due to depression. Treatment of that kind of cancer is associated with pain, frequent nausea (in the case of chemotherapy), and fatigue, which make it difficult to function and escalate depression [9].

Breast cancer changes the way women perceive their bodies [9]. Women pay particular attention to their appearance, and the need for unilateral or bilateral mastectomy lowers their sense of femininity and attractiveness. Chemotherapy leads to hair loss, which reduces their self-esteem and is mentally stressful [9]. All these aspects cause fear, anxiety, helplessness, and the constant need to cope with the uncertainty of the disease, recovery, further treatment, and

its side effects. Breast cancer increases the risk of depression, which has a poor prognosis [11]. Moreover, it impairs the proper functioning of immune cells, which is one of the causes of depression [11], but also negatively affects the level of serotonin [11], which is responsible for the feeling of happiness, as it is a key neurotransmitter in mood stabilization. Breast cancer treatment is associated with psychological distress, and studies show that younger people have a more challenging time adapting to the diagnosis, and their quality of life is more likely to deteriorate compared to older patients [12].

Marital status also affects well-being at different stages of treating this disease [12]. Studies indicate that being single or divorced is associated with increased experience of depression symptoms after breast cancer surgery, in contrast to women who are married or live with a partner [12]. Psychological distress decreases with the length of time since diagnosis [13]. It has been shown that the high level of stress experienced during the first year was not as severe after a year from mastectomy [13]. In addition, mastectomy itself lowers the feeling of attractiveness and self-esteem compared to breast-conserving therapy [13].

Looking through the prism of different stages of treatment, a significant increase in anxiety and depression was observed 2-3 months before death and the highest in the last month of life [1]. Psychological support during illness is crucial. Breast cancer patients are most likely to seek help from family members or friends, while the second most frequently mentioned person is the doctor [14]. Sometimes, a psychologist is also asked for help [14]. Psychological support and treatment of depression in women with breast cancer is essential, as it improves their quality of life and prolongs it [15]. Even after successful treatment, many women experience mild depression, which continues to affect their quality of life negatively.

SLEEP DISTURBANCE IN BREAST CANCER PATIENTS

Breast cancer and its treatment are a cause of psychological distress, which can negatively impact various aspects of quality of life [10]. Sleep can be considered one of the main aspects of life, as it is crucial in maintaining physiological and psychological health in humans. Therefore, sleep disturbance can furthermore decrease the already lowered quality of life associated with breast cancer [16]. Recent studies indicate that sleep disturbances are among the most prevalent issues for breast cancer patients. Evidence shows that 30% to 70% of adult breast cancer patients report experiencing one or more sleep disturbances, a rate that is twice as high as that found in the general population [16] [17]. The main sleep disorder in breast cancer patients is insomnia, which is manifested mainly as waking up repeatedly throughout

the night. The disruption of circadian rhythms can also manifest in breast cancer patients [16]. Many women with breast cancer already suffer from sleep disorders before receiving any treatment, but during treatment, the symptoms may be exacerbated [18]. It has been observed that women with pre-existing sleep disorders have lower survival rates, highlighting the importance of screening tests for sleep disorders before initiating therapy, which may help increase survival rates as an appropriate approach may be taken [18]. Preoperative sleep disturbances are also associated with increased acute postoperative pain [19].

The amount of sleep disturbances may differ when choosing whether to undergo adjuvant therapy that follows the initial treatment, which is most commonly surgery [20] [21]. It was found that in patients with breast cancer, there are notable differences in reported sleep disturbances between the treatment groups, with significantly higher levels of sleep disturbances observed in those undergoing radiation therapy compared to those not receiving any adjuvant treatment. Similarly, individuals receiving chemotherapy also reported a significant increase in sleep disturbances compared to those without adjuvant treatment [20] [16]. Patients might have experienced improved sleep quality in the first few months after starting treatment compared to their sleep quality before treatment. However, from about 4 months to a year after treatment began, their sleep quality worsened compared to the pre-treatment period [21].

Sleep disturbances can be connected to other common symptoms of cancer, such as cancer-related fatigue, pain, anxiety, and depression [22]. One of those symptoms can trigger the onset or worsening of the others. Recognizing the connections between these symptoms can improve strategies for managing them. For instance, pain can exacerbate sleep disturbances, which can lead to cancer-related fatigue, anxiety, and depression [22]. Additionally, chemotherapy and radiotherapy can induce feelings of nausea and vomiting that can furthermore decrease the quality of sleep and contribute to cancer-related fatigue and depression [20]. Sleep disturbances and emotional distress can furthermore reduce the chance of survival in breast cancer patients [17]. Despite sleep disorders being a widespread issue among cancer patients, they are often not adequately assessed or treated in routine clinical practice [16]. Improving the diagnosis and management of sleep disorders is essential for better control of insomnia and emotional distress, potentially leading to increased survival rates in breast cancer patients [16]. Insomnia symptoms are highly prevalent among breast cancer survivors, with over 60% reporting issues such as trouble falling asleep, frequent waking during the night, and waking up early in the morning without being able to go back to sleep [23]. Hot flashes rank

among the prevalent adverse effects linked with endocrine therapies and frequently lead to nighttime awakenings. They may coincide with increased heart rate and heightened mental alertness, hindering the ability to go back to sleep. Better management of these symptoms could lead to an increase in the quality of life among breast cancer survivor patients [23].

In terms of psychological management of sleep disorders, there are multiple recommendations proven to increase the quality of life in breast cancer survivors and patients, such as cognitive behavioral therapy for insomnia [24]. Another method to improve sleep quality is physical activity, which can significantly enhance sleep quality, align circadian rhythms, and boost immune function in breast cancer patients. Increased daytime physical activity is associated with better sleep among these individuals [24]. One more method also proven to be effective in treating sleeping disorders in breast cancer patients undergoing endocrine therapy is the long-term administration of Chinese herb decoctions, which has been found to significantly alleviate hot flashes and sleep disorders without notable toxicity or an increased risk of tumor recurrence [25]. Lorazepam and Zolpidem are frequently prescribed in breast cancer patients, but they are not recommended for long-term treatment. These medications are associated with numerous adverse effects, pose a risk of habituation, and may lead to potentially harmful interactions with other medications [24].

IMPACT OF PHYSICAL ACTIVITY ON MENTAL HEALTH IN BREAST CANCER PATIENTS

Breast cancer is one of the most prevalent cancers affecting women globally, representing a significant health burden [26]. Beyond the physical toll of the disease and its treatment, breast cancer patients often experience profound psychological distress, including anxiety, depression, and reduced quality of life [27]. The intersection of physical activity and mental health presents a critical area of study, particularly given the potential of physical activity to mitigate some of these adverse psychological outcomes.

Physical activity is advantageous at any stage of cancer treatment - whether before, during, or after- regardless of the type of cancer and for addressing various cancer-related issues [28]. Research consistently shows that physical activity can have a positive impact on the mental health of breast cancer patients. Higher levels of sedentary behavior are associated with increased fatigue, pain, and depression, especially in survivors who engage in lower levels of physical activity [29]. Various studies have demonstrated that such aspects as anxiety status and quality of life can also be affected by physical activity. For instance, a study conducted on

Korean breast cancer patients that used multiple tests showed a significant correlation between moderate physical activity and the alleviation of depressive symptoms. Patients who engaged in moderate physical activity levels reported lower scores, indicating fewer depressive symptoms, and higher quality of life scores than those with low physical activity levels. Measurements of anxiety levels showed an inverse relationship with moderate physical activity among breast cancer patients. Regarding the intensity of physical activity, a study suggests that moderate amounts, in particular, provide significant psychological benefits without the potential drawbacks associated with high-intensity exercises, such as the increased risk of injury or immune suppression. The study recommends that progressively low-to-moderate levels of physical activity could be applied to create positive effects on mental health state among breast cancer patients [26].

Another supporting data coming from a systematic review and meta-analysis examined the effects of various exercises on mental well-being in women undergoing active treatment for breast cancer. The analysis included data from 57 studies with 6,988 participants, highlighting the beneficial effects of physical activity on several mental health outcomes. The review highlighted that different types of exercise, including aerobic, strength, and combined training, can be beneficial. Aerobic exercises like walking, running, or cycling were particularly effective in improving mental health outcomes. Strength and combined exercise programs (aerobic plus resistance training) also showed positive effects. Moderate to vigorous intensity exercise, performed for at least 150 minutes per week, was associated with the most significant benefits. The analysis revealed that exercise significantly reduces symptoms of anxiety and depression in breast cancer patients. Quality of life, as measured by the Functional Assessment of Cancer Therapy-Breast Cancer (FACT-B) instrument, showed moderate improvements in women who participated in exercise interventions. This enhancement encompassed several domains, including emotional function and overall quality of life. Additionally, the meta-analysis reported small but significant improvements in body image and self-esteem, which is particularly important for breast cancer patients, who often face body image issues related to surgery and treatment side effects [30].

Numerous physical activity programs have struggled to engage breast cancer survivors due to obstacles like overall health problems and limited time. Additionally, women often lack confidence in the positive impact of physical activity on breast cancer outcomes [31]. Consequently, motivating breast cancer survivors to participate in physical activity poses a significant challenge for healthcare professionals. Despite those challenges, medical

personnel should focus on creating supportive environments and providing clear information about the benefits of physical activity to encourage more breast cancer survivors to incorporate exercise into their rehabilitation process.

CONCLUSIONS

The emotional and psychological burden of a breast cancer diagnosis is profound, leading to significant levels of anxiety and depression among patients. The physical changes from mastectomy and chemotherapy, such as loss of breasts and hair, can diminish their sense of femininity, attractiveness, and self-esteem. The psychological burden of breast cancer is influenced by age and marital status, with younger women and those who are single or divorced experiencing higher levels of distress and a more significant decline in quality of life.

This article highlights the need for comprehensive psychological support throughout the various stages of the disease and treatment. It is important to underscore the importance of recognizing and addressing sleep disturbances, which are prevalent among breast cancer patients and can exacerbate other symptoms such as fatigue, pain, and emotional distress.

Effective management of sleep disorders should be an integral part of the treatment plan to improve these patients' overall quality of life. Regular physical activity has been shown to alleviate symptoms of anxiety and depression, enhance sleep quality, and improve overall mental health in breast cancer patients. Encouraging physical activity should be a priority for healthcare providers, as it offers a non-pharmacological approach to mitigating the psychological impact of breast cancer.

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CHILDREN'S DRAWING CREATIVITY AS A TOOL EXPRESSING THE PERCEPTION OF A PERSON WITH MENTAL ILLNESS

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INTRODUCTION

Throughout history, mental illnesses have piqued public interest. The treatment of individuals with mental illnesses has been influenced by the historical era, geographical location, the level of societal advancement, and most importantly, the progress of medicine and psychiatry.

In ancient civilizations, instances of madness attributed to the influence of benevolent spirits were approached with reverence. Meanwhile, those believed to be controlled by malevolent spirits were met with suspicion, fear, and hostility. These individuals were often persecuted and, at times, even killed. Additionally, within Christian culture, it was commonly thought that individuals grappling with mental health issues were possessed by Satan, leading to unjustified accusations, harsh treatment, and cruel punishment. The following centuries did not elevate people with mental illnesses' quality of life. Finally, in the 18th century, Philippe Pinel (1745-1826), a French physician considered to be the founder of modern psychiatry, drew attention to the need for care for the people suffering from described illnesses and, above all, to respect their right to live in freedom and to decide about their fate. He also proposed new methods of therapy. Subsequent changes took place at the turn of the 19th and 20th centuries with the emergence and development of psychiatry as an independent scientific discipline [1]. A milestone in the treatment was the discovery and application of neuroleptics in the 1950s.

Still, despite the development of therapeutic methods and measures allowing for effective treatment of the symptoms of many mental disorders, as well as the increased availability of professional sources of knowledge about mental health issues, including social awareness in this regard, the stigmatization of the people with mental illnesses continues to be a significant problem for most societies.

Although the stigma of people with mental illness has been studied many times in recent years, there are still problems in the clarity of conceptualization and measurement of the stigma of these patients [2]. Most research attention was devoted to stereotypes and discrimination of people with mental illnesses, and the least to mechanisms focusing on the perspective of people with mental illnesses (e.g., experienced, anticipated, or internalized stigma). Mental illness stigma is an obstacle to well-being among people with described illnesses. A great deal of evidence demonstrates that people with mental illnesses experience discrimination in nearly every domain of their lives, including employment and medical care [3-5]. Experiences of stigma are associated with increased symptom severity, decreased treatment seeking, and treatment non-adherence [6,7].

Attempts to assess children's understanding of mental illness in adults and peers have been taken for many years. Fox's research suggested that children's understanding varied according to the specific mental illness diagnosis, social functioning, and emotional response. In addition, the children's attitudes towards mental illness vary when taking into account age [8]. Research by Spitzer and Cameron showed that age was not a significant factor in children's ability to classify deviant behavior; however, there was a sex main effect: Boys were able to identify deviant behaviors better than girls. A developmental trend was noted in children's ability to be aware of what mental illness is, to acknowledge the characteristics of people who are mentally ill, to differentiate between mental illness and mental retardation, to identify various etiologies of mental illness, and to choose appropriate treatment modalities [9]. It also turned out that children's knowledge of their parent's illness affects the perception and understanding of people with mental illness. Children’s knowledge of their parent’s mental illness is considered an important step for them to become aware of their parent’s condition, including how parental illness impacts their life at home, school, and other settings that they frequent. Children feel a sense of nervousness and apprehension when they do not know much about what is happening with their parents, as adults around them do not provide much information. Moreover, they start putting ideas together and making sense of them because adults leave them without information regarding their parent illnesses [10]. On the other hand, parents who want to protect their

children are generally of the view that they should not be given too many details about the state of their guardians' mental illness but should be provided with just enough for them to know that they are not well. Ballal's research showed that the above information was the main type of information given to children by their parents [11]. Results of multiple studies suggest that knowledge regarding parental mental illness is relevant for children to adapt to the impact of parental mental illness [12-15]. On the other hand, children often stigmatize both peers suffering from mental illnesses and those whose caregivers suffer from the above diseases. They usually intimidate, ridicule, or use hurtful words. They also reject and gossip about their peers with mental illness [16]. It is also worth emphasizing that children are a group particularly susceptible to the development of incorrect perceptions. One of the main opinion-forming sources nowadays is the mass media. Wahl's research proves that images and references to mental illnesses are common in media used by children. Moreover, they are rather negative, mainly due to the fact that people with psychiatric disorders are presented as unattractive, violent, and criminal. Furthermore, references to mental illnesses are typically used to disparage and ridicule discussed people [17]

It is a truism to say that children think differently than adults. Lack of sufficient knowledge and experience forces them to think differently about the issues related to adulthood. Antoine de Saint-Exupéry wrote: "*Only children know what they are looking for*". This statement can be related to how they perceive the world around them. Children do not seek the deep meaning of the signs sent to them from the environment. They determine in their own way whether something should be considered good or bad based on the mechanisms encoded and developed in evolution [18,19]. They evaluate directly and very openly what surrounds them through simple emotions such as joy, sadness, fear, and disgust [20]. As a result, their judgment is most in line with reality but often shocking and not necessarily in line with that of adults. As they grow up, the children's view of the world changes. The child gains experience, meets new people, starts to move in the media, and discovers new and unknown issues of life in society. The parents/legal guardians, whose attitudes and behaviour are imitated by "watchful observers of the world", play an extremely important role in growing up [21].

According to the Polish psychologist B. Hornowski, "*Drawing is one of the interesting forms of expression of a child. The drawing shows what the child is thinking and dreaming about […]. The drawing expresses its fantasy and willingness to act"* [22].

Until the end of the 19th century, children's drawings belonged to the areas that were ignored and considered worthless. The interest in the discussed subject increased with the

publication in 1885 by Ebenezer Cooke (1837-1913), a pioneer and reformer of artistic education, of the work entitled "Art Teaching and Child Nature," containing the results of the analysis of children's drawings. At that time, the work had a significant impact on teachers and researchers [23,24].

Currently, no one questions the value of drawing for the proper development of a child, as well as its importance in diagnosing problems and emotional disorders experienced by children. Drawing creativity is more than just an opportunity to shape and improve precise hand movements; a way of spending time and one of the forms of activity for a child. It is fundamental to the perceptual and emotional development of creativity, spatial thinking, and imagination, as well as the formation of social awareness. Through this type of creativity, the child reveals owned personality and expresses himself. Drawing is also a way of distinguishing from the environment some aspects with which the child identifies and organizing them into a meaningful whole [25]. A child's drawings indicate not only the level of intellectual development but are also a projection of the vision of itself and others. The effects of a child's artistic creativity based on their experience are, therefore, a valuable source of knowledge not only about a given child but also a tool of communication used by children, enabling them to learn and explore not only drawing skills but also intellectual abilities, feelings, and thoughts [26].

To understand the message contained in the pictures, it is important to consider them in the context of the child's overall development, taking into account cultural conditions and the process of socialization.

In the concept of the psychologist Lev Semyonovich Vygotsky (1896-1934), the creator of the original theory of the development of the psyche, called by some researchers "*cultural and historical psychology*", culture is of fundamental importance for cognitive development [27,28]. The abovementioned author emphasized that upbringing and education consist of acquiring specific knowledge and developing higher mental functions that determine a child's learning ability. Learning is much easier and more effective if we know how to learn. Hence, *"cultural thinking and creation tools*," i.e., non-verbal and verbal language, are essential to the learning process [29,30]. Education should, therefore, be treated as a support for young people in learning to use tools to create meanings and construct reality to better adapt to the world in which they live and, above all, to initiate an effective process of its modification by their requirements. A person's individual development takes place in interaction with the products of culture and historically shaped traditions that are characteristic of it, relating to the use of

cultural reservoirs of knowledge and skills. Polish scientist A. Męczkowska-Christiansen noticed that culture not only equips man with meanings and symbols with which his mind operates but also co-constitutes the human mind [31].

Throughout life, humans are influenced by countless cultural factors that shape personality, value systems, cultural patterns and norms, and consequently attitudes and behaviour towards other people. From the moment of birth to the end of life, humans internalize social reality, learning patterns of behaviour, including patterns of social roles. This process is called socialization and takes place through spontaneous imitation, identification, upbringing, or conscious personal self-education decisions, and it occurs through interactions with other people.

Polish sociologist Sztompka defined socialization as the process of shaping people's mentality, attitudes, and actions by society [32]. Generally, socialization is understood as human socialization, that is, introducing an individual into the "objective world" of society or some part of it. As a result of this process, individuals are equipped with specific models and patterns of action that allow them to behave following the conventions and norms of this society [33].

Socialization has two stages: primary socialization covers childhood, and secondary socialization occurs in adulthood. In primary socialization, the child is shaped by the social environment. Secondary socialization takes place in the long term and covers adolescence and adulthood. Secondary socialization is largely an individual's work and occurs through interaction with other people.

An important and extremely socially useful element of each culture and socialization process is the historically shaped area of knowledge about health and disease, constituting a complex and multidimensional whole. Understanding and expressing the disease is conditioned by the cognitive abilities of the child at a given stage of development, and these are usually descriptions of specific symptoms, behaviors, or emotions characteristic of a sick person. Since experiences related to health and illness are shared by most people from birth, almost everyone has a certain amount of knowledge about it [34]. Children also have some subjective knowledge in this regard.

AIM OF THE STUDY

The main aim of the study was to find out how people with mental illnesses are perceived by pre-school and primary-level school children. The specific objectives corresponded

with the research questions, which were formulated as follows:

- Is mental illness perceived by children in a biological or psychosocial dimension?
- What is the attitude of the surveyed children towards people with mental illnesses - do the children isolate them (is there a social distance between the mentally ill and the healthy?) and are they afraid of them?
- Does the image of a person with mental illness change with age, and in what direction?

METHODS

The research occurred in two municipal kindergartens and a primary school in one of the cities of the Silesian Province in Poland. All methods used in the study were conducted according to relevant guidelines and regulations. Furthermore, all experimental protocols in the study were approved by the Bioethics Committee of the Medical University of Silesia (KNW/0022/KB/223/17). Kindergartens, primary schools, and children participating in the study were selected randomly.

The headmasters of the educational institutions and teachers from the classes of randomly selected children gave their consent to conduct the study.

The main criterion for inclusion in the study was the children's declared willingness to participate and the fact that they obtained informed consent from their legal guardians.

The study included 140 children aged 5 to 13 years. The mean age was 8.62 years (SD: 2.51 years). During the study, the generally applicable legal provisions in science and respect for the autonomy of the respondents were observed, bearing in mind the fundamental ethical principle of research involving children: the priority of the individual respondent's well-being over the research interest [35,36]. The material presented in the work results from the implementation of one of the stages of a research project devoted to the social image of people with mental illnesses.

The study's introduction involved an interview with each child group, during which the purpose of the study was explained and a few simple questions were asked about the study's subject (Table 1).

Both the obtained answers and the observed interactions between the children and the researcher provided a lot of valuable information on the attitudes of children toward people with mental illness. The data obtained in the first part of the experiment were the subject of another study.

Table 1. Questions were asked to the children during the initial interview before the test.

Questions asked during the initial interview with the children:
Who is an ill person?;
What diseases do you know?;
What does an ill person look like?
Do you know any ill people?;
Who has heard of mental illnesses?;
Who is a person with mental illness? ;
Have you ever seen a person suffering from mental illness?;
Do you know a person living with mental health issues?
Are you afraid of people with mental illness?;
What does a mentally ill person look like?

The drawings were created in the classrooms during educational hours. Following a 10-minute introductory conversation, the remaining 35 minutes of the lesson were dedicated to drawing. The participants were tasked with creating a drawing titled "A Person with Mental Illness." A total of 143 drawings were collected. To analyze all the collected drawings, which were created using various artistic techniques, a proprietary drawing analysis questionnaire was prepared in collaboration with experienced art therapists and child psychologists. Szczepański emphasized that drawing can help determine the causes and conditions determining human behavior, patterns, and personal norms as well as the social and psychological background of their formation [37].

The drawings were grouped into categories determined by specific objectives and subjected to a qualitative analysis based on the proprietary drawing analysis questionnaire, which took into account the following features:

- drawing content - situational context,
- the location of a mentally ill person,
- social environment,
- other elements of the environment,
- the creator's emotionality is expressed by the colours used, the pressure put on the crayon during drawing, the thickness and shape of the line,

It was decided that in the results only the most exciting works of children included in the study will be presented in the order determined by the research questions:

1. The way of expressing the construct of a mental illness and a person with mental illness.
2. Features or behaviours attributed to a person with mental illness.
3. The attitude of the respondents to a person with mental illness.
4. Changes in the perception of mental illnesses and people with mental illnesses conditioned by age.

The researchers provided commentary on each work, which the specialists evaluated. The analysis is based on results from a proprietary drawing analysis questionnaire. The age and biological gender of each author are given at the end of the drawing description in brackets. The authors' identification data on the drawings have been anonymized using black quadrilaterals, which were not part of the original drawings and were not considered during the analysis. Information relating to all analyzed drawings was presented in tables and graphs before the selected works.

RESULTS

General characteristics of the studied group of children

Table 2 presents the characteristics of the studied group of children, taking into account the respondents' sex and place of study.

Table 2. Characteristics of the studied group of children, taking into account the place of study and respondents' sex.

Place of study	Sex	n	%
Kindergarten	Female	19	13,29
	Male	22	15,38
Primary school	Female	55	38,46
	Male	47	32,87

Explanation of abbreviations: n - number of respondents.

Table 3 presents the characteristics of the studied group of children, taking into account the age and gender of the respondents.

The largest part of the study group was children aged 6. Most of the study group were girls, and the highest number of students attended primary school.

Table 3. General characteristics of the studied group of children, taking into account age and gender

Age of the respondents	Sex	n	%
5 years	Female	5	3,57
	Male	8	5,71
6 years	Female	13	9,29
	Male	18	12,86
7 years	Female	3	2,14
	Male	6	4,29
8 years	Female	5	3,57
	Male	7	5,00
9 years	Female	16	11,43
	Male	14	10,00
10 years	Female	2	1,43
	Male	1	0,71
11 years	Female	11	7,86
	Male	8	5,71
12 years	Female	9	6,43
	Male	2	1,43
13 years	Female	8	5,71
	Male	4	2,86

Explanation of abbreviations: n - number of respondents.

The way of expressing the construct of mental disorders/illness and the people with mental illnesses

Table 4 presents the characteristics of the studied group, taking into account the place of presentation of a person with mental illness.

Table 4. Characteristics of the studied group, including the place of presentation of a person With mental illness.

Variables	n	%
Places where a person with mental illness is depicted with no additional people in the drawing:		
House	15	10,49
Forest/Meadow/Park	14	9,79
Hospital/ Hospital room/Closed Unit	11	7,69
City (street, square, police station)	3	2,10
Places where a person with mental illness is depicted with additional people in the drawing:		
House	48	33,57
Forest/Meadow/Park	39	27,27
Hospital/ Hospital room/Closed Unit	7	4,90
School playground/Restaurant/Shop/Church	5	3,50
Other	1	0,70

Explanation of abbreviations**:** n - number of drawings.

Most often, the respondents presented a person with mental illness surrounded by other people in a home environment.

Figure 1. MA’s drawing - 5 years old, biological gender male (own source).

In MA's drawing (Figure 1), the depiction is of a person with a mental illness set against a natural backdrop of trees and a clear, sunny sky. The person is the only human figure in the drawing, and it is difficult to determine their gender. The figure is large compared to the trees and has proportional body features. The attention is drawn to the empty, expressionless eyes, lips twisted in a grimace of sadness or dissatisfaction, and lush, light, curly, or matted short hair. One leg is detached from the ground, and the arms are asymmetrical. The figure is placed among trees, which may indicate social isolation. Darkened hollows are visible on the trees, and in the lower-left corner, an object resembles a burning fire, which can symbolize illegal behavior or aggression. The drawing is multi-colored, dominated by brown, green, blue, yellow, red, and pink. The author of the drawing perceives a person with mental illness as lonely and sad. Mental illness is perceived in a psychosocial dimension.

The artist of Figure 2 depicted three girl characters, one of whom appears to have an intellectual disability, indicated by the speech bubble saying, "I do not know and do not remember." The person on the right side of the picture is smiling somewhat exaggeratedly,

while the others have serious expressions. The proportions of the bodies are accurate, with detailed hands for each character and no visible distance between them. The backdrop of the drawing features a pleasant, sunny sky, green grass, and colorful flowers. The artwork seems to emphasize the psychosocial dimension of mental illness dominates.

Figure 2. SA's drawing - 5 years old, biological gender female (own source).

The person with mental illness presented in CH's drawing (Figure 3) is presented as lonely. The body proportions are respected, but the upper limbs are without hands. The sad and threatening facial expression is enhanced by empty, purple eyes, a pointed nose marked with a clear line, and lips twisted in a grimace of sadness, fear, or dissatisfaction. Most likely, there are various sounds around - a graphic sign of the sound is drawn at the level of the left ear of the depicted character. The legs are coloured different colours, which may be a testimony to this about a certain "character weirdness". The entire drawing is full of chaos and contradictions. Next to the figure, there are trees and coconut palms. Black smoke or steam is puffing out of the hydrant near the character's feet. A rainbow of different colors is visible in the upper left corner. A multi-colored fence (brown-yellow, blue, red, and black) runs along the

bottom edge of the drawing. The fence is not drawn continuously and does not limit the depicted form. Unenclosed free space gives you freedom and the possibility of going out. Soaring, bold, ellipsoidal lines rising upwards are characteristic. Perhaps it is gushing blue water or tropical thickets. On one of them, hovering over the head of the figure, there is an undefined creature of brown-red color. The characteristic blue coastline, parallel to the lower edge of the drawing, probably separates the land from the sea. The world of a sick person is colorful but full of sadness, fear, and chaos.

Figure 3. CH's drawing - 5 years old, biological gender male (own source).

In the foreground, the author of the work (Figure 4) drew a large female figure. The proportions of the body are preserved; the face is cheerful, smiling, eyes wide open, clearly marked black eyelashes, green shadow on the eyelids and blushes on the cheeks, and lush, long brown hair. There are dots on the skin of the face, around the cheeks and nose, and on the skin of the legs, which most likely symbolize freckles or skin eruptions. The woman is wearing a blue skirt and a pink blouse. She is holding an object in her hand and has dropped another oblong, blue one. There is a mess around - loud music flows from the receiver, and the chest drawers on the left are pulled out. A ceiling lamp shines above the woman's head. Another female figure in the background of the drawing also attracts attention, who also has very lush

brown hair but with a slightly different shade than the foreground figure (perhaps these people are related). This character is wearing a green dress. The outlined frown on her lips indicates her dissatisfaction or sadness. It can be assumed that the cause of these emotions is the noise caused by loud music and the clutter in the room. In the upper right corner of the picture is a door with a drawn black key in the lock. However, it is difficult to determine which side of the door the key is on. The person presented by the author of the drawing is not alone, she lives with other people close to her. She is cheerful, but it can be assumed that her behaviour is disturbing and burdensome for the environment. In this case, the mental illness and the person with mental illness are also perceived in the psychosocial dimension

Figure 4. CL's drawing - 6 years old, biological gender female (own source).

The drawing labeled as Figure 5 depicts a person with a mental illness staying at home. The sick person is shown lying in bed, drawn with a black crayon and featuring spiky hair, large black eyes, and dark stubble around the chin, which may indicate aggressive behavior. This

character is the only one in the room. A table with a lamp and a chair is next to the bed. On one perpendicular wall is a TV set, and on the other, there is probably a wardrobe. The ceiling lamp and the walls, painted with a brown crayon, are also clearly marked. The room emanates a sense of sadness and gloominess. In contrast, the surroundings outside the house are depicted as friendly, with a clear and sunny sky, green grass, growing trees, and blooming flowers.

Figure 5. NO's drawing - 9 years old, biological gender male (own source).

In his work (Figure 6), CR drew four characters and described a fragment of a conversation between a boy and his mother. The characters are situated on the path between rows of trees and are proportionate to the elements of the environment. The boy observes the different appearance or unusual behavior of two other people nearby, prompting him to ask his mother: "Why do people behave differently, strangely?" The mother explains to the boy that the person is sick. The boy then learns that we should accept these people as they are and not ridicule them.

Figure 6. CR's drawing - 12 years old, biological gender male (own source).

Features or behaviours attributed to people with mental illnesses.

Table 5 shows the features ascribed to the people with mental illnesses by the surveyed children. Table 6 presents behaviours attributed to people with mental illnesses by children.

Table 5. Characteristics of the studied group, taking into account the features attributed to people with mental illnesses by children based on drawings made by them.

Features attributed to people with mental illnesses by the children	n	%
Being loved/liked by someone	80	55,94
Being vulnerable / in need of care or help/ weak	70	48,95
Being sad	33	23,08
Being lonely / abandoned in sickness	29	20,28
Being confused	28	19,58
Being misunderstood	23	16,08
Being dangerous/ unpredictable	22	15,38
Being aggressive	8	5,59
Being insulted by others	3	2,10

Explanation of abbreviations: n - number of drawings.

In over 50% of the drawings, one could see features related to positive relationships between the drawn people.

Table 6. Characteristics of the studied group, taking into account the behaviour attributed to people with mental illnesses by children based on drawings made by them.

Behaviours attributed to people with mental illness by the surveyed children	n	%
The craving for contact with loved ones	60	41,96
The desire for normality	51	35,66
Embarrassment about one's illness	42	29,37
Inadequate expression of emotions / Difficulty expressing emotions	30	20,98
Dangerous behaviours	23	16,08
Arousing negative feelings	17	11,89
Lying in bed	16	11,19
Shouting inadequate words	10	6,99
Consoling one's loved ones	10	6,99

Explanation of abbreviations: n - number of drawings.

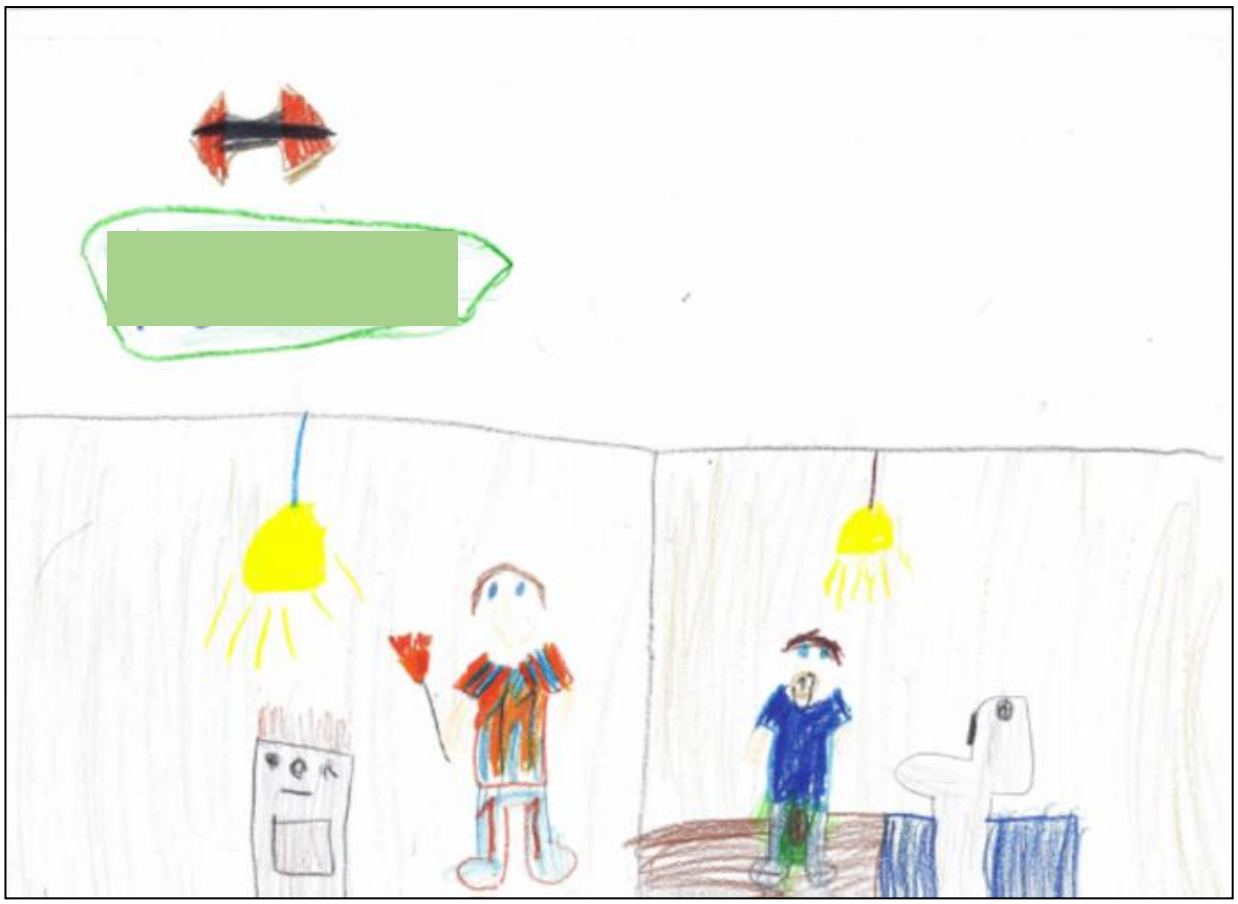

Figure 7. KU's drawing - 5 years old, biological gender male (own source).

Over 40% of the surveyed children presented in their drawings the desire for contact of mentally ill patients with their relatives, and only 10 of the surveyed referred in their drawings to the patient's comfort from the family.

KU's work (Figure 7) presents two scenes from the life of a person with mental illness or a person with an intellectual disability. The first cutscene takes place in the kitchen, but apart from a stove with flaming burners and a glowing ceiling lamp, no other kitchen utensils are visible. The depicted figure is smiling, body proportions are preserved, and clothes are complete and colourful. The boy is holding a burning torch in his hand. The second cutscene is located in the toilet. The boy is most likely contaminated with feces or is unable to use the toilet. He is terrified. Both the first and the second scenes depict illegal or undesirable behaviour. In the author's opinion, a person with a mental illness/intellectual disability misbehaves (it is unpredictable; it may be dangerous).

Figure 8. PE's. drawing - 6 years old, biological gender male (own source).

The scene in PE's drawing (Figure 8) occurs inside a house. The building's walls, roof, chimney, and window are marked. One of the characters, most likely a man, is shown destroying the equipment on a table with a hammer or an axe. His expression is hateful, and large teeth are visible in his open mouth. The face on the character's T-shirt is equally terrifying.

Next to the man, a girl with long blonde hair appears to be trying to stop him. The arrangement of her lips suggests a scream, and the word "No" is written in a speech bubble. In the window on the right side of the building, someone can be seen covering their mouth with their hands, likely trying to suppress a scream or cry. The window has curtains pinned on the sides. Another figure is visible on the roof of the building – a girl who seems to have escaped there in an attempt to hide from the aggressor. A large bird is approaching her, which could potentially save her and move her to a safe place. The body proportions of the figures shown are preserved. The dominant color of the work is blue, which symbolizes peace and tranquility and, in extreme cases, passivity and resignation. A notable feature of the drawing is the element of fantasy in the form of a large bird coming to assist.

The attitude of the respondents toward people with mental illnesses.

Figure 9 presents the characteristics of the studied group, taking into account positive or negative attitudes towards people with mental illnesses, based on the presentation in the figures by the surveyed children.

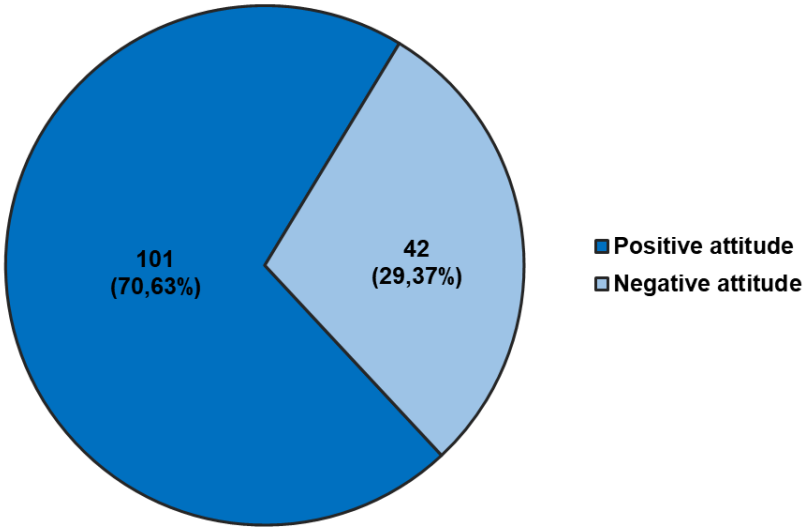

Figure 9. Characteristics of the studied group, taking into account the positive or negative attitude towards people with mental illnesses based on their presentation in the drawings by the examined children.

Most of the respondents presented in their drawings a positive attitude towards people with mental illnesses.

The drawing has two figures: a girl and a boy. Based on his facial expression and open hands, the boy appears to be trying to communicate something or is perhaps afraid of

something. The proportions of their bodies are drawn accurately, and the details of the girl's outfit, such as her handbag, colorful skirt, and bow belt, are particularly well-executed. The girl is holding the boy's hand, and a fire is burning next to the boy. The overall environment appears friendly, and it seems like the girl wants to bring the boy into her joyful world filled with flowers, butterflies, sun, and greenery. The boy says, "I haven't eaten my dinner." This may suggest that the artist understands the importance of meeting basic human needs, such as providing food, as failure to do so can have serious health consequences. The drawing uses many colors, with blue being the dominant color.

Figure 10. LE's. drawing - 5 years old, biological gender female (own source)

OL has drawn a room (Figure 11) depicting a sick person lying in bed. Next to the bed, another figure has set up a meal on the table with two plates and two tablespoons. Both characters are cheerful and smiling. There are slippers on the floor at the foot of the bed. On a nearby small table, there is a bedside lamp providing light and a sense of security, along with a box of handkerchiefs for cleaning the nose or wiping tears caused by illness, pain, or sadness. The author placed a large table and a chair in the center of the room. The walls are painted with a pink crayon, and the floor and bedding covering the sick person are blue. According to OL,

when someone is sick, it's important to take care of them, ensure peace, safety, and warmth with slippers and bedcovers, and serve meals.

Figure 11. OL's drawing - 7 years old, biological gender female (own source)

Age-related changes in the perception of mental disorders/diseases and people with mental illnesses

Table 7 presents the characteristics of the study group, taking into account the changes in the perception of mental illnesses and people with mental illnesses with the increasing age of the respondents.

IN's work (**Figure 12**) is made using the cut-out/lined-up method. It concerns alcohol addiction. The author presented two figures - an adult, a disabled man sitting in a wheelchair, and a little girl. On the table where the man is sitting is a bowl with a meal and a bottle. It can be assumed that the man has a problem with accepting his disability, and with the help of stimulants - alcohol and cigarettes (visible in the bubble) he tries to deal with it. The girl - a person most likely close to the man, tries to take care of him and support him in the fight against addiction, showing other methods of dealing with a difficult situation. The black background of the work additionally deepens the drama of the presented situation.

Table 7. Characteristics of the study group, including age-related changes in the perception of mental disorders/diseases and people with mental illnesses

As the age of the examined children increased, the following topics/changes were observed in the works:
Inclusion of addictions in the area of mental diseases
Showing the specific behaviour of people affected by various mental diseases e.g, autism
Noticing the religious needs of people with mental illnesses and their carers
Noticing the different behaviour of people with mental illnesses from the general public
Noticing unusual reactions of the environment to the behaviour/words of people with mental illnesses
Noticing the difference between mental and physical illness
Noticing the need to integrate people with mental illnesses with the rest of society

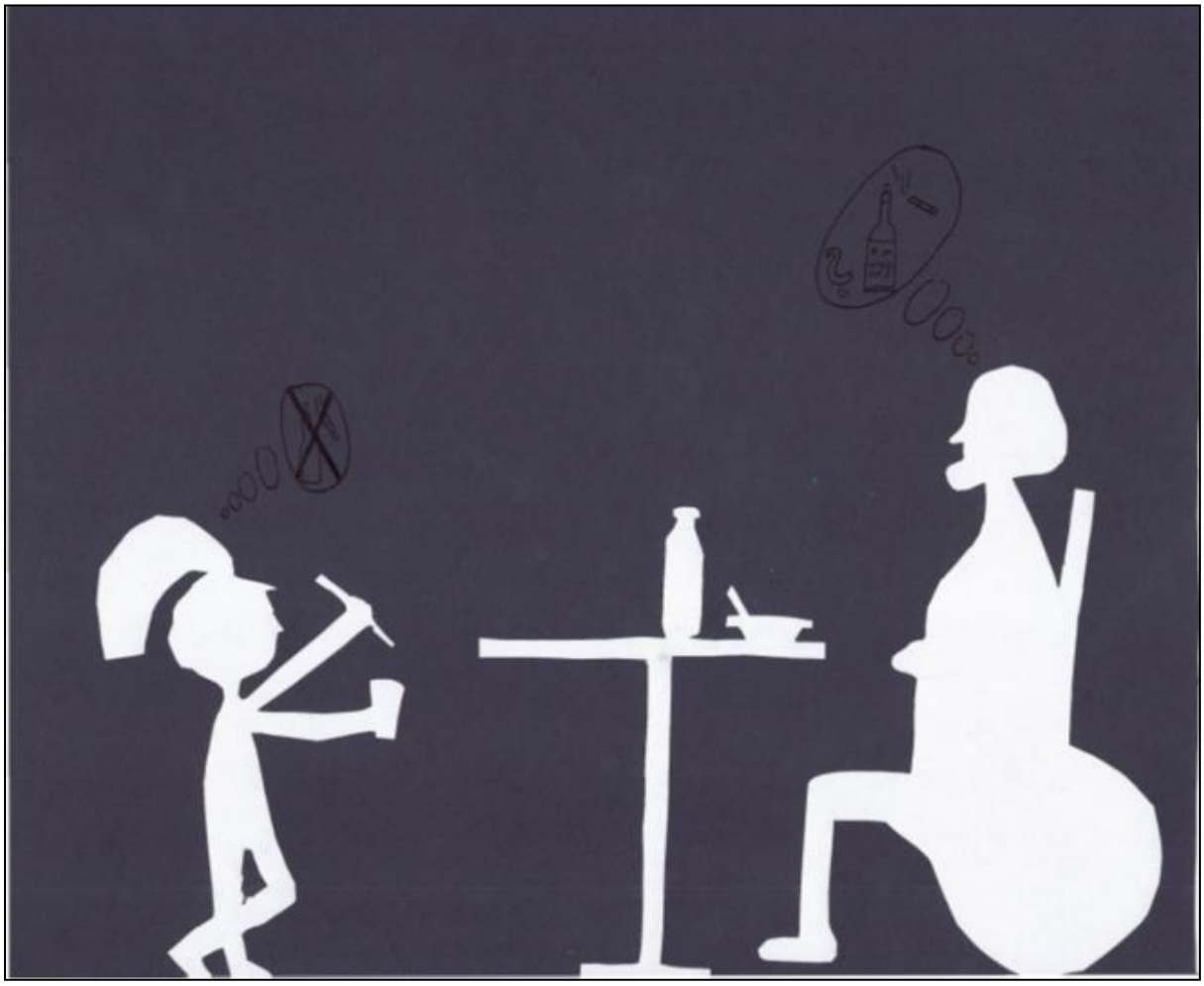

Figure 12. IN's drawing - 11 years old, biological gender female (own source).

BA's work (Figure 13) is presented as a comic book and depicts the story of a family with a child who has autism (a mental disorder related to developmental age). The child, Adrian,

exhibits specific behaviors and lives in a world filled with fear and anxiety. The comic portrays the family's compassionate support for Adrian maturely and empathetically, showing natural interactions such as the father spending time with Adrian outdoors and playing football. The author may have personal experience with this topic based on their immediate surroundings.

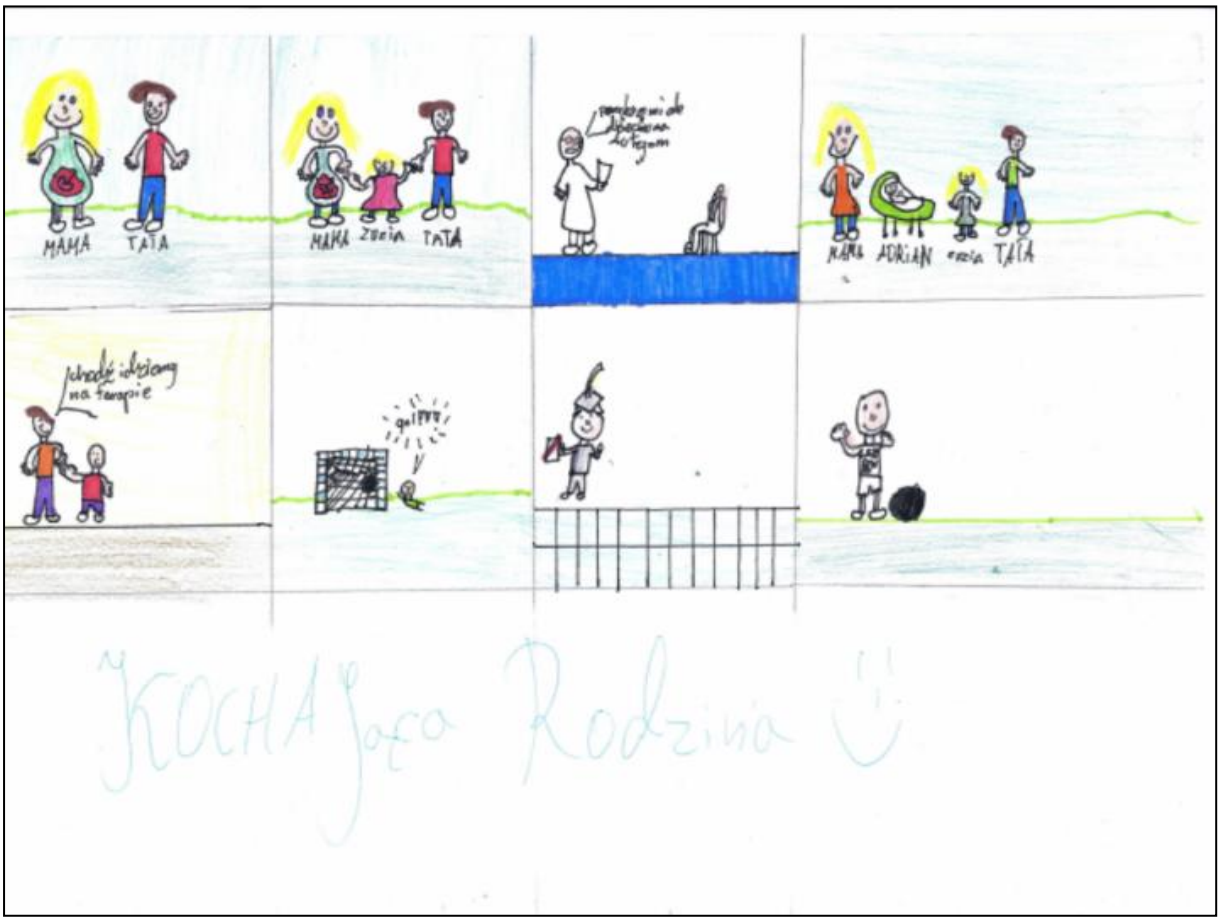

Figure 13. BA's drawing - 12 years old, biological gender female (own source)**.**

DISCUSSION

The Mental Health Protection Act, which has been enforced in Poland since 1995, recognizes that "mental health is a fundamental personal good, and the protection of the rights of people with mental disorders is the responsibility of the state." The legislation also stresses the importance of "promoting appropriate social attitudes towards people with mental health disorders, particularly understanding, tolerance, kindness, and preventing their discrimination" [38].

However, despite these efforts, mental illnesses continue to elicit strong negative emotions and are still considered a classic example of stigma, despite many actions taken to

debunk such stereotypes [39, 40].

The Polish Public Opinion Research Centre has announced that one-third of adult Poles are concerned about their mental health and lack sufficient knowledge about it. The percentage of people having personal contact with individuals suffering from mental health issues has also increased in recent years, leading to a higher demand for psychiatric help [41]. The data from the announcement revealed that mental illnesses are often regarded as embarrassing and should be kept hidden, with 73% of respondents sharing this view. In comparison, only 23% held the opposite opinion. It's important to note that most respondents chose the "rather" option. Still, the percentage of those who considered mental illnesses shameful was over six times higher than those who did not. This belief was prevalent across all socio-demographic groups. At the same time, it was observed that respondents with higher education, city inhabitants, and people who had contact with the mentally ill personally or through the media (literature, film) were more convinced about the shame of mental illness compared to those who had no contact with them. The authors of the announcement commented that the respondents who came into contact with people with mental illness were more aware of their stigmatization in everyday social life and, therefore, were more likely to include them in the category of embarrassing and hidden diseases. It is also worth noting that almost two-thirds of the respondents - 65% declared a friendly attitude towards the society above members, including over half -52% marked their attitude as "rather kind". Only a few admitted to being reluctant - 5%, and more than a quarter - 26% - to indifference. Despite the low percentage of people expressing aversion to people living with mental issues, for many years, the authors of various studies have confirmed the persistence of negative attitudes toward the environment towards the mentally ill not only in Poland but also in the world [42-45]. Research also confirms the importance of both the cognitive and motivational spheres in the process of shaping attitudes towards people with mental disorders [46].

Previous research used content analysis of children's drawings to understand various topics, such as children's perceptions of the transition to school from kindergarten, their understanding of elephants and human-elephant interactions, and their perceptions of World Heritage Sites [47-49]. These studies show how analyzing children's drawings can be used to learn their opinions and thoughts in different contexts. However, in the literature available to the authors of this article, no studies have been found that use content analysis of children's drawings to explore their opinions on the subject of mental disorders and people with mental illnesses.

The analysis of the collected drawings shows that children perceive mental illness in its psychosocial dimension. People with mental illnesses were presented as sad, lonely, and unable to meet their basic life needs. Most often, specific behaviours were attributed to them. Some of the aforementioned behaviors can be classified as reprehensible, socially undesirable, and even dangerous, such as burning fire, aggression, and destruction of objects. The authors of some works highlighted differences in appearance - spiky or matted hair, mouth open in an angry grimace showing teeth, or different clothes (e.g., two different trousers legs). People with mental illnesses were most often presented in a specific social environment, among other people, or against the background of the world around them - most often nature. No marginalization or stigmatization of people with mental illnesses has been observed. Only a few authors drew people with mental illnesses staying in bed in a room of a residential house where there were no other people. While the colors used to color the walls looked depressing, the outside environment was cheerful. A few of the children drew the people with mental illnesses staying in the hospital ward. The authors of many works dealt with helping the sick by holding their hands, caring for them, and explaining differences in behaviour. It was observed that older children more often perceived the complexity of mental health problems, including alcohol and tobacco addiction. In two drawings, the figures presented were physically disabled (one in a wheelchair, the other without one leg). Still, it is difficult to conclude on this basis that the children covered by the study did not distinguish between bodily and mental illness. Most likely, these children noticed some differences in the behaviour of people with disabilities or unusual reactions to the environment in contact with them. The oldest students included in the study attempted to define mental disorders, stressing that the phrase "mentally ill" is not synonymous with "somatically ill". They expressed their feelings and observations in the form of "speech bubbles" at the heads of the figures or descriptions found on the backs of many works. These descriptions were in the form of short opinions and concerned the need to integrate people with mental illnesses with healthy people.

Research by Spitzer et al. conducted among school-age children concerning the perception of mental illness showed that age was not a significant factor in children's ability to classify deviant behaviour. However, there was a sex-main effect: boys were able to better identify deviant behaviours than girls. Mentioned researchers also proved that cognitive development contributes to an increase in the child's ability to respond to what mental illness is, to acknowledge the characteristics of people who are mentally ill, to differentiate between mental illness and mental retardation, and to identify various etiologies of mental illness what

was also observed during drawing analysis [50].

Research by Mouratidi et al. conducted in 347 children aged 5–11 years showed that "health" is mainly perceived based on defining psychosocial elements or specific lifestyle activities regardless of age. The abovementioned researchers also found that children's ability to understand health as a complex and multifaceted situation seems to develop with age. They noticed that older children increased the number of different aspects of health presented in their drawings, which indicates an increasingly holistic way of understanding health and probably reflects cognitive development, which is consistent with the results of the analysis of the drawings conducted by the authors of this article [51].

In the study's limitations, one cannot fail to mention the small group of examined children and the influence of the surrounding environment. Both schools and kindergartens are institutional spaces. This condition could have influenced what the children revealed in their drawings. Additionally, the children approached drawing in classes in different ways. Researchers were often forced to repeat a given topic of work to children. Several expressed disappointment with their drawing skills. Finally, it has to be clearly stated that the authors have not found any standardized method to evaluate the content of the drawings, so as mentioned above, during the process of drawings assessment, their analysis with the use of a questionnaire and conclusions-making authors relied on knowledge and experience of aforementioned specialists and available literature concerning discussed topics [52-57]. Despite some limitations, children's drawing data was a rich source of information and opinions about the mentally ill. Future research should cover issues related to a better understanding of children's opinions about people with mental illnesses and attempt to standardize the evaluation questionnaires for children's drawings.

CONCLUSIONS

Previous research has used content analysis of children's drawings to understand various topics. For example, researchers have examined children's perceptions of the transition to school from kindergarten, their understanding of elephants and human-elephant interactions, and their perceptions of World Heritage Sites [47-49].

These studies demonstrate how analyzing children's drawings can be used to understand their opinions and thoughts in different contexts. Despite this, the authors of this article have not found any studies that use content analysis of children's drawings to explore their opinions on the subject of mental disorders and people with mental illnesses.

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THE RELATIONSHIP BETWEEN MENTAL HEALTH AND IRRITABLE BOWEL SYNDROME (IBS)

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INTRODUCTION

Irritable bowel symptoms (IBS), a functional disorder of the gastrointestinal tract, remain a challenge for modern medicine. IBS is a common disease globally, with prevalence ranges between 1.1 and 45% worldwide. The problem affects women more often than men, and they are the ones who visit the doctor more likely because of bothersome symptoms [1,2]. The diagnosis of IBS is based on the 2016 Rome IV criteria. IBS is currently defined as recurrent abdominal pain, occurring at least one day a week in the last three months, accompanied by 2 of the three criteria:

1) related to defecation
2) associated with a change in the frequency of bowel movements
3) associated with a change in the form (appearance) of stools.

Currently, using the Bristol scale and the Rome criteria, we identify the following subtypes of IBS:

- IBS-C—IBS with predominant constipation;
- IBS-D—IBS with predominant diarrhea;
- IBS-M—IBS with mixed bowel habits;
- IBS-U- unclassified IBS [3,4].

The majority of people with IBS are also struggling with mental health disorders. People with IBS have a three times higher risk of anxiety and depression than healthy individuals. Based on genetic studies, we know that there is a shared genetic predisposition to IBS and emotional instability disorders and that they have common pathophysiological mechanisms [1,5].

BRAIN-GUT-MICROBIOME INTERACTIONS

The cause of IBS is not known, but thanks to a wide range of research, doctors and scientists have put forward several factors to explain the simultaneous occurrence of mental and

intestinal disorders in IBS. Thus, a comprehensive disease model of brain-gut-microbiome interactions has been developed [1].

Gut: As we mentioned earlier, some genetic disorders explain the simultaneous occurrence of psychological symptoms (such as anxiety and lowering of mood) and intestinal disorders characteristic of IBS. Recent studies of the IBS patient's genome have shown that the *CADM2 gene*, which is responsible for forming members of synaptic cell adhesion molecules (SynCAMs), shows variable expression in the ENS (Enteric nervous system). This protein is essential for proper communication between glia and neurons. Poor communication between these cells can lead to abnormal ENS circuits in IBS. Interestingly, abnormal *CADM2* expression also occurs in individuals with psychological and neurological traits (risk-taking behavior, nervousness-like traits, and neurodevelopmental disorders - e.g, intellectual disability and autism spectrum disorder) [1].

Microbiome: The intestines are populated by a wide variety of microbial organisms. It is worth emphasizing that the microbiome influences endocrine, neural, and immune pathways. Despite many studies, the specific microbe responsible for the symptoms seen in IBS has not been discovered. However, stress affects the abundance of gut microbes, both indirectly by altering the secretion of substances into the gut and through the direct effect of norepinephrine on the microbiome. There are interesting results of studies which involved transplanting stool samples from depressed and healthy individuals into mice. The first group of organisms developed inflammation and anxiety, while the second group of organisms continued to function normally. This information suggests that in patients suffering from IBS, a disruption of the microbiome may be involved in the development of certain symptoms [1, 5].

Brain: More and more research is showing the involvement of the central nervous system (CNS) in the development and continuation of symptoms found in IBS. Pharmacological therapies targeting the central nervous system, as well as cognitive behavioral therapies, show the best efficacy in the treatment of IBS. Several types of networks have been identified in the human nervous system that are responsible for proper functioning in the environment. It has been shown that IBS patients have a disruption in regions and networks linked to salience detection, emotional arousal, central autonomic control, central executive control and sensorimotor processing. One of the networks in which disruption occurs is the DMN - the default mode network. The network is deactivated when focusing on sensory triggers, and it is activated when a person's thoughts are unrelated to the sensory environment. Neuroimaging of IBS patients indicates reduced activity of the DMN network in their nervous

system. A similar situation occurs in patients who suffer from chronic pain [1, 5].

SYMPTOMS

The primary symptom occurring in IBS is abdominal pain. It is the most important one since, without it, we are not able to diagnose IBS based on the Rome IV Criteria [7]. Previous criteria included the term discomfort, but due to the non-specificity of this term, as well as the different meanings of the word in different languages, it was replaced by the word pain [3]. It is worth mentioning that pain in the IBS is related to defecation. Meaning that after defecation, abdominal pain may improve but may also worsen [7].

Symptoms that may occur in IBS are diarrhea or constipation. Depending on the frequency of diarrhea or constipation, IBS can be divided into different types according to Rome IV Criteria [3]. Abdominal distension and abdominal bloating are other symptoms that the Rome IV Criteria do not consider but which occur with significant frequency in patients suffering from IBS [7]. Very often, as mentioned earlier, anxiety or depressive disorders may be present together with IBS, which should be kept in mind [1].

TREATMENT

Effective treatment for IBS is based on strong patient cooperation. Patients have to be well-informed about their condition and should be educated on the factors that can positively or negatively influence their gut health. The second important aspect of this syndrome is a diet rich in fiber and a low-FODMAP diet, which reduces the consumption of fermentable carbohydrates [9]. Even more significant is regular exercise. Yoga tends to reduce the severity of IBS and its symptoms, and walking minimizes digestive system symptoms and anxiety [10].

A huge impact on IBS can also have psychotherapy, especially CBT. Stress management is a crucial aspect of IBS symptoms manifestation.

Pharmacological treatment contains antidiarrheals like loperamide, which effectively reduces stool frequency and increases stool consistency; however, it does not alleviate abdominal discomfort and actually increases nocturnal pain [9].

Probiotics are known for their good benefits, such as minimizing gastrointestinal symptoms and reducing pain and flatulence. In the diarrhoeal form of IBS, it is recommended to use antibiotics like rifaximin for two weeks, which notably reduces bloating, abdominal pain, and stool texture. Nevertheless, in the IBS with constipation, it is recommended to use antispasmodic, which indicates patient improvement, especially in abdominal discomfort.

Over-the-counter laxatives are good for controlling constipation but do not relieve the pain. However selective C-2 chloride channel activators have an influence on both. Undoubtedly, the usage of antidepressants significantly enhanced patients' comfort. The benefits of these drugs are reduced symptoms and pain. Antidepressants help to deal with stress which strongly affects severity of IBS. Close collaboration with doctors is necessary for patients with IBS to devise a customized treatment that addresses their requirements. Furthermore, making lifestyle changes such as sticking to regular meal times, staying well-hydrated, and prioritizing sufficient sleep is also essential for the well-being of patients [6,9].

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of IBS requires a multidisciplinary approach to ensure accurate diagnosis and treatment. The most important thing is to exclude other causes of diarrhea or constipation, such as inflammatory bowel disease, celiac disease, or lactose intolerance. To diagnose IBS, evaluation includes a complete history and physical examination, laboratory tests, or colonoscopy. If alarm symptoms occur, it should be considered an organic disease [8,9].

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PANDEMIC OF DEPRESSION - A PROBLEM OF THE MODERN WORLD

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INTRODUCTION

Mental illnesses are a significant issue in today's world. The most insidious, often unnoticed, and underestimated disease is depression. It significantly impacts daily functioning and life satisfaction for many people worldwide [1]. Data published by the World Health Organization (WHO) shows an increasing trend in the incidence of this disease. Research conducted in 2021 indicates that about 5% of people over the age of 18 struggle with depression. Moreover, a significant increase has been observed over the past two decades [2].

Many factors contribute to depression, which can be divided into biological, psychological, and social categories. Genetics plays a crucial role, with abnormalities in neurotransmitter functioning and hormonal imbalances being key [3, 4]. Psychologically, childhood experiences, stressful situations, and personality traits significantly contribute to depression [5]. Social factors, such as the pace of life, pursuit of perfection, and professional pressure, also worsen mental health.

In recent years, social isolation due to the COVID-19 pandemic has played a significant role. High stress, uncertain situations, fear of illness, and confinement have significantly deteriorated many people's health [6].

Overcoming depression is a significant challenge for both the patient and the doctor. It requires an integrated approach, including pharmacology and psychotherapy. Support from loved ones is also crucial. Often underrated and ignored are the issues of healthy eating and physical activity, which should not be overlooked [7, 8].

BIOLOGICAL FACTORS

Biological factors play a crucial role in the predisposition and course of depression. Scientific research places particular value on genetics, neurobiological mechanisms, and

neurotransmitter interactions. Many studies show that mental health problems can be hereditary. Research conducted among twins and families indicates that people with a family history of depression are more at risk of developing it. Specific gene variants, especially those related to serotonin regulation, are conditions that increase the risk of developing depression [9].

The imaging of certain brain structures and functions, which differ in depressed individuals compared to healthy ones, plays a crucial role. These differences are located in the hippocampus, amygdala, and prefrontal cortex, areas responsible for emotions, mood regulation, and cognitive functions. Prolonged severe stress can cause changes in these areas, leading to depressive disorders [10].

Neurotransmitters such as serotonin, norepinephrine, and dopamine act as mood regulators. Serotonin plays the most crucial role in mood regulation. Hence, it's called the "happiness hormone." It is also a precursor for melatonin, a hormone regulating the sleep-wake cycle. Norepinephrine, also known as norepinephrine, is a neurotransmitter responsible for attention, alertness, and stress response regulation. Disturbances in this system manifest as apathy and a decrease in energy. Dopamine is responsible for the brain's reward system and motivation, and its deficiency manifests as anhedonia [9].

The hypothalamic-pituitary-adrenal (HPA) axis controls the body's stress response. In depressed individuals, this axis is disturbed, resulting in increased secretion of corticotropin-releasing hormone (CRH), which stimulates the pituitary gland to release adrenocorticotropic hormone (ACTH). ACTH, in turn, stimulates the adrenal glands to produce cortisol. High cortisol levels can lead to neurotoxicity, damaging the hippocampus and other brain areas responsible for mood. Additionally, HPA axis dysfunction can affect neurotransmitters like serotonin and dopamine, further worsening the clinical picture of depression [11,12].

SOCIAL FACTORS

The 21st century imposes many demands on individuals. Rapidly changing culture, high emphasis on self-development, and unlimited access to well-developed social media significantly impact the increase in depression rates. The contemporary lifestyle is characterized by a high level of stress both personally and professionally. High expectations, the pursuit of perfection, intense competition, and pressure lead to chronic stress, one of the main risk factors for developing depression [13].

Urbanization, characterized by high population density, environmental pollution, and

noise, can affect the mental health of city residents. Studies show that people living in cities have a higher risk of developing depression compared to rural residents. Factors such as limited contact with nature, lack of social support, and higher levels of environmental stress may contribute to this phenomenon. There is evidence that city living may increase stress susceptibility and impact mental health [14,15].

SOCIAL AND PROFESSIONAL PRESSURE

Contemporary culture often promotes high social and professional expectations, leading to pressure for achievement and success. Social media further reinforces these expectations by presenting idealized images of life and success, which can lead to feelings of inadequacy and low self-esteem. High social and professional pressure can lead to burnout, which is strongly associated with depressive symptoms. Social tensions, competition, and a lack of work-life balance can also affect mental health [16].

PSYCHOLOGICAL FACTORS

Personality predispositions to depression play a significant role in the etiology of this disease, indicating a complex interaction between personality traits and the risk of developing depressive disorders. Empirical research indicates that certain personality traits can increase vulnerability to depression by influencing emotion regulation mechanisms and stress responses.

One of the key personality factors is neuroticism, characterized by high levels of anxiety, a tendency toward negative thinking, and a propensity to experience stress easily. Individuals with high levels of neuroticism show increased sensitivity to life stressors, leading to more frequent and intense depressive symptoms. Another important aspect is low extraversion, which is a tendency toward introversion. People with low extroversion have less intense social contact and are less likely to seek social support, increasing the risk of isolation and deepening depression symptoms. Additionally, traits such as perfectionism and self-criticism have also been linked to a higher risk of depression, as they can lead to chronic dissatisfaction with oneself and feelings of inadequacy.

Another crucial factor is the coping style with stress. Individuals prone to rumination, i.e, repetitive, negative thinking about their problems and failures, are more likely to develop depression. Rumination can prolong and intensify negative emotions, hindering adaptive coping with difficult life situations. Furthermore, individuals with a high susceptibility to early trauma or chronic stress in childhood show a higher risk of developing depression later in life. Early

experiences can shape negative thinking patterns and disrupt emotion regulation mechanisms, which, combined with certain personality traits, increase vulnerability to depression.

In summary, personality predispositions to depression include high levels of neuroticism, low levels of extraversion, perfectionism, self-criticism, a tendency toward rumination, and negative early life experiences. Understanding these predispositions is crucial for developing effective preventive and therapeutic strategies for treating depression [17].

TRAUMAS, LIFE STRESSORS, AND ADJUSTMENT DISORDERS

Traumas, life stressors, and adjustment disorders play a key role in the etiology of depression, influencing its development and course through complex interactions between psychological, biological, and social factors. Traumatic experiences, especially those experienced in childhood, such as abuse, neglect, violence, or other forms of trauma, significantly increase the risk of depressive disorders in adulthood.

The mechanisms through which trauma influences the development of depression include persistent changes in the functioning of the hypothalamic-pituitary-adrenal (HPA) axis, dysregulation of the stress system, and changes in the structure and function of the brain, particularly in areas related to emotion regulation and stress, such as the hippocampus and amygdala. Life stressors, such as the loss of a loved one, divorce, job loss, financial problems, or serious illnesses, are strongly associated with depression. The response to life stressors is individualized and depends on many factors, including personality, previous experiences, and the availability of social support. Chronic stress can lead to the depletion of the individual's adaptive resources, resulting in increased vulnerability to depressive symptoms. Prolonged exposure to stress also affects neurobiological mechanisms related to mood regulation, such as neurotransmitters (serotonin, dopamine, norepinephrine) and synaptic plasticity. Adjustment disorders, defined as inadequate emotional and behavioral responses to identifiable stressors, also contribute to the development of depression. Individuals with adjustment disorders show difficulties in adapting to life changes, leading to chronic stress, anxiety, and depressive symptoms. Key symptoms of adjustment disorders, such as feelings of helplessness, powerlessness, and chronic tension, can evolve into full-blown depression, especially when stressors are prolonged or when the person lacks appropriate coping mechanisms [18].

PHARMACOTHERAPY

Pharmacological treatment of depression focuses on traditional medications and alter-

native methods aimed at improving treatment outcomes and accelerating therapy effects. The first-choice drugs are selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). These pharmacotherapies combat depression by increasing the levels of neurotransmitters in the brain synapses, resulting in improved patient mood [19].

Recent years have seen the discovery of new-generation drugs with faster and more effective action. One such drug is ketamine, used as an NMDA receptor antagonist. It shows rapid antidepressant effects, making it a good solution for patients with treatment-resistant depression. Combined therapy, which includes atypical antipsychotics with SSRIs or SNRIs, also yields good results [20]. New research also indicates a correlation between gut microbiota and mental health. Probiotics, prebiotics, and synbiotics can positively impact mood, especially in its early stages. Probiotics can affect the hypothalamic-pituitary-adrenal (HPA) axis, which plays a crucial role in the body's stress response. Normalizing HPA axis function through probiotics can reduce chronic stress and improve mood [21].

PSYCHOTHERAPY

Psychotherapy is an integral part of the fight against depression. In many cases, it is the only therapeutic method. Depending on the cause, different therapy techniques are used. We distinguish between cognitive-behavioral therapy (CBT), psychodynamic therapy, and interpersonal therapy (IPT). CBT focuses on changing the way of thinking, behavior patterns, and perceptions of the world that are responsible for mood drops and the patient's poor mental state [22, 23]. Psychodynamic therapy operates under a different scheme. Its goal is to uncover unconscious thought processes and understand how they affect the patient's psyche. The treatment's intended effect is to resolve emotional conflicts [24,25].

Interpersonal therapy is a short-term form of therapy where the therapist focuses on the patient's relationships with loved ones, turning points in the patient's life, past traumas, and the analysis of social roles [26]. The effectiveness of the discussed therapies may vary depending on the individual characteristics of the patient, the type of depression, and the therapist-patient relationship. Therefore, an individualized approach to each case is crucial.

THE ROLE OF PHYSICAL EXERCISE, DIET, AND SUPPLEMENTATION

It is common knowledge that a healthy lifestyle correlates with good health, but it is often overlooked that this also applies to mental health. Physical activity, a healthy diet, and

supplementation play an integral role in both the prevention and treatment of depression. Studies have shown that regular physical activity alleviates symptoms of depression. The mechanism of this process involves the release of endorphins and serotonin, improved brain neuroplasticity, and the reduction of oxidative stress [27].

A healthy diet is fundamental to the proper functioning of the body. Antioxidants play a crucial role in neutralizing the effects of free radicals, thereby eliminating oxidative stress. Therefore, it is important to consume vegetables and fruits rich in vitamins C and E, legumes, and whole grain products. An appropriate amount of healthy fatty acids found in fatty sea fish, nuts, and seeds is also important. These products help reduce inflammation and regulate neurotransmitter activity [28].

Supplementation with micronutrients can compensate for dietary deficiencies, especially in cases of significant nutrient deficits that affect proper brain function. The table presents a detailed breakdown [29].

Table 1. Dietary Supplements and significance [22,28,29].

DIETARY SUPPLEMENT	SUPPLEMENT SIGNIFICANCE
Omega-3 fatty acids	Anti-inflammatory and neuroprotective effects
Vitamin D	Low levels of vitamin D - higher risk of depression, supplementation especially recommended during winter periods
B vitamins	Vitamin B12 and folates (vitamin B9); deficiencies can lead to mood disorders and fatigue
Magnesium	Regulates brain function and the nervous system
Folic acid (folates)	Enhances the effectiveness of depression treatment
L-theanine	Relaxing and anti-stress properties
Green tea extract	Polyphenols - antioxidant effects, regulation of neurotransmitters

CONCLUSION

Depression is one of the most significant and prevalent mental health problems in the modern world. Despite the growing awareness of the disease and the increasing availability of treatment methods, many individuals still do not receive adequate help. Biological, psychological, and social factors contribute to the development of depression, influencing its course and prognosis. It is crucial to understand the complex nature of depression and the

necessity for an individualized approach to treatment. This approach should encompass both pharmacological and psychotherapeutic methods and lifestyle changes, including diet and physical activity. Effective treatment of depression requires interdisciplinary cooperation among various specialists and adequate support from family and loved ones. Future research should focus on identifying new, effective methods for preventing and treating depression to improve the quality of life for individuals suffering from this disease.

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PSYCHOTIC DISORDERS IN PATIENTS WITH EPILEPSY

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INTRODUCTION

Epilepsy is one of the major neurological problems, affecting around 45,9 million people worldwide, with age-standardised prevalence at 621,5 per 100,000 [1].

In the general population, 24 million people can have active epilepsy, either experiencing seizures or being on anticonvulsive medication. Despite recurrent seizures, which are distinctive symptoms of this illness, epilepsy can be connected to other conditions, such as mental disorders, including affective, psychotic, personality, anxiety, and conduct disorders. This correlation is bilateral: patients with epilepsy are at greater risk of developing mental disorders, and in psychiatric patients, epilepsy is also more likely to be diagnosed than in the general population [2]. There are many possible explanations for this phenomenon, as both epilepsy and mental disorders are manifestations of improper function of bioelectrical brain activity and neurotransmitters [3].

Epilepsy can also affect the social functioning of a patient. Stigmatization, cognitive impairment, and altered interpersonal relations can contribute to greater psychological distress and mental disorder pathogenesis. One of the most depleting conditions, which can occur in epilepsy is psychosis, a state characterised by delusions and hallucinations. In patients with epilepsy, psychosis occurs 7,8 times more frequently than in the general population, especially when epilepsy is a result of structural brain damage, such as trauma. Even though abnormalities in mesial temporal structures are connected to the greatest risk of developing psychosis of epilepsy, recent studies show that they usually aren't the only cause and coexist with distributed structural pathology and changes in frontotemporal network activation [4]. As for the clinical aspect, the psychosis of epilepsy can be divided into peri-ictal psychoses, interictal psychoses, and psychoses induced by anticonvulsive drugs. Peri-ictal psychoses occur during or shortly after an epileptic seizure, while interictal psychoses aren't chronologically connected to seizures.

In this work, we aim to review the current knowledge on pathogenesis, diagnosis, and management of the psychosis of epilepsy.

PERI-ICTAL PSYCHOSES

Rarely do ictal psychoses manifest as brief, self-limiting episodes; instead, they typically take the form of a nonconvulsive status epilepticus. Their symptoms include agitation, hostility, or "freezing," and occasionally hebephrenic or catatonic syndrome with varying degrees of altered consciousness [5]. Perception problems arise during epileptic convulsions in 30–40% of patients. The area where the epileptic focus is located determines the kind of illusions or hallucinations that occur—visual, auditory, olfactory, tactile, or general somatic feelings. Preserved insight is a characteristic of epileptic hallucinations. Around 20 percent of patients have hallucinations related to time (such as speeding, slowing, or stopping) or memory (such as déjà vécu or déjà vu). This is especially common in cases when there is an epileptic focus in the temporal area. At the same time, about 1% of epileptic patients report having a "dreamy state," depersonalisation, derealization, "thought insertion," or other mystical experiences during a seizure [6].

After a single or cluster seizure, there is a period of clear consciousness and normal functioning known as the "lucid interval." Postictal psychoses occur 24 hours to 7 days later and remain for at least 15 hours and sometimes even 7–8 weeks [6]. In addition to violent and destructive behaviour that occasionally results in automutilation, suicide attempts, or harming others, they might manifest as affective disorders (manic, depressive). Negative symptoms (alogia, anhedonia, apathy, flattened emotion, or withdrawal) are typically absent, while hallucinations and delusions are rare. Disrupted consciousness may be linked to psychotic symptoms [5,6]. Approximately 50% of patients only go through one postictal psychotic episode in their lifetime, relapses are possible for others, and 14% have interictal psychosis [7].

INTERICTAL PSYCHOSES

Interictal psychoses can last anywhere from a few weeks to several months, and they do not always indicate a direct correlation with epileptic seizures. They are frequently named schizophrenia-like. Delusions, religious and mystical experiences, and hallucinations (usually aural, less frequently visual) are characteristic symptoms. They do not come with negative symptoms or affective abnormalities, in contrast to schizophrenia. Consciousness disorders are not noted [6].

Another type of psychoses, known as alternative psychoses, is brought on by effective antiepileptic therapy. They can become visible following the introduction of a novel, effective anticonvulsant medication or the completion of a successful procedure that produces

improvements in both the EEG (forced normalisation) and clinical (absence or reduction in the frequency of seizures) [5]. Typically, anxiety or productive symptoms such as hallucinations or delusions accompany these psychotic episodes [6]. Independent of their course of therapy, about 30–40% of individuals with alternative psychoses also have episodes of interictal psychosis [8].

PSYCHOSES INDUCED BY ANTIEPILEPTIC DRUGS

Antiepileptic medication use may elicit psychotic illnesses in approximately 0.5% of epileptic patients (particularly in females and those with temporal lobe epilepsy). Phenytoin, zonisamide, and levetiracetam are the most common medications to induce psychosis, whereas carbamazepine is the least common. The prognosis is better than in other types of psychoses connected to epilepsy. The timely cessation of the offending drug and avoidance of prescription again should protect against further psychotic events [9,10].

PATHOGENESIS

Paroxysmal activity spreading within limbic system regions, which is not detectable with regular EEG but can be recorded using deep electrodes, is thought to be the underlying cause of peri-ictal psychoses [11]. Another theory states that a psychotic episode is a sign of self-limiting autoimmune encephalitis that occurs after the blood-brain barrier becomes more permeable, exposing the body to systemic blood antigens [12].

One theory about the pathomechanism of interictal psychoses is the phenomena of "kindling." Psychotic illnesses may arise as a result of repetitive bioelectrical discharges in the limbic system, overstimulating the dopaminergic system (by means of excessive dopamine release and/or enhanced sensitivity of dopamine receptors) [13].

According to a different theory, perinatal hypoxia or injury, prior neuroinfection or trauma, and reduced neuronal plasticity may lead to altered glutaminergic, GABA-ergic, and catecholaminergic transmission in vulnerable brain regions (like the limbic system), which may favour both psychotic disorders and epileptic seizures [14]. This patient group's frequent family history of mental illnesses raises the possibility that genetic variables, such as CYFIP1 mutations, play a shared background in epilepsy and psychotic disorders [15].

Patients with specific types of epileptic seizures (mostly focal temporal or secondarily generalised), early onset and prolonged disease duration, frequent or cluster seizures, and concurrent cognitive dysfunction are more likely to develop psychotic disorders [6,12].

DIFFERENTIAL DIAGNOSIS

Ictal psychosis starts suddenly, lasts only a little while, and ends when the seizure stops. When a patient has non-convulsive status epilepticus, they may exhibit strange behaviour and incoherent thoughts, either with or without loss of consciousness. This condition can lead to ictal psychosis. In contrast to postictal psychosis, patients with temporal lobe epilepsy may exhibit various seizure characteristics such as motor or orobuccal automatisms. Delusions and hallucinations are less common in this condition [16].

Making the distinction between interictal psychosis and schizophrenia is a more challenging task for physicians. Interictal psychosis can take on either a transient or long-term form. As Landolt first discovered, forced normalisation may result in certain cases of transient interictal psychosis, in which seizure control and electroencephalogram (EEG) normalisation disinhibit the limbic system [17].

The chronic forms of interictal psychosis may closely resemble schizophrenia; however, several features help to distinguish the two. Schizophrenia often begins in young adulthood. The DSM V (Diagnostic and Statistical Manual of Mental Disorders V) criteria for diagnosis are at least two core symptoms lasting for one month and a decline in social, personal, and occupational functioning during the period of symptoms. The core features of schizophrenia are positive symptoms (delusions, thought disorder, and hallucinations) and negative symptoms (apathy and social withdrawal). Delusions are passive in nature and the hallucinations tend to be third-person auditory. People with schizophrenia often have poor insight into their symptoms and show a decline in their premorbid personality and state. In contrast, interictal psychosis manifests predominantly with the positive psychotic symptoms of delusions and hallucinations, which are less likely to be third-person auditory and have better-preserved personality traits and no negative symptoms. The psychosis can last days to months but may be more protracted. It can be very difficult to distinguish between interictal psychosis and postictal psychosis, and in many patients, these coexist [18-20].

In the initial stages of clinical diagnosis, we need to consider other potential causes of psychosis. Psychosis can be seen in the context of other medical conditions; for example, limbic encephalitis (infective or autoimmune), transient psychosis following alcohol or drug misuse, delirium, neurodegenerative dementia syndromes (Alzheimer's disease) and non-convulsive status epilepticus. There are also several psychiatric conditions in addition to schizophrenia where psychosis can manifest; for example, severe depression, borderline personality disorder and mania with psychosis [16,21].

MANAGING A PATIENT WITH EPILEPSY AND PSYCHOSIS

The management of psychosis of epilepsy can present a challenge for clinicians and requires a multidisciplinary approach. Firstly, it is necessary to establish whether psychosis was preceded by a cluster of seizures in a patient with epilepsy or these are new-onset seizures. Then we need to check AED (antiepileptic drugs) compliance, any new prescribed medications, history of drugs or alcohol misuse, HIV status, and history of foreign travel. Psychiatric and neurological examination is important to establish psychotic symptoms (delusions, hallucinations, thought disorder) and their onset (acute, subacute, chronic), any associated altered or fluctuating consciousness, agitation, mood disorder, cognitive decline, headaches, and other neurological or systemic symptoms. [16] All patients should have routine blood tests for biochemical and haematological screening in the acute setting. These tests should also include urine toxicology, which can screen for drugs like alcohol, amphetamines, cannabis, benzodiazepines, opiates, and psychotropic substances, or "legal highs." It is best to arrange an MR (magnetic resonance imaging) scan of the brain with contrast and diffusion-weighted imaging or an emergency CT (computed tomography) scan of the head with contrast in order to rule out a space-occupying lesion or cerebrovascular accident. Baseline electroencephalography can help to characterise ictal events to exclude non-convulsive status epilepticus or to demonstrate specific patterns relating to limbic encephalitis [16].

Interrupting a seizure or status epilepticus in accordance with practical recommend-dations is the treatment for ictal psychoses [6]. The first step in treating a patient with interictal or postictal psychosis is to induce fast tranquilization. Benzodiazepines are utilised during its acute phase, while neuroleptics (such as risperidone, olanzapine, and quetiapine) are employed in case benzodiazepines don't work or in patients with florid psychotic symptoms [16,22]. Most patients with postictal psychosis respond well to these short-term measures; however, if symptoms have not entered into remission by this stage, then they may need a more long-term strategy, as in the case of interictal psychosis. The majority of patients with postictal psychosis-roughly 95%—have their symptoms completely resolved in less than a month, with an average duration of 9 to 10 days. As a result, the majority of individuals need treatment for no more than three months. Interictal psychosis or symptoms that persist for more than a few months may necessitate the long-term use of antipsychotics under close observation. Similar to the acute care of epilepsy-related psychosis, no particular studies have been conducted on this patient population to inform therapy recommendations for antipsychotic selection or necessary treatment duration. Although there is little data supporting the use of long-term treatment for

the prevention of psychosis, it may be necessary for individuals with recurrent postictal psychosis [16].

SCHIZOPHRENIA AND EPILEPSY

The incidence of epilepsy in patients with schizophrenia is estimated to be 4–5 times higher than that of the general population. The high incidence may indicate that patients with schizophrenia have a further specific vulnerability to epilepsy in addition to the ordinal vulnerability of the general population [23]. Some investigations have linked certain genes to the manifestation of both epilepsy and psychosis, while the evidence for each finding is still inconclusive [24]. The genes that are shared by psychosis and epilepsy may also be linked to a number of neuropsychiatric conditions, including autism, ADHD (attention deficit hyperactivity disorder), and learning difficulties [25].

Many neuroimaging studies have shown frontotemporal lobe abnormalities in patients with schizophrenia. Patients with TLE (primarily temporal lobe epilepsy) or FLE (frontal lobe epilepsy) have more distinct cortical disturbances in the frontotemporal region than patients with schizophrenia, but patients with TLE/FLE exhibit psychotic symptoms less frequently. While frontotemporal abnormalities are often observed in epilepsy and schizophrenia, the neuroanatomical relationship between the two disorders remains unclear [26,27]. Patients with schizophrenia may also have an increased vulnerability to epilepsy due to acquired factors, which may cause an increase in the frequency of epileptic seizures [28]. Patients with schizophrenia have a high risk of head injury caused by self harms, fights, or accidents during psychomotor excitements [29]. Furthermore, many patients engage in alcohol and drug abuse, or have a history of addiction [30], and these can also trigger the development of epilepsy [31]. Some elderly patients experience epileptic seizures as a complication of psychosurgery [32] or may experience epilepsy due to the administration of a high frequency of electroconvulsive therapy [33]. Furthermore, antipsychotic drugs may also contribute to epileptic seizures as they lower the seizure threshold. However, the improvement of psychiatric symptoms by APD (antipsychotic drugs) administration can regularise daily activities and AED adherence, and subsequently improve epilepsy [23].

Patients with schizophrenia with epilepsy exhibit the first psychotic episode at age 17.5 years on average and the first seizure at age 28 on average. Seizure phenomenology and pathophysiology in patients with schizophrenia can be regarded as equivalent to those in people without schizophrenia [34].

There is no specific pharmacotherapy research for this group of patients. Conducting clinical trials with the right sample size to obtain useful results is difficult. In over half of all epilepsy cases, the initial AED suppresses seizures. Most epileptic people experience few seizures during their lifetimes. Patients with schizophrenia may also be predicted to have a similar prognosis for epilepsy. With any AED, seizures in moderate epilepsy can be managed [35,36].

CONCLUSION

In patients with epilepsy, psychosis occurs 7,8 times more frequently than in the general population. Risk factors for psychosis of epilepsy include specific types of epileptic seizures (mostly focal temporal or secondarily generalised), early onset and prolonged disease duration. Making the diagnosis of psychosis of epilepsy can be a challenge since many features overlap with other medical and psychiatric conditions. Furthermore, schizophrenia may also co-occur with epilepsy. The acute management of psychosis of epilepsy involves a multidisciplinary approach with early involvement of a psychiatrist. There is currently no evidence on the pathogenesis of the psychosis of epilepsy or on the best treatment choice, therefore, more studies are necessary.

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ACCEPTANCE OF THE DISEASE IN PATIENTS WITH TYPE 1 DIABETES

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INTRODUCTION

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia caused by a defect in insulin secretion and impaired insulin action. Type 1 diabetes is an autoimmune disease associated with the absolute necessity of insulin treatment. Despite the available research, there is no clear explanation of the cause of type 1 diabetes. Moreover, no method of preventing type 1 diabetes has been recommended or implemented in clinical practice [1,2,3,4].

Type 1 diabetes mellitus causes limitations in everyday life, resulting from the necessity to perform systematic blood glucose measurements, insulin administration, adherence to a diet, regular exercise, and constant education. It requires more self-discipline and self-control than healthy people and causes a change in lifestyle as it necessitates the need to participate and be involved in the treatment process [5,6,7].

Diabetes can significantly worsen the quality of life and affect the mental and spiritual sphere. Factors such as personality, acceptance of the condition, self-esteem, and social support influence the patient's attitude towards the disease. Accepting an illness means adopting a positive attitude. It impacts the mobilization of the patient's strength and good quality of life. The degree of disease acceptance is also related to stress reduction and negative feelings about

the illness [8,9,10].

Type 1 diabetes mellitus is a chronic disease of developmental age that is quite often diagnosed in young people. The chronic nature of the disease process influences the patient's perception of the world. It reevaluates the patient's existence as they must adjust to changes in their private lives. Acceptance of the disease can be a challenge for many patients suffering from type 1 diabetes.

OBJECTIVES

The study attempts to determine the degree of acceptance of the disease among young adults with type 1 diabetes. It takes into account factors that may affect the development of acceptance.

MATERIAL AND METHODS

The study involved 121 people with type 1 diabetes, 85 women and 36 men between ages 18 and 29, thus classified as groups of young adults. The study was conducted online via Facebook. Users belonging to the "Cukrzyca 24H Info" group participated in the study. The study occurred in January 2020, when the group included 25 225 individuals with diabetes. The respondents participating in the study were informed about their voluntary participation in the project and its complete anonymity.

The study used the Acceptance of Illness Scale (AIS). The scale contains eight statements describing the negative consequences of poor health. The respondent's task is to respond to the statements using a point scale from "1" to "5," where "1" means complete agreement with a statement and "5" means complete disagreement with a statement. The sum of points on the scale ranges from 8 to 40. The higher the score on the scale, the greater the degree of disease acceptance and the better social adaptation of the patient.

The study also used a proprietary questionnaire with 28 questions on socio-demographic factors, self-control, self-acceptance of the disease, and the respondents' quality of life.

The results were statistically analyzed using Statistica 13 and MS Excel 2016. Shapiro-Wilk, Mann-Whitney, and Kruskal-Wallis tests and the Spearman rank correlation test were used. The statistical significance level was $p < 0.05$.

RESULTS

The mean age was 23.88 ± 3.5 at a median of 24 years (ranging from 18 to 29). Most of

the respondents were single (75.20%) and lived in villages (27.27%) and large cities over 100 000 (22.30%). A majority of individuals (36.36%) had secondary education. The most significant percentage of the respondents declared that they performed professional work (41.32%), including predominantly intellectual work (45.45%) in the primary system, i.e, 8 hours a day (42.98%) or study (27.27%). The disease duration in the study group was, on average, 10.64 years at a median of 12 years. Most respondents (57.02%) indicated no immediate family member with type 1 diabetes. 54.55% of the respondents used the method of continuous subcutaneous insulin infusion (insulin pump) in diabetes treatment, while 45.45% used multiple insulin injections. The respondents indicated the last glycated hemoglobin *(HB_{A1C})* result at 7.5% ± 1.83. (Most respondents attended the diabetologist's appointments every 3.5 months).

Most respondents (60.33%) did not fear other people's reactions to disclosing the disease. Most subjects (70.25%) also declared that they did not use psychological care related to their illness. The average result of the respondents' self-assessment regarding the level of knowledge about diabetes was 4 points (48.76%) on a 1–5-point scale.

As shown in Figure 1, nearly half of the respondents (47.11%) assessed their quality of life as good. In the quantitative scale that evaluated the quality of life from 0 to 100 points, the respondents' average result was 72.13 ± 17.90 points, with a standard deviation of 17.85 points.

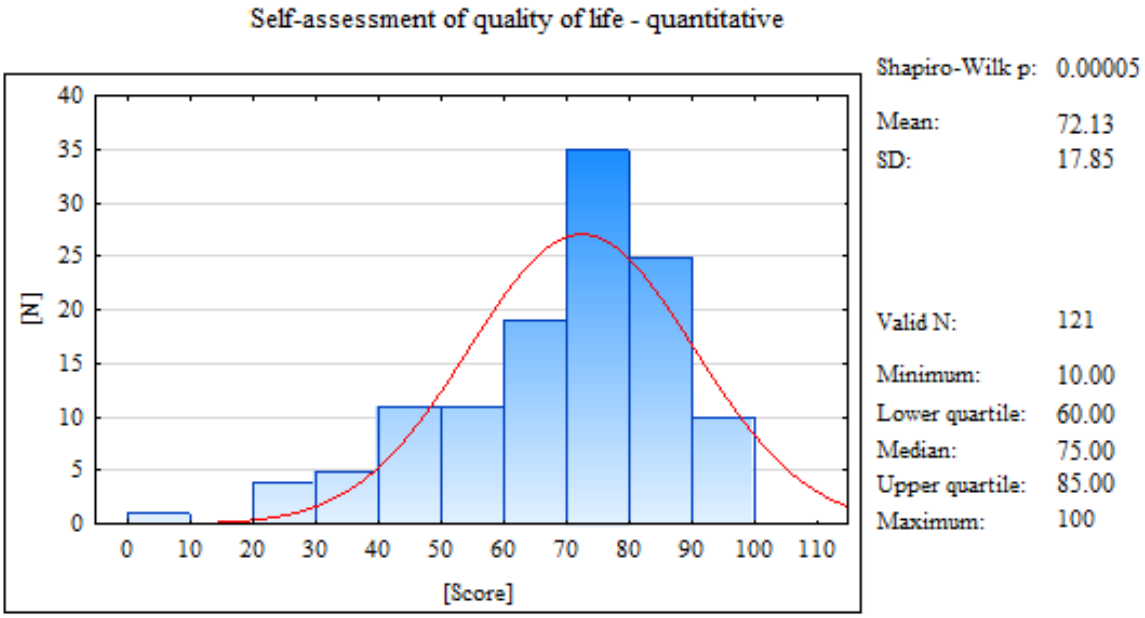

Figure 1. The distribution of self-assessment of the quality of life is done on a quantitative scale of 0 to 100 points.

As shown in Figure 2, the average result among the respondents obtained in the AIS questionnaire was 27.86 ± 8.77.

Half of the respondents showed results ranging from 20 to 35 points, with a median of 29 points. A high level of disease acceptance (over 30 points) was found in 46.28% of individuals (n = 56).

Patients who scored more points on the AIS scale accepted their disease more.

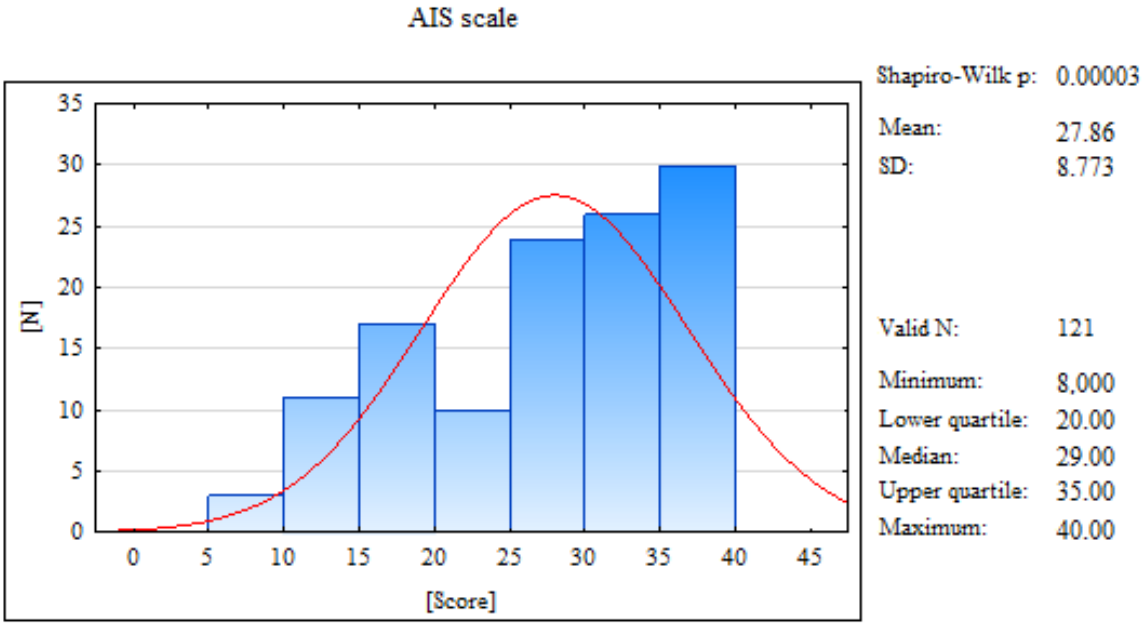

Figure 2. Acceptance of Illness Scale AIS.

Efforts were also made to identify factors that may affect self-assessment of the quality of life and the level of disease acceptance.

As presented in Table 1, gender significantly influenced the respondents' self-assessed quality of life (p = 0.002).

Women's self-assessed quality of life (69.14 ± 17.26 with a median of 70) was lower than men's (78.56 ± 17.79 at a median of 80).

However, there was no statistically significant relationship between sex and disease acceptance (p = 0.117).

Marital status as the analyzed factor didn’t alter the results in self-assessment of the quality of life in respondents (p = 0.513) or the level of disease acceptance (p = 0.399).

Similarly, the level of education in the studied group as a factor also did not significantly modify the results regarding self-assessment of the quality of life (p = 0.269) or the level of disease acceptance (p = 0.079).

Table 1. Factors influencing the self-esteem of the quality of life of the respondents and the level of acceptance of type 1 diabetes.

FACTOR		SELF-ASSESSMENT OF THE QUALITY OF LIFE				DEGREE OF ACCEPTANCE OF DISEASE			
		$\bar{x}$	SD	Me	p	$\bar{x}$	SD	Me	p
GENDER	WOMEN	69.14	17.26	70	**0.002**	27.08	8.74	27	0.117
	MEN	78.56	17.79	80		29.69	8.69	32	
MARITAL STATUS	IN A RELATIONSHIP	74.44	16.16	80	0.513	29.26	8.14	31	0.399
	LONELY	71.46	18.33	75		27.56	8.99	29	
EDUCATION	BASIC/ VOCATIONAL	62.9	22.97	65	0.269	24.18	8.12	22	0.079
	SECONDARY	71.77	18.52	75		26.52	8.98	27	
	HIGHER	73.9	16.19	75		29.36	8.53	31	
TYPE OF WORK	MENTAL	75.74	14.67	77.5	**0.006**	29	8.67	31	**0.036**
	PHYSICAL	76.87	14.1	77.5		29.4	8.82	32.5	
	NOT APPLICABLE	62.67	21.53	65.5		24.83	8.36	24	
PRESENCE OF DIABETES IN THE FAMILY	NO	74.49	16.89	76.5	0.071	28.57	8.49	30.5	0.278
	YES	68.41	18.84	70		26.74	9.18	27	
MODEL OF INSULIN THERAPY	INSULIN PUMP	73.63	18.35	75	0.232	28.35	8.45	29.5	0.551
	PEN	70.33	17.21	75		27.27	9.19	29	
RESIGNATION FROM THE ACTIVE LIFESTYLE	YES	52.18	25.91	40	**0.003**	19	6.87	18	**0.000**
	NO	76.53	15.04	80		31.44	7.35	33	
USING THE HELP OF A PSYCHOLOGIST	YES	61.59	20.6	60	**0.005**	22.56	7.57	21	**0.001**
	OCCASIONALLY	73.1	18.1	80		28.56	7.18	30	
	NO, NEVER	75.68	15.53	79		29.47	8.7	32	

The quality of life was the worst among people not taking up employment (62.67 ± 21.53 with a median of 65.5). In the case of working people, the results are significantly higher at the minimum level of 75.74 ± 14.67 with a median of 77.5 (p = 0.006). Moreover, the non-

working individuals had considerably lower acceptance of the disease than those working physically or mentally, 24.83 ± 8.36 with a median of 24 vs. 29.00 ± 8.67 with a median of 31 (p = 0.036).

There was no statistically significant relationship between the prevalence of diabetes in the family and the quality of life of the respondents (p = 0.071) and acceptance of the disease (p = 0.0278). Correlations between the applied therapeutic model of intensive insulin therapy and the quality of life (p = 0.32) and acceptance of the disease (p = 0.551) in the study group were also not statistically significant.

The disease was the reason for withdrawing from an active lifestyle and was a factor that significantly influenced the respondents' quality of life and the degree of illness acceptance. The respondents who declared the necessity to withdraw from social activity assessed their quality of life as worse (p = 0.003) and had lower acceptance of the disease (p <0.001) compared to those who decided that the illness did not limit them.

Respondents who had been seeing a psychologist assessed their quality of life as worse than those not in therapy (p = 0.005). Also, the disease's acceptance level significantly differed depending on the help of a psychologist. People who systematically consulted a psychologist demonstrated a lower acceptance of the disease (p = 0.001).

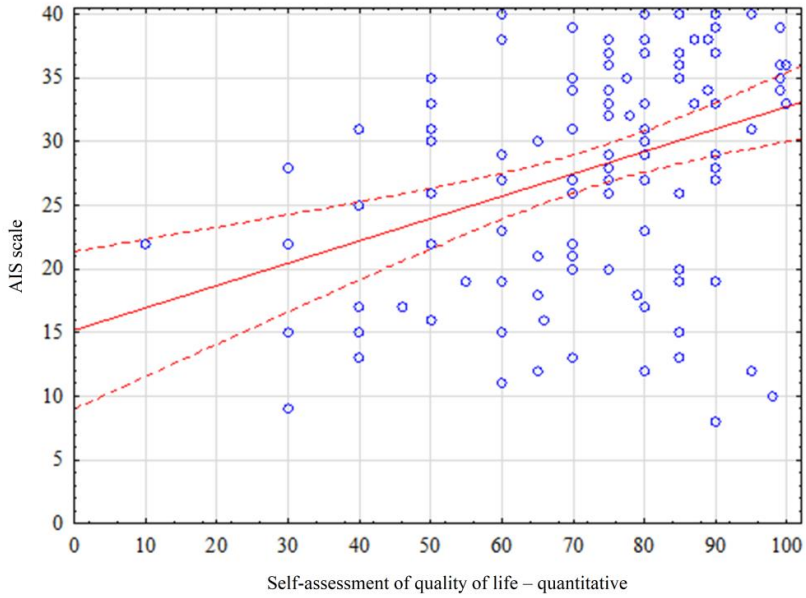

Figure 3. Graphical distribution of the results for self-assessment of the quality of life about the degree of disease acceptance (r = 0.360; p<0.001).

Figure 3 shows the analysis of the relationship between the quality of life and the degree

of disease. Correlation studies found that the degree of disease acceptance increased along with life quality improvement. The demonstrated correlation was weak ($r = 0.360$), but significant ($p < 0.001$).

DISCUSSION

Achieving good metabolic balance is a condition ensuring health safety among people with diabetes and a factor influencing their long lives. Nevertheless, more and more attention is being focused on balancing the absolute pursuit of normoglycemia and ensuring the patient's joy and quality of life. The goals of treating type 1 diabetes include maintaining normal glycemia, preventing disease complications, and accepting the disease. That allows for achieving a better quality of life [11].

Acceptance and quality of life with the disease depend on one's physical condition, mental state, attitude towards the illness, socio-economic situation, and physical experiences. Acceptance of the disease is a complex process that requires the adoption of a positive attitude by the patient. The fact of acceptance stimulates a patient's strength and prevents a reduction in the quality of life [12].

Based on the AIS questionnaire, this study attempted to determine the degree of disease acceptance among young adults who struggle with type 1 diabetes. The obtained mean point was 27.86 at a median of 29 points. On the other hand, 46.28% of the respondents achieved a high degree of disease acceptance, scoring over 30 points on the scale. Similar results were obtained by Kurpas et al., who examined patients with different types of diabetes. The researchers showed an average of 29 points on the AIS scale, where most respondents demonstrated a high level of acceptance of the disease, ranging from 30–40 points [8]. In addition, studies by Stefańska and Maida on patients with type 1 and type 2 diabetes showed that the average acceptance score on the AIS scale was 27.61, with a median of 27.5 points [13].

In the study by Kurpas et al., a higher degree of disease acceptance was found in men (average points on the AIS scale – 30 points) compared to women (average points on the AIS scale – 28 points). Rogon et al. studied patients with type 2 diabetes. They observed a similar degree of acceptance in the AIS scale between men and women (26.95 vs. 25.09 points) without, in the opinion of the researchers, having any significant impact on the relationships between variables [14]. In the presented study, similar correlations were shown, with a slight difference in points between men and women (29.69 vs. 27.08), which meant this factor was

not statistically significant (p = 0.117). However, the self-assessment of the quality of life of women (69.41 on a quantitative scale from 0 to 100 points) was significantly worse than the self-assessment of the quality of life of men (78.56 points) at the statistical significance p = 0.002. That confirms the observations of Rogon et al., who also describe women's worse quality of life than men [14]. These observations may result from an increased tendency to depressive disorders in women. As shown by Duda-Sobczak et al. research, symptoms of depression among people with diabetes are more common in women [15].

The presented study showed that people who used the help of a psychologist have a worse quality of life (p = 0.005) and a lower level of acceptance (p = 0.001) of the disease than people who used such help sporadically or never. People in therapy often struggle with unpleasant emotional states, e.g., a sense of rejection, loneliness, or lack of understanding. Unresolved psychological problems can lead to severe mental disorders in the form of depression [16]. Wojtaszek et al. conducted a study that showed that depressive disorders are a common phenomenon among people with diabetes. The first symptoms of depression are fatigue, lack of energy, and lack of motivation to exercise. Hypoglycemia and hyperglycemia are among the factors leading to depression in individuals with diabetes. They also cause the fear of harm to health [17]. There is a reason the holistic approach to patient treatment has gained more attention in recent years. Diabetologists strive to include integrated psychological consultations as part of the follow-up visits. They justify their decisions by referring to the influence of psychological problems on insufficient glycemic control [18].

The analysis shows that professional activity influences the degree of disease acceptance and the quality of life. The quality of life in people not taking up employment was worse than in people working physically or mentally (62.67 ± 21.53 vs. 75.74 ± 14.67; p = 0.006). A lower level of disease acceptance was also observed in unemployed individuals than in the respondents who worked (24.83 ± 8.36 vs. 29.00 ± 8.67; p = 0.036). Michalak et al. reached similar conclusions, showing that professionally active people obtained statistically significantly higher AIS scores at p <0.01 [10]. The consequence of unemployment among people with diabetes is a worse economic situation, which may cause difficulties in disease control and limited access to medical care. Consequently, it will contribute to the development of diabetic complications. Unemployment in people with diabetes is undoubtedly a reason for the poorer quality of life and the lack of acceptance of the disease.

Diabetes is often found to be the reason for abandoning an active lifestyle, which is not indifferent to the degree of disease acceptance and quality of life [19]. This study showed that

the respondents declaring the need to withdraw from social activity assessed their quality of life worse ($p = 0.003$) and had lower disease acceptance ($p < 0.001$). This problem, however, may reach deeper and also affect the families of people with diabetes and the patterns of behavior they convey. As the research by Podsiadło et al. shows, most parents of children with type 1 diabetes (64%) leave home to go to the cinema, theater, swimming pool, etc, without their child, often without giving a reason for it [20].

The study shows that the quality of life improves disease acceptance ($p < 0.001$). Kurpas et al. obtained similar results and concluded that acknowledging the disease affects the quality-of-life assessment. The higher the degree of disease acceptance, the better the evaluation of the quality of life [8].

CONCLUSIONS

1. Almost half of the respondents showed a high level of disease acceptance (over 30 points) in the AIS questionnaire.
2. The following factors significantly influenced the acceptance of the disease: professional work, active lifestyle, and no problems related to diabetes requiring psychological care.
3. There was a correlation between gender, education, and quality of life. Men and individuals with higher education were among those who assessed their quality of life as best.

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PATIENT WITH BORDERLINE PERSONALITY DISORDER IN GENERAL PRACTICE

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INTRODUCTION

A borderline personality disorder is a psychiatric condition defined by a persistent pattern of instability in affect regulation, impulse control, interpersonal interactions, and self-image. BPD may be present in up to 6.4% of adult primary care visits, four times greater than in the general population. A borderline personality disorder is underdiagnosed, and the majority of individuals with it also have other mental problems [1].

Clinically, these individuals may exhibit excessive healthcare usage, health-sabotaging behaviors, persistent or nonspecific somatic complaints, angry outbursts, high-risk sexual activities, and drug abuse [2]. Obesity and binge eating disorders are typical comorbidities among people with borderline personality disorder [3]. There is a known link between borderline personality disorder and increased suicide risk [4].

Patients who were not in remission had a significantly higher likelihood of obesity, diabetes, osteoarthritis, hypertension, back pain, urine incontinence, and other "syndrome-like" conditions after six years of follow-up compared to those who had been in remission [5]. They were also substantially more likely to report daily alcohol usage, smoking one pack of cigarettes per day, daily use of sleep drugs, excessive use of pain medications, and a lack of regular exercise. Furthermore, non-remitted BPD patients were considerably more likely than remitted BPD patients to have experienced at least one medically related emergency room visit, medical hospitalization, or both. At 16 years of follow-up, these same variables separated ever-recovered and never-recovered borderline individuals [6]. An extensive epidemiological investigation discovered a higher prevalence of a variety of illnesses among borderline individuals living in the community. These conditions included arteriosclerosis or hypertension, hepatic illness, cardiovascular disease, gastrointestinal disease, arthritis, venereal disease, and other evaluated medical problems [7,8].

As general practice principles, family doctors should refrain f rom over-familiarizing

themselves with patients, plan frequent appointments, establish reasonable boundaries, and be mindful of their patients' sentiments. Successful communication tactics, such as problem-solving methods and motivational interviewing, can assist in resolving problematic behaviors in individuals diagnosed with borderline personality disorder [9].

EMPTINESS

The Diagnostic and Statistical Manual of Mental Disorders (3rd edition; DSM-III) included "chronic feelings of emptiness or boredom" as one of the diagnostic criteria for BPD [10]. However, later empirical research determined that emptiness was a more discriminating criterion than boredom, as reflected in later DSM editions [11]. The International Statistical Classification of Diseases and Related Health Problems (10th version; ICD-10) lists chronic emptiness as a symptom of emotionally unstable personality disorder, specifically borderline type [12].

The clinical diagnosis of chronic emptiness is imprecise, as the classification system and rating tool descriptions make no distinction between existential components of emptiness, such as meaninglessness, and physical symptoms, such as feeling hollow [13]. Emptiness in BPD can be characterized as a visceral feeling, generally in the belly or chest,' but it has also been defined as 'without meaning, purpose, or substance' [11].

The sensation of emptiness in BPD may vary depending on age and gender; 84.8% of adults 45–68 and 64.9% of people 18–25, respectively, agreed that chronic emptiness was real [14]. Chronic emptiness is distinct in that it is linked to worse functioning in women but not in males [15].

Beyond object connections, attachment theory is increasingly being used to examine the sensation of emptiness and other core aspects of BPD [16]. Impaired mentalization, particularly in comprehending one's emotions and cognitions, has also been connected to the sensation of emptiness [17]. When talking about the idea of narrative identity, Fuchs sees chronic emptiness in BPD as a result of "the inability to integrate past and future into the present," which is a tactic used to avoid "the necessity of tolerating the threatening ambiguity and uncertainty of interpersonal relationships" [18].

There have been suggestions of links between chronic emptiness and other BPD symptoms. People who have a "hyperbolic temper," or a propensity to feel negative and reactive emotions, may be more susceptible to BPD symptoms, such as "intense and chronic

pain," which is brought on by detachment and emptiness and partially results from "giving up on the social world" in reaction to inadequate early social support [19].

For BPD, there are no clear-cut, scientifically proven treatment approaches to address persistent emptiness [20]. The acceptance component of dialectical behavior therapy may be the most helpful tactic for treating BPD's enduring temperamental symptoms, such as feelings of chronic emptiness. According to the Mentalization-Based Treatment paradigm, improving one's capacity for mentalization might mitigate the effects of emptiness and loss of self-structure, such as after an attachment loss, by guarding against "non-mentalizing" modes linked to emptiness and self-harm [13,17].

EMOTIONAL INSTABILITY

Dysregulation, or emotional instability, maybe a fundamental feature of borderline personality disorder (BPD), influencing the likelihood that symptoms may manifest [21]. The part that emotional instability plays in BPD emphasizes the detrimental effects that this cognitive process's disruption may have on day-to-day functioning [22].

The main characteristics of borderline personality disorder are impulsivity, particularly when it comes to expressing emotions, managing moods, and displaying persistent suicidal thoughts, as well as instability in interpersonal relationships and a poor self-image. In addition, several nebulous somatic symptoms, risky sexual conduct, binge eating, or persistent discomfort may be signs of borderline personality disorder [23].

Patients with BPD may exhibit impulsive conduct in general practice, including minimal persistence, lack of attention, and a fast reaction to boredom and frustration. They may also struggle to delay pleasure. Additionally, they could be ruthless (lack caution, exaggerate their talents, ignore safety concerns), untrustworthy (will not be held accountable), and deficient in planning (emphasis on present sensations, little attention given to future objectives) [24].

FEAR OF ABANDONMENT

A fundamental characteristic of borderline personality disorder (BPD) is problematic interpersonal connections, along with emotional dysregulation and identity disruption.7. One of the most effective ways to differentiate between BPD cases is through interpersonal dysfunction. One of the most crippling symptoms of BPD is the imagined or actual fear of abandonment, which frequently serves as the primary trigger for self-harm, acute crises, and

general clinical decline. Abandonment fear, coupled with desperate attempts to prevent it, can occasionally result in violent crime, particularly against intimate partners. A fear of abandonment can lead to inwardly directed suffering in addition to the externally directed pain that affects interpersonal interactions. Fear of social rejection can cause self-defeating actions that impair one's ability to think, make illogical decisions, and feel disconnected from the future [25].

Fear of abandonment may adversely affect interpersonal relationships across multiple domains. When it comes to the quantity and frequency of interaction with their therapists, people with BPD may be susceptible to boundaries and limitations being imposed. For example, a therapist who is going on leave—which entails confirming boundaries around the therapist's availability—may set off feelings of rejection and abandonment. In a similar vein, leaving a hospital may result in threats or actual self-harm, which would worry the personnel and perhaps lengthen the hospital stay. Compared to other severe mental diseases like mood or psychotic disorders, mental health professionals are more likely to respond negatively to a person with BPD. There is a great deal of stigma associated with BPD among mental health professionals [26].

IDENTITY DISTURBANCE

Identity is defined as a set of characteristics, characters, beliefs, appearances, and expressions characteristic of an individual. It appears in childhood, when the child learns about his or her self-awareness, remaining a coherent aspect of the individual in later stages of life [27]. A person with borderline personality disorder has a distorted self-image. To better understand the nature of the problem, it is worth mentioning the concept of "ego boundary"[28]. Ego boundary represents the concept in which a person can distinguish between his or her own and what is not. The lack of an ego boundary causes a blurring between the individual and others, resulting in identification with them too quickly or easily [29]. Patients may be overly sensitive, causing them to develop defense mechanisms against others to remain separate from them and close themselves off. Other patients, however, may develop excessive openness in relationships with others, adopting a hyper-suggestive, imitative role. Still, other patients show discontinuity in their sense of identity. They need to present a conformist facade in society while hiding their rebellion and alienation. Another group may be unable to notice their identity with others or stability over time [27]. As the element of the healthcare system that most often establishes a long-term relationship with a patient, a family doctor should be aware of the

possibility of the patient having the features described above. Appropriate management of the relationship with the patient will help build trust based on healthy foundations, allow for better compliance, and will also enable the doctor to maintain comfort, safety, and healthy boundaries, which translates into practical work.

IMPULSIVITY

Impulsivity is defined as the tendency to act on the spur of the moment and manifests itself in behaviors characterized by a lack of forethought, reflection, or consideration of consequences. It can threaten long-term goals and strategies. It accompanies many disorders, such as: FASD, ADHD, SUD, bipolar disorder, or borderline personality disorder [30].

In the case of BPD, it is a clinical and diagnostic feature, and comorbid ADHD may worsen impulsive behavior.

In everyday medical practice with this group of patients, risky behaviors that do not consider long-term consequences are clear [31].

The pattern of impulsivity in BPD patients is expressed in the form of suicide attempts, self-harm, substance abuse, sexual promiscuity, dangerous driving, and eating disorders [32]. There may be problems with experiencing emotions, e.g. anger, or interpersonal problems in creating chaotic relationships. The relationship between substance use and impulsive aggression is also well established, and the co-occurrence of BPD and SUD in patients correlates with higher levels of impulsivity. Problems with self-control and self-destructive tendencies [33] may be present. Clinically significant levels of impulsivity and suicidal tendencies develop over time. They become visible in the teenage years. Mood disorders are more typical of women, and substance use and criminal problems are more typical of men. The social environment is also essential in shaping disorders. Its sudden changes, instability, and loss of social cohesion, e.g., in the case of growing up in a dysfunctional family, may contribute to the development of the described disorders [34]. Also, in this case, a family doctor, in cooperation with a pediatrician, should examine their patients and patients' families to detect problems at an early stage of development.

SPLITTING

Splitting is a term used to describe a process of mental fragmentation, which typically manifests as shifts of emotional perception of other people, objects, and self with typical fluctuations between idealization and devaluation [35].

It is a typical thought pattern in which individuals tend to think in extremes (another person is perceived as only good or only bad). This interpretation is contrasted by acknowledging specific nuances known as "shades of gray" [36].

This phenomenon is hazardous in a medical setting, making the patient prone to lack of criticism regarding proposed treatment or excessive distrust of the clinician who harmed their trust. In response to this black-and-white thinking, a clinician categorized as "bad" may encounter various aggressive or disruptive behaviors, such as refusal of treatment, disproportionately angry outbursts, demands, or intimidation [37].

RAGE

People with BPD often experience significant emotional instability, frequently feeling intense negative emotions that they cannot manage. This emotional volatility can skew their perception of their surroundings, making them prone to anger and aggressive behavior when faced with perceived threats.

It is thought that individuals with BPD are predisposed to emotional dysregulation, impulsivity, and aggressive reactions to upsetting situations without considering potential negative consequences. They also find it difficult to control their strong urges [38,39].

The Diagnostic and Statistical Manual of Mental Disorders (4th ed., text rev.) indicates that the intense anger typical of borderline personality disorder (BPD) frequently arises due to perceived rejection [40].

In primary care settings, this symptom may be presented through seemingly benign situations, causing patients great upset and refusal of treatment or a follow-up. Dealing with a BPD patient requires a high conflict awareness and establishing boundaries to prevent rage outbursts which might sabotage a healthy doctor-patient relationship.

SUICIDALITY

Suicidality is a significant aspect of BPD psychopathology. Individuals with BPD typically experience an average of three suicide attempts in their lifetime, primarily through overdoses. Follow-back studies indicate that suicide occurs in up to 10% of BPD cases, while prospective cohort studies report lower rates, ranging from 3% to 6% [41]. Other research, such as the work by D.W. Black and colleagues, suggests that at least 75% of patients with BPD attempt suicide [42]. Non-suicidal self-injury (NSSI), which involves repeatedly harming the body without suicidal intent, plays a crucial role in this context. Prevalence rates of NSSI are

estimated to be around 95% for adolescents and 90% for adults with BPD [43].

It’s extremely important to be vigilant of potential signs of suicidality and NSSI. In general practice settings, it's crucial to utilize suicidality screening questionnaires and detailed physical examinations focused on nonhealing wounds or signs of cutting.

CONCLUSIONS

Every practicing family doctor will encounter patients with borderline personality disorder in their professional career. Therefore, knowledge about the problems of this group of patients is essential to establish a satisfactory relationship for both sides. Emptiness, emotional instability, fear of abandonment, identity disturbance, impulsivity, and splitting are aspects of the patient's internal life that should be taken into account. Problems with anger control or suicidal behavior and the possibility of substance abuse should also be closely monitored for the good of the patient and their surroundings.

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