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The First Pyrolysis Protocol Based on Experimental Measurements in the Atomic Level Structured Cancer Studies

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Abstract

Background: *Oxygen balance is critical for cell life and is regulated by an intricate oxygen-sensing process in the body. The same mechanism can also be used by cancer cells to survive, to grow and to disseminate what is key for cancer patients' life. We took highly advanced interdisciplinary approach Isotope Ratio Mass Spectrometry to experimentally search for methodological issues fundamental for oxygen evaluation on an atomic level of cancer tissue biology – by stable isotope ratio assessment.*

Objectives: *The aim of presented studies was to assess the reference mass of the sample for oxygen estimation in future cancer tissue studies.*

Material and Methods*: Experimental O-isotope determination in animal tissues made by IRMS (Thermo Finnigan MAT 253) following pyrolysis at 1350°C and chromatographic separation (70°C) of* H_2 *and CO in a He gas stream.*

Results: *Oxygen signals were identified in all the examined experimental animal tissue samples. The obtained oxygen isotope ratio values appeared 12,7 ± 0,5 ‰ and 11,8 ± 1,0/2 ‰ for vacuum line and the vacuum dryer experimental parts, appropriately.*

Conclusions: *Homogeneity of the tissue sample is critical for oxygen isotope ratio measurements in cancer. It must be taken in consideration when the level of homogenization of the sample allows to achieve the results versatile for cancer tissue studies with prospective clinical impact. Presented studies are the call for overcoming interdisciplinary barriers to intensify and develop isotope ratio cancer studies which give hope to understand more cancer disease and save cancer patients' lives.*

Key words: *biomarkers, isotopes, pyrolysis, structure analysis, neoplasms*

Introduction

Normal human cells need oxygen to survive and act properly. However, the amount must be right since oxygen balance is critical for cell life and because of that fact is regulated by an intricate oxygen-sensing process in the body, the discovery of which earned the 2019 Nobel Prize in Medicine. The same mechanism can also be used by cancer cells for their own survival. Hypoxic cancer cells acquire abilities key for cancer patients' health and life – the ability to metastasize and resist chemotherapy and radiation treatment. Although, it is not completely explained how hypoxic tumors gain these abilities, however it was proved that activating Hypoxia Inducible Factor (HIF) turns on genes and proteins that can degrade extracellular matrix, enabling cancer cells to disseminate. There is proved the relation of hypoxia and angiogenesis, and neovascularization in many cancer types. In oxygen deprivation states HIF expression is impaired and induces activity of the other proangiogenic factors as Stromal cell derived factor-1 (SDF-1), which recruits in turn bone marrow derived progenitor cells CD133(+), from circulatory system to the hypoxic areas which starts angio – and vasculogenesis. Epithelial to mesenchymal transition caused by HIF action makes cancer cells to be more mobile and more resistant to therapy. Hypoxia in tumors is also a major factor in their resistance to immunotherapy agents. Moreover, cancer cells can also adapt to low-oxygen environments by turning on an alternative way for generating energy – one that doesn't require oxygen [1–5].

The complex relationship between oxygen and cancer has been a subject of ongoing research. The lack of practical results of these efforts so far justifies a search for wider understanding of the problem with the use of modern methods which may alight pathways of cancer growth and metastasizing in oxygen deprivation states.

Interdisciplinary studies on cancer, highly developing today, had brought such a possibility. Awarded the four Nobel Prizes Mass Spectrometry had opened a new window on cancer studies by structured cancer tissue studies on an atomic level – the stable isotope ratio assessment.

Stable isotopes are non-radioactive atoms of the same chemical element, which differ only in their number of neutrons [6]. The studies with the use of stable isotopes are known from decades and since 1990s their popularity in metabolic studies started to increase [7].

Isotope ratio assessment by Isotope ratio Mass Spectrometry (IRMS) relies on the fact that biochemical processes cause change of isotopic profile of elements of reacting molecules due to different rates of isotopic species what is named an isotopic fractionation. The measurement of the ratio of a heavier stable isotope to a lighter one is very precisely expressed as a delta value which is 'per mil' (‰) deviation from a standard.

Stable isotopes are used for the dynamic assessment of in vivo metabolism and they may be particularly important for cancer studies and the validation of new treatment modalities. In 2015 it was successfully completed the first protocol of stable isotope ratio assessment in tumor tissues based on original research and the same year the first histoclinical studies were performed and for the first time revealed proves for prospective clinical impact of isotope ratio measurements in cancer [8, 9].

Highly developing stable isotope cancer studies during next few years had brought many intrigued findings which alight cancer biology at the atomic level as well as potential clinical implications of stable isotopes estimations, and the results of isotopic studies were published by the most demanded scientific journals e.g. Nature group, however none of them concentrated on oxygen [10, 11].

At this still early stage of isotope ratio assessments in cancer tissue it is fundamental to establish universal methodology of the studies as well as patterns of measurements and references values of samples.

The aim of presented studies was to assess the reference mass of tissue sample for oxygen estimation in future cancer studies. The standard mass was understood as the mass of the sample selected in such a way that it was possible to obtain the appropriate peak intensity (mV) of CO (the values within the linear range of the used devices).

Material and Methods

Experimental part

Material: animal tissue (meat RFN type (EU), class 1 – pork loin of the protein content in the fresh meat 16.8% (67.2% dry matter) and fat content which did not exceeded 30%, and connective tissue content which did not exceeded 20%).

Preparation procedures

Animal tissues were cut into pieces of an average size of 0.3 cm x 0.3 cm x 0.3 cm and frozen – 70°C till the time of experiment and thawed prior to drying. Drying: The pieces of animal tissue were placed on the sides of bottles 5 centimetres high and weighed. Drying was carried out using two methods: by means of a vacuum line and in a vacuum dryer. Drying in a vacuum oven took place at the temperature of 30°C for 24 hours; drying in a vacuum line lasted 5 days (120 h). Drying in a vacuum line took place in a desiccator with the use of a drying agent – phosphorus pentoxide (P_2O_5). The vacuum in the system was 0.001 mm Hg. After the drying process, the samples were weighed and on this basis the percentage of dry mass was obtained.

Homogenization

Homogenization followed drying, the pieces of animal tissue were homogenized by a vibrating grinder that had two balls made of agate. Grinding the pieces of animal tissue by hand, first with a scalpel, and then with a mortar made of percelite, was used. The samples obtained in this way – for the vacuum line and the vacuum dryer, which were determined respectively "L" and "S", were sent for isotope ratio assessment with the use of pyrolysis.

Isotope ratio measurements

Samples were first weighed (180 ± 20 µg) into Ag-foil capsules. The capsules were then folded and loaded into plastic sample trays. Samples were then loaded rapidly onto the automated carousel of a ThermoFinnigan elemental analyzer (Bremen, Germany), which was evacuated, purged with helium, and opened to the reactor. Before beginning the analysis, I monitored the background voltage on masses 28, 29, 30 until stable. O-isotope determination was made by IRMS (Thermo Finnigan MAT 253) following pyrolysis at 1350°C and chromatographic separation (70°C) of H_2 and CO in a He gas stream. Measured values were calibrated to repeat analyses of a gelatin (certified reference material) provided by Elemental Microanalysis company and caffeine (measured by different research group and published) standards and are reported to VSMOW on the VSMOW-SLAP scale. Analytical precision, based on repeated analysis was 0,5 ‰ (δ18OVSMOW;1σ n = 5).

One needs to pay attention to the fact, that N-containing compounds could yield less accurate results, despite quantitative conversion of the standard oxygen into CO. Analysts believe that the problems is partially caused by interfering gases (third peak on the chromatogram) produced by a secondary decomposition of N – and C-containing polymers formed during the decomposition of the analyte [12–14].

Results

Oxygen signals were identified in all the examined experimental animal tissue samples.

Obtained results of oxygen isotope ratio assessment regarding the conditions of performed experiments are presented in Table 1, identification of the method and summary of the procedure and results are presented in Table 2 and Figure 1.

Table 1. Characteristic of results of oxygen isotope ratio measurements in experimental animal tissue studies

	Samples	Animal tissue mass (g)	Animal tissue mass after drying (g)	% of dry animal tissue mass	% of dry animal tissue mass (mean value)
Vacuum dryer	1	0,03188	0,00898	28,16813	30,21254
	2	0,03344	0,00975	29,1567	
	3	0,02434	0,00742	30,4848	
	4	0,03068	0,00894	29,1395	
	9	0,41910	0,14297	34,11358	
Vacuum line	5	0,06190	0,01709	27,609047	28,93006
	6	0,07765	0,02282	29,38828	
	7	0,06820	0,01986	29,12023	
	8	0,06594	0,01952	29,60267	

Identification of used method and the summary of oxygen isotope ratio measurement procedure and results plus EA-Py-CF-IRMS chromatogram of gelatin are presented in Table 2 and Figure 1.

Table 2. Identification of used method δ18OVSMOW/EA-Py-CF-IRMS

"L" analysis			
Analysis	Parameter	Result±s	Unit
1.	δ 18OVSMOW	12,7 ± 0,5	‰
"S" analysis			
Analysis	Parameter	Result±s	Unit
2.	δ 18OVSMOW	11,8 ± 1,0/2	‰

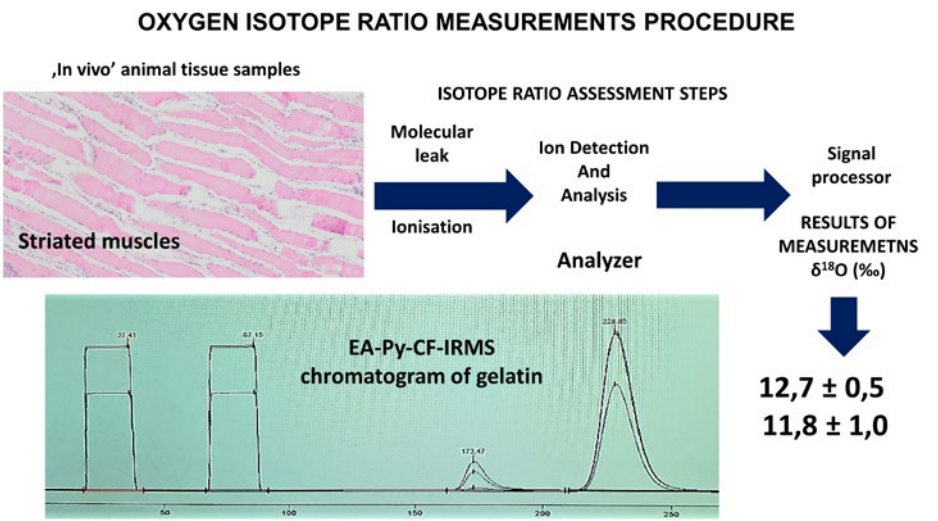

Figure 1. Oxygen isotope ratio measurement procedure and results plus EA-Py-CF-IRMS chromatogram of gelatin

Discussion

The stable-isotopic composition of the body tissues depends on the isotopic composition of food sources and on shifts due to isotopic fractionation during metabolism. It already have been demonstrated that cardiovascular diseases, smoking, anaemia, liver diseases, obesity and pregnancy affect the isotopic composition of human tissues [15–21].

The research in literature strongly suggests a relationship between stable isotope biochemistry, and human pathology, including cancer [10, 11, 22–25].

Nitrogen and carbon highly predominate as the subject of isotopic studies on cancer regarding their part in cell life sustention and proliferation [10, 11, 24]. A little is known about the other elements e.g. copper and zinc in cancer, the studies on oxygen fractionation in cancer had not been found in the literature according to the authors knowledge [23, 25, 26].

Isotopic studies on oxygen reflects in the literature environmental studies on water resources and oxygen fractionation is analyzed with hydrogen as one of the two elements of water chemical structure. Growing risk of climatic

changes makes this area of studies highly developing. Isotope ratios of tap water have previously been studied as a potential tool to link public supply waters with water source characteristics at local to continental scales, providing information on the footprint of and potential risks associated with the water sources used. The tap water isotope signatures identified here could be widely applied to characterize water supplies and associated sustainability challenges in different regions worldwide [27, 28]. Stable isotopes in water (δ 2 H and δ 18 O) are important indicators of hydrological and ecological patterns and they are incorporated into geological and biological systems in a predictable manner. Physical processes result in spatial variation of δ 2 H, δ 18 O in water across the landscape (so-called "isoscapes") and provide the basis for hydrological, ecological, archaeological and forensic studies [29].

The relation of oxygen and cancer biology is complex and not completely known. In cancer patients tumor hypoxia leads to a poor prognosis due to the potential of increased aggressiveness, metastatic potential and resistance to chemo – and radiation therapy [30, 31]. Although HIF-1α transcription does not require oxygen, in normoxia, HIF-1α is rapidly degraded [32].

HIFs also stimulate cancer stem cells (CSCs) [33]. Furthermore, one mechanism of therapy resistance can be attributed to the special capacities of CSCs.

Regarding the part of oxygen in cancer cell survival, growth, dissemination and resistance to universal therapies and taking into consideration promising results of already performed IRMS studies on the other elements it seems to be reasonable to choose oxygen fractionation as the current aim of evaluation which may benefit in better understanding of cancer biology and triggers for metastasizing.

In presented studies the oxygen signals were successfully identified in all the examined samples, however a large standard deviation can indicate that samples were not enough homogenous. Regarding the obtained results homogeneity of the sample reveals as the condition of expected precision in oxygen studies and the evaluation of stable isotopes of oxygen seems to be much more challenging than previously performed with the use of continuous low isotope ratio mass spectrometry (CF-IRMS) estimations of nitrogen and carbon.

Finally, some general methodical issues may be underline. To improve the precision of the results, the intensity of the peak that comes from the sample should be close to the intensity of the standard gas. The mass of the sample should be selected to obtain the appropriate peak intensities (mV) of CO (at appropriate dilution), so that they fall within the linear range of the introducing device (elemental analyzer) and the mass spectrometer. To improve the precision of the results, the intensity of the sample peak should be close to that of the reference gas.

Conclusions

Homogeneity of the tissue sample is critical for oxygen isotope ratio measurements in cancer. The use of a vibrating grinder for homogenization did not give satisfactory results. It must be taken in consideration when the level of homogenization of the sample allows to achieve the results versatile for cancer tissue studies with prospective clinical impact. Presented studies are the call for overcoming interdisciplinary barriers to intensify and develop isotope ratio cancer studies which give hope to understand more cancer disease and save cancer patients' lives.

The authors declare no conflict of interest.

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The Role of Diet in Rheumatoid Arthritis Therapy – A Review of the Literature

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Abstract

Rheumatoid arthritis (RA) is an autoimmune chronic systemic connective tissue disease characterized by symmetrical arthritis, abarticular changes and systemic symptoms. The most characteristic symptoms are pain, stiffness and symmetrical swelling in the joints.

Including nutritional treatment in RA patients as a permanent component of therapy may have benefits in terms of weight regulation, reducing the risk of cardiovascular disease and osteoporosis, and an overall improvement in the patient's quality of life. Chemical compounds that exhibit anti-inflammatory effects include polyunsaturated fatty acids, polyphenols, and antioxidants. The use of herbal raw materials with anti-inflammatory properties is also becoming popular, but there is a need for further analysis to create official recommendations. Studies analysing the effect of consumption of anti-inflammatory bioactive substances on the disease activity have contributed to the search for a specific nutritional model optimal for patients with RA. Due to the high supply of anti-inflammatory substances and protective nature against the development of cardiovascular diseases, a balanced diet based on the principles of the Mediterranean diet is recommended. The aim of this review was to present the current knowledge on the role of diet in rheumatoid arthritis including the effect of bioactive substances supplementation on disease activity.

Key words: *rheumatoid arthritis, diet, antioxidants, polyphenols, polyunsaturated fatty acid*

Introduction

Interest in diet supporting the treatment of autoimmune diseases has increased over the past few years, which has contributed to the development of scientific research devoted to this topic. Rheumatoid arthritis (RA) is an autoimmune chronic systemic connective tissue disease characterized by symmetrical arthritis, abarticular changes and systemic symptoms. The most characteristic symptoms are pain, stiffness and symmetrical swelling in the joints of the hands and feet, but inflammation can also affect other joints. Patients with RA have an increased risk of developing diet-related diseases, including obesity [1, 2].

Physical disability and the pain associated with it, with inadequate caloric supply, may contribute to the growth of adipose tissue, which in turn may cause joint pain and deformity. In a prospective cohort study conducted on the basis of the Canadian Early Arthritis Cohort registry, it was shown that overweight and obese patients were less likely to achieve sustained remission (sREM) during the first three years of disease [3]. The authors of the meta-analysis conducted in 2016 drew a similar conclusion. Obese patients were 40% less likely to achieve remission of the disease than patients of normal weight. Most of the studies included in the analysis also showed higher values of disease activity scores, including DAS and DAS28, calculated on the basis of the examination of 44 or 28 swollen and painful joints, red blood cell sedimentation rate and C-reactive protein concentration. The assessment also takes into account the general health of the patient, determined by the visual analogue scale (VAS). Reduced mobility has also been observed in obese RA patients. However, there was no association between obesity and increased mortality. Nevertheless, the authors of the study emphasize the need for further analysis to assess the impact of obesity in the treatment of RA [4]. Also important, in the context of nutrition therapy in RA, is the increased risk of cardiovascular diseases in patients with RA, due to the ongoing generalized, chronic inflammatory process influencing the development of premature atherosclerotic lesions in the coronary, cerebral and peripheral vessels [5].

In the recommendations created by the European League Against Rheumatism (EULAR) involving the prevention and treatment of cardiovascular diseases in patients with RA, lifestyle modifications such as healthy diet, regular exercise and smoking cessation were also recommended with appropriate pharmacological treatment [6].

Adequate nutrition is also important in preventing osteoporosis. Patients with active RA are at increased risk of bone loss, bone fractures and increased bone resorption. Another important osteoporosis risk factor is a low body mass index (BMI). Therefore, for the prevention of fractures, in addition to introducing pharmacological methods, appropriate nutritional treatment based on the proper supply of energy, calcium and vitamin D is recommended in patients with RA [7].

Including education-based dietary intervention, reducing excess body weight, and introducing healthy eating habits into RA therapy can improve the patient's quality of life and reduce the risk of comorbidities.

Health promoting properties of Omega-3 fatty acids

Polyunsaturated fatty acids are one of the most researched groups of bioactive compounds in the treatment of RA. Polyene fatty acids (PUFAs) are present in both animal and plant-based foods, but the metabolism of these substances in the body differs from one another. Due to the location of the first double bond from the end of the carbon chain, they are divided into the following families: n-9, n-6 and n-3 [8]. The first clinical trials investigating the effect of a diet rich in PUFA were made in 1985 by Kramer et al. [9]. It was shown then that the number of painful joints was reduced and morning stiffness was shortened in RA patients from the intervention group who were on a diet rich in polyunsaturated fatty acids, low in saturated fatty acids and additionally supplementing eicosapentaenoic acid (EPA) at a dose of 1.8 g/day. The study lasted 12 weeks. In turn, a randomized, double-blind, controlled trial showed that daily omega-3 supplementation in RA patients has clinical benefits and may reduce the need for pain medication. The experiment included 60 patients with an active form of RA and randomly assigned either

to a placebo group or one supplemented with omega-3 acids in the form of 2 capsules containing 1.8 g of eicosapentaenoic acid (EPA) acid and 2.1 g of docasahexaenoic acid (DHA). The study lasted 12 weeks for which the standard pharmacological treatment of patients was continued. A significant reduction in the symptoms of the disease and the intake of painkillers was observed in the group supplemented with omega-3 acids. Among patients reducing the dose of painkillers, 32% discontinued the use of painkillers altogether. There were no statistically significant differences in body weight change in patients from the intervention group [10].

Research analysis on the effect of polyunsaturated fatty acid supplementation in RA patients was also the subject of a meta-analysis by Gioxari et al. [11]. The analysis included 20 randomized controlled trials of at least 3 months duration. It has been proven that oral omega-3 fatty acid supplementation significantly improves the values of disease activity markers including early morning stiffness (EMS), tender joint count (TJC), erythrocyte sedimentation rate (ESR) and pain scale. Among the inflammation markers, only the concentration of leukotriene B4 was significantly decreased. The positive effect of supplementation was also noticed on the lipid profile. A significant decrease in triglycerides levels has been demonstrated in patients in the intervention groups, which may be beneficial in reducing the risk of developing cardiovascular disease in patients with RA.

The analysis also includes the intake of products rich in omega-3 acids in patients with RA. In a cross-sectional study by Tadeschi et al. [12] the relationship between fish consumption and disease activity was investigated. The data of the ESCAPE-RA cohort were used for the study. Based on the analysis of the Food Frequency Questionnaire (FFQ) collected from the RA patients, it was observed that patients who consumed 2 or more portions of fish per week had a significantly lower DAS28-CRP index compared to those who did not eat fish at all or one portion per month.

The pro-health properties of omega-3 acids are believed to be in their anti-inflammatory action as precursors of lipid mediators of inflammation, modelling the inflammation. Moreover, many studies on animal models have shown a lower production of pro-inflammatory cytokines: TNF-α, IL-1β and

IL-6, and a decrease in leukocyte migration when EPA and DHA acids are supplemented [13, 14].

Polyphenols and antioxidants

Other tested bioactive substances in RA therapy are polyphenolic compounds and antioxidants, commonly found in foods of plant origin, including turmeric, cinnamon, green tea leaves, citrus and berry fruits. The health-promoting properties of polyphenols are related to their antioxidant activity by participating in the inhibition of the production of reactive oxygen species, as a result of which they limit the transformation of organic compounds related to oxidation [15, 16].

An example of a phenolic compound with such an effect is quercetin, whose supplementation was the subject of studies by Javadi et al. [17]. Fifty women who did not smoke and did not take other supplements were randomly assigned to the study group receiving a supplement of quercetin at a dose of 500 mg/day as a capsule or the control group receiving a placebo. Physical examinations and biochemical measurements to assess disease activity were performed both before and after the intervention. Daily quercetin supplementation (500 mg/day) was shown to have a positive effect on pain and morning stiffness, and decreased disease activity. Additionally, after the end of the study, there was a difference between the groups in the concentration of tumour necrosis factor ($p = 0.04$) and in the erythrocyte sedimentation rate, but it was not statistically significant.

Similar results were obtained by the authors of a randomized, double-blind study analysing the effects of a pomegranate extract supplement in people with RA. Patients from the placebo group took 2 capsules with cellulose daily, while those from the research group took 2 capsules containing 250 mg of pomegranate extract. Compared to the control group, the study group showed a significant reduction in the DAS28 index and the Health Assessment Questionnaire (HAQ) score. In the intervention group, a reduction in the number of swollen joints, the intensity of pain and the erythrocyte sedimentation index were also observed [18].

Beneficial therapeutic effects were also observed in the case of supplementation with micronutrients with antioxidant properties. In an Iranian study in 2014, a group of 39 women with RA took a daily supplement of 50 g of selenium, 8 mg of zinc, 400 g of vitamin A, 125 mg of vitamin C and 40 mg of vitamin E for 12 weeks. The aim of the experiment, apart from showing the effect of supplementation with antioxidant compounds on disease activity, was also to analyse the concentration of enzymes involved in the reduction of oxidative stress. The results of the conducted studies showed a decrease in the DAS28 index and C-reactive protein concentration in sick patients, while the change in the number of painful and swollen joints was not statistically significant. In turn, the concentration of antioxidant markers – glutathione peroxidase (GPX), superoxide dismutase (SOD) and catalase (CAT) – increased significantly after the intervention [19].

In recent years, there has also been an increase in interest in phytotherapy, that is the use of herbal preparations, as an element supporting the therapy of joint diseases. Many plant materials have been shown to have unique anti-inflammatory and immunostimulatory properties. Such plants species are, among others: field horsetail (*equisetum arvense*), Indian ginseng (*withania somnifera*) and ginger (*zingiber officinale*). In addition, their use can alleviate the feeling of side effects caused by pharmacotherapy, especially digestive side effects. However, attention should be paid to the need for further research in order to create official recommendations of herbal preparations as a therapy supplementing standard treatment due to many aspects of concern, such as: drug interactions, low bioavailability, insufficient standardization and legal regulations introducing the supplement to the market [20, 21].

Nutrition models in RA

The effectiveness of supplementation with bioactive compounds in clinical trials contributed to the search for specific nutritional models that could support the treatment of RA. Most attention is paid to the Mediterranean diet due to its high supply of polyunsaturated fatty acids, fruits, vegetables, whole grains and low consumption of red meat. Literature data also indicate

its high effectiveness in the prevention of cardiovascular diseases, metabolic disorders and neurodegenerative diseases [22, 23].

A systematic review of randomized clinical trials conducted in 2018 analysed the effects of the Mediterranean diet on the prevention and the treatment of rheumatoid arthritis. Two prospective studies and two clinical trials were included for the evaluation. There was insufficient evidence to support the thesis that the Mediterranean diet was effective in preventing RA, and there was limited evidence for pain reduction as measured by the visual analogue scale (VAS). One study reported a reduction in DAS28 after the intervention. The authors of the analysis recommend conducting further studies with a longer duration and greater diversity of the population covered by the intervention. Nevertheless, the implementation of nutritional recommendations based on the principles of the Mediterranean diet may bring secondary benefits in patients with RA, e.g. reduce the risk of cardiovascular diseases [24].

Similar conclusions were drawn during the ADIRA study analysing a diet based on products with anti-inflammatory properties. RA patients were divided into an intervention group and a control group whose diet was based on the dietary recommendations for the Swedish population. The intervention group received products to build a diet rich in omega-3 acids, dietary fibre, fruit, vegetables and probiotics (*Lactobacillus plantarum 299v*). The study lasted 4 months, then participants switched diets. It has been proven that an anti-inflammatory diet changes the lipid profile in RA patients towards a less atherogenic profile. The same study also analysed the effect of this nutritional model on disease activity, but no significant reduction was achieved [25, 26].

Another popular diet today is a vegan diet that excludes animal products. Current literature data suggest it has a beneficial effect in the treatment of RA through a high supply of dietary fibre and antioxidants, increasing the bacterial diversity in the intestinal microbiome, which may potentially reduce inflammation. In a study published in *Nutrients* in 2019, a favourable ratio of Th1 lymphocytes to Th17 lymphocytes and a reduction in bone erosion markers were observed in RA patients who were on a high-fibre diet for 28 days. Moreover, a properly balanced vegan diet may have a positive effect on the regulation of body weight and lipid metabolism [27, 28].

Conclusions

Diet is currently a widely discussed aspect in supporting the therapy of autoimmune diseases. Numerous studies show a positive effect of bioactive compounds in the treatment of rheumatoid arthritis. A properly balanced and varied diet including products with anti-inflammatory properties can bring many therapeutic benefits, especially in reducing disease complications and the risk of obesity and cardiovascular disease in patients with rheumatoid arthritis.

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Urinary Incontinence as a Significant Problem in Neurological Diseases

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Abstract

Background: *Urinary incontinence is a common problem among the general population. In patients with neurological diseases, this phenomenon is much more common; its diagnosis and treatment are often overlooked due to other symptoms that are easier to perceive. In neurological diseases, urinary incontinence can have various causes, related to brain damage as well as damage to the peripheral nerves or the spinal cord.*

Objectives: *The aim of this study is to draw attention to the often-overlooked problem of urinary incontinence among neurological patients.*

Material and Methods: *The data was analysed from the many articles available using Google Scholar and PubMed. The mechanisms have been discussed, so that the work is better understood and provides a complete analysis of the problem of urinary incontinence in neurological diseases.*

Results: *Urinary incontinence is an often-overlooked problem associated with neurological diseases. The various mechanisms that lead to urinary incontinence pose a challenge to effective treatment. There are many therapies used in treatment, including drug therapy, neurostimulation, surgery, but also behavioural therapy and treatment of the underlying disease.*

Conclusions: *Due to the various causes of urinary incontinence in patients with neurological diseases, more studies should be done to improve patients' quality of life.*

Key words: *urinary incontinence, neurology, multiple sclerosis, Alzheimer's disease, Parkinson's disease*

Introduction

Urinary incontinence [UI] is defined as the involuntary, uncontrolled leakage of urine from the urethra. Among patients with neurological diseases, this problem is quite common – a meta-analysis showed that the incidence of UI was 50.9% in patients with multiple sclerosis, 52.3% with spinal cord injury, 33.1% with Parkinson's disease and 23.6% with a stroke [1]. According to the International Continence Society (ICS), there are three main types of urinary incontinence: stress urinary incontinence, overactive bladder (or urge incontinence) and mixed incontinence. Stress urinary incontinence is associated with the weakening of the pelvic floor muscles, which do not properly clamp the urethra, while urgent incontinence is caused by abnormal and excessive bladder activity – there is, often a very strong, urgent need to urinate and it usually takes a few seconds to urinate outflow. In the mixed form, we observe both these mechanisms overlapping each other. UI can manifest as a constant leakage of urine, realizing a small amount of urine and a lack or less of an urge to urinate. Risk factors for urinary incontinence include female gender, Caucasian, age, obesity, smoking, pregnancy, natural childbirth, pelvic surgery, pelvic radiotherapy, and neurological diseases.

UI related to neurological causes may result from damage to the brain, peripheral nervous system, or spinal cord. This applies to people with diseases such as multiple sclerosis, Alzheimer's, Parkinson's disease, diabetes, tumours of the central nervous system and congenital spinal defects, or a history of spinal cord injury, spine surgery, stroke, or heavy metal poisoning such as mercury. Drugs used in neurological diseases also contribute to the development of UI (drug-related urinary incontinence) [2]. Urinary incontinence in the course of neurological diseases is often referred to as NLUTD – neurogenic dysfunction of the lower urinary tract (neurogenic bladder). Urine loss in these patients may also be due to factors that impede toilet use, including problems such as cognitive impairment, movement disorders, and deregulated micturition. Adequate diagnosis can be useful in finding the specific location of a neurological impairment [3].

Urinary incontinence is an important disease entity that is a complication of neurological diseases – it is not only a medical challenge, but also significantly worsens the patient's quality of life.

Multiple Sclerosis (MS)

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system that also affects the urinary system, leading to dysfunction of the lower urinary tract (LUT). It is estimated that 8 years after the diagnosis of MS, patients report symptoms of LUT dysfunction [4].

In the course of MS, the myelin sheaths of nerve fibres are lost, mainly in the white matter, manifested as injures (plaques). This process leads to multifocal (disseminated) damage to the brain and spinal cord, and thus to numerous neurological disorders. Clinical symptoms of MS include: paraesthesia, motor weakness, inflammation of the retrobulbar nerve, unsteady gait, dizziness, double vision and urination disorders [5]. The most common manifestation of urinary disorders is urinary incontinence (UI), which, as a factor causing inconvenience in everyday activities and limiting trips, often leads to a reduction in social life and a reduction in Quality of Life (QOL) [6]. In patients with MS, the main reason leading to UI is the lack of control over the muscles responsible for urinary incontinence and the detrusor hyperactivity [7]. It is an often overlooked problem which, if left untreated, may lead to recurrent urinary tract infections, repeated hospitalizations and, moreover, a deterioration of the patient's clinical condition, which is why proper management of these disorders is so important [8].

The selection of appropriate treatment should take into account the patient's mobility, disease phase, manual dexterity, comorbidities and the degree of urinary disorders [4].

Pelvic floor muscle training

Pelvic floor muscle training is of benefit only to patients with preserved pelvic floor muscle contraction. This training activates the reflex inhibiting the

activity of the detrusor muscle with voluntarily contracted pelvic floor muscles [9]. Research on the effectiveness of such treatment is ambiguous due to the small number of patients and the discussion of gender-specific methods [10].

Pharmacological treatment

The choice of pharmacological treatment depends on whether the patient has a problem with voiding or with urine storage [11].

In the treatment of problems with voiding, alpha-blockers are used, which, by inhibiting the action of the sympathetic system on the internal urethral sphincter and the smooth muscle of the bladder neck, reduce the degree of bladder obstruction [12]. In cases of resistance to pharmacological treatment, catheterization or neuromodulation may be proposed.

Antimuscarinic drugs and beta-3 agonists are used in the pharmacological treatment of urine storage problems. By blocking detrusor muscarinic receptors, antimuscarinic drugs inhibit its activation [13]. The use of oxybutynin and solifenacin in urine storage disorders in MS was tested in comparison with a placebo, and an improvement in urination frequency, urinary incontinence and an increase in QoL was demonstrated [14]. Unfortunately, antimuscarinic agents bind non-selectively, which is responsible for the side effects of these drugs: constipation, blurred vision and a dry mouth [15]. A representative of beta-3 receptor agonists is mirabegron, which significantly improves the frequency of urination and incontinence episodes [16].

In pharmacological treatment, desmopressin, Phosphodiesterase Type 5 Inhibitors and Cannabinoids may be considered [17–19]. In case of the ineffectiveness of pharmacological treatment, intravesical treatments may be considered. The most commonly used botulinum toxin inhibits detrusor activity and thus significantly improves QoL and reduces urinary incontinence episodes in MS patients [20]. The most common complications of the procedure were urinary retention and urinary tract infections [21].

The treatment of urinary system disorders in the course of MS includes neuromodulation (stimulation of the tibial nerve, stimulation of the sacral nerve), surgery and catheterization [22].

Alzheimer's disease

Lower urinary tract dysfunction is a common phenomenon in patients with dementia, often accompanied by multiple morbidity and multiple social and economic burdens.

Lower urinary tract symptoms lead to restricted activities of daily life and, consequently, a deterioration in the quality of life of the patients [23]. Urinary incontinence is common in the group of patients with Alzheimer's disease and may lead to numerous complications in the course of this disease [24]. Urinary incontinence in patients with dementia is not only the result of cognitive impairment, but may also result from urological disorders such as detrusor overactivity [23].

Despite the existence of international guidelines for the treatment of urinary incontinence, they often do not address the complex comorbidities of Alzheimer's patients and are rarely followed. Most dementia patients can be successfully treated with standard treatments, both pharmacological and non-pharmacological. The diagnosis of dementia does not exclude the treatment of urinary incontinence, but options may be narrowed in patients with advanced dementia who are unable to understand and remember the information given to them [25].

According to a study conducted by Hae Ri Na et al., the incidence of urinary incontinence in patients with Alzheimer's disease was 24.8%. The most common types of urinary incontinence were urgent urinary incontinence (44.3%) and functional incontinence (25.3%). Urinary incontinence in patients suffering from Alzheimer's disease was clearly correlated with the Barthel scale [26]. A study conducted by Robert L. Grant and colleagues also provided conclusive data; urinary incontinence is three times more common in patients with dementia than in non-demented primary care patients in the UK [27].

Treatment of urinary incontinence in patients with dementia is conditioned by factors such as comorbidities, the use of multi-drug therapy and other urological ailments. The first step of the treatment is behavioural therapy, but this will not be appropriate for all patients. Behavioural programmes such as timed voiding, habit training, and prompted voiding can reduce the

problem of urinary incontinence in cognitive-impaired elderly people. Electrostimulation, biofeedback and pelvic floor muscle exercises are reccomended elderly people without advanced cognitive and physical disorders [22]. Drug treatment should be considered when behavioural therapy is not producing the desired results. The type of treatment depends on whether the patient has problems with urination or storage. Anticholinergic drugs or mirabegron, a beta-3 receptor antagonist, are used to treat urinary incontinence [23]. The mechanism of action of antimuscarinic drugs is to inhibit bladder contraction, while mirabegron, by activating beta-3 adrenergic receptors in the detrusor muscle, results in bladder relaxation and an increase in its capacity [28]. Unfortunately, the use of antimuscarinic drugs in the geriatric population carries the risk of cognitive deterioration due to side effects with long-term use [23]. Cognitive decline is associated with a blockade of the M1 muscarinic receptor in dementia patients who initially have low levels of acetylcholine in the brain [29]. The disturbances resulting from the use of antimuscarinic drugs are reversible upon their withdrawal. However, there are reports that antimuscarinic drugs may lead to an increased risk of dementia [30].

In the case of patients with problems with urination, only alpha-blockers are currently used [22, 23].

Parkinson's disease

With over 6 million cases [31], the second most common neurodegenerative disorder after Alzheimer's belongs to Parkinson's disease (PD) [32]. It is a progressive disorder of the central nervous system that leads to the death of the patient [33]. It has been noticed that its incidence increases with age and is more common for men than women. The aetiology relates to the loss of dopaminergic neurons in the substancia nigra of the midbrain, the occurrence of Lewy bodies inside nerve cells and increased neuroinflammation. Moreover, cholinergic, GABAergic and noradrenergic cells can be damaged, such as the primary ones [34–36].

Diagnosing Parkinson's disease is about examining the patient and knowing the history of his illness because of the heterogeneous nature of this

disorder. Progression can be slow or very rapid depending on each patient [31]. There are typical symptoms of PD normally defined by motor perturbations and disease is typically diagnosed when the first one appears. Many of these include bradykinesia, rest tremor, rigidity of muscles or postural instability [35]. PD also has non-motor symptoms and one of them is urinary incontinence which may occur first, before traditional symptoms [37].

Urinary incontinence (UI) is an embarrassing problem for patients with Parkinson's disease, which significantly affects quality of life [36]. As a neurodegenerative disorder PD impacts the nerve function of the bladder which causes neurogenic bladder dysfunction [38]. Unfortunately this symptom does not always respond to treatment with levodopa which suggests the cause of this problem is complex [39]. Urinary problems also include frequent nocturnal urination, daytime pollakiuria, and urgency [40].

Thirty-eight to 71% of patients with PD complained because of lower urinary tract symptoms [41]. However, it is not possible to conclusively determine whether this problem is due to Parkinson's disease or some other cause. This symptom is also reported by patients with clinically silent cerebral ischemia, with benign prostatic hyperplasia and women with stress urinary incontinence [42, 43].

Videourodynamic examinations, pressure-flow analysis and electromyography have been used to diagnose bladder problems. Patients with PD have reduced bladder capacity with excessive detrusor activity, consisting of phasic and involuntary detrusor contraction, and unstoppable relaxation of the external sphincter due to the voluntary reduction of its electromyographic activity, which usually exists with excessive detrusor activity [43, 44]. The last one may therefore be the main factor of excessive bladder activity [45]. The pressure-flow analysis of the voiding phase in PD shows weak detrusor activity during voiding and a slightly decreased urethral patency [46, 47].

Regarding treatment, levodopa and other antiparkinsonian drugs may affect the way the bladder works. In research with apomorphine and levodopa a positive effect was obtained in the form of bladder enlargement and disturbing symptoms were much less frequent. In others studies switching bromocriptine with pergolide reduced nocturnal urination [48]. However,

the use of dopaminergic drugs can be unpredictable [49]. Parasympatholytics are generally used as the first line treatment of an overactive bladder. They should be taken carefully because too high a dose may cause urine retention [50, 51].

Studies on Studies on pharmacological treatment have also shown the positive effect of mirabegron (β3 adrenergic agonist) on patients with Parkinson's disease. Most of the respondents report improvement in treatment so this drug is safe and effective for them if they are resistant to anticholinergic medications [32].

It is not only drugs that can be used in the treatment of urinary incontinence. Research has shown that behavioural therapy can also have a positive effect. In a randomized study, it was proved that regular pelvic floor exercises, bladder training, and constipation and fluid control management improved the quality of life of patients [52]. In the treatment of urinary incontinence, you can also try deep brain stimulation. It involves stimulation of the globus pallidus pars interna or the nucleus of the hypothalamus. In a twelve-month study, a positive effect was found in urinary retention and the frequency of urination regardless of gender. Unfortunately, the stimulation showed no effect on nocturia and nocturnal urinary intrusion [53].

Brain stroke

Studies imply there is a significant correlation between urinary incontinence (UI) and being a post-stroke patient. Therefore, UI often causes long term disability and may lead to the institutionalization of these patients [54]. We can distinguish full, partial and no UI symptom states. During the acute stage of a stroke the proportions between those three is as follows: 41%, 12%, and 47%. We can observe the change in the 12 following months, where the percentage of full UI drops to 16%, partial UI moves to 16% and no UI grows to 68%. Worth mentioning is the fact that during those 12 months (following the stroke incident) 45% of patients that experienced full or partial UI were institutionalised compared to 5% of patients who developed no symptoms of UI. The logistic regression model shows that we can differentiate three

independent factors creating a higher risk of institutionalizing a patient during the 12 months after a stroke. Those factors are: severe disability at 12 months, age and urinary incontinence at day 7 [55].

These results are confirmed in data collected from a population of unselected stroke survivors, of whom more than 50% experience UI in the acute stage of a stroke. This number drops to one third in the next 12 months. In this case the risk of being institutionalised is also significantly higher for stroke survivors who were incontinent during the acute stage of a stroke [56].

The researchers of urodynamic studies agree that the main cause of post-stroke urinary incontinence is the overactivity of a detrusor. The exact number varies between 28% and 79% [57]. While diagnosing a type of UI it is crucial to conduct a physical exam and study the case history.

The numbers presented above are from one of the few studies from one of the few studies conducted in this field. The authors of those which exist emphasize the need for further investigation of post-stroke UI as well as the risks and symptoms [58]. Furthermore, there is still a lack of data showing the effects of pharmacologic and non-pharmacologic treatments in post-stroke UI patients. Pharmacological treatment includes beta adrenergic medications and antimuscarinics but its use is still experimental. There is also no hard proof of behavioural therapy being effective [59]. Obtaining such data could become crucial in creating treatment allowing post-stroke survivors to elevate their life comfort.

Urinary incontinence can become an issue reducing life quality causing further behavioural disorders. The lack of ability to control the urine flow can discourage a patient from participating in social activities. It may furthermore lead to social distancing and depression [60].

Existing research and collected data support the thesis that assessment of the severity and type of post-stroke urinary incontinence is significant for the patient [55]. Acknowledging the connection between occurrence of the UI in the acute stage of a stroke and the risks it brings should encourage stroke health professionals to study this field more thoroughly [38]. This could create an individually tailored treatment strategy to reduce the symptoms of urinary incontinence.

Discussion

The problem of urinary incontinence in neurological diseases occurs largely in poorly treatable or untreatable conditions. Another link can be seen; the diseases mentioned above have a strong correlation with the age of the patient, namely their incidence increases in increasingly older patients. The exception here may be multiple sclerosis, MS, which primarily affects young people, but also to some extent, stroke, as its occurrence is also associated with comorbidities such as hypertension, atherosclerosis, overweight/obesity. It can be concluded in this situation that stroke is predominantly influenced by an unhealthy diet and static human lifestyle, which can be related to age, although there is an increasing incidence in people in the group of 20–64 years [61, 62].

In developed countries, one can see ongoing social changes such as declining birth rates, increasing wealth, a focus on educating individuals, and increasing life expectancy due to rapid medical advances. The consequence of this is the increasing percentage of elderly people over 65 years old among the citizens of European countries [63]. It can be deduced that incontinence resulting from Alzheimer's, Parkinson's and stroke will increase and become a more and more common problem over the coming years.

In the aforementioned neurological conditions (Alzheimer's disease, Parkinson's disease, stroke and MS), a variety of pharmacological and physiotherapeutic treatments are tested and used. The results of the study are promising, but so far, no fully effective method has been found to eliminate urinary incontinence in seniors, and there are too few data on the effectiveness of treatment methods in the elderly and in people with neurological diseases. Surgical treatment is considered to be an effective method only in the case of stress urinary incontinence [64].

The lack of fully effective treatment methods and the consequent persistent incontinence may lead to episodes of urinary tract infections [65]. A population-based study of 157 men and 322 women aged 85–86 published in 2011 noted that urinary incontinence and cognitive impairment of daily living (ADL) were independent risk factors for urinary tract infection (UTI) in older

adults aged 85–86 years [66]. In addition, a history of urinary tract infections can lead to increased incontinence among women [67]. This is dangerous because, UTI can have a real impact on mortality in elderly people [65].

Reduced quality of life in these patients is also an important consideration. One of the most common conditions of old age, in addition to those mentioned above, is depression. Urinary incontinence can result in decreased life satisfaction, making it a risk factor for depression in seniors [68]. A 2018 study of 510 women with different types of incontinence found that increasing the severity of the condition, not the type of incontinence itself, increased stress, but also anxiety and depression [69]. Additionally, it was noted that in addition to incontinence, Parkinson's disease is also a common comorbidity with depression [70].

Seniors with Alzheimer's, Parkinson's, MS and stroke may have difficulty or be unable to perform activities of daily living, thus requiring additional assistance from others, often family members. Such a relationship can cause a sense of shame and lead to lower self-esteem, but it is also an additional risk factor for skin infections, largely due to poor hygiene of the genitourinary area [71].

The emerging consequences significantly underline the importance of finding and refining a fully effective treatment method that not only eliminates the problem of urinary incontinence, but also indirectly prevents the development and aggravation of other currently serious diseases of old age.

Conclusion

Incontinence is a common problem in patients with neurological diseases, affecting up to 50% of them. UI significantly deteriorates the patient's quality of life. Possible causes of this condition are brain damage caused by the disease, medications and other disorders associated with the disease.

In the course of MS, multifocal damage to the brain and spinal cord results, inter alia, in the lack of control over the muscles responsible for urinary incontinence and detrusor hyperactivity, leading to UI. Alpha-blockers, antimuscarinics, beta-3 agonists, desmopressin, phosphodiesterase type

5 inhibitors, and cannabinoids may be effective in MS patients. In the event of ineffectiveness of pharmacotherapy, neuromodulation, surgery or catheterization can also be used.

Patients with AD suffer from UI due to cognitive impairment and urological disorders such as detrusor overactivity. A problem in the treatment of urinary incontinence in AD patients may be a disturbance in remembering and understanding information. The first step in treatment will be behavioural therapy. In patients with preserved cognitive functions, electrostimulation, biofeedback and pelvic floor muscle exercises can be used. Drug treatment should be considered when behavioural therapy is not producing the desired results. Anticholinergic drugs or mirabegron, beta-3 receptor antagonists, are used in the pharmacotherapy of UI in patients with AD. It should be remembered that antimuscarinic drugs in the geriatric population may contribute to the deterioration of cognitive functions with long-term use.

UI in PD is caused by neurodegeneration affecting bladder function, resulting in neurogenic bladder dysfunction. Patients with PD have reduced bladder capacity with excessive detrusor activity. Treatment with levodopa and anti-Parkinsonian drugs, e.g. apomorphine, bromocriptine and pergolide, had a positive effect on reducing the frequency of disturbing symptoms. Parasympatholytic drugs used in the treatment of an overactive bladder and beta-3 adrenergic agonist mirabegron were also positive. Non-pharmacological treatments for UI include behavioural therapy and deep brain stimulation.

Stroke patients suffer from UI mainly due to detrusor overactivity as a result of brain damage. Pharmacological treatment includes adrenergic and antimuscarinic beta-drugs, but there is no evidence that such treatment is effective in patients after a stroke. There is also no unequivocal evidence of the effectiveness of behavioural therapy in stroke patients with UI.

Due to the high prevalence of the problem, more data should be obtained on possibly effective therapies that could improve the quality of life of neurological patients with UI, such as pharmacotherapy, behavioural therapy, pelvic floor muscle training and deep brain stimulation.

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Safety and Efficacy of Using NOAC as Prevention of Ischemic Stroke in the Geriatric Population with Atrial Fibrillation – Review Article

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Abstract

Introduction: *Atrial fibrillation is a common arrhythmia in the elderly population, which may lead to thromboembolic events complicated by ischemic stroke. The frequency increases with age along with other chronic diseases such as diabetes or hypertension. Non-vitamin K antagonist oral anticoagulants (NOACs) are the main drugs used in the prevention of stroke, taking the place of vitamin K antagonists (VKAs).*

Materials and Methods: *The article reviews the literature using the Pubmed and Google Scholar databases. Articles were analyzed using keywords: atrial fibrillation, elderly, NOAC, VKA, ischemic stroke.*

Results: *Many studies have shown that NOACs are a groundbreaking achievement in treating thromboembolic events such as ischemic stroke, even in the elderly. Their efficiency and safety surpasses VKAs as they have better pharmacokinetics and pharmacodynamics along with a wider therapeutic index, no need for monitoring, less risk of interactions and fatal bleeding, but with higher risk of gastrointestinal bleeding.*

Conclusion: *NOACs are efficient and safe in the elderly with atrial fibrillation for ischemic stroke prevention. Caution should be kept in patients with renal failure or a prosthetic valve. Interactions are not serious but possible when taking NOACs with drugs such as carbamazepine. Investigation is still indicated for reviewing this issue further.*

Key words: *atrial fibrillation, elderly, NOAC, VKA, ischemic stroke*

Introduction

Atrial fibrillation (AF) is the most common arrhythmia. Estimated data indicate that in 2016 it affected 46.3 million people worldwide. Age is the main risk factor, which is confirmed by the increasing trends in the elderly.

Morbidity is increasing because appropriate treatment of chronic diseases in the elderly population extends their lives, which however, results in an increased incidence of atrial fibrillation. In addition to age, risk factors include high BMI, hypertension, heart attack, heart failure, smoking and genetic predisposition [1, 2].

Atrial fibrillation results from atrial fibrosis and enlargement, which lead to the wrong conduction of electrical impulses and the chaotic work of the heart. This arrhythmia is one of the major risk factors for stroke. This is due to the disturbed mechanical work of the atria and blood stagnation, which serves to form a blood clot in the left atrium. The embolic material is a cause of ischemic stroke, the probability of which is increased 4–5 times in patients with AF [1, 3]. Therefore, appropriate treatment should be implemented to prevent stroke. The main therapy is oral anticoagulation (OAC). Among the drugs, vitamin K antagonists (VKAs) have dominated for many years but there is an increasing trend of using non-vitamin K antagonist oral anticoagulants (NOACs), which have quickly become first choice drugs.

OAC, especially the use of NOACs, reduces mortality, the occurrence of ischemic stroke and hospitalizations. In connection with all these expected results OACs are indicated to prevent stroke especially in the elderly. However, during the therapy, people are in danger of major bleeding, mainly intracranial hemorrhage (ICH). Despite that, the benefits outweigh the risks, which show the need to use them even in the geriatric population [4].

Results

NOAC – characteristics

Oral anticoagulants are used to prevent ischemic stroke in patients with atrial fibrillation. It is especially important to use them in the elderly. However, this raises many concerns, mainly due to multiple diseases, multi-drug use or the presence of geriatric syndromes. The main concern is the risk of major bleeding, and special attention is given to intracranial bleeding (ICH), especially because of the risk of falls in this age group. As a result, some elderly patients are excluded from anticoagulation therapy or are treated less effectively, e.g. by administering acetylsalicylic acid (ASA) [5, 6].

Many European and American societies (AHA, ESC, EHRA) indicate the need for anticoagulant treatment of patients with AF, especially the elderly. Despite the fact that, in the studies, people over 75 years of age do not constitute the majority, the obtained results allow for drawing conclusions and recommendations as to the safety and efficacy of OAC in this age group. Treatment discontinuation is recommended only when there is a low risk of stroke. The CHA2DS2-VASc scale, which takes into account e.g. cardiovascular diseases, age, sex and thromboembolic events is crucial in assessing the necessity of stroke prevention. According to the gender scoring, OAC should be used in men with ≥ 2 points and in women with ≥ 3 points [7, 8].

In addition to the CHA2DSc-VASC classification, the acronym ABC (A – avoid stroke / anticoagulation, B – better symptom control, C – cardiovascular risk and comorbidity optimization) highlights the role of anticoagulation in the treatment of AF. It is equally important to assess the risk of bleeding using the HAS-BLED scale (Hypertension, Abnormal liver / renal, Stroke, Bleeding, Labile INR, Elderly, Drugs and alcohol). Obtaining ≥ 3 points means a high risk of bleeding and is the basis for considering the withdrawal from OAC [9, 10].

For several decades, the main drugs have been VKAs, mainly warfarin. Drugs in this group are characterized by several mechanisms of action, primarily blocking the production of vitamin K-dependent coagulation factors. However, their use is associated with many problems, such as slow onset

of action, a narrow therapeutic index, drug and food interactions, and the need to monitor coagulation parameters. To avoid this, NOACs were created, which are distinguished primarily by the fact that they block only one coagulation factor. Apixaban, rivaroxaban and edoxaban block factor Xa, while dabigatran blocks thrombin (factor II). These drugs have the advantage of a quick onset of action, favorable pharmacodynamics and pharmacokinetics, no food interactions, and little drug interaction. In addition, they are characterized by a wide therapeutic window and no need to monitor coagulation parameters. Their use is limited by liver diseases and kidney failure. Many studies show their greater effectiveness and safety, mainly compared to VKAs. So far, based on research, they have been recognized as the drugs of choice for the treatment of non-valvular atrial fibrillation, deep vein thrombosis and pulmonary embolism and for the prevention of thromboembolic complications after hip and knee arthroplasty [5, 11, 12].

The RE-LY, ARISTOTLE, ROCKET-AF, ENGAGE-AF studies showed at least the same or even higher efficacy of each drug when separately compared to VKAs. A better therapeutic effect was demonstrated for apixaban and dabigatran. A statistically significant reduction in the risk of major bleeding was demonstrated primarily for apixaban, but also for edoxaban. However, most importantly, when using NOACs, there is a lower risk of ICH compared to VKAs, also in people over 75 years of age. Apart from ICH, an important issue is the occurrence of gastrointestinal bleeding – among NOACs, apixaban shows the greatest reduction of this risk. Additionally, this effect can be achieved by not using ASA and NOACs together and by including PPIs – mainly pantoprazole [4, 13].

Renal failure and the related creatinine clearance are an important issue with the use of NOACs. With age, kidney function deteriorates, which limits the use of certain medications. This also applies to NOACs, the dosage of which depends on the creatinine clearance. In this case, the dose should be reduced (usually by half), which, however, reduces the anticoagulant efficacy and increases the frequency of thromboembolic events. In contrast, the risk of major bleeding does not decrease with dose reduction. In the absence of concomitant renal failure in people over 80 years of age, the dose of the

NOAC should not be reduced, except for dabigatran. Even with dose reduction, a higher efficacy of NOACs over VKAs was demonstrated, except for rivaroxaban [4, 7]. Table 1. shows the standard and reduced doses as well as the indications for dose reduction [3, 13].

There are also important contraindications to anticoagulant therapy, including hemorrhagic diathesis, subarachnoid hemorrhage, gastrointestinal bleeding and liver failure (Child-Pugh C). Moderate/severe mitral stenosis and the presence of a mechanical heart valve are also contraindications to NOAC therapy. In this case, a VKA is recommended for therapy [9, 14]. Moreover, the manifestation of even major bleeding is not a contraindication to return to NOAC therapy later [13]. Absolute contraindications to OAC may be an indication for the closure of the left atrial appendage [15].

Until recently, there was concern about the lack of an antidote to the treatment of NOACs in the event of bleeding, which was particularly severe and life-threatening. Currently there are antidotes. For dabigatran it is idarocizumab and for factor Xa inhibitors it is andexanet alpha. This is another premise for their use instead of VKAs [5].

NOACs compared to VKAs

NOACs (new oral anticoagulants) are drugs used increasingly in the prevention of thromboembolic events in atrial fibrillation as a relatively safe and convenient option; however, VKAs (vitamin K antagonists) are still a popular choice – primarily due to their lower cost, which is an important determining factor, especially in the elderly population. Warfarin, introduced in the 1950s, was the basic anticoagulant drug; it effectively protected against venous thrombosis and pulmonary embolism, and for many years it had no suitable alternative. Due to the fact that NOACs were introduced only in 2009, VKAs have been used for a considerable period of time, and their therapy is often still continued in patients who have been taking them for so long and do not want to switch to NOAC therapy, which mainly concerns the geriatric population [16].

VKAs work by inhibiting the Y-carboxylation of factors II, VII, IX, X (dependent on vitamin K) by blocking vitamin K epoxide reductase, which leads

to the formation of the so-called PIVKA (protein induced by vitamin K absence) with reduced activity. The main representatives are warfarin and acenocoumarol. They are administered orally, once a day, and the dose must be adjusted to the INR value [17]. Due to the fact that the anticoagulant action is delayed – therefore, when the effect must be obtained immediately, bridge therapy is used, i.e. together with low-molecular-weight heparin for at least 5 days, until the INR is 2–3 for 2 consecutive days. INR should be measured regularly (usually every 4–6 weeks), because VKAs have a narrow therapeutic index, and elevated INR may lead to bleeding [17, 18].

The convenience of using NOACs is not having to determine any laboratory values and carry out such strict controls. This limits the number of necessary medical visits and examinations. It is worth emphasizing that patients often do not follow the rules defined in the case of VKAs, which may pose a risk of bleeding. Studies have shown that it is more common in people taking VKAs, especially in the elderly population with atrial fibrillation [19]. Major NOAC bleeding was also less frequent in patients aged 85 and over and in those with a low BMI [20]. According to the meta-analysis published in the European Heart Journal, Cardiovascular Pharmacotherapy, which included 22 studies and over 440,000 patients, in elderly patients with AF, the use of NOACs is associated with a lower risk of events such as intracranial bleeding, cerebral hemorrhagic stroke and fatal bleeding than VKAs, but the risk of gastrointestinal bleeding increases [21, 22]. NOACs cannot be used in patients with end-stage renal failure and those on dialysis [23, 24].

VKAs are metabolized by cytochrome P-450, which is associated with another problem, namely numerous interactions with other drugs and chemicals (more than 200 of them have been described for warfarin) – much more intense than in the case of NOACs [17]. It is a huge obstacle for the elderly, who are most often affected by polypragmasy. Drugs such as amiodarone, statins, paracetamol and antibiotics like ciprofloxacin or metronidazole, enhance the anticoagulant effect of VKAs. Diet also has a great influence, because the consumption of green, leafy vegetables, such as cabbage or lettuce, which are after all a rich source of vitamin K, will lead to a reduction in the activity of vitamin K antagonists [25]. This can be a problem for seniors,

for whom vegetables should be an important part of the diet, especially if they suffer from atherosclerosis, diabetes or arterial hypertension, often co-occurring with atrial fibrillation. NOACs do not have clinically significant interactions with food, and drug interactions are less frequent. It should be remembered that in people with a prosthetic heart valve, VKAs are the first choice. In addition, they are safer in the case of renal failure [23, 26]. Table 2. shows VKAs and NOACs compared to each other [27, 28].

NOAC – interactions

Knowledge about NOAC interactions with other drugs is constantly evolving and requires the construction of new, wider clinical trials. NOACs do not show numerous interactions, and if they do, they are not as significant as in the case of VKAs. One Turkish study by Ersoy and others obtained information on NOAC interactions with other drugs and the impact of these interactions on adverse events and deaths. 704 patients with atrial fibrillation participated in the study. All drugs used were tested for drug interactions using the Lexicomp software. Each drug interaction was described according to a risk assessment. A total of 9,883 drugs were analyzed for interactions. Most drug interactions were negligible; therefore they were assigned to group A (80.7%). The clinically significant drug interaction groups were as follows: 256 C class (2.7%), 1168 class D (11.8%) and 23 class X (0.2%). The majority (66%) of group X are antiepileptic drugs (carbamazepine, phenytoin) [29].

After a stroke, seizures occur frequently, so medications to prevent seizures are indicated. There have been reports of interactions suggesting a reduction in the effect of NOACs by antiepileptic drugs, resulting in further strokes or pulmonary embolism. Carbamazepine, levetiracetam, phenobarbital, phenytoin and valproic acid may reduce the effect of NOACs by inducing P-glycoprotein (P-gp) activity. Carbamazepine, oxcarbazepine, phenytoin, phenobarbital and topiramate may reduce the effect of NOACs by induction of CYP3A4. As a result, the anticoagulant effect is weakened [30].

The antiepileptic drugs recommended by the European Heart Rhythm Association for people using NOACs are lamotrigine, zonisamide, pregabalin

and gabapentin. It should be noted that almost all the evidence to date on the risk of recurrent thromboembolic events comes from individual cases. Therefore, it makes sense to create more complex studies to solve a given problem and provide solid evidence. Until then, caution should be exercised when combining antiepileptic drugs and NOAC, especially levothyracetam, carbamazepine, phenobarbital, phenytoin, topiramate and valproic acid [31].

A common group of drugs used among the elderly are SSRIs (serotonin reuptake inhibitors), i.e. drugs with an antidepressant effect. These drugs when combined with the NOAC group increase the risk of bleeding due to their effect on platelets. Therefore, caution should be exercised when combining these groups of drugs [32, 33].

Another group of drugs that may hinder anticoagulant treatment are azole antifungal drugs. In one Danish study, apixaban users had a significantly increased risk of bleeding following exposure to systemic fluconazole. However, there was no increased risk in people taking rivaroxaban and dabigatran. Topical application of azoles did not increase the risk of bleeding [34, 35].

Theoretically there are inhibitors/inducers of CYP3A4 or P-glycoprotein in foods or herbs, but no direct evidence of such interactions has been shown. St. John's wort is a strong inducer, so caution should be exercised when combining this herb with NOAC medications. It is expected that this interaction would lower the concentration of the new oral anticoagulants and would not produce a satisfactory effect. Rivaroxaban shows increased bioavailability when taken with food, so it is best to do so. It has been postulated that citrus, especially grapefruit, affects the bioavailability of rivaroxaban, but this has not been confirmed by clinical studies [36]. Further investigation is needed regarding this important issue due to elderly people taking many medications because of their co-occurrent chronic diseases. Therefore, their safety is also affected by interactions problems.

Discussion

In recent years, there have been some groundbreaking events for NOACs, resulting from large and numerous studies. In 2020 NOACs were added to the

WHO's Essential Medicines List thanks to the work of a team of international experts in various fields, such as cardiology, neurology and public health, who issued an appeal to the WHO, emphasizing the noticeable improvement in safety and efficiency in the prevention of stroke in the treatment of non-valvular atrial fibrillation, with a significant reduction in the number of hemorrhagic strokes, intracranial hemorrhages and, above all, a decrease in mortality with this group of drugs. These conclusions are based on the results of large, randomized studies, primarily published in the NEJM in the years 2009–2013 [37].

A previous attempt to add NOAC to the EML was unsuccessful. The application was rejected on the grounds that evidence based solely on study populations would not be representative of patients who would actually receive such treatment. In addition, attention was then paid to the lack of specific antidotes and the costly nature of such therapy. As we know today, substances are available that are able to reverse the effects of NOACs. Adding NOACs to the List of Essential Medicines increased their therapeutic significance and initiated the course of activities increasing their worldwide availability. Perhaps this significant change will allow the treatment costs to be reduced over time, which will contribute to more frequent conversion of VKAs to NOACs also in the geriatric population [37]. In 2021, NOACs are still on the list [38].

In 2021, Anna Plit, Thomas Zelniker and colleagues conducted a large meta-analysis published in the European Heart Journal – Cardiovascular Pharmacotherapy covering approximately 60 thousand patients with atrial fibrillation coexisting with type 2 diabetes, which is a common problem in the elderly group. The effects of NOACs and warfarin were compared, as well as the benefit-risk balance of their use. It was questioned whether diabetes could be a significant variable, with the result that the outcome would indicate an older class of drugs as the preferred one. However, it turned out as expected – NOACs are safer and more effective, also in diabetics [35, 39, 40].

Summary

The use of NOACs in the prevention of ischemic stroke in the geriatric group is very important and should be the preferred choice. A large part of the

article has been devoted to determining the benefits of this type of anticoagulant treatment. The reason for expanding and delving into this topic is the fact that nearly 50 million people suffer from AF and need effective and safe anticoagulant treatment. Such therapy should also involve minimal or no drug interactions, and this is the pattern shown by NOACs. Still, a large group of elderly people use VKA drugs and we should strive to withdraw them in most cases and replace them with NOACs. This is a debatable topic and when choosing a specific drug, we should take into account the medical and economic aspects together with the patient. There are many advantages to using NOACs, but the most important is the lack of routine monitoring of blood clotting parameters and a relatively low risk of fetal bleeding.

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Table 1. Standard and reduced doses of NOACs in appropriate indications

Drug	Standard dose	Reduced dose + indications
Apixaban	2 x 5 mg/day	2 x 2,5 mg/day (≥ 2 criteria: > 80 yrs, GFR 15–30, body mass < 60 kg, creatinine clearance < 1,5 mg/dL)
Dabigatran	2 x 150 mg/day	2 x 110 mg/day (> 80 yrs, GFR 30–50)
Edoxaban	1 x 60 mg/day	1 x 30 mg/day (GFR 15–49, body mass < 60 kg, concomitant use of verapamil / dronedarone / quinidine)
Rivaroxaban	1 x 20 mg/day	1 x 15 mg/day (GFR 30–49)

GFR – glomerular filtration rate (ml/min per m^2)

Source: [3, 13].

Table 2. Comparison of VKAs and NOACs

Anticoagulants	VKAs	NOACs
Representatives	Acenocoumarol, warfarin	Rivaroxaban, apixaban, edoxaban, dabigatran
Year of introduction	1954	2009
Effect	Inhibition of the reduction of vitamin K and thus the activity of coagulation factors II, VII, IX and X, proteins C and S Factor	Xa factor inhibitors Direct inhibition of thrombin-dabigatran
The way of taking	For the first 2 days – acenocoumarol 6 and 4 mg, warfarin 10 and 5 mg (the elderly can start with 4 mg and 5 mg respectively), then depending on the INR. Therapeutic action after 3–5 days	A tablet up to twice a day depending on the specimen. In patients > 80 years of age < 60 kg or when GFR < 15 ml/min, do not use, < 30 reduce the dose
Monitoring	INR approximately every 4 weeks (target 2.0–3.0, with prosthetic heart valves 2.5–3.5)	Unnecessary
Interactions	Many with drugs (e.g. antibiotics, painkillers, antiarrhythmics) and food (green vegetables)	Few with drugs (e.g. antibiotics, carbamazepine)
Bleeding risk	Increased risk of intracranial bleeding, cerebral hemorrhagic stroke, and fatal bleeding	Increased risk of gastrointestinal bleeding
Cost of therapy	Low cost – PLN 10–20 / package	High – PLN 60–150 / package

Source: [27, 28].

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Using Professional Support when Quitting Smoking
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Abstract

Introduction: *Smoking is defined as a chronic disease with periods of use and abstinence. Reducing tobacco consumption is of key importance to the overall health of the population. The combination of therapeutic education, behavioral support, and pharmacotherapy are key ingredients in smoking cessation. Clinical guidelines recommend cognitive-behavioral intervention together with the administration of first-line drugs (bupropion, varenicline, NRT).*

Interventions of as little as 3 minutes by primary care physicians can help patients to quit smoking successfully. Quitting smoking advice by GPs has been shown to increase rates of quitting smoking.

Aim: *The aim of the study was to assess smoking cessation frequency and the frequency of smoking cessation counseling in primary care.*

Material and Methods: *A cross-sectional study was conducted in 2015 among 114 smokers from the Piotrków district who were referred to a primary care physician. The Bioethics Committee of the Medical University of Lodz issued a positive opinion on the study (RNN/243/15/KE). The research tool was a questionnaire.*

Results: *57% of respondents had tried to quit smoking, the most common number of attempts being 1–2 (32.5% of respondents); 66.7% of respondents intended to quit smoking in the next month, and 22.8% were considering quitting smoking in the next 12 months; 45.6% of respondents had been advised to quit smoking in the last 12 months; and only 38.6% of respondents had ever been given advice on stopping smoking by their GP. In the previous 12 months: 14.9% of respondents had used nicotine replacement therapy, incl. slices or chewing gum; 3.5% of people had benefited from therapeutic help, including the anti-smoking clinic; 3.5% of respondents had used traditional drugs (e.g., champix); and 5.3% of respondents had used prescription drugs (e.g., bupropion).*

Conclusions: *The results suggest that the time spent advising patients on smoking should include helping them to quit smoking. GPs should discuss smoking cessation with more patients who smoke.*

Key words: *smoking cessation, counseling, family doctor, tobacco control, smokers*

Introduction

According to the World Health Organization (WHO), smoking kills more than 8 million people worldwide each year, including about 1.2 million non-smokers as a result of secondhand smoke [1]. The 2018 WHO report on the health of Europeans identified tobacco smoking as one of the main public health problems in the European Region [2]. Smoking is defined as a chronic disease with periods of use and abstinence [3]. Most adult smokers start smoking in adolescence; 88% of them smoke their first cigarette before the age of 18 [4]. The consequences of smoking have a huge impact on public health costs. Reducing tobacco consumption is of key importance to the overall health of the population [5].

The number of people quitting smoking in Poland increases with age (the largest age group among people quitting smoking is people over 60, the smallest group are people aged 15–19). Young people believe that the possible negative effects of smoking will not appear until the distant future and are often not willing to give up smoking permanently [6].

The combination of therapeutic education, behavioral support, and pharmacotherapy are key ingredients in smoking cessation [7]. Clinical guidelines recommend cognitive-behavioral intervention together with the administration of first-line drugs (bupropion, varenicline, NRT) [5].

In the non-pharmacological treatment of smoking cessation, there are psychological therapies that include, inter alia, short counseling, and individual and group cognitive-behavioral therapy [5]. Individual counseling is a commonly used method for people trying to quit smoking [8]. Research indicates the benefits of combined pharmacotherapy with behavioral treatment in comparison with the usual care or short advice [9, 10]. Recently, new technologies and social networks have been incorporated into smoking cessation interventions [11, 12].

One way to reduce tobacco consumption is to offer smoking cessation counseling in primary care settings [13, 14]. Interventions of as little as 3 minutes by primary care physicians can help patients to quit smoking successfully [5]. Minimal intervention by GPs may bring benefits in terms of promoting abstinence as well as creating smoke-free places [5].

GPs under the guidelines must routinely advise smokers to stop smoking, offer them help to stop smoking, and prescribe the use of available stop smoking medications. Moreover, they are to record the patient's behavior in his or her medical records and, if necessary, refer patients to specialist therapy and counseling [7]. Quitting smoking advice by GPs has been shown to increase rates of quitting smoking [15]. However, research suggests that smoking cessation counseling in primary care is not being sufficiently implemented [16]. The aim of the study was to assess smoking cessation frequency and the frequency of smoking cessation counseling in primary care.

Materials and Methods

In 2015–2016, a cross-sectional study was conducted which included all smokers from the Piotrków district who gave their written consent to participate in the study. A detailed description of the study area has been published elsewhere [17, 18]. The respondents were referred to a primary care physician to encourage them to quit smoking. The study received a positive opinion and was approved by the Bioethics Committee of the Medical University of Lodz (project identification code: RNN/243/15/KE). The study used a research tool in the form of a questionnaire, which consisted of socio-demographic data (gender, age, marital status, education, professional status, average monthly net income per family member). In addition, the questionnaire questions concerned: smoking; trying to quit smoking; and using professional support when quitting smoking. Current daily smokers (who had smoked one or more cigarettes a day in the last 30 days) as well as those who smoked less frequently (occasional smokers) were included in the study.

Results

114 people smoking cigarettes in the Piotrków district participated in the study, of which men constituted 44.7%, and women 55.3%. The most numerous group of respondents were people in the 30–39 age group (23.7%) and in the 55–59 age group (33.3%). 38.6% of the respondents had secondary education,

28.9% higher education. 46.5% were married and 24.6% were unmarried. Every fifth person was a pensioner, and 59.7% of the respondents were hired employees. Every fourth respondent had a monthly family income of over PLN 1000 to PLN 1500. 7% of smokers smoked less than daily, and 93% of smokers were daily smokers. The average age of the respondents when they lit a cigarette for the first time was 19 years. Smokers most often smoked slim cigarettes (24.6%) and filtered cigarettes (69.2%). The most numerous group (32.5%) were people who started smoking daily at the age of 20–21. As many as 12.3% of respondents started smoking daily 16–20 years ago, and 15.8% 21–25 years ago. Every fourth respondent had smoked cigarettes for 21 to 30 years; every third respondent had smoked cigarettes for 10 to 20 years. The most numerous group (53.5% of respondents) among smokers were people who smoked more than 10 to 20 cigarettes a day. Every fourth respondent (28 people out of 114) smoked more cigarettes in the morning than in the rest of the day. 32.5% of the surveyed smokers would wake up at night and light a cigarette. 54.4% of people would smoke cigarettes even while lying in bed while sick. 70.2% of respondents (80 people out of 114) smoked their first cigarette within 30 minutes after waking up. 51.8% of respondents (59 people out of 114) had the hardest time giving up their first cigarette of the morning. 28.1% of respondents (32 people out of 114) found it difficult to refrain from smoking in public places where smoking is prohibited. 57% of respondents had tried to quit smoking. 32.5% of the respondents had made 1–2 attempts to quit smoking (Table 2). 19.3% of respondents (22 out of 114) had tried to quit smoking in the previous 12 months. These people most often made 1–2 attempts to quit smoking (42.9% of the respondents). In their last attempt to quit smoking, 11.4% subjects stopped smoking for up to 1 day and 16.7% for more than 2 weeks to a month. 4.4% of the surveyed smokers used professional support while quitting smoking, and 93.8% did not. Among the reasons why the respondents had not used professional smoking cessation support so far, the most frequently mentioned ones were: I did not know where to turn for such help (29.8%) and I did not know what professional help in quitting smoking there was (16.7%). Other reasons were: I thought that using professional help would require a lot of work and effort (15%) and I did not want to admit to myself that I needed

professional help to quit smoking (14%). Fear of being ill (27.2%) and current health problems (19.3%) were the most common reasons that had prompted smokers to try to quit smoking. Other reasons mentioned were financial considerations (17.5%) and family wishes (17.5%). 66.7% of respondents (76 out of 114) intended to quit smoking in the next month, and 22.8% (26 out of 114) were considering quitting smoking in the next 12 months. In the case of their current willingness to quit smoking, as many as 36% were definitely convinced of their success, and 48.2% were fairly convinced of their success in quitting smoking. 79.8% of the surveyed smokers had visited a doctor or other health care representative within the previous 12 months, most commonly consisting of 1–2 visits (53.5% of the respondents). 59 respondents (51.8%) were asked during a visit to a doctor or other health care representative whether they had smoked tobacco in the last 12 months. 52 subjects (45.6%) during such a visit in the previous 12 months had been advised to quit smoking. In the previous 12 months, 14.9% of respondents had used nicotine replacement therapy, incl. slices or chewing gum. 3.5% of people had benefited from therapeutic help, including the anti-smoking clinic. 3.5% of respondents had used traditional drugs (e.g., champix) and 5.3% of respondents had used prescription drugs (e.g., bupropion). The helpline for people trying to quit smoking was used by 3.5% of respondents. 7.9% of people tried to switch from smoking to other ways of using tobacco products, the most common being e-cigarettes (14.9%). 39.5% of respondents were very concerned about the harmful health effects of smoking, and every second person was somewhat concerned about the harmful effects. A GP gave advice on smoking cessation to 38.6% of the subjects. 11.4% of the surveyed (13 out of 114) smokers received support in quitting smoking from the workplace where they worked. 46.5% of respondents (53 out of 114) were somewhat concerned and 36.8% (42 out of 114) were very concerned about the harmful health effects of passive smoking.

Discussion

Our study supplements the literature on the use by smokers of the professional support of a doctor or other health care representative when quitting

smoking. In our survey, which was conducted among daily smokers, men accounted for 44.7% and women 55.3%. These results are higher than in Poland. According to data, in 2018 in Poland, 27.8% of men and 23.1% of women declared using traditional tobacco products at least once a day; in 2020 they amounted to 23.1% and 14.9% respectively [19]. 14.9% of the respondents in our study tried to switch from smoking to e-cigarettes. As shown by the data from 2020, the percentage of users of electronic tobacco substitutes in all age groups has significantly increased in Poland. The exception was the age group of 70 and more [19]. In our study, 57% of people had tried to quit smoking, with the most common number of attempts to quit being 1–2 (32.5% of respondents).

A systematic review of 17 randomized controlled trials showed that smokers who received medical advice were 66% more likely to quit smoking than those who did not [20]. Another study by Lancaster et al. showed that individual counseling can increase the chances of quitting smoking by 40–80% compared to minimal support [8]. In tobacco dependence treatment guidelines, one of the recommended ways to reduce tobacco consumption is primary care counseling [21–23].

The FCTC (Framework Convention on Tobacco Control) has recognized the important role of healthcare professionals in quitting smoking. Article 14 of the FCTC emphasizes screening and smoking cessation advice by healthcare providers. Moreover, it requires the inclusion of tobacco dependence treatment in the healthcare system [22, 23].

The scheme of minimal anti-smoking intervention is based on the 5xA principle. Each 'A' (ask, advise, evaluate, help, organize) represents the next step of an intervention [26]. As shown by the data, this procedure is not commonly used in practice [24, 25]. Behavior corresponding to 5A ask and advise was reported more often than subsequent strategies: evaluate, help, arrange. On average, 63% of physicians used the 'Advisory' intervention in practice, 65% the 'Ask' procedure, 44% 'Help', 36% 'Assessment', and 22% 'Organize', whilst the measurement and reporting of each of these counseling practices differed depending on the research [16]. Regular contact with a family doctor has been shown to build trust in the doctor-patient relationship, which helps and facilitates the

provision of smoking cessation counseling and allows the implementation of individualized smoking cessation advice [26, 27]. In a study by Shahawa et al. it was shown that only 15% of subjects in primary care were provided the recommended advice given their willingness to quit smoking [28]. Earlier literature shows that approximately 20% of unmotivated smokers will attempt to quit smoking when advised by their GP [29]. Evidence-based measures that increase the chances of smoking cessation include, in addition to direct medical advice, structural counseling, approved drug therapy and a follow-up plan. Varenicline, bupropion, or nicotine replacement therapy in the form of long-acting patches, and short-acting forms of nicotine such as gum, lozenges, prescription nasal spray or prescription inhaler are an approved pharmacotherapy [30].

51.8% of our respondents were asked during a visit to a doctor or other health care representative if they had smoked in the last 12 months, and 45.6% of subjects were advised to quit smoking. This shows that GPs advise smokers to quit smoking according to the guidelines, which may increase the rates of quitting smoking [7, 34].

Only 5.3% of our respondents used prescription drugs (e.g., bupropion) to quit smoking, and 3.5% of the respondents used traditional drugs (e.g., champix). Only 3.5% of the respondents benefited from therapeutic help, including the anti-smoking clinic; 14.9% of the respondents used nicotine replacement therapy, including slices, or chewing gum.

In a cross-sectional study by Tibuakuu et al. in the US in 2006–2015, the percentage of people who reported having received medical advice to quit smoking increased from 60.2% to 64.9%, whilst prescription drug use decreased from 6.0% to 4.6% [31]. Numerous studies suggest that smoking cessation counseling is not sufficiently implemented in primary care [17, 32–39].

A review by Ahluwalia et al. found that in the 31 countries assessed, quitting smoking without any assistance was the most common method of quitting smoking (from 52.7% in Pakistan to 92.4% in Greece). The second most popular method was counseling (from 1.3% in Romania to 23.7% in the Republic of Tanzania), then NRT (from 0.02% in Bangladesh to 26.7% in Indonesia), prescription drugs (from 0.5% in Indonesia to 14.3% in Kazakhstan) and traditional medicines (from 0.1% in Bangladesh to 11.4% in Senegal) [35].

In the Netherlands, only 22.6% of smokers received advice on smoking cessation, and only 20.9% of patients had their GP prescribed or order medications. 58.9% of English smokers received smoking cessation advice from their GP [36]. In a study by Guydish et al., 53% of smokers were recommended to quit smoking, 41% benefited from counseling, 26% received drugs to help quit smoking, and 17% received counseling and medications [37]. In the study by Sipos et al. 25% of smokers were provided with a brief intervention, 7% with programmed non-pharmacological support, and 2% with pharmacotherapy [38].

The study by Zhang et al. showed that people who received smoking cessation advice were more likely to use smoking cessation medications compared to those who did not receive such advice (21% and 13%, respectively) [39].

A review by Owusu et al. based on the Global Adults Tobacco Survey conducted in 12 countries found that 52% had not received any intervention, and 40% of participants had been advised to quit smoking. Smoking cessation advice has been associated with an increased use of telephone quitline advice, WHO prescribed medications, and counseling [23]. Research shows that smoking cessation interventions by healthcare professionals, such as counseling and the use of nicotine replacement therapy (NRT), are cost effective [40]. The Ankabi review showed that nicotine replacement therapy (NRT) improved rates of smoking cessation, and behavioral counseling was more effective than minimal interventions [41]. High availability and low cost of NRT make it an ideal pharmacotherapy for smoking cessation compared to other drugs to help stop smoking [42]. Pharmacological support has been proven effective in quitting smoking [43]. However, the knowledge of smokers and the perceived efficacy of these pharmacotherapies is low [44–49].

Awareness of the availability of smoking cessation treatments in primary care should be increased [49]. Our research also shows that every third respondent did not know where to turn for professional help in stopping smoking, and every sixth respondent did not know what professional help there was to quit smoking. The study has some limitations that should be considered when interpreting the results. One limitation of the study is the small size of the group who participated in the research. The study also used

a cross-sectional design that tends to be observable at one point in time, making it impossible to observe changes over longer periods of time.

Conclusions

The results suggest that the time spent advising patients on smoking should include helping them to quit smoking. GPs should discuss smoking cessation with more patients who smoke. Behavioral counseling, quick advice, and nicotine replacement therapy appear to be effective in helping people quit smoking in low – and middle-income countries.

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Table 1. Characteristics of the studied population (N = 114)

	N	%
Sex		
female	63	55.3
male	51	44.7
Age (years)		
< 30	14	12.3
30–39	27	23.7
40–49	9	7.9
50–59	38	33.3
≥ 60	26	22.8
Marital status		
unmarried	28	24.6
married	53	46.5
divorced	18	15.8
widower/widow	15	13.1
Education		
basic	2	1.8
basic vocational	21	18.4
average	44	38.6
post-secondary	14	12.3
higher	33	28.9
Professional status in the last 12 months		
salaried employee	68	59.7
self-employed person	11	9.6
pupil/student	3	2.6
housewife	2	1.8
pensioner/annuitant	23	20.2
unemployed	7	6.1
Monthly net family income per person		
up to 500 PLN	11	9.7
over 500 to 700 PLN	8	7.0
over 700 to 1000 PLN	18	15.8
above 1000 to 1500 PLN	29	25.4
above 1500 to 2000 PLN	26	22.8
above 2000 to 2500 PLN	13	11.4
above 2500 PLN	9	7.9
Smoking tobacco		
Yes, everyday	106	93.0
Yes, less than every day	8	7.0

	N	%
What kind of cigarettes do you currently smoke?		
With filter	79	69.2
Unfiltered	1	0.9
Slim	28	24.6
Menthol	6	5.3
How old were you when you **first smoked** tobacco?		
10–12	2	1.8
13–14	5	4.4
15–16	25	21.9
17–18	27	23.7
19–20	25	21.9
21–22	6	5.3
24–25	11	9.6
28–30	11	9.6
above 30	2	1.8
How old were you when you started smoking tobacco **every day**?		
14–15	3	2.6
16–17	12	10.5
18–19	21	18.4
20–21	37	32.5
22–24	8	7.1
25–27	14	12.3
28–30	11	9.6
31–32	4	3.5
35–40	2	1.7
above 40	1	0.9
no data	1	0.9
How many years ago did you start smoking tobacco **every day**?		
Up to 1 year	3	2.6
from 2 to 5 years	6	5.3
from 6 to 10 years old	11	9.6
from 11 to 15 years old	8	7.0
from 16 to 20 years old	14	12.3
from 21 to 25 years old	18	15.8
from 26 to 30 years old	12	10.5
from 31 to 35 years old	12	10.5
from 36 to 40 years old	14	12.3
over 40 years old	16	14.1

	N	%
How many cigarettes do you smoke in total during the day? (pieces)		
< 1	2	1.7
1–5	5	4.4
over 5 to 10	27	23.7
above 10 to 20	61	53.5
above 20 to 30	18	15.8
above 30	1	0.9
Number of years of regular daily smoking? (after deducting any interruptions for abstinence)		
< 10	17	15.0
10–20	36	31.6
21–30	29	25.4
31–40	20	17.5
> 40	11	9.6
No data	1	0.9
How quickly do you light up the first cigarette (pipe, cigar, cigarillo, another tobacco product) **after you wake up**?		
in the first 5 minutes	26	22.8
after 6–15 minutes	31	27.2
after 16–30 minutes	23	20.2
after 31–60 minutes or	16	14.0
after more than 60 minutes	17	14.9
no data	1	0.9
Do you wake up at night and light up a cigarette?		
Yes	37	32.5
No	77	67.5
Do you smoke **more cigarettes in the morning than the rest of the day**?		
Yes	28	24.6
No	86	75.4
Which cigarette is the most difficult for you to give up?		
The first of the morning	59	51.8
Every other cigarette	55	48.2
Do you find it **difficult to refrain from smoking in non-smoking public places** (e.g. library, cinema, church)?		
Yes	32	28.1
No	82	71.9
Do you smoke cigarettes even when you are **so sick that you have to stay in bed**?		
Yes	62	54.4
No	52	45.6

Table 2. Use of professional support when quitting smoking (N = 114)

Variable	N	%
Have you ever tried to quit smoking?		
No	49	43.0
Yes	65	57.0
If you have ever tried to quit smoking, how many times?		
0	2	1.7
1–2	37	32.5
3–4	30	26.3
5–6	6	5.3
6+	3	2.6
No data	36	31.6
Have you tried to quit smoking in the last 12 months?		
Yes	22	19.3
No	82	71.9
No data	10	8.8
If in the last 12 months you have tried to quit smoking, how many times?		
0	7	6.1
1–2	49	42.9
3–4	5	4.4
5–6	1	0.9
6+	2	1.8
No data	50	43.9
During the last attempt to quit smoking, for how long did you stop smoking?		
1 day	13	11.4
from 2 days to a week	12	10.5
over a week to 2 weeks	5	4.4
over 2 weeks to a month	19	16.7
over a month to 6 months	11	9.6
over 6 months to 1 year	3	2.6
no data	51	44.7
Have you ever benefited from professional support when quitting smoking?		
Yes	5	4.4
No	107	93.8
No data	2	1.8

Variable	N	%
Which of the following statements best describes the reason for which you have so far NOT used professional support in quitting smoking?		
I did not know where to turn for such help	34	29.8
I was ashamed of what others would think of me	11	9.6
I thought that using professional help would require a lot of work and effort from me	17	15.0
I didn't want to admit to myself that I needed professional help to quit smoking	16	14.0
I was too proud to ask for professional help	5	4.4
I did not feel able to talk to another person about my smoking	4	3.5
I was afraid that professional help would be very expensive	8	7.0
I did not know what professional help there was to stop smoking	19	16.7
What prompted you to now try to quit smoking?		
current health problems	22	19.3
fear of disease	31	27.2
doctor's recommendations	7	6.1
family wishes	20	17.5
belief in the harmful effects of smoking	11	9.7
financial considerations	20	17.5
no smoking in the workplace	2	1.8
other reason	1	0.9
Which of the following best describes your intention to stop smoking?		
I'm going to quit smoking in the next month	76	66.7
I'm considering quitting in the next 12 months	26	22.8
I'll quit smoking, but not in the next 12 months	5	4.4
I'm not going to quit smoking	1	0.9
I do not know	6	5.2
Which of the following best describes your **current approach to quitting smoking?**		
I'm definitely convinced of success	41	36.0
I'm rather convinced of success	55	48.2
I'm not convinced of success	18	15.8
Have you visited **a doctor or other health care representative** in the last 12 months?		
Yes	91	79.8
No	23	20.2

Variable	N	%
How many times have you visited a doctor or other health care representative in the last 12 months?		
1–2 times	61	53.5
3 to 5 times	28	24.6
6 or more times	18	15.8
No data	7	6.1
During a visit to a doctor or other health care representative in the last 12 months, were you asked if you smoke?		
Yes	59	51.8
No	49	43.0
No data	6	5.2
During a visit to a doctor or other health care professional in the last 12 months, were you advised to quit smoking?		
Yes	52	45.6
No	49	43.0
No data	13	11.4
In the last 12 months, have you used the following measures to help you quit smoking?		
Therapeutic help, including help from the anti-smoking clinic		
Yes	4	3.5
No	110	96.5
Nicotine replacement therapy, such as patches or chewing gum?		
Yes	17	14.9
No	97	85.1
Other prescription drugs, for example (Bupropion)?		
Yes	6	5.3
No	108	94.7
Traditional drugs, for example (Champix)?		
Yes	4	3.5
No	110	96.5
Quit Smoking Helpline?		
Yes	4	3.5
Well	110	96.5
Switching from smoking to other ways of using tobacco products?		
Yes	9	7.9
No	105	92.1
e-cigarettes		
Yes	17	14.9
No	97	85.1

Variable	N	%
Are you concerned about the harmful effects of smoking on your health?		
I am very concerned	45	39.5
I'm a little worried	57	50.0
I'm not very worried	11	9.6
I'm not at all concerned	1	0.9
Have you ever been given any smoking cessation advice by your GP / family doctor?		
Yes	44	38.6
No	70	61.4
Have you received help / support to stop smoking from the workplace where you work?		
Yes	13	11.4
No	101	88.6
Are you concerned about the harmful effects of passive smoking on your health?		
I'm very concerned	42	36.8
I'm a little worried	53	46.5
I'm not very worried	14	12.3
I'm not at all concerned	5	4.4

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Assessment of Functional and Gait Efficiency in Patients after Knee Endoprosthesis

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Abstract

Background: *Osteoarthritis is a perennial and progressive disease, and its progression can only be slowed down. The disease incidences increase with age and are a large problem of the elderly. Women and people doing physical work are more often ill. Knee arthroplasty is the procedure carried out most often for advanced degenerative changes. The disease causes severe pain and limits joint movement, thus impairing professional and social life and hindering everyday activities. Replacing the knee joint reduces pain, improves the biomechanical conditions of the joint and gait, and allows to undertake physical activity, and thus positively impacts on the quality of life of patients. The aim of the research was to determine the functional and gait capabilities of patients rehabilitated after knee arthroplasty.*

Material and Method: *The research involved 60 patients, including 30 women and 30 men, who were subject to two researches: before and after surgery followed by rehabilitation. The author's questionnaire, Laitinen scale was used for the research. The range of flexion and extension in the knee joint was assessed, and the "Up & Go" test was carried out. Statistical analysis of the collected data was carried out in the Statistica 13.0 program.*

Summary and Conclusions: *The research revealed that rehabilitation treatment positively impacts on improving functionality and gait in patients' daily lives. The rehabilitation applied after knee arthroplasty significantly improved the range of flexion and extension movements in the knee joint. Moreover, a statistically significant increase in the level of balance and a decrease in the risk of falls in the researched persons was observed. In terms of all pain indicators assessed in the Laitinen questionnaire, statistically significant improvement was noted after the use of surgical treatment supplemented with rehabilitation.*

Key words: *knee, grthrosis, physiotherapy*

Introduction

Functional efficiency is the ability to independently carry out basic everyday activities in a controlled and safe way as well as without excessive effort [1]. Due to the individual ageing process, the assessment of functional efficiency is often a very difficult element of diagnostics, which should be multi-faceted and should include careful observation [2].

Gait assessment as the basic form of human mobility is one of the best indicators of the patient's functional status. Gait is largely individual, primarily influenced by age and pathologies associated with the musculoskeletal system.

Functional efficiency and gait function assessment are basic determinants in the overall assessment of the patient and significantly impact on the level of his/her quality of life.

Degenerative changes in the musculoskeletal system progress with age and increased multi-morbidity. The most common cause of these changes is developing osteoarthritis that destroys anatomical structures such as articular cartilage, the subchondral layer of the bone, meniscus, ligaments, synovium, and joint capsule. The disease process is often accompanied by severe pain, muscle weakness and reduced range of motion in the joints. In addition, there can be distortions within the joint itself (e.g. valgus, varus formation) and fixation of contractures [3]. All these irregularities adversely impact on the function of gait.

Osteoarthritis is a perennial and progressive disease, and its progression can only be slowed down. The disease occurs most often in the age range from 40 to 60 years old. It concerns both men and women; however, epidemiological data show that the more severe forms of this disease concern women. It arises as a result of both mechanical and biological degenerative changes, and recently, the influence of genetic factors is also being considered [4].

Depending on the severity of the disease, as clinical symptoms increase, conservative management of osteoarthritis is not effective enough, as it only slows down the progression of disease changes. Currently, the only effective method of treating people with advanced knee osteoarthritis is

knee arthroplasty, which, supplemented with rehabilitation, restores the correct range of motion parameters and enables re-education of the correct gait pattern [5].

The main purpose of surgery is to improve the quality of life of patients by reducing pain, correcting the disturbed axis of the limb – if it occurs, restoring joint stability and improving the range of mobility [3].

The effectiveness of knee endoprosthesis implantation in patients with advanced degenerative joint changes in reducing pain intensity, improving joint function and quality of life has been confirmed in scientific publications [3]. The improvement of the functional condition of patients after total knee replacement surgery depends on many factors, including appropriate physiotherapy. Relieving pain and improving functional efficiency, including restoring the appropriate range of motion in the knee joint necessary to achieve independent gait are important goals for rehabilitation.

Nowadays, medicine has extensive treatment options. The selection of rehabilitation procedures depends on the type of pain, experience gained from previous rehabilitation and the tolerance of treatments by the patient.

Intensive functional rehabilitation carried out already in the early postoperative period reduces pain, improves gait efficiency and functioning of patients in everyday life, which results in an increase in patients' quality of life [6, 7].

Material and Methods

Respondents

The research consisted of 60 patients, including 30 women and 30 men. They were patients with osteoarthritis of the knee who qualified for an endoprostheoplasty (31 researched people – right knee joint, 29 – left knee joint).

The research was carried out twice: for the first time before the surgery, for the second time after the endoprosthesis and rehabilitation. Rehabilitation was carried out from Monday to Friday, once a day for 5 weeks. The researched group consisted of 11 people (18.3%) aged 35–50 and 49 people

(81.7%) aged 51–75. The average BMI in the researched group was 26.3 ± 2.1. The BMI value was within the normal range for only 28% of the researched group (Table 1).

Research tool

All patients were subjected to the research using the author's own questionnaire. An additional Laitinen scale test was carried out twice, the range of flexion and extension movement in the knee joint was assessed, and the 'Up & Go' test was carried out. The first research was carried out before knee arthroplasty; the second research took place in the postoperative period on the day of completion of the rehabilitation procedure.

Statistical analysis was carried out using the Statistica 13.0 PL program. The Wilcoxon pair order test was used for the analysis of dependent variables, the dependence of quantitative variables was assessed using Sperman rank correlation, whilst the analysis of independent variables was carried out using the ANOVA test. The distribution normality assumptions were checked using the Shapiro-Wolf test, and the variance using the Levene test. Statistical dependences were significant if their level of significance was $p < 0.05$.

Results

The research showed that in all the analysed cases there was pain in the knee, which the subjects classified in three ranges, with almost 75% of people reporting the presence of pain for at least 2 years (Table 2). In the analysed group, almost all respondents (98.3%) had joint pain while carrying out basic daily activities and while walking (Table 2).

Among the methods of dealing with pain, 65% of respondents indicated the use of pharmacological agents, and less than 30%, physical therapy procedures.

In the group of patients, 96.7% had used physiotherapeutic procedures in the past, and on average every fifth respondent definitely confirmed that the applied treatments improved his/her comfort of life. Patients most often

indicated the TENS procedures, iontophoresis and cryotherapy as those that impacted on reducing pain experienced during conservative treatment (Figure 1). In addition, all respondents declared their willingness to use physiotherapeutic procedures in the postoperative period.

The treatment effect obtained during previous rehabilitation was maintained for all patients for no more than half a year. Most often from two weeks – 46.6%, to approximately a month – 43.1%.

Analysis of the obtained results showed a relationship between the duration of the treatment effect and the BMI index. The treatment effect lasted the longest in patients with the lowest body mass index (Figure 2).

The research assessed the range of motion in the knee joint and the level of balance and gait of the patients, using the 'Up & Go' test. Analysis of the researched variables showed statistically significant differences in the scope of all parameters ($p < 0.001$). The range of flexion movement in the knee after treatment increased on average from 81 to 113.42 degrees, and the effect of the therapy was determined at 32.42 degrees ± 10.52 (Table 3).

In the first measurement of extension in the knee joint, prior to the treatment, a limited range of motion was pointed out, an average of 9.38 degrees, which meant the lack of full extension in the knee joint. After the treatment, the range of limitation of joint mobility decreased to an average of 1.83 degrees ± 3.44 degrees (Table 3).

The assessment of dynamic balance and gait was carried out using the 'Up & Go' test, where the duration of the motor task was determined. Patients carried out the pre-treatment test at an average time of 18.92 seconds, and after treatment at an average time of 10.92. In the next two measurements, the subjects improved the test time by an average of 8 seconds (Table 3).

The intensity of pain, the frequency of pain occurrence, the frequency and amount of painkillers taken, as well as the level of physical activity limitation due to pain were determined in the study group with the Laitinen pain index questionnaire. The listed categories of the questionnaire were rated on a five-point scale, from 0 to 4 points, where a higher number of points meant a greater severity of the problem. The intensity of pain sensations was assessed by the subjects in the measurement taken before treatment at an

average level of 2.8 ± 0.94 points. After treatment, the intensity of pain decreased to an average of 0.85 points. The difference between the assessment of pain intensity in two subsequent measurements was 1.95 ± 0.79 points on average. The observed change was statistically significant ($p < 0.001$) (Table 4).

Discussion

Knee osteoarthritis is a growing socio-economic-social problem, which is also a major medical challenge. It applies mainly to the elderly, in whom, due to multiple diseases, therapeutic management and improvement of the quality of life may be difficult. As the recognition of the disease increases, younger and younger patients are undergoing joint endoprosthesis surgery, which aims to improve the quality of life. Therefore, research on the quality of life and assessment of the functional state of patients before and after endoprosthesis surgery is widely used in assessing the effectiveness of medical activities [8, 9].

Osteoarthritis of the knee is the source of a number of local and systemic lesions with varied dynamics and clinical images. It results not only in pain and limitation of mobility, increasing contractures, deformation of the axis of the limb, impairment of gait performance and aesthetics, but also changes in body posture resulting from disturbances in the spatial orientation of individual elements of the osteoarticular system.

Osteoarthritis is the result of overlapping diseases that, despite different aetiologies, lead to similar biological, morphological and clinical effects. Clinically, osteoarthritis is manifested by joint pain, pressure soreness, restricted mobility, crackling, occasional exudate and inflammation of varying severity without systemic symptoms.

Knee arthroplasty for the treatment of advanced degenerative changes is currently the most common method, because its main goal is to restore functional independence in daily activities of the patient by reducing the intensity of pain and increasing mobility in the knee joint.

Our conducted research proved that in patients after arthroplasty the range of motion in knee joints significantly increased ($p < 0.05$). The flexion improved by an average of over 30°, while the extension by 8°. In the research

of Majewska et al., the passive range of the operated joint in the control research improved by an average of 10.7°. Researchers noted that an important factor affecting the size of the postoperative range of motion was the range of motion of the operated knee joint prior to joint replacement surgery. In patients with significantly reduced joint flexion (below 90°) before surgery, the postoperative results were significantly worse than in those patients whose knee flexion before surgery was above 90° [5].

The carried-out 'Up & Go' test for able-bodied persons should last approximately 10 seconds, and an increased risk of falls occurs for persons with a score over 14 seconds [10]. The research has shown that the time of 'Up & Go' test was significantly shortened from an average of 18.9 seconds before treatment to 10.8 after surgery. The obtained improvement indicates good functional efficiency of the subjects and a significantly reduced risk of falls in the postoperative period [11, 12].

Respondents in the research of Gajewski et al. reported almost daily pain in the osteoarticular system. The score was on a scale of 1 to 5, where 1 corresponded to very weak or weak ailments, and 5 described the pain as very strong. Approximately 11% of respondents felt low pain, approximately 35% medium, and 48.5% suffered large pain [13]. In our research, the patients complained of pain every day. The pain usually occurred during the day during the basic activities of everyday life – in 40.0% of respondents, and while walking – in 58.3%. In addition, our research showed that in all pain indicators assessed in the ***Laitinen questionnaire, statistically significant improvement was observed after the use of surgical treatment supplemented with rehabilitation.*** The largest difference was observed in reducing the frequency of pain and in reducing the need to take painkillers.

One of the risk factors for developing knee osteoarthritis is excessive body weight, which can contribute to accelerating the destruction of articular cartilage and the occurrence of degenerative changes. Still, the results of the research on the effects of obesity on the development of osteoarthritis and the results of total joint replacement surgery are not always unambiguous. In the research on the assessment of the functional state of patients with gonarthrosis, Jastrzębiec-Święcicka and co-authors showed that 80%

of respondents had a BMI above the accepted norm, i.e. > 25, and the average value of the indicator was 28.55. This indicates a relatively frequent occurrence of excess weight or obesity of various types [14]. In the research of Kiełbasa et al. the BMI value was at a similar level, also indicating the existence of excess weight and obesity among people diagnosed with osteoarthritis of the knee [15]. Similar average values were obtained in the research of Krekor et al., where the majority of the subjects had abnormal body weight (73%) compared to those with normal BMI (27%) [16].

The carried-out research proved the existence of a relationship between the duration of the therapeutic effect after physiotherapeutic procedures and the body mass index. ***The lower the BMI value, the longer the therapeutic effect experienced by the patient. Similar conclusions were reached by*** Bugała-Szpak et al. who demonstrated a significant influence of patients' BMI on the results of treatment [17].

In the research of Jastrzębiec-Święcicka and co-authors, respondents mentioned physiotherapeutic procedures (98%), followed by the use of analgesic and anti-inflammatory drugs and ointments as a method of coping with symptoms of knee osteoarthritis the most often [14]. In our research, ***most respondents cope with pain by using painkillers – 65.1%.*** Far fewer respondents applied physiotherapy procedures – only 28.3%. ***However***, out of all respondents, 96.7% had physiotherapeutic procedures in the past, and on average every fifth respondent definitely confirmed that the physiotherapeutic procedures applied in his/her case contributed to the improvement of his/her life comfort.

Conclusions

Surgical treatment of osteoarthritis of the knee combined with physiotherapeutic treatment positively impact on improving gait and functioning in everyday life, thus improving the quality of life of patients.

Rehabilitation applied after knee arthroplasty had a beneficial impact on increasing the range of flexion and extension movements in the knee joint, increasing the level of balance and reducing the risk of falls in the subjects.

In terms of all pain indicators assessed in the Laitinen questionnaire, statistically significant improvement was noted after the use of surgical treatment supplemented with rehabilitation.

Rehabilitation after knee arthroplasty impacted on reducing the incidence of pain and the need to apply painkillers.

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Table 1. General characteristics of the research group of the respondents

Characteristics		n		%
Gender (n – 60) **– female/male**		30 / 30		50.0 / 50.0
Age (n – 60) [years] **– 35–50 / 50–75**		11 / 49		18.3 / 81.7
Place of residence (n – 60) – village / city		18 / 42		30 / 70
Professional status (n – 60) **– professionally active / professionally inactive / pensioners**		34 / 2 / 22 / 2		56.7 / 3.3 / 36.7 / 3.3
Type of performed work (n – 34) **– intellectual work / light physical work / hard physical work**		14 / 11 / 9		41.1 / 32.4 / 26.5
Variable	$\bar{x}$	**SD**	**Reference**	**Me**
Age (n – 60) [years]	67.4	5.2	35–75	67.0
BMI (n – 60)	26.30	2.1	21.3–30.5	26.1

* $\bar{x}$ – mean; SD – standard deviation; Reference – minimum to maximum; Me – median

Table 2. Parameters of pain in patients

	n	%
Occurrence of pain (n – 60) [months] **– over 12 months / 24 months / over 24 months**	16 / 20 / 24	26.7 / 33.3 / 40.0
Activities that intensify pain (n – 60) **– walking / everyday activities / sleep**	35 / 24 / 1	58.3 / 40.0 / 1.7
Methods to relief pain **– pharmacology / physical therapy / relief positions / not used**	39 / 17 / 2 / 2	65.1 / 28.3 / 3.3 / 3.3
Impact of physical therapy on the patient's condition **– improvement / partial improvement / no improvement**	12 / 35 / 13	20.0 / 58.3 / 21.7
Duration of the effect of the applied rehabilitation (n – 58) **– two weeks / month / half year**	27 / 25 / 6	46.6 / 43.1 / 10.3

n – number of observations; % – percent

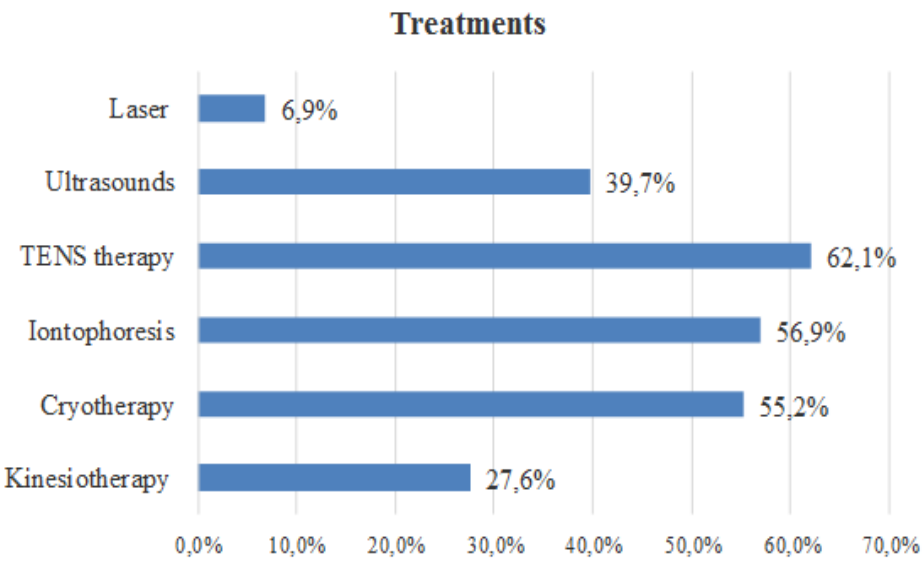
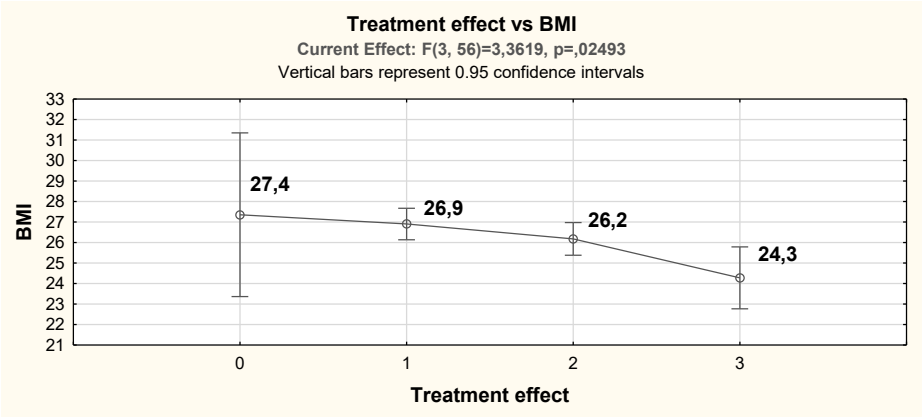


Figure 1. Treatments regarded as significantly impacting on reducing pain

* possibility of indicating several answers



** Treatment effect: 0–2 weeks; 1 month; 2 – half a year; 3 – a year*

Figure 2. The duration of the lasting treatment effect of the applied rehabilitation, considering the BMI of the researched patients

Table 3. Changes in the range of motion and assessment of the level of balance

Variable	$\bar{x}$	SD	Reference	Me	Q1	Q3
The range of bending movement in the knee joint [degrees] n = 60	p < 0.001					
Before treatment	81.00	12.78	55–100	80.00	70.00	90.00
After treatment	113.42	11.29	90–135	115.00	102.50	120.00
Difference	32.42	10.52	15–55	32.50	25.00	40.00
The range of extension in the knee joint [degrees] n = 60	p < 0.001					
Before treatment	-9.83	9.83	-40–0	-10.00	-15.00	0.00
After treatment	-1.83	3.44	-10–0	0.00	-2.50	0.00
Difference	8.00	8.50	0–40	5.00	0.00	10.00
'Up&Go' [sec.]	p < 0.001					
Before treatment	18.92	3.04	14–27	19.00	16.50	21.00
After treatment	10.92	1.88	8–16	10.00	10.00	12.00
Difference	-8.00	1.66	-12–(-5)	-8.00	-9.00	-7.00

n – number of observations; $\bar{x}$ – mean; SD – standard deviation; Reference – minimum to maximum; Me – median; Q1 – lower quartile; Q3 – upper quartile

Table 4. Laitinen pain index questionnaire

Laitinen Pain Indicator Questionnaire [0–4 points]	Descriptive statistics			
	n	$\overline{x}$	Me	SD
pain intensity				
Before treatment	60	2.80	3.00	0.94
After treatment	60	0.85	1.00	0.63
Difference	60	-1.95	-2.00	0.79
frequency of pain occurrence				
Before treatment	60	2.88	3.00	1.04
After treatment	60	0.88	1.00	0.67
Difference	60	-2.00	-2.00	0.82
taken painkillers				
Before treatment	60	2.85	3.00	1.07
After treatment	60	0.85	1.00	0.71
Difference	60	-2.00	-2.00	0.86
limitation of physical activity				
Before treatment	60	2.45	3.00	0.79
After treatment	60	0.78	1.00	0.69
Difference	60	-1.67	-2.00	0.71

N – number of observations; $\overline{x}$ – arithmetic average; Me – median; SD – standard deviation

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Effects of Cardiac Rehabilitation in Patients after Myocardial Infarction – A Case Report

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Abstract

Purpose: *The objective of the study was to evaluate the effects of cardiac rehabilitation in a patient after myocardial infarction (MI).*

Methods: *The participant in the study was a 58-year-old male with a medical history of myocardial infarction. The participant underwent a 25-day course of cardiac rehabilitation, with pre – and post-intervention outcome measures to assess his physical performance; the evaluation involved a treadmill exercise stress test according to the Bruce protocol. The total time and load of the test, maximal heart rate, systolic and diastolic blood pressure and the reason for discontinuing the study were determined. The rehabilitation protocol included cycling a cycloergometer, active exercises, resistance exercises and relaxation exercises. The level of exercise difficulty was increased weekly, starting from 2 METs (60% of the MET obtained during the stress test).*

Results: *During the exercise stress test performed following the completion of the rehabilitation management, the total stress test time was prolonged by 353 s, while the load of the test was increased by 5.64 METs as compared to the results obtained during the first examination. The maximal heart rate decreased by 12 beats/min, the systolic blood pressure by 15 mm Hg and the diastolic blood pressure by 10 mm Hg. The reason for discontinuing the test was fatigue (the score of 16 using the Borg Rating of Perceived Exertion scale).*

Conclusions: *Cardiac rehabilitation with a higher-intensity training program supplemented by resistance training in patients after myocardial infarction is recommended.*

Key words: *cardiac rehabilitation, myocardial infarction, exercise stress test*

Introduction

Cardiovascular diseases, including myocardial infarction, are recognized as the leading cause of death and disability worldwide [1]. According to the WHO statistics, 17.9 million people die each year because of cardiovascular diseases, 85% of which are caused by myocardial infarction and stroke [2]. In 2019, 2.2 million women and 1.9 million men in Europe died from cardiovascular diseases; 38% of deaths among women and 44% cases of demise among men were due to ischemic heart disease [3].

It is estimated that there are approximately 800,000 American residents who suffer from myocardial infarction every year; of this number, 16.7% result in death [4, 5, 6].

The therapeutic options for reducing mortality and morbidity, and thus improving the quality of life of patients with cardiovascular diseases, include cardiac rehabilitation [7, 8].

It is a secondary prevention management method, which is a comprehensive and multidirectional intervention with documented effectiveness [9]. Strong and consistent evidence of its efficacy in such diseases presenting as stable angina pectoris or myocardial infarction is reported in the literature [10–12].

Comprehensive cardiac rehabilitation significantly reduces the risk of recurrence, positively affecting the function of the coronary vessels and the heart [10]. Despite the benefits of cardiac rehabilitation programs, there are still some barriers that keep many patients from participating in such interventional management [13]. Furthermore, access to these services is not standard in all countries [10].

There are three phases of cardiac rehabilitation. Phase I begins immediately after the vital functions are stabilized and the hospitalized patient undergoes inpatient rehabilitation. It is of crucial importance to begin the physiotherapy program immediately after the life-threatening condition has been resolved [8]. Phase II refers to outpatient therapy consisting of an exercise program with a graded level of difficulty. Stage III involves an unmonitored set of exercises [8, 14]. In addition to physical training, Stage III also concentrates on psychosocial activity, lifestyle modification and patient education

[8, 9, 15]. As a result, cardiac rehabilitation is gaining in importance today and in many countries it is considered the key element of the treatment process in patients with cardiovascular disorders [14, 15].

The objective of the study was to evaluate the effects of cardiac rehabilitation in a patient after myocardial infarction.

Organization and course of the study

The program of cardiac rehabilitation extended over 25 days and was based on recommendations of the Section of Cardiac Rehabilitation and Exercise Physiology, Polish Cardiac Society [16]. Prior to commencing the therapy, during the first session, the patient's medical history was taken and a physical examination was carried out. Subsequently, the tolerance of physical exercise was assessed using the exercise test on a treadmill in keeping with the Bruce protocol, evaluating the following parameters: time [s] and load during physical exercise [MET], maximum heart rate, systolic and diastolic blood pressure, as well as fatigue level as measured by the Borg scale. Prior to commencing each session, blood pressure and heart rate were measured; the parameters were periodically controlled during the exercises. Each 1.5-hour long rehabilitation session was divided into four parts, representing aerobic training, i.e. cycling a cycloergometer, active exercises, resistance exercises and relaxation exercises. The level of training difficulty was gradually increased and matched the individual abilities of the patient as determined by the results achieved in the exercise stress test. Every week exercises characterized by a higher level of advancement were introduced and thus the cycling time was prolonged and the MET load was increased starting from 60% of the MET achieved initially during the exercise stress test. The patient repeated each exercise 10–15 times. A physiotherapist was present with the patient during the preliminary examination and the entire rehabilitation session. Having completed the rehabilitation cycle, the patient's tolerance of physical exercise was again tested using a treadmill. The rehabilitation program additionally included a session with a dietician aiming at developing proper nutritional habits and maintaining appropriate body mass, as well as another session offering psychosocial support.

Case report

The patient recruited to the study was a 58-year-old professional driver. Due to myocardial infarction, he underwent coronary angiography, after which he was referred to cardiac rehabilitation. Two months after hospitalization, the patient began a course of physiotherapy, following his granting written informed consent to participate in the study.

During the first assessment, the subject was interviewed to obtain information about his lifestyle. He was reported to smoke 6 cigarettes a day, follow a heavy diet, and not regularly perform any physical activity. The exercise stress test was performed according to the Bruce protocol (Table 2). Subsequently, the subject proceeded to a cycle of cardiac rehabilitation procedures following the designed protocol. The participant underwent a 25-day course of cardiac rehabilitation, in a series of 5-day meetings, with the level of exercise difficulty starting from 2 METs. After the final intervention, the treadmill stress test was repeated. The results obtained pre – and post-cardiac rehabilitation were compared with respect to the total time and load of the test, maximal heart rate, systolic and diastolic blood pressure, as well as the reason for discontinuing the study (Table 2).

A considerable improvement was observed in the parameters illustrating the physical exercise time and load. The post-cardiac rehabilitation stress test was discontinued due to physiological factors. Following the completion of the rehabilitation program, the authors noted lower values of maximal heart rate, systolic and diastolic pressure. The results indicated improved exercise tolerance in the patient.

Discussion

The available studies on patients after myocardial infarction who were subjected to cardiac rehabilitation as complementation of the therapeutic process prove the effectiveness of the therapeutic intervention [10, 17]. The investigators observed decreased mortality rates and a decreased risk of repeated infarction, while the clinical effect was described as "considerable"

as compared to other forms of treatment not employing physical therapy [10]. Improved quality of life was also noted [18]. Finally, employing cardiac rehabilitation decreased long-term costs associated with the process of convalescence [19–21]. Sjölin et al. demonstrated that patients after myocardial infarction who were subjected to cardiac rehabilitation achieved a marked improvement of their cardio-vascular factors as compared to patients not included in physical therapy programs [22].

The development of medical science has positively affected the survival of patients after myocardial infarction; nevertheless, complications associated with the disease continue to constitute a considerable burden to the patient and the state [13]. The possibilities offered by cardiac rehabilitation have not been sufficiently exploited, while the patients' interest in this type of therapy is low [23, 24]. Therefore, the activities are constantly modified [23]. In spite of significant health-associated and economic benefits, the percentage of countries offering such a rehabilitation program is as low as 40% [10]. The recommendations employed in these countries differ significantly [10]. The divergencies predominantly address exercise intensity, duration and frequency of training sessions [10]. Many countries continue to recommend training sessions with a moderate degree of intensity, without any weight-bearing components [10].

The most current reports emphasize the important role of aerobic training of increased intensity and resistance exercises in programs of cardiac physical therapy [10, 14]. Studies performed to date have been mostly based on a group of patients participating in moderate intensity cardiac rehabilitation programs [14, 25]. The present investigation addresses newly introduced exercises that follow the most recent recommendations. The exercise time has been prolonged and the load increased, starting from moderate exercise and ending with the recommended intensely difficult training. In addition, resistance exercises have been employed from the very start; such exercises are recommended in primary and secondary prevention [13]. The results confirm the validity of offering such a rehabilitation program. The change in the level of the tested parameters indicates the increased capacity of the patients and their adaptation to physical effort.

Conclusions

Cardiac rehabilitation employed in patients after myocardial infarction should be a therapeutic standard. It is the key element of convalescence that allows for decreasing therapy-associated costs. The training should include resistance exercises and activity characterized by an intense degree of difficulty.

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Table 1. Distribution of exercise time (in minutes) in particular weeks of cardiac rehabilitation

Weeks		I	II	III	IV	V
Exercises	Cycling a cycloergometer	15 min	20 min	25 min	30 min	30 min
	Active exercises	30 min	30 min	25 min	20 min	20 min
	Resistance exercises	10 min	15 min	20 min	25 min	30 min
	Relaxation exercises	35 min	25 min	20 min	15 min	10 min

Source: own elaboration.

Table 2. Pre-and post-cardiac rehabilitation results of treadmill stress test according to the Bruce protocol

Factors	Pre-rehabilitation	Post-rehabilitation
Physical exercise load	3,44 MET	10,21 MET
Physical exercise time	187 s	722 s
Maximal heart rate	138 beats/min	126 breaths/min
Systolic blood pressure	150 mm Hg	135 mm Hg
Diastolic blood pressure	85 mm Hg	70 mm Hg
Reason for discontinuing the test	Chest pain	Fatigue (score 16, Borg scale)

Source: own elaboration.