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WPŁYW SELENU NA ZAPOBIEGANIE NOWOTWOROM PRZEWODU POKARMOWEGO I PŁUC – CZĘŚĆ II

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Summary

Background. Persistently high incidence of 'diseases of affluence' (including cancer) motivates numerous research teams to look for causes of morbidity, as well as to search for preventive methods and effective therapeutic measures. The paper aims to present the literature on effects of selenium (Se) on prevention of gastrointestinal and lung cancer.
Material and methods. Based on national and international literature, the paper presents information on the role of selenium (Se) in prevention of cancer – with special consideration given to gastrointestinal and lung cancer.
Results. The results of national and international research show the importance of selenium in prevention and treatment of cancerous diseases, including digestive tract cancer and lung cancer. Numerous studies have shown that the risk of cancer for people with low selenium levels is twice as high as for people with high levels of selenium in blood serum. The most prominent relationship between low selenium level in serum and cancer is observed in gastrointestinal cancer, lung cancer, breast cancer in women, and prostate cancer.
Conclusions. Many clinical and experimental studies carried out nationally and internationally gathered evidence which indicate the vital role played by selenium in prevention and treatment of diseases – especially of cancer. It should be emphasised that the intake of selenium in amounts necessary for proper functioning - given numerous deficiencies (first in the soil, then in food products coming from selenium-deficient soil) – is merely the first step, as it has already been proven in numerous publications that carbohydrates (especially simple sugars, sweets, cakes, etc.) 'destroy' selenium in the human body.

Keywords: selenium, cancer, lung cancer, digestive tract cancer, prevention

Streszczenie

Wprowadzenie. Wysoka zachorowalność na choroby cywilizacyjne (w tym na choroby nowotworowe) skłania liczne zespoły badawcze do poszukiwania odpowiedzi dotyczącej przyczyn zachorowalności na nowotwory, jak i poszukiwania metod prewencji i skutecznych środków terapeutycznych. Celem niniejszej pracy jest przedstawienie w świetle literatury przedmiotu wpływu selenu (Se) na zapobieganie nowotworom przewodu pokarmowego i płuc.
Materiał i metody. W pracy zaprezentowano na przykładzie dostępnej literatury przedmiotu (krajowej jak i zagranicznej) informacje dotyczące roli selenu (Se) w profilaktyce chorób nowotworowych – ze szczególnym uwzględnienie chorób nowotworowych przewodu pokarmowego i płuc..
Wyniki. Wyniki badań krajowych i światowych pokazują jak ogromne znaczenie ma wpływ selenu w profilaktyce i leczeniu chorób nowotworowych, w tym: przewodu pokarmowego i płuc. Liczne badania wykazały, że ryzyko raka dla osób z niskim poziomem selenu jest dwa razy większe niż dla osób z wysokim poziomem selenu w surowicy krwi. Najwyraźniejszy związek między niskim poziomem selenu w surowicy krwi a nowotworami jest dla nowotworów przewodu pokarmowego, płuc, gruczołu piersiowego u kobiet i prostaty.
Wnioski. W wielu badaniach klinicznych i eksperymentalnych przeprowadzonych w kraju i na świecie zebrano dowody wyraźnie wskazujące na dużą rolę, jaką odgrywa Se dla profilaktyki i leczenia, zwłaszcza chorób nowotworowych. Podkreślić należy, że dostarczenie do organizmu Se w ilości niezbędnej do prawidłowego jego działania, w sytuacji licznych niedoborów (najpierw w glebie, potem w produktach spożywczych pochodzących z gleb z niedoborem Se) jest tylko pierwszym krokiem, gdyż udowodniono już w licznych publikacjach, że węglowodany (a zwłaszcza cukry proste, słodycze, ciasta itp.) spożywane – „niszczą" selen w organizmie człowieka.

Słowa kluczowe: selen, choroba nowotworowa, nowotwór płuc, nowotwór przewodu pokarmowego, prewencja

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Introduction

In the 1960s, attention was drawn for the first time to the correlation between selenium deficiency and the risk of cancer, based on previous epidemiological work indicating co-occurrence of certain cancers and deficiency of selenium in soil in specific areas [1,2].

Höghberg and Alexander in their monograph devoted to selenium (pub. 2007), collected a whole series of epidemiological data, developed by other epidemiologists and reported that the high supply of selenium in food translates into a lower incidence of some cancers, among others lung cancer [3]. The protective role of selenium in carcinogenesis has been confirmed in numerous experiments that have shown inhibition of the initial (early) stages of this process [4,5].

Presently, a whole range of signalling pathways is suggested that could potentially provide some insight into how selenium can block cell progression and induce their death [6].

Research by Willet et al. showed that the risk of cancer for individuals with low selenium levels is twice as high as for those with high levels of selenium in their blood serum [7,8]. The most prominent relationship between low selenium level in serum and cancer was observed in gastrointestinal cancer, lung cancer, breast cancer in women, and prostate cancer [9]. The following paper aims to present the literature on effects of selenium (Se) on prevention of gastrointestinal and lung cancer.

Selenium versus large intestine cancer

A large group of cancers (after breast cancer), for which the relationship between selenium and development of cancer is sought, are cancers of the gastrointestinal tract, especially of the large intestine. The development of large intestine cancer in first-degree relatives (parents, children, siblings) under the age of 40 indicates the possibility of a genetic condition of cancer. Colonoscopy is recommended for other members of the immediate family (ideally before the age of 40), as well as consultation with a Genetic Clinic. The most common causes of hereditary cancer of the large intestine are mutations in the *APC* gene or the DNA repair genes. Research by Yu et al. showed that selenium reduces the incidence of developing an experimentally-induced large intestine cancer in Wistar rats and interferes with a high-fat diet that affects the development of this type of cancer [10]. These results correlate with earlier research by Reddy and Tanaki [11].

Mikac - Devic et al., based on their research and studies conducted by other research groups, analysed the level of selenium in blood serum in large intestine cancer cases and concluded that significant differences in selenium level in serum of patients with large intestine cancer – in comparison to healthy individuals – justify the use of this micronutrient as a marker for large intestine cancer [12]. Additionally, Clark et al. showed that a decreased selenium concentration in serum may be a significant risk factor for polyp changes in the large intestine [13].

Epidemiological studies conducted in Shanxi province, China, on a substantial clinical material showed that selenium concentration levels in serum were significantly lower in a group of patients with large intestine cancer, compared to a healthy control group [14].

It should be noted that there are also relatively few reports in the literature whose authors did not find lower selenium concentration in people with cancer [15, 16].

Research by Schober and colleagues did not support the relationship between low levels of vitamin A and E, and selenium concentration in serum (and subsequent increased risk of developing large intestine cancer) [15]. Furthermore, in a study published in 1995, Nelson et al. did not find a protective effect of higher selenium concentration in serum on the occurrence of malignant or benign tumours of the large intestine [16].

Many transplantable tumours are insensitive to selenium. The cause of this phenomenon is not yet clarified, although Medina and Lane stated that it results from the differences in the existing inverse correlation between selenium concentration in serum and cancer risk in particular types of cancer. The strongest relation between selenium concentration in the body and the risk of cancer is shown by studies conducted to demonstrate GSH-P_x activity in various types of cancer [17].

Generally, it may be concluded that undoubtedly there is a relation between low selenium concentration and an increased risk of cancer. However, there may be differences in optimal selenium levels for particular populations or countries [18]. For example, in the United States, the level of selenium associated with the lowest risk of colorectal adenomas is ≥150 μg/l. Such differences between Europe and the United States may be associated with a number of genetic and environmental factors, including exposure to chemical agents [15,18].

Selenium versus lung cancer

The main reason for lung cancer is inhalation of carcinogens contained in cigarette smoke. This covers 80-90% of cases. Amongst non-smokers, lung cancer is rare. Lung cancer develops as a result of a very long biological process. It rarely appears in smokers who smoked for only ten years. The 'delay' between the start of smoking and the onset of the disease is 20, 30 or even 40 years. Currently, Poland has the lowest rate of smokers in the last 50 years. Unfortunately, cigarettes are still smoked by 28% of men and 18% of women.

Several prospective studies identified an inverse association between selenium concentration and the risk of lung cancer [3,19].

As experimental work by Liu et al. suggests, selenium plays an outstanding role in prevention and inhibition of proliferation not only of breast and prostate cancer but also of lung cancer. Objective studies showed that methylselenic acid displays anti-cancer activity. Methylselenic acid (MSA) can significantly inhibit proliferation and ability to form metastases in the L9981 cell line of highly metastatic lung cancer, as well as induce apoptosis. The anti-cancer effect of MSA may be associated with regulation of expression related to cell cycle related genes, and genes associated with apoptosis in humans with highly metastatic lung cancer of the L9981 cell line [20].

Available literature clearly indicates that the identification of low selenium concentrations may be very helpful in selecting patients for control exams, such as computed tomography, aimed at early detection of lung cancers. Over 20 studies have shown that low selenium levels in serum are associated with an increased likelihood of lung cancer. Studies conducted by the International Hereditary Cancer Centre in Szczecin, in which serum concentrations in the serum of 86 subjects with lung cancer and 86 healthy individuals were assessed, also showed a strong correlation between the amount of selenium and lung cancer [21].

Among lung cancer cases, the average selenium level was 63.2 μg/l, compared to the average level of 74.6 μg/l in the control group ($p<0.0001$). Among throat cancer patients, the average selenium level was 64.8 μg/l, compared to the average level of 77.1 μg/l in the control group ($p<0.0001$). There was also a 10x lower incidence of lung cancer in patients with selenium level in serum of >80 μg/l, compared to those with selenium concentration of <60 μg/l.

In the above-mentioned comparison, patients displayed an approximately 3x lower incidence of laryngeal cancer accompanied by a higher selenium concentration in serum. The comparison of selenium level in serum of <60 μg/l with >80 μg/l was linked to the odds ratio 0.1 for lung cancer and 0.23 for laryngeal cancer [22]. Individuals in the study group and control group were selected with regard to age, gender and smoking addiction. The risk of developing both the lung cancer and laryngeal cancer decreased along with increased selenium concentration in the blood, and this relation appears to be linear. It should be emphasised that the average selenium level in the Polish population is 75.8 μ/l. This level is far lower than the optimal level, which according to Rayman's proposition should be 120 μg/l since that level would allow optimal expression and activity of selenoproteins [23].

Thus far, a whole series of studies assessing the impact of selenium on the risk of lung cancer was carried out. Four studies showed selenium's protective effect against lung cancer, other four studies did not show such relationship, while two other studies showed an adverse effect of higher doses of selenium on lung cancer incidence [22]. However, it must be emphasised that the comparison of the above-mentioned study results is very difficult. The studies differed in terms of plans and designs (population studies, specific control groups, with or without selenium supplementation), high/low initial selenium level in the population, selenium measurement methods (dietary intake of selenium, determination of selenium concentration in serum or nails) and the length of the observation period [14].

Among the publications, the most cited one is a meta-analysis of 16 studies on the relationship between selenium and lung cancer, made by Zhuo et al. [14]. These authors showed in their collective analysis a relative risk of 0.74 for individuals with high exposure to selenium, i.e. these people had a smaller chance of developing lung cancer. However, this protective effect was more significant for individuals with lower average selenium level (RR =0.72), who came from regions with low selenium concentration in soil, than for subjects from areas with higher concentration of selenium in soil, who had a higher average level of selenium in their blood serum (RR=0.86).

The results of this comparison correlate with the results obtained by the authors of a project entitled: Nutritional Prevention of Cancer Trial (NPC). The project confirmed that the protective effect of selenium may be limited to people with low baseline (pre-study) selenium level in blood. The study was conducted on 1,312 Americans who received 200 μg/day of selenium or placebo in a randomised trial. In the follow-up study after 7.9 years, the odds ratio for the incidence of lung cancer was 0.70. The beneficial effect, to a large extent, was limited to those with a low baseline selenium level, as per the American population (<106 μg/l). In this subgroup

of subjects, the correlation between selenium supplementation and a lower risk of lung cancer was the strongest, and the odds ratio was 0.42. This protective effect occurred only in men with a basic PSA level in serum of ≤4 μg/ml. and whose level of PSA in the blood was low (less than 123.2 μg/ml) [24].

It should be noted, however, that a clinical trial entitled: *The Selenium and Vitamin E Cancer Prevention Trial (SELECT)* published in 2009 in the JAMA journal, found no benefits for men in a randomised trial who were given 200 μg of selenium per day versus placebo in terms of the incidence of lung cancer (RR 1.12). However, in that study, the mean baseline level of selenium was 137 μg/l, and the study results were not divided in terms of selenium in blood serum [25].

In 2008-2011 in Szczecin, an *Early Pulmonary Detection Programme* was carried out. The programme involved participants of both sexes, aged 55-65, with a history of tobacco smoking equal to at least 20 pack-years. The most recent addition to the protocol of this programme (in 2012) was adding pre-selection of participants in the form of measurement of selenium concentration in their blood serum. Only those with low selenium levels (<75 μg/l) were invited for computed tomography. This resulted in more than two-fold increase in the detection of lung cancer. The inclusion of selenium level in serum into prophylactic examinations for lung cancer yields tangible clinical and economic effects [26].

Conclusions

Many clinical and experimental studies conducted nationally and internationally gathered evidence which indicates the important role played by selenium in prevention and treatment of diseases – especially of cancer.

The search for factors causing the formation of cancer, as part of the epigenetic research, was largely focused on demonstrating the role of micronutrients (especially selenium). Many aspects have been clarified, but there is still a need for observational and diagnostic studies to clarify many issues raising doubts, as indicated for example in *Cochrane Database of Systematic Reviews.*

Several clinical and experimental animal tests suggest that improving the supply of selenium to the body may reduce the incidence of several types of cancer, such as lung, colon and breast cancer. The results of recent clinical trials also indicate the anti-cancer effect of selenium on the prostate gland. Data from epidemiological, experimental studies on animals and molecular biology data are convergent in terms of the anti-cancer function of selenium. The obtained data indicate that there are essentially two models of selenium's anti-cancer effect: firstly, the functional model is related to the fact that selenium is a micronutrient that provides catalytic centres for numerous selenoenzymes, including antioxidant and reductive-oxidative functions; while the other model sees selenium as a source of selenium metabolites which act differently. To obtain the maximum protective effect of selenium in the prevention of cancer, selenium supplementation should start at an early stage of life and should be maintained throughout life.

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REVIEW PAPER
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ETIOPATHOGENESIS OF ALLERGIC DISEASES

ETIOPATOGENEZA CHORÓB ALERGICZNYCH

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Summary

Allergic diseases are the most common chronic diseases, particularly widely spread among children, adolescents and young adults. The problem is that there is an increasing incidence of allergic diseases. The causes of such a sudden increase of incidence rate are not well known. Complex interactions of environmental factors seem to play their role in the phenomenon. These include: change in the dietary and hygienic habits, progressing industrialization and increased use of numerous chemical agents. It was shown that inhabitants of highly industrialised nations, as compared to those from the developing countries, suffer from allergic diseases more frequently (most often in USA, Australia, Great Britain, Ireland and New Zealand, least frequently in Eastern Europe, Russia, China, India and Ethiopia), inhabitants of cities rather than those of rural areas, children who have no siblings rather than those from large families [1]. Knowledge of the factors that cause or influence the course of allergy is significant as it can help prevent and properly treat this disorder. It seems especially vital as in some patients allergy can manifest itself in the form of severe anaphylactic reactions, including an anaphylactic shock burdened with high risk of death.

Keywords: environmental factors, genetic factors, allergic diseases

Streszczenie

Choroby alergiczne są jednymi z najczęściej występujących schorzeń przewlekłych, szczególnie rozpowszechnione wśród dzieci, młodzieży i młodych dorosłych. Problem stanowi fakt, że częstość występowania tych chorób stale wzrasta. Przyczyny tak gwałtownego wzrostu zachorowań nie są do końca poznane. Podkreślana jest rola złożonych interakcji czynników środowiskowych takich jak: zmiana nawyków żywieniowych i higienicznych, postępujące uprzemysłowienie i wzrost stosowania wszelakich środków chemicznych. Wykazano, że na schorzenia alergiczne częściej chorują mieszkańcy krajów wysoko uprzemysłowionych niż krajów rozwijających się (najczęściej w USA, Australii, Wielkiej Brytanii, Irlandii i Nowej Zelandii, najrzadziej w Europie Wschodniej, Rosji, Chinach i Indiach i Etiopii), mieszkańcy miast niż wsi, dzieci nieposiadające rodzeństwa niż dzieci z licznych rodzin [1]. Znajomość czynników, które wywołują lub wpływają na przebieg alergii jest bardzo ważna, aby móc zapobiegać i odpowiednio leczyć te schorzenia . Tym bardziej, że u części pacjentów alergia może objawiać się ciężkimi reakcjami anafilaktycznymi, w tym wstrząsem anafilaktycznym obarczonym wysokim ryzykiem zgonu.

Słowa kluczowe: czynniki środowiskowe, czynniki genetyczne, choroby alergiczne

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Introduction

A steady increase in the incidence of allergic diseases can be observed around the world, including Poland. This concerns both children, youth and adults. In the last three decades, the incidence has grown 2-3 fold and relates to all atopic diseases, despite the fact that during this time there has not been noticed any substantial change in human genome[1,2].

According to the White Book of Allergy in Europe, currently allergy affects every third person. It is estimated that in 2010 these disorders will take the third place after cardiovascular diseases and neoplasms [3,4].

The findings of the first stage of Epidemiology of Allergic Diseases in Poland study (ECAP), which began in 2005, were published in April 2008. They were based on personal questionnaires conducted among more than 22,5 thousand people from nine regions in Poland, out of whom one forth underwent detailed medical

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examinations. A rigorous analysis showed that 45-52% of the Polish population, more than 15 million Poles, at least once in their lifetime suffered from an allergy, whereas 28% of the surveyed people are in need of systematic treatment because of an allergic medical condition. The findings resulting from the ECAP study place Poland among the countries with the highest percentage of patients suffering from an allergy [5].

Epidemiology of allergic diseases

It is commonly known that the main factor determining the occurrence of allergy is atopy, genetic predispositions of the body to increase the production of characteristic antibodies in IgE class directed against the environmental antigen (allergens). Atopy does not necessarily indicate a disease, but an increase in susceptibility to the development of an allergy. If an allergic disease is to occur, some kind of interaction of genetic factors (atopy) and environmental ones is needed. Further, the influence of genetic predisposition on the prevalence of an atopic disease, passed onto next generations, as well as a constant increase in the number of unfavourable external factors modifying the occurrence, development and the course of an allergy cause that the problem of a constant increase in incidence of allergic diseases becomes more acute[2].

Genetic factors

Because there is an incontestable contribution of genetic factors to the rise of the factors determining atopy, there are currently ongoing studies aiming to determine them precisely. These studies are hindered by the fact that even in the same family allergy can manifest itself in different clinical form, such as rhinitis, asthma or atopic dermatitis. Individual family members may also be allergic to totally different allergens. Another disturbing fact is that children descendent from families burdened with atopy show an increased risk of morbidity for such diseases. The risk of an atopic disease in children of healthy parents is around 10-15%. When one parent is affected, the risk increases to 30-40%, whereas when both of the parents suffer from an atopic allergy, the risk is over 60% [2].

Atopy is caused by multigenic inheritance. Until now, we have identified tens of gens determining the occurrence or modifying the course of an allergy, localized in different regions on particular chromosomes. Among others, a correlation was shown between a gene localized on chromosome 4 with bronchial hyperactivity; on chromosome 6 with total concentration of IgE in serum and eosinophilia; on chromosome 7 with total concentration of IgE in serum and bronchial hyperactivity; on chromosome 11 with total concentration IgE in serum, positive skin test results with allergens and asthma; on chromosome 13 with atopy characteristics; and on chromosome 16 with total concentration of IgE in serum, bronchial hyperactivity and asthma [6,7]. Detailed characteristics of particular genes are shown in table 1.

Table 1. Characteristics of genes linked with different phenotypic traits of atopic allergy [2]

Chromosome region	Trait linked to a gene	Correlation coded by the gene
5q	high level of total IgE bronchial hyperactivity asthma severity of asthma bronchial hyperactivity high level of total IgE atopy	IL-3, IL-4, IL-5 receptor $_{\beta}2$
6p	specific IgE, total IgE asthma	HLA-DR TNFα
7q	specific IgE, total IgE	TCRB, TCRG
11q	atopy, asthma	receptor for IgE FcεRI CC16
12q	asthma	IFNγ
14q	specific IgE, total IgE	TCRA
16p	atopy, atopic dermatitis	IL-4R
17q	asthma	chemokine

Environmental factors

Environmental factors play a big role in the etiopathogenesis of allergic diseases. Allergens are definitely the most important of them. Not only is their presence significant, but also their concentration and exposition time. An example could be the fact that in children descended from families with atopy, asthma develops all the more frequently and earlier, if higher concentration of household dust allergens (mites) are present in the direct surroundings [2,8].

The significance of a constant rise in the air pollution is also being emphasized [9]. Germany, which was divided into two countries after 1945, is a good example. Both of the territories were characterized by radically different environmental factors. In the former East Germany, where the industrial activity developed, an increase in carbon dioxide in the atmospheric air was observed. In the former West Germany, however, the atmosphere contained significant amounts of nitrogen dioxide because of the intensive vehicle traffic. The studies conducted by Heinricha et al. showed that the incidence of allergic diseases in West Germany increased significantly in people born after the year 1960. Such an increase was not noted in East Germany though. After the unification of both countries, atmospheric pollutants became more uniform and the inhabitants' way of life became similar on the whole German territory. Then, it was noticed that the differences in frequency of atopic allergic diseases both in the eastern and western territories were slowly diminishing [2,10]. It should also be mentioned that the presence of motor vehicles fuel particles in the atmosphere was significant as it contributed to the changes.

Formation of toxic substances such as sulphur dioxide, nitrogen oxides, carbon monoxide, ozone, benzene, formaldehyde, hydrocarbons and diesel exhaust particles (DEPs) results from incomplete fuel and diesel oil combustion [11]. The emissions from diesel engines produce more than 90% of such particles. Their size is usually smaller than 1 millimicron and therefore they can easily get into the respiratory tract. Further, these particles absorb plant pollens on their surface, which aid the penetration of nasal mucous membranes as well as the penetration into the lower respiratory tract. The exposure to diesel emission particles, after the prior provocation by an allergen, causes an increased expression of IL-4, IL-5, IL-10 and IL-15, enhances adhesion of eosinophils to the epithelial cells and leads to their degradation, as well as activates production of IgE in nasal mucosa [12].

The emissions of diesel fuel not only exacerbate the symptoms of the already existent allergic disease, but also aid in the development of new ones. This would explain the increased incidence of pollinosis in city inhabitants as compared to the people who inhabit rural areas and the exacerbation of symptoms in patients with the already existent pollinosis. That is why, so many studies on the role of rural environment highlight its role as a factor decreasing the risk of allergy development [10,13].

It is not only environmental pollution that plays a significant role in etiopathogenesis of allergic diseases. As a consequence of change in lifestyle, living space hygiene has also become more important, because modern people spend on average 30-80% of their time indoors. This causes that not only an increased level of nitrogen dioxide is dangerous, its sources being gas stoves, coal heaters, fireplaces as well as cigarette smoke, but also the presence of numerous volatile substances derived from materials used for building, decoration and conservation of houses, such as for example formaldehyde [14]. Lack of natural air ventilation, particularly in air-conditioned spaces, favours an increase of the above mentioned substances. It also causes a higher concentration of allergens, disease causing microorganisms, including bacteria, moulds, house dust mites as well as cockroach allergens. Furthermore, a long-lasting stay in indoor spaces, as well as the common use of UV skin filters is connected with a decreased exposure of the skin to sun, which results in a decreased synthesis of vitamin D[15].

Another notable development is greenhouse effect caused by an increase of CO_2 in the atmosphere due to human industrial activity, which results in global warming. Higher air temperature stimulates earlier and longer blooming, which increases the risk of exposure to airborne allergens. Besides, an additional exposure to pollutants that acts synergistically intensifies the overall allergic response [13,16].

How the above mentioned factors affect people was shown on the two populations: Finish and Russian, who inhabit the same geographic area of Karellia. The comparison was conducted at two distinct points in time, i.e. in 1997/98 and 2007. It was determined that morbidity for allergic diseases in subsequent Finnish generations was increasing both in children and in adults, while in the Russian population such an increase in morbidity for allergic diseases was not observed. This could be explained by the differences between the areas. The area inhibited by Russians is characterised by a smaller degree of industrial development, and greater exposure to a more varied bacterial environment, including bacterial endotoxins derived from the farm animals environment, which are typical surroundings of the Russian population [17].

It is bacteria of Acinetobacter (gammaproteobacteria) species that showed a particularly protective action, which has anti-inflammatory genetic modification properties, and which showed a decrease in the risk of allergy as well as pneumonia development in the conducted in-vitro studies. In one of the studies on skin microbiota in healthy people without atopy, a higher concentration of Acinetobacter and anti-inflammatory molecule expression was found, as compared to the skin of those with atopy. Bacteria of the Acinetobacter group promote anti-inflammatory Th1 cell type response [18].

In the Sandin et al. study of children population with positive skin test results, it was observed, that in those in whom higher concentration of IgA in saliva was found, allergic diseases developed less frequently, as compared with children who had a low concentration of this immunoglobulin. High concentration of IgA occurred more often in children who had older siblings as well as in those who had at least several infections in the period of

their early childhood [19]. In the study conducted by Kusunoki et al., on the group of eleven thousand children, a decreased risk of food allergy development was observed along with the corresponding increasing number of older siblings, which most probably is related with more frequent infections among large family [20].

The European project GABRIEL carried out on the population of Polish children aged 7-12 years, in the region of Lower Silesia, showed a more frequent occurrence of atopy in children living in the city environment as compared to those inhibiting the rural areas, but no changes were observed in this study with regard to the frequency of bronchial asthma occurrence [21].

Other factors affecting the intestinal microflora, which accompany humans from the beginning of their existence, are parasites. It was observed that parasitic infections have a protective action in regard to the development of allergic diseases, and the treatment of the parasitic infestation favours the development of allergies and autoimmunological diseases. This finding was confirmed by many studies in different world populations. In the developed countries, where parasites are relatively rare in comparison to the developing countries, allergic and autoimmunological diseases constitute a common health problem [22].

The advancement of medicine is also causing a wide use of medications, whose long term effect is being studied only now. It is believed that many substances which exist today may be the cause for allergy development in the future.

The frequent use of paracetamol and/or antibiotics during pregnancy and in first years of life may increase the risk of development of allergic diseases in children, including bronchial asthma, atopic dermatitis and allergic rhinitis, which was observed in a few cohort studies in different populations [23,24,25]. However, not all of those studies confirm such correlations [26].

The use of medications increasing the pH of the stomach in pregnant women is related to an increased risk of development of asthma in children. It is also believed that a long term use of medications neutralizing the acidity of the gastric juice increases the frequency of food allergy occurrence, which was also confirmed on a mouse model [27].

The use of substances containing plant protein on a damaged skin may induce an allergy toward the same protein that is caused when it is contained in some foods. Therefore, the selection of substances for skin care in children with atopic dermatitis is so crucial [28, 29].

Allergic contact dermatitis is another allergic disease caused by environmental factors. Many metals, especially nickel, chromium, copper and cobalt, are used in jewellery, coins, parts of clothing (e.g. belts, trousers), mobile phones, dental materials, leather dyes, etc. Nickel contact allergy dermatitis is one the most frequent allergic skin problems due to the high use of this metal in daily life and its presence in drinking water in different quantities [30].

Unfavourable life style changes also impacted nutrition adjustments, including in particular an introduction of new products into diet, industrially processed foods, food additives (such as for example: dyes and preservatives), which all affected changes in the intestinal flora [31,32]

Besides, the importance of travel abroad, during which exposition to new allergens might take place, is being emphasized in discussing the ethiopathogenesis of allergic diseases. It is believed that the following factors also play their own role: the exposition to disease causing microorganisms; interference within human immunological system, which includes among others anti-infectious immunizations; the use of immunomodulating drugs, as well as an increased exposition to stress. However, these data need further research in order to fully confirm their role in the development and course modification of allergic diseases [2, 10, 33].

On the other hand, environmental factors may have an influence on an increased frequency of allergies occurrence, which is shown in table 2.

Table 2. Environmental factors which may influence an increase in frequency of allergies [2, 7]

Pollution of external environment
• Atmospheric pollution • Vehicle traffic (emissions) • Ozone • Chemical and biological pollution • Cigarette smoke • Building construction (new materials, thermal insulation, diminished ventilation, increased room humidity)
Lifestyle changes
• Longer stay indoors • More frequent travel – exposition to different allergens

Change in the way of nutrition
• New products • Manufactured processed foods • Food additives (among others pigments, preservatives, additives) • Change in the bacterial flora
Exposition to allergens
Size and socio-economic status of the family
Role of infections
Iatrogenic factors
• Preventive vaccinations • Antibiotics • Discrimination of aspirin
Exposure to stress and ways of fighting it

As for food allergy, it has been found so far that the risk factors include: male gender among children, female among adults, black and Asian races, vitamin D insufficiency, low consumption of omega-3 fatty acids and antioxidants as well as obesity, high level of hygiene and the time when new products are introduced into child's diet [2].

Food served either too early or too late may be the reason for the development of an allergic reaction. It is currently believed that the so called „window of immunological tolerance induction" is between the 4th and 6th month of life and during this period the largest variety of different foods should be introduced into the child's diet so that the immunological system may get acquainted with them without developing an allergic reaction [34].

Conclusions

It seems obvious that the allergy development occurs only in people with genetic predisposition, the so called atopy. According to this premise, the allergy is currently defined as a TH2 type hypersensitivity for non-harmful antigens (allergens) of complex genetic background. The basis for the development of the so-called hygienic atopy theory is explained by the mutual interdependence of genetic and environmental factors. Individuals with a Th1 response defect (independent of a tendency for atopy) are also susceptible to many infections (bacterial and viral) because of the deficit of INF-γ, IL-12 and IL-2, which are essential for the activation of cytotoxic cells. It may therefore be speculated that those people who lived before antibiotics were introduced died in the early period of life as a result of infections and, in consequence, could not pass on the above mentioned immunological anomaly to their offspring. This in turn resulted in a natural selection in the population with effective Th1 response in the the first half of the 20th century, while most of the carriers of the Th2 type response were unable to survive. According to one theory, the moment antibiotics were introduced for therapeutic purposes on a wide scale, the above mentioned natural selection succumbed to modification, which finally led to an increase in carriers with genetically predominant type Th2 response, vulnerable to the development of atopic disease. In some individuals of the present day population, the lack of Th1 incentives resultant from „sterile" conditions in which children grow up may have contributed to the intensification of allergy. Although presently the hygiene theory seems to be the most convincing interpretation of the atopy genesis in the light of current knowledge of its mechanism, many aspects of the condition still remain to be discovered in this area [35].

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ORIGINAL PAPER
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QUALITY OF LIFE IN OBESITY AT PERIMENOPAUSAL AGE IN OBESE WOMEN AND WOMEN WITH PROPER BODY MASS INDEX

JAKOŚĆ ŻYCIA W WIEKU OKOŁOMENOPAUZALNYM W GRUPIE KOBIET Z OTYŁOŚCIĄ ORAZ Z PRAWIDŁOWĄ MASĄ CIAŁA

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Authors' contribution
Wkład autorów:
A. Study design/planning
zaplanowanie badań
B. Data collection/entry
zebranie danych
C. Data analysis/statistics
dane – analiza i statystyki
D. Data interpretation
interpretacja danych
E. Preparation of manuscript
przygotowanie artykułu
F. Literature analysis/search
wyszukiwanie i analiza literatury
G. Funds collection
zebranie funduszy

Summary

Background. Obesity is a global-scale epidemic of the 21st century, leading to numerous psychophysical complications. The objective of this paper is to analyse the quality of life at perimenopausal age in the group of obese women, and to compare the findings with those obtained in the group of women with proper body mass.
Material and methods. There were two equal research groups included in the study. In the first group there were 50 obese women BMI (m) = 36.5, patients of the Obesity Treatment Ward. In the other group, there were 50 normal-weight women BMI (m) = 24.1, primary care patients from Warminsko-Mazurskie Province. The research tool used in the study was The World Health Organization Quality-of-Life Scale – WHOQL-BREF.
Results. Differences between the group of obese women and the one with healthy body mass turned out to be statistically significant $p<0.05$ in the general quality of life t(sd) = -3.21(98), general quality of health t(sd) =-3.96(98), physical health t(sd) = -3.11(98), psychological health t(sd) = -3.67(98), social relationship t(sd) = -2.76(98) and environment t(sd) = -2.86(98).
Conclusions. Results of the study showed significantly lower quality of life in all measured domains in obese women in comparison to those with proper body mass.

Keywords: obesity, quality of life, WHOQOL-BREF

Streszczenie

Wprowadzenie. Otyłość jest epidemią na skalę globalną XXI wieku, prowadzącą do licznych komplikacji psychofizycznych. Celem pracy jest analiza jakości życia w wieku okołomenopauzalnym w grupie otyłych kobiet oraz porównanie wyników z wynikami uzyskanymi w grupie kobiet z prawidłową masą ciała.
Materiał i metody. W badaniu wzięły udział dwie równoliczne grupy badawcze. W pierwszej grupie było 50 otyłych kobiet BMI (m) = 36,5, pacjentów Oddziału Leczenia Otyłości. W drugiej grupie było 50 kobiet o prawidłowej masie ciała BMI (m) = 24,1, pacjentek podstawowej opieki zdrowotnej z województwa warmińsko-mazurskiego. Narzędziem badawczym zastosowanym w badaniu była Skala Jakości Życia Światowej Organizacji Zdrowia - WHOQL-BREF.
Wyniki. Różnice między grupą otyłych kobiet a grupą kobiet z prawidłową masą ciała okazały się statystycznie istotne $p <0,05$ w ogólnej jakości życia t (sd) = -3,21 (98), ogólnej jakości zdrowia t (sd) = - 3,96 (98), zdrowiu fizycznym t (sd) = -3,11 (98), zdrowiu psychicznym t (sd) = -3,67 (98), związkach społecznych t (sd) = -2,76 (98) i środowisku t (sd) = -2,86 (98).
Wnioski. Wyniki badania wykazały znacznie niższą jakość życia we wszystkich mierzonych domenach u otyłych kobiet w porównaniu do osób o prawidłowej masie ciała.

Słowa kluczowe: otyłość, jakość życia, WHOQOL-BREF

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Introduction

Obesity is a global-scale epidemic of the 21st century [1]. In Poland, every second adult is overweight, and one in six is obese [2]. According to the available research, 16.4% of Polish teenagers and children are overweight or obese [3]. Moreover, the increase in the percentage of child obesity is faster in Poland than in the USA [4]. It is also worth mentioning that the costs of treating obesity poses an additional burden on the Polish budget. According to the assessment by the Food and Nutrition Institute, excessive body weight account for approximately 1.5 million hospitalisations annually. This consumes 21% (approximately 11 million PLN) of the budget allocated to health protection [5].

Obesity may considerably reduce the quality of human life, leading to numerous psychophysical complications [6]. It is recognised as a social-cultural problem within Polish society. This is confirmed among others by research

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on the stigmatisation of obese Polish women [7]. It is also common knowledge that certain modern psychosocial and educational problems of juveniles result from the stigmatisation of overweight children and teenagers, particularly girls [8]. Research conducted by Sola et al. [9] showed that high body weight in children and youth has a negative effect on the quality of their life related to the state of health with simultaneously the strongest impact of the physical functioning on the psychosocial sphere. In this domain, the problem is particularly evident in the sphere of contact with others. Moreover, the research evidenced that the group of obese children and youth demonstrate health-related quality of life-HRQL comparable to children and youth with cancer [10]. Similar research conducted by Serrano-Aguilar et al. [11] confirmed the impact of body weight on life quality. Patients with average BMI suggesting II degree obesity in comparison to the norm in society reported considerably lower results in eight domains of life quality. Patients with extreme obesity achieved significantly worse results in the physical and social domain, assessed the general state of health worse and experienced pain more intensely than obese persons with a lower BMI value. Obese persons also reported significantly higher disability due to experiencing physical pain than patients with other chronic diseases. The above research showed that obesity has a negative effect on HRQL even in the case of lack of accompanying chronic diseases.

The objective of this paper is to analyse the quality of life at perimenopausal age in the group of obese women at perimenopausal age, and to compare it the one in the group of women with healthy body weight. Due to the physiological changes in the organism and the related psychoemotional problems, women at the perimenopausal age tend to gain body weight [12]. This, in consequence, results in a considerable increase in the frequency of obesity. Finally, targeting the proposed research at women is due to the fact that the problem of overweight and obesity in the social-cultural context predominantly concerns women [13].

Material and methods

The research covered two equal research groups. All participants gave verbal consent to participate and the study was approved by the Bioethics Committee of University of Warmia and Mazury, Olsztyn, Poland. The first research group comprised 50 obese women (table 1) of the Obesity Treatment Ward. The mean age of the patients was 49.8 (range: 39-65 years of age). The mean body mass index amounted to 36.5 (range: 25-51.2). All patients were inhabitants of town. All subjects had been admitted to an obesity management clinic which organises weight loss programmes teaching patients to make healthy lifestyle choices with the assistance of an interdisciplinary team of experts, including a dietician, physician, psychologist, physiotherapists and physical education trainers.

The other research group comprised 50 women (table 2) with proper body mass from the Primary Care Centres in Warminsko-Mazurskie Province. All of them were inhabitants of town. The mean age of the patients was 48.7 (range: 38-60 years of age). The mean body mass index (BMI) amounted to 24.1 (range: 22.3-24.9).

Table 1. Characteristics of the research groups

Variable	Obese women (n, %)	Women with proper body mass (n, %)
Education	Vocational: 4, 8	Vocational: 5, 10
	Secondary: 16, 32	Secondary: 18, 36
	Higher: 30, 60	Higher: 27, 54
Marital status	Single: 5, 10	Single: 4, 8
	Married: 35, 70	Married: 34, 68
	Divorced: 8, 16	Divorced: 9, 18
	Widow: 2, 4	Widow: 3, 6

The applied research tool was The World Health Organization Quality-of-Life Scale – WHOQOL-BREF [14]. The questionnaire comprises 26 items. It measures the following broad domains: physical health, psychological health, social relationship and environment. Individual assessment of the patient covers: in the physical domain: everyday activities, dependency on medicines and treatment, stamina and tiredness, mobility, pain and discomfort, rest and sleep, ability to work; in the psychological domain: outward appearance, negative feelings, positive feelings, self-assessment, spirituality, religion, personal faith, thinking, learning, memory, concentration; in the domain of social relations: personal relationships, social support, sexual activity; in the environment of functioning: financial resources, freedom, physical and psychological safety, accessibility and quality of health care, household environment, possibility to obtain information and skills, possibility to participate in rest and recreation. Moreover, WHOQOL-BREFF includes items analysed separately: question 1: individual general quality of life; question 2: individual general quality of health. Respondents provided their

answers on the 5-degree scale and could score up to 20 points in each domain. The results were presented in the form of the arithmetic mean, standard deviation and percentage calculation. The statistical assessment of the results obtained was performed using SPSS 22 programme on the basis of Student t-test.

Results

General quality of life of obese persons amounted to m=3.25 (0.90) on the 1-5 scale. Among the patients, 13% assessed the quality of their life as very good, 15% good, 19% bad, and 6% very bad. The remaining 47% of persons assessed the quality of their life neutrally – "neither good nor bad". Regarding the assessment of own health in obese persons, 5% were very satisfied, 15% satisfied, 21% dissatisfied, and 14% very dissatisfied. 45% provided a neutral answer "neither good nor bad" to the question concerning own health. In comparison, in the group of persons with proper body weight 18.5>BMI<25, general quality of life amounted to m=3.85 (1.03). Among the patients, 26% assessed the quality of their life as very good, 41.5% good, 38% bad, and 2% very bad. The remaining 42.5% evaluated the quality of their life as "neither good nor bad". As for the assessment of own health in persons with proper body weight, 22.5% were very satisfied, 36% satisfied, 11% dissatisfied, and 2% very dissatisfied. The remaining 29% assessed the quality of their life neutrally, i.e. "neither good nor bad". The differences between the obese group and the one with healthy body weight in the general assessment of the quality of life and own health turned out to be statistically significant in both cases $p<0.05$.

The differences in the quality of life in particular domains (physical, psychological, social, and environmental) between both study groups were presented in Table No. 2.

Table 2. The results obtained in the WHOQOL-BREF test in the group of obese (n=50) and proper body mass women (n=50) at the level of significance of $p < 0.05$

Quality of life domains	Obese women m (sd)	Women with proper body mass m (sd)	Student t-test (df)
General quality of life	3.25 (0.90)	3.85 (1.03)	-3.21 (98)
General quality of health	2.50 (1.02)	3.65 (1.02)	-3.96 (98)
Physical health	13.25 (3.03)	15.31 (3.21)	-3,11 (98)
Psychological health	11.67 (3.21)	14,52 (3,91)	-3,67 (98)
Social relationship	13.14 (3.03)	16,31 (3,21)	-2,76 (98)
Environment	13.48 (3.05)	16,95 (3,71)	-2,86 (98)

m-mean, sd-standard deviation, df-degrees of freedom

Moreover, the statistical data from WHOQOL-BREF showed no correlation between the demographic variables of the studied persons (place of residence, marital status, level of education) and the level of quality of life.

Discussion

The term quality of life has had special prominence in recent years both in psychology and medicine. There has been observed an empowerment of the patient as more attention has been paid not only to their situation, but also the subjective perception of the disease. Clinicians took interest in domains of life related to the state of health and psychological and physical functioning, which is related to the concept of quality of life determined by the state of health – HRQL. Quality of life determined by the state of health has become an important indicator of the ill patient's position. It is a clinicians' response to a higher real prevalence of chronic diseases. The assessment of quality of life is performed subjectively, i.e. by the interested person themselves. It constitutes the most valuable and properly obtained source of information. In the presented research, the general quality of life and health of obese persons, and quality of life in all of the analysed domains (physical, psychological, social, environmental) turned out to be statistically significantly lower than the quality of life of persons with proper body weight. A decrease in the quality of life in the physical sphere probably results from the co-morbidities associated with obesity – numerous diseases and pathologies [6, 15]. As the statistics indicate, obesity in women at post-menopausal age increases, among others, the probability of uterus cancer, oesophageal cancer, kidney cancer, colorectal cancer, and breast cancer. A health-related effect of obesity, which usually resulting from sedentary lifestyle, is type II diabetes [16]. Moreover, a large part of the western society, and particularly persons with excessive body weight, have been determined to suffer from non-alcoholic fatty

liver disease causing damage to the organ [17]. Obesity is also the cause of atrial fibrillation, which considerably increases the risk of heart attack. Extreme obesity may lead to pulmonary thrombosis, deep vein thrombosis, chronic abdominal compartment syndrome, and heart enlargement, often leading to death [6, 16]. The incidence of such diseases may also be largely determined by the so-called metabolic syndrome, often occurring in the obese. Its consequence can be type II diabetes, coronary heart disease, or stroke [6, 16]. A decrease in the quality of life of obese patients in the psychological, social, and environmental sphere can be related to more frequent co-occurrence of obesity with depression-anxiety disorders, eating disorders, and personality disorders [18, 19, 20].

Moreover, the obesity stigma and the resulting discrimination lead to social isolation and contribute to the devalued social identity of the overweight persons. They are discriminated and victimised in many different spheres of life, including education, workplace and health care [21]. They face contempt, verbal or physical abuse and social repression, becoming subject to isolation, neglect, ridicule and gossip [22]. People with BMI>30, in particular women, find it more difficult to enter into romantic relationships [13]. Stress and low self-esteem increase the probability of emotional overeating and adopting a sedentary lifestyle. Those behaviours perpetuate obesity and additionally create a risk of developing somatic disease caused by weight gain [21]. Victims of weight stigma are also more susceptible to psychological disorders such as depression and are more likely to attempt suicide [23].

The obtained results in the presented research are consistent with results of other studies focused on the quality of life of the obese [9, 11]. Among others, the research conducted by Groessl et al. [24] shows that obese persons demonstrate a lower quality of life compared to those with proper body weight. Moreover, a non-linear correlation is observed between the quality of life and BMI value, and in the case of healthy BMI, the quality of life has a positive value. BMI exceeding the normal range generates the risk of deterioration of the state of health [25]. Also among persons at the age of 55-75, the BMI value strongly determines the quality of life [26]. Comparable results were also obtained by the Polish research team who applied the WHOQOL-BREF questionnaire while assessing the quality of life of the obese and those overweight [27]. In the above study, the obese reported a significantly lower assessment of own state of health and quality of life in comparison to the overweight. It was visible in the following general domains: physical health, psychological health, social relationships, and environment.

Research on the quality of life in the population of obese persons provides essential information concerning their subjective perception of self. This has valuable practical implications in the development of therapeutic, prophylactic, and treatment programmes with consideration of the quality of life in chronic disease. As the approach by de Walden-Gałuszko [28] stresses, the quality of life concerns the perception of own life position of a person in a temporal space, emphasising the necessity of doing medical research from two_perspectives, namely objective and subjective, which would simultaneously indicate the correlation between the quality of life and feeling of happiness.

Regarding ways of improvement of the psychophysical welfare of persons with excess weight, research by Prat et al. [29] evidences that body weight reduction programmes involving the cooperation of the patient with the doctor, psychologist, and dietician result in a considerable increase in quality of life of such patients. Also according to other research teams [30], the most efficient methods of improvement of the psychophysical functioning of persons with excess weight include multidisciplinary interventions aimed at facilitating a change of lifestyle. Moreover, the above study evidences that training of self-regulatory skills as an element of organised treatment for obesity results in an improvement of the body image and, therefore, the quality of life in persons with body mass index exceeding 30.

The weak point of the present study is the small size of the research group, which limits the ability to generalise the results. Therefore, the obtained results should be treated with special caution. Future research focusing on the quality of life in obese women should cover a far more significant number of subjects.

Conclusions

Results of the study showed a significantly lower quality of life in all measured domains (general quality of life, general quality of health, physical health, psychological health, social relationship and environment) in obese women compared to those with proper body mass.

Obese persons should receive multidisciplinary support during weight loss treatment programmes due to the level of quality of life and associated psychophysical disorders.

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MANAGEMENT OF CHILD INJURIES IN TRAFFIC AND OTHER ACCIDENTS: THE WHO POLICY GUIDELINES

URAZY U DZIECI W ZDARZENIACH DROGOWYCH I INNYCH WYPADKACH: WYTYCZNE WHO

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C. Data analysis/statistics
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D. Data interpretation
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Summary

Children injuries are one of the biggest problems in modern medicine that require vigorous and preventive actions. All kinds of injuries resulting from road accidents are the most common cause of death in children, more common than cancer and birth defects. In the years 1995-2009, there were 113 211 accidents involving 959 children aged 0-14 years in Poland in which 3791 children died and 117 730 were injured. Most fatalities were recorded in children in the age range 7-14 years. The following study presents the main problems of road safety and the nature, causes and consequences of injures in children in Poland and worldwide. It discusses the risks associated with children involved in traffic as well as ways of reducing the number of accidents in children based on the WHO report.

Keywords: injuries, children, accidents

Streszczenie

Urazy i ich następstwa u dzieci są jednym z największych problemów współczesnej medycyny, które wymagają działań energicznych i zapobiegawczych. Obrażenia spowodowane wypadkami drogowymi są najczęstszą przyczyną zgonów wśród dzieci, częstszą niż choroby nowotworowe i wady wrodzone. W Polsce w latach 1995-2009 doszło do 113 211 wypadków drogowych z udziałem dzieci w wieku 0-14 lat. 3791 dzieci zmarło, a 117 730 zostało rannych. Większość ofiar śmiertelnych odnotowano wśród dzieci w wieku 7-14 lat. Praca przedstawia główne problemy związane z bezpieczeństwem ruchu drogowego, charakter, przyczyny i konsekwencje wypadków drogowych wśród dzieci w Polsce i na świecie. Omówione w niej zostały także zagrożenia związane z udziałem dzieci w ruchu drogowym, jak również sposoby na zmniejszenie liczby wypadków wśród dzieci na podstawie raportu WHO.

Słowa kluczowe: obrażenia, dzieci, wypadki

Introduction

According to the WHO, each year about 75 million people suffer from injuries in the world, and 23% of trauma victims die or suffer permanent injury. Such a large number of injuries is due to, inter alia, changes in the pattern of life, transformation of economic systems, developments in the automotive industry and mechanisation of agriculture. Further, there are noticeable a constant pursuit of work, wish to move from place to place, insufficient rest, violation of road safety rules, poor quality of road infrastructure and poor technical condition of vehicles. Many of the threats facing the contemporary world also concern the children to a large extent. Injuries in children older than 2 years are the cause of more deaths than all other childhood diseases combined. More than 20% of the population experience trauma, and about 10% of accidents cause some sort of disability in children. Further, road injuries are among the predominant causes of deaths. Falls from height, drowning, burns, beatings and the use of physical violence (i.e. child abuse) are rarely causes of injuries. The damage resulting from traffic accidents is the leading cause of death among children, more frequent than cancer and birth defects. As the WHO report of 2007 – "Youth and road safety" – shows, road accidents are the leading

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cause of death among young people. According to the WHO, about 400 000 people under 25 years are killed in road accidents each year, and millions suffer from various injuries [1,2,3,4].

Currently, a fatal road accident occurs on average every 50 seconds in the world, and every two seconds it causes damage in humans. As a result of injuries sustained in road accidents, mortality is 2.2% of all deaths worldwide. Road accidents cause more deaths than wars, and millions of people become handicapped. The economic consequences of such a large number of fatal accidents and injuries leading to disability are significant. In many countries, low-and middle-income costs of road accidents consume 1.5-2% of gross domestic product, and some exceed the value of international aid [5,6,7].

Injury and violence is a major cause of fatality resulting in about 950,000 deaths in children and young people under the age of 18 years each year. Unintentional injury (road traffic collision, drowning, burn, falls and poisoning) account for about 60% of all child deaths in the world. Other unintentional injuries (smothering, asphyxiation, choking, animal and snakebites, hypothermia and hyperthermia) account for 23% of childhood deaths. It is well known that children in poorer countries and those from poorer families are the most vulnerable. The rate of child injury death is 3.4 times higher in low-income and middle-income than in high-income countries. The child-injury pyramid showed that, for each child under 19 years who was fatally injured, 45 children required hospitalisation and further 1,300 needed medical care at outpatient emergency clinics. A non-fatal injury not only causes suffering but also constitutes a financial burden for the health care system. It is also worth noting that 50% of those under 12 years who were treated in emergency departments remained with some form of disabilities (physical, mental, sociological), which has an impact on their lives as well as members of their families and the society. It is due to their inability to attend school, find suitable work or engage in an active social life.

Since children are not small adults they have different physical and cognitive abilities. They are curious and ready to experiment. They can be exposed to injury risk at different age in different countries while entering the formal workplace. Also some legal aspect connected with driving a car or drinking alcohol may influence the problem. For example, alcohol can be legally consumed at the age of 15 in Belgium, 20 in New Zealand; a car can be legally driven in New Zealand at the age of 15, and 18 in Sweden. A small stature is another factor making children particularly vulnerable to injury; they are less visible than adults and when hit by a vehicle, they are more likely to get a head or neck injury. Since they have smaller airways, they are particularly susceptible to aspiration than adults. Their skin is thinner, so they get deeper burns more quickly, even at lower temperature. In children below 15 years, a fatality rate is 24% higher in boys than in girls due to the fact that boys behave more impulsively, demonstrate higher activity levels and engage in more risky behaviour. There are certain socioeconomic factors associated with the risk of injury in children such as economic factors (family income), social factors (maternal education), family structure (single parenting, maternal age, number of occupants of the household, number of children), accommodation (type of tenancy, housing, overcrowding) and access to high quality medical services that can influence not only the likelihood of survival but also its long–term consequences. The studies conducted in the centres involved in the biomechanics of transportation and injury show that the risk of injury and the effects of impact increase proportionally to velocity. Body overload in the moment of vehicle collision impact is so great that the passenger's weight of increases a few or even several times. At a speed of 50 km / h, the collision effects are the same as when a body falls from a height of 10 feet (3 floors). At the speed of 80 km / h, it corresponds to the weight dropped from a height of 24 meters (8 floor). At a speed of 100 km / h, the collision effects are the same as when a body falls from a height of 40 meters (12-13 floor). A person weighing 90 kg, driving with unfastened seatbelts, in a collision at 50 km / hr. hits the windshield with the force of the concrete block weighing 3.5 tons [8,9,10].

Another threat to the Polish roads are young drivers (18-25 years). According to the Police Headquarters data, young drivers in Poland are the perpetrators of 18% of all accidents in which 18% of those involved die. The causes of excessive risk associated with the involvement of young people in traffic are a lack of experience and driving skills, willingness to take risky behaviours, driving in times and places of particular risk (night time, weekends) and driving under the influence of alcohol. Young people are confident of their abilities, i.e. receiving and processing stimuli. However, being too inexperienced, they do not leave any margin for error. A young driver is the most reasonable when driving alone. With an increasing number of friends, the chances for survival decrease. If a teenager takes one person, the chances of their safe arrival fall by 39%. When driving with two people, the risk doubles. Recklessness occurs in the presence of peers. It causes that s/he desires to impress others and show that s/he can control speed [6,11,12].

Aim of the study

The need for preventive measures to reduce the number of road accidents is indisputable and yet, at present, it seems impossible to eliminate road accidents entirely. Therefore, whole communities and those in charge of rescue systems should focus their attention on increasing the chances of saving lives on the site of road accidents to reduce the number of fatalities or limit the extent of post-traumatic disabilities.

There are three cooperating institutions on the site of a road accident that are responsible for pre-hospital activities in the Polish rescue system. These include medical units (medical rescue teams), the Fire Brigade units and the Police. Effective work of the rescue system should be based on integration and close cooperation of all services involved in the rescue action, which guarantees unfailing functioning of all links of the so called "survival chain".

Proper coordination of the activities on the site of a road accident is possible due to regular training including the specificity of tasks of every service and the possibility of cooperation in emergency situations.

The above mentioned services undertake professional actions on road accident sites. However, each of the services has own separate guidelines, most often following narrow specialist proceedings, which results in an inefficient use of all rescue possibilities. The aim of this training is to increase the quality and efficiency of rescue activities based on the guidelines involving cooperation, understanding and completion among all the rescue services on the road accident sites. This programme is dedicated to those who are responsible for the organisation and coordination of actions in such situations as road accidents, and those responsible for the programmes aimed at increasing professional qualifications. In assessing this programme, we followed the general guidelines outlined by the World Health Organisation [13,14,15], Polish legal regulations [16,17] and the analyses of the WHO project entitled „Improving rescue services activities in different types of accidents", which has been run in Poland as a 5-year strategy of improving road traffic safety.

Since each child has the right to live in a safe environment and be protected from injury and violence, there are many issues to resolve in order to prevent child injury. It is also a matter of global improvement of child health by involving the issues into child health strategies and child survival programmes that should include legislation, regulation and their enforcement; product modification; environmental modification; supportive home visit; the promotion of safety devices as well as education and teaching of skills.

Common child injury prevention strategies suggested for five major unintentional injuries (traffic, drowning, burns, falls, poisoning) are listed in Table 1.

Table 1. Key approaches to addressing child injuries

Key approaches	Traffic	Drowning	Burns	Falls	Poisoning
Legislation regulations, and enforcement	Speed limits; comprehensive drink-driving laws, child restraints laws	Four-sided pool fencing	Hot water tap temperature; legislation; smoke alarms	Playground equipment standards	Manufacture, storage and distribution of harmful substances requiring safe packaging
Product modification	Vehicle-front Modification, child restraint systems	Personal flotation devices	Non-tip lanterns and candle holders	Baby walker modification; safety glass	Medication packaging; child resistant closures
Environmental modification	Child friendly infrastructure; safer routes to school; safer play spaces	Barriers: coverings and fencing	Separation of cooking area from living area	Window guards on tall buildings, roof railings, non-climbable banisters	Safe storage of potentially harmful substances
Education and skills development	Helmet wearing; using child restraints	Swimming training and supervision	First aid – "cool the burn"	Supportive home visitation to identify fall hazards	Immediate first aid
Emergency medical care	Child-sized equipment; child-friendly environment	Immediate resuscitation	Burns centres	Appropriate paediatric acute care	Poison control centres

Source: World report on child injury prevention, the WHO, Geneva 2008, p. 166.

Each of these approaches should be implemented based on the countries characteristics and abilities.

According to the WHO rapport, there are three phases of child injury prevention. These include:

A. Primary prevention: preventing a new injury,

B. Secondary prevention: reducing the severity of injuries,

C. Tertiary: decreasing the frequency and severity of disability after an injury.

It is worth pointing out that the cost of primary prevention programmes within a public health strategy of the country is much cheaper that any kind of prolonged treatment and care a child might need as a result of injury, e.g. it has been estimated that for each 1 US dollar spend on a child car seat, savings in direct and indirect health care cost and other costs to society amount to 29 US dollars. Besides, it should not be forgotten how many lives are saved as well.

In order to prevent an unintentional injury, one has to consider three aspects: education, enforcement and engineering. The first step in preventing injuries is legislation in the area of:

- road environment (child passenger restrains, seat-belts, bicycle helmet, motorcycle helmet),
- home environment (smoke alarms, hot water temperature legislation, child resistant containers),
- leisure environment (isolation and fencing of swimming pools).

A public health model that combines four area of injury prevention shows a holistic approach to the issue of child injury. In this model, different national and local agencies as well as organisation can work together to achieve the goal.

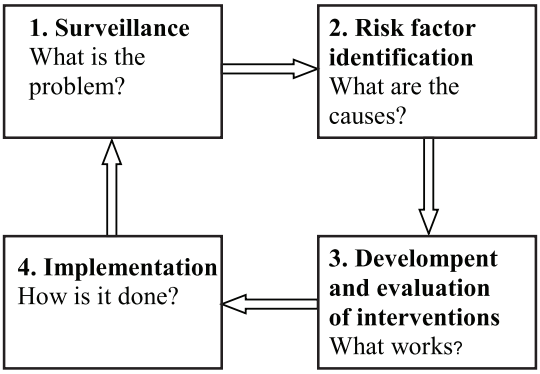

Figure 1. Public health approach to injury prevention
Source: World report on child injury prevention, the WHO, Geneva 2008, p.31

To achieve the goal, governments, nongovernmental organisations, academic institutions, international agencies, media, teachers and community leaders, parents and the business sector should work together. The public health sector plays a major role in the process and should be responsible for:

Collecting and analysing data, caring out research on risk factors; implementing, monitoring and evaluating interventions; delivering appropriate primary, secondary and tertiary care and campaigning for greater attention to the issue of child injuries.

Basing on the WHO report findings, each country should start developing child injury prevention programmers which would follow seven general recommendations.

1. Integrate child injury into a comprehensive approach to child health and development: a child injury prevention programmes should be part of generally recognised child health service;
2. Develop and implement a child injury prevention policy and a plan of action: each county should prepare its own programme including agencies responsible for transport, health, planning, consumer product safety, agriculture, education and law;
3. Implement specific actions to prevent and control child injuries: the list of the proposed interventions is included in Table 1;
4. Strengthen health system to address child injuries: special emphasis should be placed on efficient system of pre-hospital care, child-specific equipment and drugs to manage a small patient, rehabilitation programmes (physical and psychological), coordination in delivering holistic care;
5. Enhance the quality and quantity of data for child injury prevention, i.e. the system on child injuries should be simple and cost effective, understandable for the staff that uses it, calibrated in accordance with national and international standards;
6. Define priorities for research and support research on the causes, consequences, cost and prevention of child injuries; it should involve an economic analysis, intervention trials, information on the fate of the children who survived, and implementing the idea of prevention into child health programmes;

7. Raise awareness of and target investments towards child injury prevention by letting well-known people and political leaders campaign for child injury prevention and introducing these ideas into school and university curricula.

Children are not "little adults." Their different anatomical structure, maturity, variety of interests, need for fun and safe passage to school mean that children require special security measures. The ways of reducing the risk of children in road traffic include, inter alia, setting a good example of compliance with traffic rules by adults, providing adequate care to the youngest children (especially during the holidays), prohibiting the play in the nearby roads or creating safe playgrounds. Further, the child should be woken early enough not to hurry to school, dressed in bright clothes, especially during autumn and winter, supplied with reflectors (reflective elements secured in a child is visible from a distance, giving the driver time to reduce the car's speed and adequate pedestrian evade), leaving a self-ban on the way for children under the age of 12 years (cycling). Besides, collision-free cycle paths (especially in cities) should be developed and cyclists obliged to equip the bike with lights and reflective elements. Finally, cyclists and motorcyclists should wear helmets, those driving cars should fasten seat belts even on the shortest route and children are to be safely placed in child safety seats [5,8,18,19,20].

A programme on transportation and moving around can play a major role in reducing the number of injuries. Accordingly, such a programme is an investment in the future. By introducing it, one can educate not only well-behaved and safe future drivers, but above all informed citizens who exhibit appropriate values, understand others' needs, not necessarily in traffic.

Conclusions

It is essential to accept the fact that an injury is not the result of random, uncontrolled factors (although many people may think so). Injuries are preventable! France sets a good example with a 34% reduction in road traffic deaths as a result of introducing speed reduction, traffic calming, control of drinking and driving and increased seats-belts use between 2002-2004. It is the public health responsibility to collect data, analyse risk factors, intervene, or implement some proven prevention method s (for example: speed reduction, traffic calming, control of drinking and driving, etc.). Injury as an issue to be solved and should be discussed on a global but also national and local level. Each country should develop its own action plan involving different bodies and agencies (non-governmental organisations, academic institutions and industry). Preventing child injury is also very cost effective from an economic perspective of each country. It is also absolutely necessary to understand that unless injury prevention is included in health care programmes for children, the impact of the large investment in immunisation, nutrition and maternal care may be lost due to number of unintentional injuries or deaths. Having that information in mind, one might hope that necessary activities mentioned above may be taken and, as a result, the number of killed or injured children decreased each year in the world.

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VASCULAR RELATED PATHOLOGIES IN CARDIOVASCULAR DISEASE AND CANCER

PATOLOGIA NACZYŃ KRWIONOŚNYCH W CHOROBACH UKŁADU KRĄŻENIA I CHOROBACH NOWOTWOROWYCH

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Wkład autorów:
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zaplanowanie badań
B. Data collection/entry
zebranie danych
C. Data analysis/statistics
dane – analiza i statystyki
D. Data interpretation
interpretacja danych
E. Preparation of manuscript
przygotowanie artykułu
F. Literature analysis/search
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Summary

Cancer and Cardiovascular diseases (CVD) are the two most prominent causes of death worldwide. Emerging evidence indicates shared risk factors and a common biology between these diseases. For instance, chronic inflammation has a significant role in contributing to both diseases. An alteration of the vasculature and the endothelial cells plays a key role in pathogenesis of CVD and cancer. The widespread overlap regarding disease prevention and risk factors for these diseases suggest a common mechanism in terms of molecular pathways. The goal of this tutorial is to present common problems and mechanism of these two mayor diseases.

Keywords: cancer, vascular, mechanism, diseases

Streszczenie

Choroby nowotworowe i sercowo-naczyniowe (CVD) to dwie najczęstsze przyczyny śmierci na całym świecie. Pojawiające się dowody wskazują na wspólne czynniki ryzyka i wspólną biologię między tymi chorobami. Na przykład przewlekły stan zapalny ma znaczącą rolę w przyczynianiu się do obu chorób. Zmiana układu naczyniowego i komórek śródbłonka odgrywa kluczową rolę w patogenezie CVD i raka. Czynniki ryzyka tych chorób sugerują wspólny mechanizm pod względem szlaków molekularnych. Celem tego artykułu jest przedstawienie typowych problemów i mechanizmów tych dwóch chorób.

Słowa kluczowe: rak, miażdżyca, śmiertelność, mechanizmy

1. General Introduction

Cancer and Cardiovascular diseases are the two most prominent causes of death worldwide [1]. Emerging evidence indicates shared risk factors and a common biology between these diseases. For instance, chronic inflammation has a significant role in contributing to both diseases [2, 3]. An alteration of the vasculature and the endothelial cells plays a key role in pathogenesis of CVD and cancer [4]. The widespread overlap regarding disease prevention and risk factors for these diseases suggest a common mechanism in terms of molecular pathways [5].

1.1.1. Vascular Ageing

A key factor that contributes to vascular dysfunction is ageing reliant injury of normal endothelial functioning. This is responsible for numerous age-related diseases of the vascular system and other organs. All organs undergo a progressive decline of function and structure over time due to ageing. Endothelial cells undergo senescence during this process and display substantial changes in their properties ensuing damage to the vascular functionality and neo-angiogenic capability. Thus, changes to mechanical and structural properties of the vascular wall result in damage of arterial elasticity and reduced arterial compliance [6, 7].

Evidence suggests that different disease state like diabetes, hypertension and end stage renal failure show a reduced arterial compliance. These changes could also be present before the manifestation of CVD. Vascular ageing contributes to the ageing dependent growth in atherosclerotic disease and hypertension. More than traditional risk factors like lipid levels, smoking, diabetes, and sedentary lifestyle, ageing is a factor that deliberates a greater risk for the disease. Mitochondrial dysfunction, microRNAs and micro environmental

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stressors like hypoxia, Mechanisms like mitochondrial dysfunction and micro environmental stressors, are defined to be involved in ageing-related endothelial cell senescence control [8, 9].

The process of ageing is characterised by a functional decline in the cells and tissues and the diminished ability to suitably respond to environmental distress, including metabolic stress and reduced oxygen supply. This results in deterioration of the total fitness of the organism, which is often associated with the individual's life style [10-12]. As the vasculature is the major source of oxygen and nutrient supply in the body, endothelial cells are extremely susceptible to deviation in oxygen pressure. The age-related injury of the response to oxygen and nutrients level variation is considered a key factor contributing to arterial dysfunction that leads to age related vascular diseases, for example, atherosclerosis [13-16].

1.1. Cardiovascular Disease

Cardiovascular diseases are a set of diseases involving the heart or the blood vessels [17, 18] and are the foremost cause of death and disability in the world. CVDs include, coronary artery diseases such as myocardial infarction and angina, congenital heart disease, heart arrhythmia, heart failure, stroke and peripheral heart disease to name a few. The underlying mechanisms vary depending on the disease. For example, coronary artery disease, peripheral artery disease and stroke involve atherosclerosis [15, 16, 19, 20].

1.1.1. Causes

1.1.1.1. General Mechanism

Many years ago, atherosclerosis was thought to be a lipid storage disease. Lipid deposits were moulded on artery's surfaces and grew until they became large enough to hinder blood flow and eventually result in a cardiac event such as a myocardial infarction or a stroke [3]. Current mechanisms involve inflammation, which play a key role in atherosclerosis formation, right from its initiation and development to its endpoint-thrombotic complications. [21] ECs, which form the innermost layer of the arterial wall, normally resist the attachment of leukocytes such as macrophages and T lymphocytes from binding to its wall. But triggers like consuming high saturated fat diet, hypertension or smoking can initiate this binding. One factor is vascular endothelial growth factor-1 (VCAM-1) [22].

Lesions also develop due to type of blood low they experience. Shear stress occurs due to laminar blood flow and this result in several atheroprotective mechanisms [22, 23]. For example, it produces an antioxidant enzyme, superoxide dismutase or an increased expression of nitric oxide synthase. This limit VCAM-1 expression by inhibiting nuclear factor kappa beta(nF-Kbeta) production and thus combat platelet clumping [24].

Once adhered, the monocytes penetrate the endothelium and infiltrate the intima by diapedesis a process that requires a chemoattractant gradient such as monocyte chemoattractant protein -1(MCP-1) [25]. Within the intima, monocytes change into macrophages, and express scavenger receptors and engulf lipid particles, thus transforming into foam cells characteristic of atherosclerotic lesions.[26-28]. In the intima through lesion evolution the T lymphocytes join macrophages and secrete cytokines and growth factors that may nurture the migration and proliferation of smooth muscle cells [29-32]. T lymphocytes also excite macrophages to produce collagen-degrading enzymes and secrete cytokines and growth factors that may promote the migration and proliferation of smooth muscle cells. This leads to the fibrous cap that protects the blood from the thrombogenic core of the plaque, to weaken. This results in rupturing of the plaque leading to thrombosis which is the complication in most atherosclerotic cases [31, 33, 34].

1.1.1.2. Dysfunctional endothelium

A normal vasculature has an organised network of blood vessels maintained by a balance between pro and anti-angiogenic factors. A healthy tissue also displays a systematic network of lymphatic vessels that allows for transport and draining of blood and metabolic waste from the interstitium. This intricate architecture consisting of mature vessels make up the normal vasculature. These vessels allow the adequate transport of nutrients, oxygen and blood supply required to sustain the vasculature [35, 36] An alteration to the vasculature plays a significant role in the pathogenesis of various diseases.

The endothelium plays a significant role in governing the circulation as a physical barrier and as a variety of different regulatory substances. For example, the endothelium derived prostacyclin and nitric oxide inhibit platelet function and induce vascular relaxation when they are released in response to physical stimuli, platelet derived substances or hormones. The endothelium is also a good source of heparins, heparin

sulphates, thrombospondins and platelet derived growth factor. Also, several vasoactive substances produced by the endothelium such as nitric oxide, angiotensin- 2 and endothelin-1 might play a role in vascular tension. Dysfunction of these endothelium dependent factors could lead to CVD such as atherosclerosis and hypertension and is thought to be involved in stroke, tumour angiogenesis, vascular leakage and infectious diseases [37, 38].

Endothelial dysfunction occurs when the endothelium shifts to a pro inflammatory, reduced vasodilatory and pro thrombotic state. This state is associated with most forms of cardiovascular diseases. When free radicals disrupt the balance of NO in the body, damage to the endothelium occurs leaving them excessively permeable allowing for toxins to pass into the tissues.[39] When the action of NO is inhibited, endothelial signalling is weakened resulting in widespread disease, since in the human body, the endothelium actively maintains, around 66,000 miles of blood vessels. A normally functioning endothelium also supports the body's immune response, helps regulate blood clotting, controls the volume of fluid and the number of electrolytes and other substances passing from blood into the tissues, and produces dilation or constriction of the blood vessels.

1.1.1.3. Hemodynamics

The dynamics of blood flow is called hemodynamics. Blood, being a non-Newtonian fluid, is best studied with rheology [40].

Normal blood flow ensures the transportation of nutrients, oxygen, CO2, metabolic waste throughout the body thus enabling regulation of different functions such as maintaining cell metabolism, pH and osmotic pressure and temperature regulation along with protecting the body from harmful stimuli. These are key factors that help the body adapt as per the environment. A laminar blood flow thus ensures proper functioning of the body while a turbulent flow and local hemodynamic factors like flow disturbances at bends and bifurcations contribute to the formation of atherosclerosis or other pathological conditions. A laminar flow occurs when the vessel wall is smooth whilst a turbulent flow occurs when there is a decrease in wall smoothness. This is due to fatty deposits on the vessel wall.

The vascular ECs form the innermost layer of the vessel wall with direct contact to blood flow and are involved with vital homeostatic functions to various mechanical and chemical stimuli. Not only do they provide a selective barrier for permeability but the ECs also influence hemostasis and thrombosis through secretion of pro and anti-coagulants, fibrinolytic agents and mediate inflammatory responses via the release of cytokines and chemokines. The EC's also regulate smooth muscle migration through the release of vasodilators and constrictors and influence vascular remodelling using growth promoters and inhibitors. Hence hemodynamic forces are needed for normal physiological functioning of the ECs while some forces induce a dysfunction of the endothelium by modulating EC gene expression and signalling leading to the development of pathological states which contribute to the formation of atherosclerosis, thrombosis and its complications.

The role of hemodynamic forces in endothelial dysfunction was first proposed when observations of initial atherosclerotic lesions were credited to a nonrandom pattern of development. These were observed typically at arterial bends and branches with a disrupted flow. This flow pattern included recirculation eddies and change in direction with respect to space (reattachment and flow separation) and time (reciprocating flow).

Recent research show that this kind of flow and the associated reciprocating and low shear stress bring about a constant activation of several atherogenic genes in ECs. for instance, the monocyte chemoattractant protein (MCP-1) that induces monocyte infiltration into arterial wall, and platelet derived growth factor (PDGF) that augment EC turnover and SMC migration, into the subintimal space [28].

On the contrary, the straight portion of the artery, usually safe from the atherosclerotic lesions, is exposed to constant laminar blood flow and high shear stress, all with a definite direction of flow and the associated downregulation of atherogenic genes and upregulation of growth arrest genes and anti-oxidants in EC's. Hence these findings propose that laminar and turbulent flow patterns might induce a variety of molecular responses in ECs which result in sparing of the straight parts of the arteries and formation of lesions at the curvatures.

1.2. Blood and Blood Vessels

1.2.1. Blood

Normal tissue functioning requires an adequate supply of oxygen, nutrients and blood vessels to facilitate their transport. Virchow, around a hundred and fifty years ago, explained vascular diseases in terms of cellular mechanisms, most of which stand valid till date ®. However, more recently the vessel wall has been visualized as a channel containing blood, which is provided by the heart pumping around blood in a circuit that is optimized to exchange and distribute oxygen and nutrients.

Blood is a body fluid that delivers oxygen and the essential nutrients to cells and tissues [41]. In vertebrates, blood is comprised of blood cells suspended in blood plasma. Blood has various functions such as, supplying oxygen to different tissues, supply of nutrients like amino acids, fatty acids and glucose, waste removal (CO2, urea) etc. Blood cells constitute the following components; erythrocytes, leukocytes, platelets. The most abundant are the erythrocytes, which has the iron containing protein, the hemoglobin which facilitates transport of oxygen [42-44].

The cellular components of blood are formed through a process known as hematopoiesis, which is a process that occurs during embryonic development and throughout adulthood. All the cells are derived from the hematopoietic stem cells. In a healthy adult, around 10^11-10^12 new cells are formed every day. The process occurs in two waves. The primitive wave consists of an erythroid progenitor which appear in blood islands, giving rise to macrophages and erythrocytes during initial stages of embryonic development. The main purpose of this stage is to provide tissue oxygenation since the embryo grows rapidly. This wave is transitionary. In humans, foetal haematopoiesis begins in the yolk sac and shifts to the liver temporarily before establishing in the bone marrow and thymus when the baby is born.

Bone marrow is the tissue encompassing the centre and the epiphysis of bones. It is also the place for production and maturation of B cells. It is an organ composed of trabecular and cortical bone, cartilage, hemopoetic and connective tissues. The trabecular bone is composed of a framework of fine bone plates filled with hematopoietic marrow, fat containing marrow or blood vessels. The bone marrow consists a vascular component (stroma) and a hematopoietic component (parenchyma) The parenchyma includes hematopoietic stem cells (HSCs) and hematopoietic progenitor cells, localized near the endosteum of the bone and more around blood vessels. The stroma comprises multipotential non-hematopoietic progenitor cells as well which can differentiate into various tissues of mesenchymal origin, including, endothelial cells, osteoblasts, reticular cells, adipocytes and fibroblasts. The stromal cells including ECs deliver signals for migration of specific leukocytes into and out of the bone marrow, involving in rolling/extravasations along the vascular endothelium [45-48].

1.2.2. Blood Vessels

Angiogenesis is a process through which fresh blood vessels are formed from existing vessels. It is a normal and key process that occurs throughout life and is involved in development and growth, disease as well as wound healing. Oxygen plays a critica l role in this process along with hemodynamic factors that are essential for the survival of vascular networks and for structural adaptations of vessel walls.

The blood vessels originate through a process beginning with the mesodermal layer. The first system to develop in the embryo is the cardiovascular system. The luminal surface of this system that is in close contact to the blood is made up of a single layer of endothelial cells derived from the mesoderm. It is formed by the following processes. Hematopoietic stem cells and angioblasts arise from the differentiation of hemangioblasts followed by vasculogenesis which is the de novo formation of blood cells from angioblasts. It is an active process that involves cell to cell interactions along with cell to extracellular matrix interactions. This process is directed spatially and temporally by morphogens and growth factors. Vasculogenesis includes differentiation of mesoderm stem cells into angioblasts followed by migration of angioblasts to form blood islands where they give rise to endothelial cells [45-48].

There are two types, the sprouting and intussusceptive angiogenesis. Sprouting angiogenesis occurs when sprouts of endothelial cells migrate towards a stimulus, in this case VEGF-A. It thus adds vessels to parts of tissues that previously lacked blood supply. Intussusceptive, on the other hand forms blood vessels by splitting vessels due to which interstitial fluids invade an existing blood vessel [49, 50].

The steps involved in sprouting angiogenesis process are: Basement membrane degradation followed by endothelial cell (EC) proliferation, focused migration of the cells, formation of new vessels (tubulogenesis), fusion of the vessels, vessel pruning and pericyte stabilization. The process begins in response to a hypoxic environment. VEGF-A initiates the process. An endothelial tip cell responds to this stimulant by guiding the sprouting EC through the ECM towards VEGF-A. The ECs migrate through the ECM via filopodia, which are long, thin projections which extend from the migrating tip of the cells. These secrete proteolytic enzymes which degrade the basement membrane. When a sufficient number of filopodia on have anchored to the substratum, the tip cell is aligned with the VEGF-A receptor through contractions of actin filaments within the tip cell. Meanwhile, the capillary sprout elongates due to endothelial stalk cell proliferation, since they follow the tip cell causing the elongation process. A lumen is formed within a series of stalk cells due to vacuoles developing and coalescing. These stalk cells form the trunk of the recently formed capillary. When the tip cells of two or more capillary sprouts meet at the source of VEGF-A secretion, the tip cells merge together forming a continuous lumen via which oxygenated blood can flow. VEGF-A levels return to near normal, when the local tissues receive suitable amounts of oxygen. Pericyte recruitment induces maturation and stabilization of the capillary [7, 31, 32, 48].

Intussusceptive angiogenesis also called splitting angiogenesis, is a process where a single vessel splits in two due to an extension of the vessel wall into the lumen. This type is considered to be quick and effective compared to sprouting angiogenesis since, initially, it only requires restructuring of existing ECs and does not require immediate EC proliferation or migration. Intussusceptive angiogenesis occurs lifelong but plays an important role in vascular development in embryos where growth is quick and resources are limited. Intussusception mainly causes new capillaries to develop from existing capillaries.

All blood vessels except for capillaries are made up of three layers, tunica intima, tunica media and the adventitia. The tunica intima, the thinnest layer is comprised of a monolayer of endothelium cells that line the vessel wall, surrounded by an elastic connective tissue called the internal elastic lamina, whose function is to related to elastic resilience to sustain blood pressure [34, 51-53]. The tunica media is made up of numerous layers of elastic lamina and smooth muscle cells. This is the thickest layer. The SMC's present in the medial layer influence blood pressure through the production of multiple ECM components (elastin, collagen) [54]. The adventitia is comprised of loose connective tissues made up, primarily of collagens and elastic fibres, fibroblasts and macrophages. The fibroblasts play an important role in fibrognesis. The adventitia also plays a significant role in vascular remodelling and development of vascular diseases such as transplant vasculopathy, atherosclerosis, hypertension and restenosis [55, 56].

1.3. Vascular Remodelling

Vascular remodelling is an intricate process of structural changes that involve at least four different process – cell growth and death, cell migration and degradation of extra cellular matrix (ECM). The process is dependent on an interplay between locally generated growth factors, hemodynamic stimuli and vasoactive substances.

Generally remodelling is an adaptive process which occurs in response to long term changes in the hemodynamic conditions, but it might eventually contribute to pathophysiology of circulatory disorders and vascular diseases [57, 58]. For instance, physiologically, vascular remodelling occurs during pregnancy. Adequate uteroplacental blood flow is needed for a normal pregnancy outcome. This process takes place with the growth and remodelling of the uterine circulatory system along with growth of a new organ, the placenta.

Vascular remodelling involves various patterns and the nomenclature used to denote these patterns is circumferential remodelling. It is normally called inward or outward to signify narrowing vs. widening of the vessel wall. The term expansive remodelling is used to denote increase in circumference and it is employed as a substitute for outward Also, taken into consideration is the wall mass, which can increase (hypertrophy), decrease (hypotrophy) or remains unchanged (eutrophy). For example, the remodelling of vessel to larger lumen with the same wall thickness occurs during pregnancy in the uterine circulation. This is called outward hypertrophic because the cross-sectional area is increased. This is due to the diameter of the chief uterine artery almost doubling in magnitude in humans during pregnancy and the enlargement occurs with or without the thickening of the vascular wall. Another study on human myometrial radial arteries from preeclamptic women the pattern of remodelling was inward eutrophic since there was no change in cross-sectional area indicating a rearrangement of existing wall elements around a smaller lumen.

Several factors contribute to vascular remodelling resulting in pathological implications. For example, when pulsatile blood flow and pressure induce various kinds of hemodynamic forces such as shear stress, hydrostatic pressure, constantly on blood vessels. Since the ECs are in direct contact with the blood, they bear most of the shear stress as a result of frictional forces arising from blood flow acting parallel to the vessel luminal surface. This increase or decrease in shear stress plays a key role in vascular remodelling and homeostasis. During the process of remodelling, for a compensatory arterial response towards changes to occur, a functional and intact endothelium is required to undergo adjustments in function and structure in response to alterations in shear stress.

Vasoactive factors also play an important role in vascular structure determination. They have an acute effect on vascular muscle tone and they may also impact matrix production and migration of cells. Angiotensin 2, for example, induces growth of vascular smooth muscles cells through PDGF AA and TGF beta 1. They are also involved in activation of EC through receptors coupled to ion channels which in turn modulate intracellular calcium concentration.

Vascular remodelling can also occur in response to increased arterial pressure, in which case, the structure of the vessel wall is modified such that the ratio of the width of the wall to the width of the lumen is raised either, by an increase in muscle mass or rearrangement of cellular and non-cellular elements. This results in heightened peripheral resistance typical for hypertension [59-61].

Another form of remodelling includes reduction in lumen diameter and is related to other diseases such as cardiac allograft vasculopathy and restenosis post percutaneous intervention [62]. Alternatively, remodelling

could also lead to higher lumen diameter and compensate for increased plaque load [63]. Vascular remodelling also involves changes primarily in lumen dimensions due to active reorganization of wall components. This type is associated with constant high blood flow, observed in patients -an arteriovenous fistula and was shown in animal models [64, 65].

Remodelling of vessel wall also occurs in response to vascular injury. A neointima forms in a sequential process as part of a reparative answer to injury. This involves thrombosis, migration and proliferation of vascular cells, matrix production, and inflammatory-cell infiltration. Mechanical injury results in vessel constriction and smaller vascular lumen in response to the scarring in the outer vessel layer [66]. Key features of transplant vasculopathy include inflammation and formation of intimal hyperplasia [62, 67, 68].

1.3.1. Vascular injury

Vascular trauma is the injury caused to a blood vessel- the artery, that carries blood to an organ, vein, which returns blood back to the heart.[69] Hemodynamics, hypoxia, ischemia and endothelial dysfunction are factors that contribute to vascular injury. Vascular injury is brought about by mechanical injury due to surgical manipulations and from tissue ischemia due to obstruction of the vasa vasorum. The level of the resulting neointimal lesion is related to the extent of vascular injury.

Distressed flow patterns contribute to pathogenesis of various clinical disorders such as atherosclerosis, arterial aneurysm, post-surgical intimal hyperplasia, ischemic/reperfusion injury. This is due to disturbances of blood flow in arteries generated due to surgical interventions like end to end anastomosis in bypass graft or stent insertion in balloon angioplasty. Additional flow disturbances that facilitate endothelial dysfunction is the termination or inactive flow and its recovery later in clinical conditions related with ischemia/reperfusion and hypoxia injury. Hence myocardial recovery following acute infarction becomes complex and the outcome could be cell damage, arrhythmia and death. Tissue injuries induced by solid organ transplantation, tissue resuscitation and key vascular surgical intrusions could also result in a dysfunctional endothelium. This results in inflammatory responses with recruitment of WBCs from circulation.

Another mode of injury occurs through ischemia/hypoxia. Hypoxia is a vital component of an ischemic result. Hypoxia is the reduction of oxygen while ischemia is the lack of perfusion. Ischemia is a process which occurs when the tissue's demand for energy substrates is not met with supply. Reperfusion injury or ischemic/reperfusion injury occurs when blood flow and oxygen resume to a tissue after a hypoxic/ischemic event. HIF 1 alpha is stabilized in response to limited oxygen. This is worsened by modification of locally released vasoactive mediator such as NO and its action. Sudden re-oxygenation post hypoxia activates the release of free radicals, like reactive oxygen species (ROS) and reactive nitrogen species(RNS), which modify EC homeostasis and cause swelling and tapering of the blood vessel lumen along with a host of other damaging effects. ROS and RNS are highly reactive molecules and include hydrogen peroxide, peroxynitrite, hydroxyl radical, and superoxide resulting in oxidative stress, disparity between the production of reactive species and antioxidant defences that causes tissue damage. Tissue injury is characterized by a loss of tight junctions, leading to augmented permeability, detachment from the basement membrane, and, often, EC apoptosis or necrosis. Eventually all of these structural changes contribute towards microvascular perfusion impairment.

1.3.2. Intimal hyperplasia

Intimal hyperplasia is the universal response of a vessel to an injury. It is the thickening of the tunica intima [70]. It is connected to increased cell number and the amount of ECM in the intimal layer of the vessel[71]. Physiologically, it occurs in the involution of the uterus, during closure of the ductal arteriosus post birth (DA) In the foetus, the process of intimal thickening starts in the second trimester of pregnancy with the build-up of glycosaminoglycans in the sub endothelial region (SER). This is followed by separation of ECs from the internal elastic lamina, followed by migration of SMCs into the sub endothelial region. This phenomenon was also observed in the mature DA in the neonate, indicating that this is a constant process [71].

Pathologically, it occurs post balloon angioplasty, transplantation, artery bypass conduits, in pulmonary hypertension and pre-atherosclerotic lesions [15, 16, 34, 51, 72].

Intimal hyperplasia occurs in a few stages. The key stimuli are inflammation, injury and enhanced vessel wall stress. For instance, balloon injury to the rat carotid artery does not incite a marked inflammatory response but nonetheless generates intimal hyperplasia. Inflammation is, nevertheless, a confounding feature of most other models of vascular injury and therefore may contribute to the extent of intimal hyperplasia. Direct effects of inflammatory mediators on early transduction events, mainly the NF-κB pathway, have been implicated. Synergistic communication between growth factors and inflammatory cytokines to cause MMP induction and

activation is another probable mechanism. In addition, proteases and growth factors directly derived from macrophages possibly play key roles.

Two situations which evidently demonstrate a relationship between increased mean wall stress and intimal hyperplasia are vein grafting and pulmonary hypertension. The mediators involved remain largely undefined but increased MMP and PDGF expression has been observed in experimental vein grafts and was reversed in parallel with intimal hyperplasia when the grafts were supported by an external stent.

The injured artery recruits inflammatory cells such as macrophages and leukocytes and mobilizes vascular progenitor cells from their niches. Another important factor in the neointima formation, platelet-derived growth factor (PDGF), FGF along with additional factors, is produced by platelets, smooth muscle cells, endothelial cells and macrophage foam cells. These factors along with PDGF act as chemo attractants which promote cell migration of the SMC's into the neointima from the media. Also, PDGF promotes production of collagens and proteoglycans. In parallel, the ECM is remodelled by MMP's which further promote SMC migration. Thus, the neointima grows in response to cell proliferation, increased ECM synthesis, apoptosis and fibrosis [73-75].

Various sources of cells contribute to neointima formation. They can originate from the adventitia from cells such as pericytes, fibroblasts and vascular progenitor cells or from circulating progenitor cells, for example-endothelial progenitor cells, smooth muscle progenitor cells or bone marrow derived cells.

1.4. Cancer

Cancer is a disease involving abnormal cell growth, which arises when cells undergo uncontrolled proliferation and lose their ability to control apoptosis. More than two hundred diverse types of cancer exist, and their etiology remain uncertain. Current hypothesis state that cancer is a genetic disease and numerous mutations in various genes are considered as cancer promoting genes. Additional factors such as lifestyle, obesity, tobacco, alcohol consumption and virus infections constitute risk factors for cancer development [72, 76-79].

Dysfunctional endothelium is a hallmark of many diseases like diabetes mellitus, atherosclerosis and cancer. Endothelial cell migration is an essential component of angiogenesis and requires a tight regulation of the contractile and noncontractile conditions of the cell. These processes require the combination of signals elicited by hepatotactic, chemotactic and mechanotactic stimuli. This movement is in turn, related to the activation of intracellular pathways that congregate on cytoskeleton remodelling.

There are several types of malignancies that affect humans and they are classified based on the type of cell that the tumour cells resemble. These include carcinomas representing a group of cancers originating from epithelial cells, including the most common cancers breast, colon, lung and prostate cancer, - Sarcomas a neoplasm derived from connective tissue (e.g. bone, cartilage, fat), originating from mesenchymal cells outside the bone marrow and lymphomas and leukaemia's: neoplasm arising from blood cells that leave the bone marrow and mature in lymph nodes and blood.

1.4.1. Normal and tumour vasculature

There are fundamental differences between the normal and tumour vasculature. The normal vasculature has an organized network of blood vessels maintained by a balance between pro and anti-angiogenic factors. A healthy tissue displays a systematic network of lymphatic vessels that allows for transport and draining of blood and metabolic waste from the interstitium. This intricate architecture consisting of mature vessels make up the normal vasculature. These vessels allow the adequate transport of nutrients, oxygen and blood supply required to sustain the vasculature [36, 80].

The tumour microenvironment consists of different cell types such as endothelial cells, pericytes, and fibroblasts. These cells contribute through the rearrangement of the ECM and secretion of various growth factors and cytokines to tumour progression.

In tumours, aggressive neoplastic growth is accompanied by an over expression of pro angiogenic factors which lead to the formation of aberrant blood vessels. These blood vessels are immature and highly permeable and give rise to a disorganized vascular structure comprised of irregular vessels with different shapes and diameters. This is due to the scarcity in smooth muscle cells and possible discontinuous endothelial cell lining with an abnormal basement membrane. Augmented vessel permeability leads to deviation in osmotic forces that results in build-up of vascular contents and high interstitial fluid. Blood flow is hindered due to resistance caused by the defective shape of the blood vessels. This, in turn, leads to insufficient oxygen supply with a localized hypoxia.

Other aberrant characteristics of the tumour vasculature include arteolar-venous shunts abnormal bulges and plasma channels lacking red blood cells. The typical blood vessel arrangement found in the healthy tissue (consisting of arterioles, arteries and venules) sometimes cannot be identified. The vessel endothelial cells are dysfunctional

and loose their expression of endothelial markers. The lymphatic vessels in tumours are also leaky, unstable and dilated. Due to this type of arrangement, various functional processes within the tumours are drastically different to those of the healthy tissue. For instance, the normal processes of nutrient delivery through these dysfunctional blood vessels and of metabolic waste removal via the lymphatic system are greatly reduced [36, 81].

1.4.2. Angiogenesis in cancer

Angiogenesis is a process through which new blood vessels form from existing vessels. It is a normal and key process involved in development and growth, as well as in wound healing. It is however, also involved in cancer, since it is the fundamental step for a tumour to grow in size and metastasize. Tumour angiogenesis was first reported in 1971 by Judah Folkman. He suggested that tumour growth is dependent on angiogenesis [82-85].

For a tumour to grow (more than 1-2 mm in diameter), it needs an independent blood supply, hence angiogenesis is a necessary step. The tumour secrets growth factors that recruit new blood vessels. The process continues after a tumour matures and is a vital step in sustained tumour growth and for tumour metastasis [86-88].

The newly formed vessels provide an exit route for tumours cells, through which cells may detach from the primary tumour and enter the blood stream. The angiogenesis process is regulated by the production of various angiogenic stimulators. This includes members of the VEGF and FGF families along with regulating angiogenic inhibiting factors like angiostatin and endostatin. The latter regulate and modulate the process both at the primary and metastatic sites. Vascular density plays an important role as a prognostic factor for many tumours. Highly vascular tumours are more metastatic [89, 90].

Regulation of angiogenesis occurs through hypoxia or ischemia. Many proangiogenic factors and their receptors maybe modulated by this process. For example, factors like VEGF, FGF, and TGF-beta, PIGF and angiopoietins and HIF. Oxygen deficiency stimulates and regulates HIF which in turn triggers genes for VEGF-A and VEGFR 1. The VEGF family is the most important player in angiogenesis [91-97].

VEGF induces vascular endothelial cell proliferation and growth and survival. The VEGF family consists of various receptors, namely VEGF- A, VEGF-B, VEGF-C and VEGF-D with their receptors VEGF -1, VEGF-2 and VEGF-3. VEGF-A along with the receptor VEGF -2 are important regulators of angiogenesis.

VEGF initiates angiogenesis by binding to specific receptors. When a tumour needs to grow, it releases growth factors, VEGF which binds to the extracellular receptor on the endothelial cell on the blood vessel. VEGF A, B and PIGF bind to VEGF 1, while VEGF A, C and D to VEGF -2. VEGF C and D bind to VEGF 3 on the endothelial cell of the lymph vessel thereby stimulating lymph angiogenesis [87, 98].

Once VEGF binds, dimerization of the receptors takes place which activates intracellular tyrosine kinase domain (ITK) thereby inducing auto phosphorylation. This further activates downstream signals required for the angiogenesis process [73-75, 99].

1.4.3. Colon cancer

Colon cancer is one of the foremost causes of cancer-related deaths worldwide. The chief cause of mortality in colon cancer patients is liver metastasis, either present already at cancer diagnosis stage, or developing after primary tumour resection. Survival rates of patients continue to increase with time, mainly because of improved diagnostics and treatment. Colonic epithelium consists of roughly ten million invaginations, called crypts whose base of contain multiplying daughter cells and dividing stem cells and form the starting point for the cell migration towards the epithelium surface. Here the cells die and become replaced by continuously streaming new cells.

One of the factors or an amalgamation of chromosomal instability(CIN), CpG island methylator (CIMP) phenotype, microsatellite instability(MSI) contributes to colon cancer progression. Genetic variability is usually caused by loss of heterozygosity and aneuploidy. Alternatively, mutations in the cell cycle genes or tumour suppressor gene may also lead to cellular transformation. Similarly, microsatellite instability and mutator phenotype are caused due to epigenetic and/or genetic modifications resulting in impaired cellular pathways, such as DNA repair mechanism. Non-coding RNAs, more prominently microRNAs and long non-coding RNAs have also been implicated at numerous CRC stages.

The acquisition of mutations in the adenomatous polyposis coli (*APC*), followed by the mutational activation of oncogene *KRAS* and the inactivation of the tumour suppressor gene, *TP53* signals the beginning of the CIN pathway. The major players in CIN tumours are loss of heterozygosity (LOH) and aneuploidy. This not only constitutes most of the sporadic tumours (85%) but also involves familial adenomatous polyposis cases

linked with germline mutations in the *APC* gene. Promoter hypermethylation of several tumour suppressor genes is a characteristic feature of CIMP pathway most importantly *MGMT* and *MLH1*. This is often associated with *BRAF* mutation and microsatellite instability. Inactivation of genetic alterations in short repeated sequences contributes to the MSI pathway. Also, hypermethylation of DNA mismatch repair gene might lead to MSI.

Both genetic and environmental factors contribute to histopathological changes. Key environmental factors involve toxins, pathogen invasion, polyamines, ROS (reactive oxygen species) production and stress. The growth of adenomas is triggered by adverse conditions like bacterial or viral invasions, subsequently causing mutation in the APC (Adenomatous Polyposis Coli) regulatory pathway usually affecting either APC or β-catenin. APC represses β-catenin, which diminishes the tendency to abnormal tissue expansion by augmenting protein expressions that promote and affect cell division and cell adhesion. As cells migrate from base crypts towards the epithelium surface, APC expression increases and hinders β-catenin. This in turn promotes apoptosis at the surface and provides optimal balance in production from the crypt base in parallel.

Transformation of dysplastic epithelium (stage I) to early adenoma phase (stage II) takes place due to COX2 mutations and appear in most human colorectal adenocarcinomas. This is followed by mutations in RAS genes, with K-RAS being the most common gene and less H-RAS the least. K-RAS mutations, next to common mutations in DCC, MLH1 and MSH2 facilitate the transition from early to late adenoma (stage III). Lastly, progression to tumour metastasis (stage IV), involves genes such as BAX, E2F4, MSH3, MSH6, TGF-βR2, BAX and MMPs, p53 and SMAD4 affecting liver, lungs, bone and brain.

1.4.4. Metastasis

Metastasis is a multi-step process involving a modulation of phenotype of cancer cells, invasion of cells to enter circulation and form distal metastasis. It is one amongst the three hallmarks of malignancy with circulating tumour cells being the prime cause in the formation of distal metastasis.

Metastatic disease accounts for majority of cancer related deaths. Metastases are believed to develop from dormant circulating tumour cells that are seeded into various organs. The process of metastasis formation involves an invasion-metastasis cascade of events. A stepwise progression is proposed. First, the normal cells undergo genetic alterations leading to the formation of pre-malignant lesions [100]. These steps are clinically recognized. Several types of pre-malignant lesions such as hyperplasia or dysplasia, can be detected in different organs prior to the formation of a malignant tumour. The lesions are caused either by genetic alterations or by an external factor (for example, a virus infection); the former causes a monoclonal expansion of cells, whereas the latter causes a polyclonal expansion of cells. Unknown factors precipitate pre-malignant lesions to develop into cancer. Further progression leads to invasive cancer, with a substantial risk of metastases.

A metastatic tumour is composed of cells that are phenotypically different and heterogeneous, when compared to a noninvasive tumour. They are believed to origin form circulating tumour cells that have left the primary tumour and can reach distal organs through the lymphatic system or via the blood circulation. Once there, they extravasate and invade the parenchyma and form micro -metastasis that can later develop into macroscopic metastasis. Loss of endothelial cell integrity and a selective permeability of the endothelium provides for the transmigration process [101-106] and several factors including an inflammatory environment are believed to aid in the survival of tumour cells in other organs.

Angiogenesis also provides an exit route for metastasis. This is due to the nature of permeable and immature vessels formed within the tumour leading to cells detaching and entering circulation. Thus, a highly vascular tumour gives rise to more metastasis compared to a less vascularised tumour. Butler. TP showed that about 2x10^6 mammary carcinoma cells are shed from the primary tumour each day, giving rise to metastasis [107].

The most important correlation between angiogenesis and metastasis are the studies on vascular density of the tumour and patient survival. A study by Weinder et al showed a direct a link between tumour vascularisation and metastasis, and indicated that it can function as an independent prognostic factor for outcome. This study was repeated by others and the findings were confirmed and the study is not limited to breast cancer. Thus, these studies show the importance of vascular density [104, 108].

The blood system is considered as the main mode for metastatic spread, but increasing evidence shows that the lymphatic system could play an important role in metastasis [109].

Lymphangiogenesis is the process of formation of new lymphatic vessels from preexisting vessels. It plays an important role in homeostasis. An impaired vessel or excessive formation of the vessel leads to metastasis. Generally, lymphatic vessels were thought to be indirect participants in tumour metastasis They provide conduits for tumour cells to transit into draining lymph nodes, but recently the discovery of several key lymphatic-specific molecular markers and an increased accessibility of *in vitro* and *in vivo* experimental systems to study lymphatic

biology have highlighted a more dynamic role for the lymphatic vasculature in metastatic tumour spread [110-112].

The lymphatic capillary is a thin walled structure consisting of single layer of endothelial cells lacking inter -endothelial tight junctions. They do not have smooth muscle cells and a basement membrane as the blood capillaries. The main function of lymphatic vasculature is regulation of tissue fluid homeostasis, antigen collection from peripheral tissues, and mediate immune cells such as antigen-presenting dendritic cells from the periphery to lymph nodes. It also provides a unidirectional transport system that relies on skeletal muscle contraction and respiratory movement for the transport of lymph. This is a process which occurs in adults only during pathological conditions such as inflammation, tissue repair or tumour growth. Many molecular factors that contribute to lymphangiogenesis have been studied recently, among which VEGF C and D bind to the VEGF-3 receptor expressed on the endothelial cells of the lymphatic vessels [112-114].

More recently, several factors with pro lymphangiogenic activity have been identified. These include hepatocyte growth factor, which binds to the c-met receptor, angiopoietin-1 together with its endothelial cell–specific receptor Tie-2, FGF1 and -2, PDGF, insulin-like growth factor-1 and -2, and endothelin-1 [115-119].

Tumour-induced lymphangiogenesis is mediated by lymphangiogenic growth factor produced and secreted by the tumours. The role of VEGF-C and VEGF-D in cancer progression has been extensively studied. The overexpression of either of the two factors in tumours significantly increased tumour-associated lymphatic vessel growth (mainly at the tumour margin) and increased incidence of lymph node metastasis. The lymphangiogenic growth factors along with increasing vessel density, also enlarge and dilate vessel size. VEGF 2 receptor is important in this process, while VEGF 3 receptor is involved in endothelial cell sprouting [119-124].

1.4.5. Cytomegalovirus and cancer

Emerging evidence indicate that cytomegalovirus (CMV), which is not considered as an oncogenic virus, is highly present in several types of cancer. CMV belongs to the family *Herpesviridae* and the subclass *Betaherpesviridae.* CMV remains latent in the body for the life time of its host after a primary infection without causing any clinical disease in healthy individuals. It can reactivate from time to time, but is kept under control by the immune system However, in immunocompromised individuals CMV infection may be life threatening; it causes major morbidity and mortality in stem cell and organ transplant patients as well as in AIDS patients. It is also a common cause of birth defects in children who suffer from a congenital infection. Emerging evidence suggest that the virus is detected in high prevalence in tumours of different origin. Over 90% of glioblastoma, neuroblastoma, medullblastoma, colon, breast and prostate cancers are positive for CMV proteins and nucleic acids. The virus is also detected in lymph node and brain metastases of colon and breast cancer patients. However, it is rarely found in healthy tissue surrounding the primary tumour. Although HCMV is found in lymphnode and distant metastases, the potential virus related mechanisms of metastasis promotion are not understood [125, 126].

1.4.5.1. CMV in tumour dissemination

HCMV is known to play a role in tumour dissemination. For example, HCMV infection of neuroblastoma cells leads to enhanced tumour cell adhesion to endothelial cells resulting in the disruption of EC monolayer integrity. This leads to enhanced neuroblastoma invasiveness and higher trans-endothelial migration.[127] [128]. Studies also show the role of HCMV in EMT related to metastasis. A study by Shimamura et al examined the role of HCMV in the induction of TGF-β and its role in EMT. Upon infecting human renal tubular epithelial cells were *in vitro* it was observed that these cells underwent morphologic and transcriptional analogous related to EMT. Also, TGF-β and MMP-2 expression was induced. HCMV IE proteins probably control this process as their overexpression summarized these effects and targeting late gene expression did not inhibit these changes.

Several factors involved in EMT are similarly modulated by HCMV. This includes growth factors and signalling pathways. Further studies are required to comprehend the role of HCMV infection in EMT transition and metastasis formation.

1.5. Cancer Immunology

Metastasis is the key factor for cancer related deaths. Thus, understanding the mechanism of tumour dissemination is the central factor of cancer research. In cancer patients, the disseminated tumour cells are detectable in the peripheral blood as circulating tumour cells (CTC's) while in the lymph nodes they are detected as disseminated blood cells (DTC's). Hence the identification and characterization of these cells have resulted in perceptions of the molecular mechanisms of metastasis [129].

Cancer cells that exist in the primary site of a tumour are immune protected, cells which exit this site and enter circulation are compromised and vulnerable to immune surveillance, hence the survival of these cells are essential for metastatic spread. Thus, immune escape mechanisms are required for cell survival [129].

Immune escape mechanisms or immunoediting are important aspects for cancer cell survival. Immunoediting is a process which comprises of immune surveillance and tumour progression. It consists of three phases leading to cancer progression. The first phase is called elimination, here neoplastic cells are contained and destroyed by innate and adaptive immune cells. The second phase equilibrium is attained following escape the neoplastic cells escape from elimination and their interactions with immune cells reach an equilibrium with the immune system exerting a constant pressure. Hence even though the immune system wants to prevent the cells from progressing, it unwillingly contributes by selective clonal selection. This leads to the third stage, the escape phase, where the colonies which survived the previous phases, gain the ability to grow in an immune competent environment [130-132].

Tumours which escape immune evasion acquire resistance to immune factors, for example interferon gamma. Insensitivity to interferon gamma, enhances tumour resistance to immune attacks. Also, tumours evade immune cells either by shedding or restricting presentation of their ligands for recognition by NK cells and cytotoxic T lymphocytes. The tumours also downregulate other factors that elicit a tumour-immune response, for example pro inflammatory cytokines and chemokines [133-138].

1.5.1. Immune surveillance

NK cells and macrophages are the most studied cells with respect to tumour suppression and surveillance. NK cells are an important part of the innate immune system and they play a major role in defence against tumours and viruses. The interactions of these cells with tumours is mediated by a network of receptors and ligands including the major histocompatibility complex (MHC) class 1- related inhibitory molecules. Inhibition of NK cell signalling leads to tumour lysis through cytolytic granules release and apoptosis induction. These effects of the NK cells are decreased in CTC positive patients with metastatic colon, breast and other types, compared to CTC negative patients [138-141].

Macrophages, along with NK cells have an important role in controlling metastatic progression. Macrophages are vital for antibody dependent phagocytosis of tumours. This process is mostly governed by macrophages in the liver. A study by Denève et al showed comparisons of CTC counts between peripheral and mesenteric blood samples in patients with colorectal cancer confirmed that a significant proportion of the viable CTC population seem to be filtered and trapped in the liver. Thus, these findings highlight the importance of the liver microenvironment in mediating the outcome of interactions between tumour cells and immune cells. This often promotes tumour-cell death and sometimes facilitates DTC survival and growth [142-144].

1.5.1.1. Immunoediting

The immunological elimination of tumour antigen is driven by T- cell recognition, which is the chief principle of cancer immunoediting. Studies have validated this finding, one study on genetic mapping of a highly immunogencic and unedited sarcoma derived from methylcholanthrene (MCA)-treated Rag2−/− mice, to determine its mutational landscape showed that cancer immunoediting is the consequence of a T-cell-dependent immunoselection process which leads to outgrowth of tumour cell clones that lack immunodominant rejection antigens displaying reduced immunogenicity. A study by DuPage et al reached a similar conclusion. Studies also show the involvement of innate immunity in the immunoediting process. They showed that NK cells (apparently activated by local amplification of endogenous IL-12) can produce IFN-γ which in turn induces activation of $CD45^{+}CD11b^{+}MHCII^{hi}CD206^{lo}Ly6C^{lo}$ M1 macrophages. These act as important effectors of cancer immunoediting. Thus, these results show that the degree of immunocompetence of the host plays an important role in the extent to which a tumour undergoes immunoediting. [5,16].

1.5.1.2. Elimination:

Many reviews have described and summarized the mechanisms that take place in the elimination phase. The role of host recognition molecules such as NKG2D; IFN-γ, perforin, effector molecules like Fas/FasL, and TRAIL; and an intact lymphocyte compartment in protective anti-tumor immunity, are well recognized. Both type I (IFN-α/β) and type II interferons (IFN-γ) are essential for development of anti-tumour immune responses but play diverse roles in the cancer immunoediting process, while IFN-γ targets both tumour cells

and hematopoietic cells and tumour cells, IFN- α/β acts primarily on host cells. Recently, two studies showed that type I IFNs are mandatory for initiation of the early anti-tumour response and act on CD8α/CD103$^+$ DCs to enhance cross-presentation of tumour antigens to CD8$^+$ T cells [18,19]. Type I IFN sensitivity was not required for tumour rejection in macrophages, NK cells and granulocytes, all of which express type I IFN receptors.

1.5.1.3. Equilibrium

Adaptive Th1-like immunity plays an important role in the equilibrium phase and this was described in two studies, one using an immune-mediated dormancy model of fibrosarcoma and a follow up study using the same mouse model of MCA- induced fibrosarcoma and p53 mutant tumours. Both showed that immune-mediated tumour dormancy may be a very lengthy process. Significantly, the balance of IL-12 promoting elimination, and IL-23 (sharing the common subunit IL-12 (p40) maintains tumours in equilibrium and promotes persistence. Along with a minor tumor-promoting role for IL-10 many other pathways (e.g. IL-4, IL-17A, TNF, IFN-αβ) were shown to be dispensable for this phase.

Tumours that escape go on to metastasize. Specific mechanisms are involved in this process.

1.5.2. Immune evasion mechanism

As mentioned before, CTCs leaving the immunosuppressive primary tumour microenvironment are exposed to the active immune surveillance mechanisms. In addition, the possibility that CTCs will be lysed by tumour-specific immune cells increases significantly outside the immunosuppressive reserve of the tumour since peripheral immune cells are more numerous than CTCs. Hence the circulatory system is considered a hostile environment for cancer cells. Primary tumours are predicted to shed thousands of cells into the bloodstream every day, but evidently only a very small percentage develop the ability to grow into distant metastases supports this assumption. However, studies have identified new pathways through which CTCs might evade or survive encounters with immune cells. The most established mechanism of tumour evasion includes the ones previously described (NK cells and macrophages), CD 47 signalling, FAS/FASL signalling and hypoxia induced apoptosis [145].

1.5.2.1. MHC molecules and NK-cell ligands:

MHC I molecules that expressed on the surface of basically all nucleated cells present peptide epitopes that are processed from intracellular proteins for examination by immune cells. Thus, presentation of tumour-associated antigens (TAAs) to T-cell receptors (TCR) in the context of MHC I molecules is crucial for initiation of an adaptive CD8$^+$ CTL response. Hence, downregulation or entire loss of MHC I expression at the cell surface is a mechanism used by tumour cells to ‹hide› from CTLs and thereby evade death. As a standby to counteract this mechanism, NK cells become activated when MHC I molecules are under expressed or absent. Therefore, to escape both NK-mediated and CTL-mediated cytotoxicity, CTCs have to find a way to present MHC I molecules without presenting TAAs [146-149].

Cytokeratin 8 (CK8), along with its heterodimeric partners CK18 and CK19, have been shown to inhibit MHC I interactions with TCRs on CD8$^+$ CTLs. Overexpression of these cytokeratins has long been detected in malignant tissues. This mechanism demonstrates how cancer cells develop new methods of immune evasion, and that interfering with MHC-mediated antigen presentation seem like a critical approach to immune escape [150, 151].

1.5.2.2. FAS/FASL induced apoptosis

This apoptotic pathway is highly important to immune evasion. The transmembrane receptor FAS can initiate apoptosis, and activation of this receptor on T cells via binding to FASL is a suggested mechanism of tumour-mediated immunosuppression in several malignancies. For example, histopathological analyses have shown that FASL is upregulated in metastases compared to the primary tumour in patients with melanoma or colorectal cancer. Also, in patients with breast cancer, upregulation of FASL has been associated with increased apoptosis of T cells. Hence FASL expression on tumour cells may actively induce apoptosis in immune cells. Vice versa, tumour cells that express FAS will most likely be vulnerable to apoptosis evoked by tumour-specific immune cells, which can also express FASL. Hence, instantaneous loss or downregulation of FAS and upregulation of FASL on tumour cells might add to tumour evasion of immune-mediated cytolysis and increase the prospective for metastatic progression [152-156].

1.5.2.3. CD47-mediated signalling

Exhaustive studies by Irving Weissman and colleagues have emphasized the role of the leukocyte surface antigen CD47 in cancer, mostly, in cancer-cell evasion of phagocytic clearance. CD47 binds to its ligand signal-regulatory protein α (SIRPα, also known as macrophage fusion receptor), expressed on macrophages and dendritic cells, subsequently inhibiting phagocytosis by these cell types. Therefore, upregulation of CD47, an antiphagocytic 'don't eat me' signal, might confer CTCs with a non-immunogenic profile by allowing them to escape the consequences of cell-damage-induced upregulation of pro-phagocytic signals and, thus, the immune sequelae evoked after CTC recognition in the context of adaptive immunity. Steinert *et al* have associated the gene-expression profiles of primary tumours and CTCs from patients with colorectal cancer. Notably, CD47 was the only gene upregulated in CTCs versus the matched primary tumours, signifying a survival advantage conferred by CD47 expression for peripheral blood CTCs. Therefore, these findings along with others propose that CD47 is part of a potential metastasis-initiator cell signature, but functional analysis is required to describe the exact role of CD47 expression on CTCs [157-162].

1.5.2.4. Hypoxia-induced immune escape

Various genes are expressed during EMT, in cancer-stem cells, or in response to hypoxia. They have been shown to be upregulated in CTCs, and many of the encoded proteins can control the immune response. Specific metabolic and molecular changes enable DTCs to adapt to and survive in a microenvironment with a lower oxygen concentration, such as the bone marrow. Evidence investigating HIF-1αexpression in CTC's and functional studies of DTC's on bone marrow patients with lung, breast and prostate cancer show that many CTCs and DTCs exhibit a hypoxia-associated phenotype, and can adapt well in hypoxic condition. For example, upon hypoxic stress, glucose-regulated protein 78 (Grp78) is upregulated in cell lines established from the bone marrow of patients with cancer, and expression of Grp78 is linked with mesenchymal characteristics and poorly differentiated primary breast and lung tumours. Ongoing studies are investigating if adaptation to hypoxia also promotes CTC and/or DTC evasion of immune cells. Nonetheless, the hypoxia-resistant phenotype of DTCs has implications for immunotherapeutic strategies [163-165].

1.5.2.5. Metastasis promotion by immune cells

Studies show that metastasis can be supported by immune cells. Immune cells can, hence, be regarded as both protagonists and antagonists in the metastatic process [166-168].

1.5.2.6. Promotion of CTC seeding

Preliminary studies of CTCs have established a positive correlation between an acute inflammatory condition and formation of metastasis in the target organ of metastatic spread. For instance, using an allergic pulmonary inflammation model indicated that for CTCs to extravasate and form tumour filiae, take advantage of the augmented vascular permeability and adhesion molecules expression at the site of metastasis. They also showed that for CTC's to metastasize to the lung, they required the presence of $CD4^+$ cells at the site of metastasis. Along these lines, data from a murine colorectal cancer model indicated a positive correlation between CTCs formation and serum levels of IL-17A, a proinflammatory cytokine. In addition, the presence of IL-17A augmented tumour-cell motility. This occurs by triggering MMP-9 expression in CTCs, hence possibly supporting CTC mobilization and extravasation [169, 170].

Put together, escape from and variations in peripheral immune responses outside the local tumour milieu, are critical steps in metastases development.

1.6. C/EBPβ

C/EBPβ is a protein belonging to the C/EBP family [171, 172]. The family consists of six transcription factors from C/EBPα to C/EBPζ in total and is characterized by a basic leucine zipper at the C-terminus required for binding and dimerization. The family of proteins regulate different gene expressions involved in cell differentiation, proliferation inflammation and metabolism.

C/EBPβ can form heterodimers with members of the C/EBP family, such as C/EBPα, C/EBPγ and C/EBPδ, along with other transcription factors like Sp1or CREB1. It can also bind as a homodimer to some DNA regulatory regions thereby controlling the expressions of various target genes.

As a transcription factor, C/EBPβ interacts with several target genes and is required for a variety of biological processes, such as, granulopoiesis, adipogenesis, muscle repair, embryogenesis, and osteoporosis. It is involved in controlling autophagy, cell growth and antibacterial defence, along with regulating insulin level and insulin receptors expression. C/EBPβ is also involved in regulation of multiple genes responsible for immune and inflammatory responses. Evidence show its binding to cytokine coding genes such as IL-4, IL-6, IL-5 and TNFα. It is also responsible for activation and terminal differentiation of macrophages, an important immune cell subtype.

Our studies emphasize the involvement of C/EBPβ in breast cancer here its gene is usually non- mutated. A few rare mutations that have been found are questioned in its contribution to epithelial tumours. However, C/EBPβ might be amplified in a small subgroup of breast neoplasia, described as lobular carcinoma in situ. Elevated levels of C/EBPβ mRNA are linked to metastatic breast cancer, higher tumour grade and overall worse prognosis [171, 172].

1.7. Cancer progression and EMT

Epithelial-Mesenchymal transition is a process by which epithelial cells transform into mesenchymal cells. This occurs due to the loss of cell polarity and cell-to-cell adhesion molecules. This process is important in wound healing and embryogenesis. The reverse process mesenchymal epithelial process is also essential for various organ developments. It is also known to be involved in cancer progression and metastasis. Epithelial cells are single or multilayer cells with various functions. They depict apical-basal polarity and through specialized intracellular junctions, adhere and communicate with adjacent cells. Their position and interaction of the basement membrane proteins with integrins help define their physiology. The transition of the cells follows certain hallmarks and patterns. The plasticity of the epithelial phenotype enables cell transition through multiple EMT and MET rounds.

EMT increases the invasive phenotype of the cancer cells. They lose their cell-cell adhesion molecule, E-cadherin and the basement membrane. TGF-beta is a major factor that induces this property in tumour cells when it acts on activated RAS- expressing cells, leading to EMT and inhibition of apoptosis[173]. Evidence suggests that activated platelets have a direct contribution to the invasive phenotype of the cancer cells at the primary tumour site. In breast carcinoma, higher levels of TGF beta 1 and TBRII can be found. Similarly NOTCH and WNT signaling are associated with CSC's. In colon cancer, nuclear beta catenin is visible in scattered tumours [174]. The expression of TGF- beta varies with different cell types, thus understanding and quantifying the process is difficult [173, 175, 176].

There are three types of EMT based on the physiological context. Type 3 EMT leads to cancer progression and cancer stem cell properties. Type 1 EMT is the differentiation of epithelial cells to mesenchymal cells with no prior history of transition. Type 2 EMT is a process where cells have already undergone transition followed by reversion and initiation of a new EMT. Similarly, following dissemination, cancer cells revert to epithelial cells through MET and secondary carcinomas are generated having similar phenotypes. Pro invasive function of cancer cells is attributed to the expression of avβ3 integrin that is increased due to EMT [177, 178].

Various transcription factors like SNAIL, TWIST and ZEB have prominent roles in EMT and cancer progression. They have different profiles and functions based on the cell type. TWIST 1 down regulates epithelial gene expression and enhances expression of mesenchymal genes. SNAIL 1 and 2 has a similar role. Other transcription factors such as forkhead box (FOX) and GATA family and growth factors such as VEGF and FGF are also involved in EMT regulation [173, 175].

1.8. Death mechanisms and survival

Sudden cardiac death, a major problem worldwide is an unexpected natural cause of death due to cardiac failure. The time usually accounts for less than an hour from onset of symptoms without any prior condition would appear fatal. Such a quick death is attributed to cardiac arrhythmia. It is the most common and often, the first appearance of coronary artery disease. It is also the cause of 50% of cardiovascular deaths. The incidence increase with age in both men and women.

Sudden cardiac death may perhaps be considered as an electrical accident since, even though many patients have transient events that could influence the initiation of ventricular tachycardia or ventricular fibrillation and many individuals have anatomic and functional substrates favourable to developing a life-threatening ventricular tachyarrhythmia, only a relatively small percentage develop sudden cardiac death. This interplay between the anatomic and functional substrates (such as CAD, cardiomyopathy dilated and hypertrophic) modulated by the

transient events (like neuro& endocrine drugs, ischemic & reperfusion injury) that disturb the balance, and the impact of all 3 on the underlying potential arrhythmia mechanisms possessed by all hearts triggers sudden cardiac death. For instance, the combination of the 3 factors, i.e., coronary artery disease, scarred myocardium, and hypokalaemia, might be sufficient to provoke a ventricular tachyarrhythmia, causing sudden cardiac death in a patient had pre-existing re-entry pathways in the ventricular myocardium, likely due to an old infarction.

Variations in the anatomic substrate can modify the susceptibility of the myocardium to that of transient initiating events. For example, experimental studies show that arrhythmogenic response in a hypertrophied myocardium, and a healed myocardium post a myocardial infarction, is greater than normal tissue to the same extent of acute ischemia.

Another factor that can modulate some of the effects of acute coronary occlusion and reperfusion is catecholamine release along with reduction in sympathetic action with drugs presented to the pericardial sac to super fuse sympathetic nerves results in prevention of ventricular arrhythmias. Acute ischemia alone, involving a sufficiently large area of myocardium in an otherwise normal ventricle, can cause ventricular fibrillation without interplay with other factors though it is interesting to reflect the many balloon angioplasties performed and the infrequent occurrence of ventricular fibrillation during that procedure. Possibly the duration of ischemia is too short and inefficient to initiate. Re-entry along with regional changes in automaticity, as well as triggered activity due to afterdepolarisations, are probably important mechanisms to trigger ventricular fibrillation. Reperfusion can also be arrhythmogenic.

Another mechanism for cardiac arrest could be due to severe asystole, bradycardia, or pulseless electrical activity (electromechanical dissociation). In severely diseased hearts, this is more common and probably represents more global myocardial dysfunction.

Another major electrophysiological feature accountable for the initiation of ventricular fibrillation seems to be electrical heterogeneity. A heart that is entirely homogeneous electrically, i.e., all cells are at the same stages of repolarization and depolarization and conduct normally without block or delay, most probably does not develop ventricular fibrillation.

Essentially, even under normal circumstances these conditions do not exist, since various cell types, e.g. ventricular muscle versus Purkinje fibres, exhibit different refractoriness, action potential characteristics, and conduction velocities. But when heterogeneity becomes extreme, for instance, if one region of the myocardium exhibits ischemia-induced conduction block or delay differing from neighbouring regions, or when there is an unequal stretch or regional dysfunction causing regional electrophysiological alterations, the stage becomes set for development of ventricular fibrillation. These changes can be provoked by anatomic/functional substrates, transient initiating events and can moderate basic arrhythmia mechanisms of automaticity, re-entry and triggered activity to provoke ventricular arrhythmia.

1.8.1. Mechanism of death in cancer

Cachexia is a major recognized syndrome and a critical factor for cancer death. It is a multi-step process involving skeletal muscle and adipose tissue atrophy, leading to weight loss. It is attributed to poor physical function, lifestyle and prognosis in cancer patients. The classical clinical feature of cachexia is weight loss in adults and failure of growth in children. Various factors such as anorexia, inflammation, insulin resistance and muscle breakdown are also associated with cachexia. This problem, common to cancer patients has not been clearly defined.

The steps involved in this process include; widespread metabolic changes, proinflammatory signals arising from tumour cells and systemic inflammation in the host. Loss of body weight is a key signal and a loss greater than 5-10% is the defining limit. A weight loss above 30% results in death. The degree of loss on prognosis and outcome has not yet been clearly defined.

Until a while ago cancer cachexia was defined as a wasting syndrome that involves loss of fat and muscle, and it may or may not be attributed directly to tumour factors. This is due to the host's unusual immune response to it. More recent definitions state the cancer cachexia is a metabolic syndrome that is related to an underlying illness. It is characterized by muscle loss with or without loss of fat mass, thus emphasizing a unique property which is muscle wasting thereby, establishing it as a hallmark of cachexia. The metabolic syndrome is the result of protein synthesis, lipid metabolism and its degradation. These factors eventually result in cachexia. The changes occur due to an infection rather than starvation. These changes are complex and depend on various factors.

Decreased muscle strength is useful as a diagnostic criterion for patients with cancer cachexia, it is also used to differentiate between other forms of anorexia and the ones related to cancer. Patients who lose weight have a systemic inflammatory response [179, 180].

In a cancer patient, the main reason for weight loss is attributed to total loss of skeletal and adipose tissue mass. An increase in intracellular proteolytic activity is the reason for weight loss in the body. A complete catabolism of muscle tissue takes place leading to net loss of mass. Normal weight loss is due to depletion of adipose stores owing to starvation and the greatest contributor for cachexia is the ATP dependent ubiquitin pathway.

Clinical consequences of cachexia are determined by various factors such as host tumour interactions and metabolic syndromes, both leading to endpoints resulting eventually in cachexia. Each of these factors involves various trivial interactions. For instance, when a tumour is formed, the host initiates immune responses to deal with the tumour. An acute phase response is launched leading to the formation of a systemic inflammation.

The inflammatory cytokine response of the host against the tumour could possibly drive the cachexia process. Pro inflammatory cytokines include IL 6, TNF α and IL 1. It is not clear if the cytokine production is from the tumour or the host cell. A theory suggests that, it could be either produced by the tumours or occur due to the host's immune response against the tumour as a source of an acute phase protein response seen in various malignancies and in cachexia. Mouse models show that the systemic inflammatory response against the tumour correlates with weight loss and an interchange between IL1β and IL 6 inside the tumour microenvironment.

The tumour produces both pro cachectic and pro inflammatory factors that lead to an immune response. The pro cachectic factors include proteolysis inducing (PIF) and lipid mobilizing (LMF) factors. PIF and TNF α are the major competitors in skeletal muscle atrophy in patients with cachexia. Both of them increase protein degradation through an ubiquitin – proteasome pathway and downregulate protein synthesis through the phosphorylation of the eukaryotic initiation factor 2 alpha [179, 181, 182].

PIF has been found in the urine samples of weight loss patients having breast, colon, lung and ovarian cancer. In animals, the signaling occurs though NFκβ and STAT 3 pathways. If these pathways are incited, they lead to proteolysis in the muscle through a ubiquitin-proteasome pathway. In the hepatocytes, it concludes in the production of IL-6, 8 and CRP. LMF is found in patients with cancer related weight loss and not in patients with stable weight [179, 183].

Changes in lipid metabolism are due to lipolysis and are driven by LMF along with the tumour and a host factor known as zinc-2-alpha glycoprotein. This has a direct effect and sensitizes adipocytes to lipolytic stimuli resulting in an overexpression in cachexia. Another implicating factor is the resting energy which disrupts and dis-regulates the energy regulation. This has been found to be higher in cancer patients compared to non-cancer patients. A theory for this could be an altered gene expression in the mitochondria of the uncoupling proteins resulting in uncoupling of respiration from ATP production. This leads to loss of energy as heat.

Thus, the metabolic changes leading to cachexia are due to the interplay between tumour host interaction factors [179, 183].

1.8.2. Red blood cell distribution width (RDW)

Red blood cell distribution width or anisocytosis refers to the uneven size of the red blood cells with a higher RDW than normal. It is usually denoted in combination with red blood cell corpuscular volume in diagnosis of chronic inflammatory status in the body. Anisocytosis is commonly found in anemia and other blood disorders [184, 185].

Besides many blood disorders, RWD is associated with various acute and chronic cardiovascular diseases such as peripheral artery disease, acute coronary syndrome and ischemic cerebrovascular disease. Many studies have a shown an interesting relationship between carotid atherosclerosis or stroke. A reason for consistent increase in RDW in CVD is attributed to active stimulation of erythropoiesis by erythropoietin (EPO) a hormone, secreted during hypoxic conditions. This promotes the release of enflamed RBCs from the bone marrow [186]. Another hypothesis for high RBC could be due to a slight reduction in RBC turnover. Since size of RBCs gradually reduces with ageing of the cells, a decreased rate of RBC turnover would allow smaller cells to continue longer in circulation.

1.8.3. Survival

Post-secondary malignancies, CVD is the foremost cause of morbidity and mortality among cancer survivors. CVD risk factors are predominant in cancer patients. A study by Mertens et al[6] showed that among childhood cancer survivors, cardiovascular events are the principal non-malignant cause of death. It is responsible for a higher risk of death, about 7-fold high, among these patients when compared to their peers. After effects of cardiotoxic cancer therapy is thought to be the fundamental cause for this. Alternatively, a study by Enright and

Krzyzanowska[10] reiterated the necessity for precise individualized cardiovascular disease prevention program for cancer survivors. They showed that the subpar control provided for traditional measure of risk factors like cholesterol monitoring and blood pressure among survivors.

Recent developments indicate an increasing interest in a hypothesis for development of CVD in cancer patients. This proposed that CVD development in cancer patients takes place when they are exposed to a series of sequential or simultaneous events that together make them more susceptible to cardiovascular reserves and ultimately result in death. Another risk factor for pathogenesis of CVD is psychological distress in non-cancer populations. Put together the multiple-hit hypothesis has been conceived.

Cancer treatments include chemo, radiation, immuno or hormone targeted therapies or a combination of these. Some amongst them are cardiotoxic. For instance, for lymphoma or breast cancer treatments, chemo with anthracyclines as well as radiation therapy to the chest are cardiotoxic. These can lead to a reduction in cardiovascular reserves and eventually different sets of CVDs ranging from benign to possibly fatal. CVDs associated with cancer treatment can occur within few days, months or years. They include arrhythmias, myocardial infarction, thrombosis, congestive heart failure and cardiomyopathy.

Lifestyle factors also contribute to process. Due to cancer treatments patients might develop an unhealthy life style which includes physical inactivity and weight loss. This might lead to reduction of CV reserves and augments CVD risk and death. Psychological distress another important risk factor, whose presence is a bad for health outcome of patients. independent of traditional biomedical risk factors, depression symptoms, fatigue and anxiety have shown to forecast CVD onset and prognosis in patients with established CVD. This was validate based on a meta-analysis of 20 studies which showed the value of anxiety prediction for coronary heart disease occurrence in formerly healthy individuals. It showed that there is 26% higher risk of coronary heart disease development and a 48% increase in risk of cardiac death among anxious individuals.

Thus, research on adapted multiple-hit hypothesis for CVD development among cancer patients could contribute to advances regarding their care. An immediate necessity for CVD preventive procedures to reduce the delayed adverse effects of cancer therapies such as radiation and chemotherapy and early intervention could possibly help improve CVD's risk profile.

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PART II. PHYSICAL ACTIVITY OF SOCIAL AND PROFESSIONAL GROUPS
DZIAŁ II. AKTYWNOŚĆ FIZYCZNA GRUP SPOŁECZNYCH I ZAWODOWYCH

HEALTH AS A SOURCE OF HAPPINESS AND HEALTH-RELATED BEHAVIOUR OF YOUNG PEOPLE

ZDROWIE JAKO WYZNACZNIK SZCZĘŚCIA A ZACHOWANIA ZDROWOTNE MŁODZIEŻY

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Wkład autorów:
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B. Data collection/entry
zebranie danych
C. Data analysis/statistics
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D. Data interpretation
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Summary

Background. Proper human behaviour is needed to maintain health. Healthy lifestyle patterns develop specifically during childhood and adolescence, a process which helps shape young people, and one which significantly affects various life choices, including those regarding health. The aim of the study was to evaluate the health-related behaviour of young people, and to determine the hierarchical position of health as a symbol of happiness and its interrelations with related symbols. Differences in the postulated sources of happiness were also determined in patients with favourable and adverse health-related behaviour.
Material and methods. The study involved 209 high school students. The age of respondents ranged from 17 to 19 (M = 18, SD = 0.48). The study involved 114 girls (representing 54.5% of the group) and 95 boys (45.4%). The variables were measured using two techniques by Juczynski (2009): the Health Behaviour Inventory (IZZ) and Part I of the Personal Value List (measurement of the symbols of happiness).
Results. The respondents indicated that good health is positioned third in the hierarchy of the determinants of happiness, slightly lower than a large circle of friends. The respondents regard a successful family life as being the greatest determinant of happiness. Higher ratings for health in the hierarchy of the symbols of personal happiness were associated with more favourable adopted health-related behaviour. Similarly, people with favourable health-related behaviour are more likely to choose health as the source of a positive life than those with adverse behaviour.
Conclusions. The high position of health in the scope of a happy life is a positive factor in the health-related behaviour of young people.

Keywords: health behaviour, youth, health, happiness

Streszczenie

Wprowadzenie. Odpowiednie zachowania człowieka stanowią podstawę utrzymania jego zdrowia. Kształtowanie prozdrowotnych wzorów stylu życia ma miejsce szczególnie w okresie dzieciństwa i młodości. Proces ten powiązany jest z budowaniem struktury wartości młodych ludzi, która oddziałuje istotnie na wybory życiowe, także zdrowotne. Celem przeprowadzonych badań było ustalenie poziomu zachowań zdrowotnych młodzieży oraz miejsca zdrowia w hierarchii źródeł szczęścia w tej grupie, a także ustalenie ich wzajemnych powiązań. Określono także różnice w zakresie postulowanych wyznaczników szczęścia w grupie osób z korzystnymi i niekorzystnymi dla zdrowia zachowaniami.
Materiał i metody. W badaniach wzięło udział 209 uczniów szkół licealnych w Łodzi. Wiek badanych mieścił się w zakresie 17-19 lat (M= 18; SD=0,48). Badaniami objęto 114 dziewcząt (co stanowi 54,5 % całej grupy), oraz 95 chłopców (45,4 %). Do pomiaru zmiennych wykorzystano dwie techniki autorstwa Juczyńskiego (2009) – Inwentarz Zachowań Zdrowotnych oraz Listę Wartości Osobistych (cześć I do pomiaru symboli/wyznaczników szczęścia).
Wyniki. Przeprowadzone analizy wykazały, że dobre zdrowie zajmuje wysoką trzecią pozycję w hierarchii symboli szczęścia w deklaracji badanych, nieznacznie tylko niżej ocenione niż duży krąg przyjaciół. Według młodzieży o szczęściu przede wszystkim decyduje zaś udane życie rodzinne. Im wyżej cenione jest zdrowie w hierarchii źródeł osobistego szczęścia, tym bardziej korzystne dla zdrowia zachowania podejmuje młodzież. Podobnie, osoby o korzystnych dla zdrowia zachowaniach znacznie częściej niż badani o zachowaniach niekorzystnych wybierają zdrowie jak wyznacznik szczęśliwego życia.
Wnioski. Wysoka pozycja zdrowia w obrazie szczęśliwego życia jest czynnikiem sprzyjającym zachowaniom promującym zdrowie młodzieży.

Słowa kluczowe: zachowania zdrowotne, zdrowie, młodzież, szczęście

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Introduction

Optimal diet, physical activity, avoidance of stimulants and drugs of abuse, adequate sleep and a positive mental attitude ensure that children develop properly. In order to enter adulthood in good health, young people need to develop proper health-related behaviour: forms of human activity that remain, on the basis of objective knowledge about health and subjective beliefs, closely related to health [1]. These forms of health-related behaviour have been classified as habitual and intentional, and pro-health and anti-health. They include such aspects as healthy consumption, physical activity, preventive behaviour, making use of medical care and having a positive mental attitude [2, 3].

Harmful forms of health behaviour have been identified as leading risk factors for the most common causes of mortality, i.e. cardiovascular diseases and cancer [4, 5]. Lifestyle is of fundamental importance to health [6, 7].

However, recent studies have examined the developmental risks to children and teenagers. Younger people demonstrate a number of unsatisfactory lifestyle habits, especially in the fields of physical activity and diet, and examples of higher risk behaviour, such as drinking alcohol and smoking, are growing in popularity among this group [8, 9, 10].

The period encompassing childhood and the teenage years is crucial for the development of behaviour patterns engaged in later on in life. For example, health-compromising behaviour and poor perceived health in adolescence was found to predict low educational level in adulthood [11]. What is more, healthier students are better learners – healthy nutrition and team sports participation were found to have a positive effect on academic performance, whereas the effects of alcohol use, smoking, early sexual intercourse, bullying, and certain screen time behaviour were had an overall negative effect [12].

In response, a number of prevention initiatives have been targeted at children and teenagers. However, in an attempt to improve their effectiveness, recent studies have examined the psychosocial determinants of health-related behaviour in adolescents [13, 14, 15, 16]. The results highlight the role of subjective variables in the prediction of health-related behaviour in young people, such as their sense of coherence, but also the role of such factors as family support and parental attitudes, and the health-related patterns exhibited by parents [15, 17, 18].

The health motive, that is to say the degree of interest in one's own health and the willingness to act on its behalf, is the most important for the development of health-related behaviour. A lack of interest in one's own health results in negligence. The health motive itself stems, in turn, from the values assigned to health [19]. Life goals predict as motives, and they predict health behaviour [20].

Generally speaking, health as a value is a crucial factor for making life decisions and its perception has a decisive influence on the choice of behaviour aimed at improving or maintaining optimal health [21]. Health also enjoys a relatively high position in the hierarchy of values in teenagers, and there are important correlations within the structure of values of family members, with teenagers assigning similar priorities as their parents [22]. However, the correlation between the valuation of health and the adoption of pro-health behaviour is not so clear. For some people, health happens to be only a declarative value. It has been indicated that people who attribute a great value to health are more involved in pro-health behaviour, i.e. diet, quitting smoking, medical behaviour and refraining from risky behaviour [23, 24, 25]. An understanding of the core values may improve the ability to predict decisions related to behaviour such as healthy eating [26].

However, not all studies confirm that health evaluation plays a role in adopting health-related activities. Research conducted by Juczyński and Ogińska-Bulik [27] found varied correlations between the value attributed to health by teenagers and their avoidance or adoption of behaviour adverse to health. It is possible that behaviour perceived to be healthy did not necessarily correspond with actual behaviour [28].

When learning about the world, young people weigh up values, recognize them as their own and multiply. According to the Ajzen [29] theory of planned behaviour, they implement normative values such as symbols of happiness through their own behaviour and actions.

The period of youth is one characterised by the laying down of the foundations of adult life, and the fostering of patterns of behaviour including those related to health. It is also the most essential time for the development of value systems, beliefs about happiness and personal views affecting various spheres of life.

The aim of the study was threefold:

- to determine the level of health-related behaviour and the hierarchy of the predictors of happiness chosen by adolescents;
- to determine the types of correlations between the declared sources of happiness and health-related behaviour in adolescents;
- to identify differences in the postulated sources of happiness in the group of people with regard to favourable and adverse health-related behaviour.

Material and methods

The study involved 209 high school students lived in central Poland (Lodz city): 114 girls (54.5%) and 95 boys (45.4%). The age of the respondents ranged from 17 to 19 years (M = 18,00, SD = 0.48).

Inclusion to the group was voluntary and all surveys were anonymous. Research was conducted during lesson hours, with the teacher not present. Questionnaires were preceded by an explanatory statement which urged the respondents to give accurate answers.

The Health Behaviour Inventory (IZZ) authored by Juczyński [19] was used to measure the health-related behaviour. The tool contains 24 statements describing various types of health-related behaviour, the intensity of which is assessed on a scale from 1 ("almost never") to 5 ("almost always"). The overall health-related behaviour score is obtained by adding up the individual behaviour scores. It is also possible to calculate the intensity of four categories of health-related behaviour: i.e. preventive behaviour (adherence to health recommendations and obtaining information about health and disease), correct eating habits (the kind of consumed food), health practices (habits associated with sleep, recreation and physical activity) and a positive mental attitudes (avoiding too strong emotions, tension and stress). A higher score implies greater intensity of declared behaviour.

The second technique used was the Personal Value List by Juczyński [19]. The first part of the tool describes nine symbols of happiness, out of which the respondents are asked to select the five most important for them, answering the question: "What do you think determines personal happiness?"). The selected determinants then are ordered from 5 - the most important to 1- the least important. These assessments are treated as weights enabling interpretation. The symbols that are not selected are awarded 0 points.

Results

In the first stage of the statistical analysis, the means and standard deviations of variables were calculated. The mean health-related behaviour score for the whole study group (M = 72.4, SD = 11.4) was 5 Sten, indicating an average level [19].

Figure 1 shows the means for the symbols of happiness in the whole group.

Figure 1. Symbols of happiness in the whole group of respondents (ranked from the most to the least frequently selected)

In the study group, good health, as a determinant of happiness, takes the third highest position (average of 2.56), only slightly below a large circle of friends (2.73). The respondents indicated that happiness is primarily determined by successful family life (3.53). Fame and popularity were indicated as determinants of happiness by the lowest number of people (0.08).

Health was rated higher in relation to the Juczynski [19] study, in which "good health" was awarded an average weight of 1.85, taking fifth position.

The relationship between sex and the intensity of the studied variables is presented in tables 1 and 2.

Table 1. Comparison of the mean results of the general score and the different types of health-related behaviour between boys and girls

Variables – Health-related behaviour	Boys (N= 95)		Girls (N=114)		Test t p
	M	SD	M	SD	
General index of health behaviour	70.4	12.1	74.1	10.6	2.3 *
Correct eating habits	15.8	4.1	18.2	3.9	4.3 ***
Prevention behaviour	16.1	4.3	18.2	3.6	3.8 ***
Positive mental attitudes	19.2	4.4	19.0	4.4	-0.4 n.s
Health practices	18.8	3.8	18.8	3.8	0.1 n.s

M – mean; SD – standard deviation; t – value of test t, p – significance level
* p < 0.05, ** p < 0.01, ***p<0.001, ns — not significant

The data indicates that there is a difference between boys and girls in terms of the overall score for health-related behaviour and the indicators of healthy consumption habits and preventive actions. Boys are characterised by more adverse health lifestyles than girls.

Table 2. Comparison of the mean rates of the symbols of happiness in the groups of boys and girls

Variables – symbols of happiness	Boys (N= 95)		Girls (N=114)		Test t p
	M	SD	M	SD	
Large circle of friends	2.7	1.6	2.7	1.6	-0.0 n.s
Happy family life	2.9	1.8	4.0	1.5	4.4 ***
Having one's favourite job, profession	1.7	1.7	1.5	1.4	-0.8 n.s
Success in learning, work	1.3	1.5	0.9	1.4	-1.7 n.s
Good health	2.7	1.8	2.5	1.7	-1.0 n.s
Being needed to other people	1.2	1.6	1.6	1.7	1.7 n.s
Good material conditions	1.6	1.7	1.1	1.5	-2.3 *
Life full of adventure, travel	0.6	1.3	0.6	1.2	0.1 n.s
Fame, popularity	0.2	0.7	0.0	0.1	-2.1 *

M – mean; SD – standard deviation; t – value of test t, p – significance level
* p < 0.05, ** p < 0.01, ***p<0.001, ns — not significant

Among the studied symbols of happiness, the two groups of respondents differ most with regard to the selection of successful family life, with this being more highly rated by girls. Boys, in comparison to girls, are more likely to perceive good material conditions and fame and popularity as synonymous with happiness. In terms of the choice of health as a predictor of happiness, there were no differences between the two groups. However, as the differences in the overall rate of health-related behaviour and the declared symbols of happiness are not large, further analyses were conducted on the entire study group.

In order to verify the correlations between health-related behaviour and the symbols of a happy life declared by the respondents, correlation coefficients were calculated (Table 3).

Table 3. Correlation coefficients between health-related behaviour and the declared symbols of happiness for the whole group of respondents

Variables	General index of health behaviour	Correct eating habits	Prevention behaviour	Positive mental attitudes	Health practices
Large circle of friends	-0.05	0.07	-0.12	-0.04	-0.01
Happy family life	0.13	0.11	0.12	0.08	-0.00
Having one's favourite job, profession	0.02	0.05	0.01	-0.02	0.08
Success in learning, work	0.01	0.03	**0.14**	-0.06	-0.13
Good health	**0.21**	0.06	0.12	**0.22**	**0.18**
Being needed to other people	-0.01	-0.05	0.05	-0.04	-0.02
Good material conditions	**-0.22**	**-0.22**	**-0.18**	-0.12	-0.10
Life full of adventure, travel	**-0.15**	-0.05	**-0.18**	-0.11	-0.06
Fame, popularity	0.00	-0.06	-0.05	0.08	0.04

The selected correlations are significant at of $p < 0.05$

The data in the table indicates that the choice of good health as a source of happiness is associated with the indicator of health-related behaviour: higher values assigned to health correspond to a more favourable view of health behaviour by the respondent. A similar correlation also exists between positive mental attitudes and health practices: the choice of health as an important part of a happy life goes hand in hand with avoiding stresses and strains, and the preference for healthier habits in everyday life.

A correlation was also observed between health-related behaviour and the selection of good material conditions and a life full of adventure; however, this correlation is negative in that a higher position in the hierarchy for the two characteristics is associated with less favourable health behaviour. Choosing success in learning and work was found to have a positive correlation with preventive behaviour, although this relationship was the weakest observed.

The groups of respondents demonstrating favourable and adverse health-related behaviour were the compared with regard to their postulated symbols of happiness, according to their overall health-related behaviour. Three groups of young people were formed: one with adverse health-related behaviour (n=64; 30.62% of all respondents) (M - 0.5 SD), another with favourable behaviour (n=60; 28.71% of all respondents) (M + SD 0.5) and another with an average level of health-related behaviour (n=85; 40.67% of the whole group). The results are presented in Table 4.

Table 4. A comparison of groups with favourable and adverse health-related behaviour with regard to their preferred symbols of happiness

Variables	Adverse health-related behaviour (N= 64)		Favourable health-related behaviour (N= 60)		Test t p
	M	SD	M	SD	
Large circle of friends	2.8	1.6	2.7	1.5	0.4 ns
Happy family life	3.2	1.9	3.7	1.7	-1.6 ns
Having one's favourite job, profession	1.6	1.5	1.6	1.5	0.0 ns
Success in learning, work	1.3	1.5	1.0	1.5	0.9 ns
Good health	2.1	1.9	2.9	1.5	-2.8 **
Being needed to other people	1.4	1.7	1.5	1.8	-0.2 ns
Good material conditions	1.6	1.8	1.1	1.4	1.9 ns
Life full of adventure, travel	0.9	1.5	0.4	0.9	2.3 *
Fame, popularity	0.1	0.7	0.1	0.6	0.1 ns

M – mean; SD – standard deviation; t – value of test t, p – significance level
*$p < 0.05$, **$p < 0.01$, ns — not significant

The data suggests that people with favourable health-related behaviour are more likely to regard health as a predictor of a happy life than respondents with adverse behaviour. Another significant difference, though less so, is that a life full of adventure and travel is assigned greater importance by those with adverse health-related behaviour.

Conclusions

In reference to the study aims, the results indicate that:

- The respondents rate good health in the third position in the hierarchy of the sources of happiness, only slightly lower than having a large circle of friends. Happiness is primarily determined by a successful family life. No differences were observed between the groups of boys and girls in terms of choosing health as a symbol of happiness.
- The obtained data show that the higher that health is valued in the hierarchy of the determinants of personal happiness by younger people, the more favourable to health their behaviour is.
- Respondents with favourable health-related behaviour choose health as a source of a happy life much more frequently than those with adverse behaviour,.

According to the surveyed teenagers, "good health" was rated higher in relation to the Juczyński [19] study, which recorded the average weight of 1.85, ranking the fifth position.

Other studies confirm the high position of health in the values hierarchy of young people [22]. Similar data were obtained in studies on adolescents by Juczyński [30], where "good health" occupied the high second position in the ranking of values, and neither gender nor age significantly differentiated the value of health.

The average result of health-related behaviour obtained in the study group (M = 72.4, SD = 11.4) highlighted the average level of the variable. Significant, though small, differences in the overall rate of health-related behaviour were noted between boys and girls, an observation which has been confirmed by other studies [31].

Torres and Fernández [24] also report that the value attributed to health influences the prediction of pro-health behaviour in adolescents. In addition, research conducted by Kristiansen [32] and Huxley and Grodan [33] found that the perception of health as a value, among other things, was related to overall preventive health behaviour. Teenagers often take up risky behaviour following peer pressure, and should they rate health highly in the pursuit of happiness, this could have a protective influence against the adverse effects of the environment. Assigning a low value to health may predispose them to engaging in behaviour adverse to health in high-risk situations [34].

The above data reinforces the need for a purposeful impact on the value system of young people so as to shape and strengthen their perception of health as a value. Such a course aimed at modifying values in teenagers and children is not only possible but would also reap rewards [35]. Parents and teachers should emphasise the value of health in the normative sense, so that adolescents include the standard in their own system of values. The important role of health in the pursuit of personal happiness should be emphasized, even when it has not deteriorated, and perhaps especially so in this case. The role of education and prevention programmes can be observed from an early age. The role of the family should not be underestimated, as parental influence on the attitudes and behaviour of children is critical. Transferring and strengthening the value of health is one of the ways of shaping the health potential of the new generation.

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ORIGINAL PAPER
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KNOWLEDGE ON PHYSICAL ACTIVITY AND NUTRITION BEHAVIOURS IN PATIENTS WITH INCREASED BODY WEIGHT AND CARDIOVASCULAR DISEASES

WIEDZA W ZAKRESIE AKTYWNOŚCI FIZYCZNEJ I NAWYKÓW ŻYWIENIOWYCH CHORYCH ZE ZWIĘKSZONĄ MASĄ CIAŁA I CHOROBAMI UKŁADU KRĄŻENIA

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Authors' contribution
Wkład autorów:
A. Study design/planning
zaplanowanie badań
B. Data collection/entry
zebranie danych
C. Data analysis/statistics
dane – analiza i statystyki
D. Data interpretation
interpretacja danych
E. Preparation of manuscript
przygotowanie artykułu
F. Literature analysis/search
wyszukiwanie i analiza literatury
G. Funds collection
zebranie funduszy

Summary

Background. Low physical activity and the increasing number of overweight and obese people contribute to the prevalence of cardiovascular diseases in society. Classic risk factors and improper lifestyle increase the risk of their occurrence, progression and mortality in patients. The aim of the study was assessment of physical activity and nutrition behaviours in people with abnormal body weight and cardiovascular diseases.
Material and methods. The study involved 152 patients including 70 men and 82 women aged 23-95 years (mean 55.4 ± 14.04 years). The study used the International Physical Activity Questionnaire IPAQ in its seven-day version and an original questionnaire. The data were collected in a database and Statistica v.10 was used for a statistical analysis.
Results. The average energy expenditure amounted to 1.422 MET. 50% of the participant demonstrated sufficient physical activity, 36% low, and only 14% high. Only 15% of the respondents did exercises. Despite being overweight and obese, 66% of the respondents did not follow a diet and only 17% of them consumed 5 meals a day.
Conclusions. Despite the occurrence of cardiovascular diseases and abnormal body weight, physical activity was low in the study group, and the knowledge in this regard was limited. In addition a significant number of respondents did not exhibit healthy behaviours.

Keywords: obesity, risk factors, cardiovascular diseases, physical activity

Streszczenie

Wprowadzenie. Niewystarczająca aktywność fizyczna oraz stały wzrost liczby osób z nadwagą i otyłością przyczyniają się do występowania w społeczeństwie chorób układu krążenia. Rozpowszechnienie klasycznych czynników ryzyka i nieodpowiedni styl życia zwiększają ryzyko ich występowania, progresji oraz odsetka śmiertelności wśród chorujących. Celem pracy była ocean aktywności fizycznej oraz nawyków żywieniowych chorych ze zwiększoną masą ciała i chorobami układu krążenia.
Materiał i metody. Zbadano 152 chorych, w tym: 70 mężczyzn i 82 kobiety w wieku 23-95 lat (średnio: 55.4 ± 14.04). Do badań wykorzystano autorski kwestionariusz ankiety, a do oceny aktywności fizycznej standaryzowany Międzynarodowy Kwestionariusz Aktywności Fizycznej w wersji siedmiodniowej. Analizę statystyczną wykonano przy użyciu programu Statistica v.10.0.
Wyniki. Średni wydatek energetyczny badanych chorych wynosił 1.422 MET. Wśród nich, 50% badanych uzyskało wystarczający poziom aktywności fizycznej, 36% niski, a 14% - wysoki. Spośród badanych 15% respondentów uprawiało sport. Pomimo występującej nadwagi lub otyłości, 66% badanych nie stosowała diety, a jedynie 17% spożywało 5 posiłków dziennie
Wnioski. Pomimo występowania chorób układu krążenia oraz nieprawidłowej masy ciała aktywność fizyczna w badanej grupie była zbyt mała, a wiedza w tym zakresie – niewystarczająca. Ponadto znaczna grupa badanych osób nie przestrzegała prawidłowych nawyków żywieniowych.

Tables: 7
Figures: 1
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Słowa kluczowe: otyłość, czynniki ryzyka, choroby układu krążenia, aktywność fizyczna

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Introduction

The development of technology and mechanisation contributed to a significant reduction of physical activity in society. The most common devices linked to daily use such as washing machine, dishwasher, elevators, mobile phones and public transport caused that people move less frequently. Insufficient physical activity in combination with the omnipresent stress, the fast pace of life, poor nutrition or use of drugs contributed to an increasing prevalence of cardiovascular diseases [1].

Cardiovascular diseases are the leading causes of death in the world [2]. While in 1960 cardiovascular incidence accounted for 23.4% deaths, in 2013 it was already 45,8%. Projections for morbidity are also not optimistic. As the forecasts of the Central Statistical Office have shown, the number of deaths from cardiovascular causes in Poland will increase from 177 thousand (45.8% of the total mortality) in 2013 to 218.9 thousand in 2050 (51.1% of the overall mortality). To a large extent, the risk factors that contribute to the dissemination of cardiovascular diseases contribute can be divided into two groups: modifiable and non-modifiable [3].

The group of non-modifiable risk factors include age, sex, and positive family history, and the group of modifiable risk factors: smoking, hypertension, improper diet, stress, alcohol abuse, unsatisfactory physical activity, hypercholesterolemia, overweight, obesity and diabetes [4,5,6,7]. The presence of modifiable risk factors can be eliminated, and people can modify their habits and lead a healthy lifestyle. Then, such an elimination of risk factors reduces the risk of cardiovascular disease from 50 up to 70% [1,8].

The recommendations by American Heart Association on the prevention of cardiovascular diseases indicate that one of the significant factors is regular physical activity. Each type of exercise has a positive effect on risk factors of cardiovascular disease [9]. Daily physical activity leads to the reduction in cardiac load by slowing the heart rate in rest, lowering resting blood pressure, speeding up the return of the pulse rate after exercise to the resting level [10]. In addition, it improves emotional state and mental health, regulates body fat distribution and helps maintain a diet regimen.

Under the influence of regular exercise, there also occurs lower concentration of cholesterol, i.e. LDL, while the level of HDL, which has a significant effect of physical activity, increases. Consequently, physical activity combined with a healthy diet can help to keep the correct body weight or reduce its excess [11]. In the developed and developing countries, a significant increase in the number of the overweight or obese contributed to recognising obesity as a civilisation disease. It concerns not only older people who, for various reasons have limited their physical activity, but more and more often youth and younger persons, in particular children. The problem has become a global issue. In Europe, as many as 50 – 65% of the population have increased body weight, of which about 16% are obese. In Poland, 52% men and 29% women suffer from an increased body weight [12,13,14]. Overweight and obesity are in themselves risk factors for cardiovascular disease [15]. In patients who are burdened with cardiovascular diseases, overweight or obesity, incorrect nutrition habits, an unsatisfactory level of physical activity and coexisting diseases have negative influence on their prognosis.

The main aim of the study was an assessment of physical activity and nutrition behaviours in patients with increased body weight and cardiovascular diseases. Additionally, knowledge concerning physical activity, principles of proper nutrition and their application in daily life was assessed.

Material and methods

The study involved 152 patients including 70 men and 82 women aged from 23 to 95, average 55,4±14,04. Characteristics of the study group are shown in Table 1.

Table 1. General characteristics of the study group

Variable	Average	Min	Max	SD
Age [year]	55.4	23	95	18.45
Body weight [kg]	81.7	55	135	14.04
Height [m]	1.69	1.48	1.96	0.097
BMI [kg/m^2]	28.2	25	42	3.13

The study was conducted at the Department of Physiotherapy and Hydrotherapy in MSWiA Hospital in Katowice, Poland. The study used the International Physical Activity Questionnaire (IPAQ), a seven-day self assessment format, and an original questionnaire.

The IPAQ consisted of 4 parts testing hard work, moderate work, walking and time spent sitting during the day. On the basis of the collected data, the total energy expenditure was calculated in MET (Metabolic Equiva-

lent). The original questionnaire included 29 questions relating to physical activity, knowledge in this regard, nutrition behaviours and lifestyle of the surveyed participants. All the individuals expressed their agreement to participate in the examination. The inclusion criteria for the study were the occurrence of cardiovascular disease and a BMI above 25 kg / m2. The data were collected in a database and for statistical analysis (Statistica v.10 was used).

Results

General characteristics of the study group patients with increased body mass and cardiovascular diseases

The general characteristics of the study group of patients with increased body mass and cardiovascular diseases are presented in Table 1.

The characteristics of the study group of patients with increased body mass and cardiovascular diseases regarding BMI are presented in Table 2.

Table 2. Characteristic of the study group regarding BMI

Variable	N=152	100%
Underweight (BMI < 18.5)	0	0%
Correct range (BMI 18.5-24.9)	0	0%
Overweight (BMI 25-29.9)	118	78%
Obesity Class I (BMI 30-34.9)	30	20%
Obesity Class II (BMI 35-39.9)	2	1%
Obesity Class III (BMI ≥ 40)	2	1%

It turned out that body mass index exceeded 25kg/m^2 in each person and every fifth tested individual was obese.

Table 3 presents characteristics of the study group of patients regarding the occurrence of cardiovascular diseases.

Table 3. Occurrence of cardiovascular diseases in the study group

Variable	N=152	100%
Hypertension	106	69%
Coronary artery disease	18	12%
Myocardial infraction	29	19%
Coronary angioplasty	12	8%
Heart failure	7	4.5%
Valvulopathy	13	8.5%
Arrhythmia	19	12.5%
Peripheral vascular disease	14	9%
Stroke	7	4.5%
Other	6	4%

Most patients in the study group, i.e. 106 (69%), suffered from hypertension, subsequently myocardial infarction and coronary heart disease. A few patients had a stroke and were struggling with heart failure – 7 persons (4.5%).

Physical activity of patients with increased body mass and cardiovascular diseases

The characteristics of the study group with increased body mass and cardiovascular diseases took into account the data provided by the International Physical Activity Questionnaire: the load of hard work, moderate work, walking, total physical activity in MET (Metabolic Equivalent) and time spent sitting during the day. The data were shown in Table 4.

Table 4. Characteristic of the study group taking into account data of IPAQ

Variable	Average	Min	Max	SD
Hard work (MET)	333.4	0	4320	657.9
Moderate work (MET)	338.2	0	6720	680.1
Walking (MET)	746	0	5148	1020
Total Physical Activity (MET)	1422	0	9200	1607.4
Sitting (min.)	320	50	850	147

The total energy expenditure in the study group was diverse and ranged from 0 to 9200 MET. Furthermore, the surveyed participants spent their time sitting even 14 hours a day.

Taking all the data of total energy expenditure into account, the surveyed participants were qualified into three groups, those demonstrating low, moderate and highly physically activity (Figure 1).

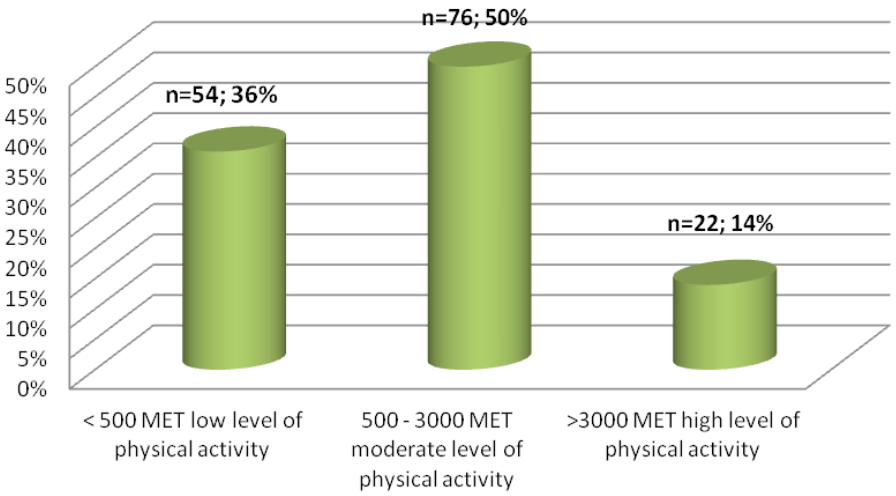

Figure 1. Characteristic of the study group regarding total physical activity based on IPAQ

The study indicated that, although half of the patients achieved a sufficient level of physical activity ranging from 500 to 3000 MET, the physical activity level of 54 respondents (36%) was too low (less than 500 MET). Only 22 tested persons (14%) achieved a high level of physical activity.

The characteristics of the study group of patients with increased body mass and cardiovascular diseases also measured the knowledge on the role of physical activity in the prevention of cardiovascular disease. The findings are presented in Table 5.

Table 5. Level of knowledge taking into account physical activity in study group

Variable	**N=152**	**100%**
Should patients which suffering from heart diseases be physically active?		
Yes	137	90%
No	3	2%
I don't know	12	8%
How often should people with cardiovascular disease be physically active?		
Just once a week	15	10%
Few days a week	58	38%
Everyday	33	22%
I don't know	46	30%
How long should one exercise to achieve beneficial changes in the circulatory system?		
Two weeks	6	4%
At least a month	21	14%
At least three months	47	31%
I don't know	78	51%

How long should an exercise last?		
At least 30 minutes	96	63%
At least 60 minutes	13	8%
Above 60 minutes	2	1%
I don't know	41	27%

The characteristics of the study group with regard to activities performed during leisure time are shown in Table 6.

Table 6. Characteristic of the study group taking account preference of leisure time activities

Variable	N=152	100%
Watching TV	91	60%
Reading books	50	33%
Napping	23	15%
Solving crosswords	35	23%
Playing on computer	26	17%
Walking	43	28%
Working in the garden	27	18%
Meeting with friends	35	23%
Exercising	23	15%
Other	0	0%

Only 23 patients from the study group (15%) did exercises in leisure time, whereas 91 persons (60%) watched TV or read a book – 50 respondents (33%).

Characteristics of the study group of patients with increased body mass and cardiovascular diseases regarding BMI

The **c**haracteristics of the study group regarding assessment and control of body mass as well as dietary habits are presented in Table 7.

Table 7. Characteristic of the study group regarding assessment and control of body mass

Variable	N=152	100%
Everyday	5	3%
Once a week	15	10%
Once a month	36	24%
Once of three months	30	20%
Semi-annually	30	20%
I do not control the process	35	23%
Subjective assessment of their own body weight		
Correct	47	31%
Slightly too large	74	49%
Definitely too large	17	11%
I cannot determine it	14	9%
Using a diet		
Yes	52	34%
No	100	66%
Regular eating		
Yes	37	25%
No	84	56%
I do not pay attention	29	19%
Number of daily meals		
2 meals	6	4%
3 meals	54	36%

4 meals	49	32%
5 meals	26	17%
I'm eating when I'm hungry	17	11%
Snacking between meals		
Yes	117	77%
No	35	23%

The examination of the study group showed that, despite overweight and obesity as well as cardiovascular diseases in the patients, 100 respondents (66%) did not follow a diet, 117 (77%) snacked between meals, and only 26 (17%) ate five meals a day. Moreover, 47 patients (31%) estimated their body weight as correct, although it was not the case, and 14 patients could not evaluate their body weight.

Discussion

The results of the studies on physical activity patients with cardiovascular diseases and increased body mass confirmed the findings documented in numerous publications, which shows that the level of physical activity in these groups of patients is too low. During an average week, the patient's expenditure for walking is on average 746 MET.

A one-time moderate physical activity lasted on average 37 minutes on three days a week. As for moderate work, average weekly energy expenditure was 338 MET per week.

One-time physical activity at the intensive level lasted on average 31 minutes for 2.9 days per week. The average weekly energy expenditure related to an intense activity amounted to 333 MET. Such a result is considered insufficient. Physical activity at moderate level was demonstrated by 100 patients (66%). Intensive physical exercises were performed the least often, i.e. 67 (44%) of the surveyed, which means that the majority of respondents did not do any exercises required to accelerate the pulse and breathing.

An average for the total weekly expenditure of energy amounted to 1417 MET. When compared to the scale of the IPAQ Q, the result seems sufficient, but it should be kept in mind that this average physical activity concerns all the respondents.

The sufficient level of physical activity was exhibited only by one in two patients. The results are consistent with those published in 2013 research in which Puciato et al. examined 2,053 people using the IPAQ short version, which showed that the level of physical activity during leisure time in the studied population was low [15]. Similar results were obtained in the study conducted by Wozniak et al., which assessed physical activity and diet behaviours of people with cardiovascular diseases. Most of the patients (81% women and 66% men) showed a sufficient level of physical activity, but their nutrition behaviours did not follow the recommendations [16]. However, the study by Woźniak et al. indicated a higher percentage of those who achieved a sufficient level of physical activity compared to our results. This may indicate that the prevalence of overweight or obesity in people with cardiovascular disease is an important factor which decreasing their physical activity. What seems comforting is the fact that 90% of the surveyed realize that patients with cardiovascular diseases should be physically active. There remains a very large group of patients who do not know this.

Further, the study assessed the number of meals consumed a day as well. It was shown that the numbers varied. Some patients consumed 2 meals: 6 (4%); others 26 (17%) – 5 meals, despite an increased body weight. The biggest groups of respondents consumed 3 meals– 54 persons (36%); and 4 meals – 49 respondents (32%). The results are consistent with the already mentioned research, which concludes that few people consume only 2 meals per day (3% of the respondents) or 5 meals (17%). However, by far the most numerous groups of respondents consumed 3 meals – 46% of the respondents or 4 – 35% of the surveyed.

The study by Platta et al. assessing nutritional behaviours of patients with regard to prevention of cardiovascular diseases showed that 40% of the surveyed are overweight and 13% were patients in Obesity Class I, whereas 1% – in Obesity Class II [17]. The results of the presented study are not consistent with our findings, maybe because the former group featured 118 overweight patients (77%), which was twice higher than in our study. However, very similar results were recorded in terms of Obesity Class II, which was found in 30 of the respondents (19%). The study showed that 2% of the patients could be classified as belonging to that class, which was close to our findings.

As for lifestyle and knowledge on healthy behaviours in obese people with hypertension, a publication from 2009 reported that up to 66.7% of the surveyed women and 87.1% of the men did not follow any diet, despite the increased weight and accompanying hypertension [18]. Interestingly, these results are consistent with our studies in which up to 100 of the surveyed patients (66%) did not follow any diet despite increased body weight.

It is worth emphasising that a significant number of patients in the study group also suffered from hypertension, which is regarded as a lifestyle disease related to one's diet, unhealthy lifestyle and insufficient knowledge on nutrition [19].

Thus, despite the fact that the half of the surveyed persons achieved a sufficient level of physical activity, their knowledge in this regard was limited. What is worse, they do not follow the healthy recommendation in their daily life. The burden of cardiovascular diseases, overweight and obesity adversely affects health outcomes in this group of patients and; therefore, the results of the presented studies point to a need of introducing health education programme in the groups with the same or similar disorders as those in the study group.

Conclusions

Basing on these results, the following conclusions have been formulated:

1. Physical activity of half of the patients with increased body weight and cardiovascular diseases was sufficient, although their knowledge in this regard was unsatisfactory.
2. Patients of the study group show incomplete knowledge on healthy behaviours and, in most cases, they did not follow them in daily life.
3. Most of the patients exhibited improper nutrition habits and did not pay attention to proper nutrition, which mainly contributes to their increased weight and, consequently, predisposes them to cardiovascular diseases.
4. Improper health behaviours and low physical activity in patients with increased body mass and cardiovascular diseases result not only from insufficient knowledge in this field but also a lack of desire and motivation to apply it in daily life.

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PART III. OTHER
DZIAŁ III. RÓŻNE

EFFECTIVENESS OF HEMOPERFUSION IN TREATMENT OF PATIENTS WITH NON-BILIARY MODERATELY SEVERE PANCREATITIS

SKUTECZNOŚĆ ZASTOSOWANIA HEMOPERFUZJI W LECZENIU PACJENTÓW Z OSTRYM MARTWICZYM ZAPALENIEM TRZUSTKI

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Wkład autorów:
A. Study design/planning
zaplanowanie badań
B. Data collection/entry
zebranie danych
C. Data analysis/statistics
dane – analiza i statystyki
D. Data interpretation
interpretacja danych
E. Preparation of manuscript
przygotowanie artykułu
F. Literature analysis/search
wyszukiwanie i analiza literatury
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Summary

Background. Acute pancreatitis morbidity has been rising annually all around the world. In case of acute necrotic pancreatitis, the mortality reaches 40% in the majority of hospitals. The therapy is effective if the efferent methods involve complex therapy of this disease. One such method is hemoperfusion, i.e. extracorporeal blood purification, which is widely used in toxicology. The authors of the article used hemoperfusion in a complex therapy in patients with severe acute pancreatitis. The following research presents an evaluation of the results of hemoperfusion used in a complex therapy of patients with acute pancreatitis. **Material and methods.** The study involved 38 patients with acute non-biliary moderately severe pancreatitis who were treated at an intensive care unit of Ternopil University Hospital in Ukraine. 18 patients were treated following the protocol for treatment of acute pancreatitis. In 20 patients, this treatment was additionally combined with hemoperfusion. We determined the levels of amylase, diastase, procalcitonin, bilirubin, malonic dialdehyde, and diene conjugates in blood serum and the level of leukocytes in the blood. **Results.** The levels of procalcitonin, amylase, bilirubin, leukocytes number, malonic dialdehyde, and diene conjugates were stabilised in patients of both groups, but in those who received hemoperfusion demonstrated much better results. These were manifested by significantly better levels of the amylase, bilirubin, creatinine, urea, procalcitonin, malonic dialdehyde, and diene conjugates in patients who received hemoperfusion ($p < 0.005$) than in the other group undergoing standard drug therapy. **Conclusions.** Hemoperfusion can be used as an effective method in the complex treatment of patients with acute pancreatitis.

Keywords: acute pancreatitis, hemoperfusion, amylase, procalcitonin

Streszczenie

Wprowadzenie. Corocznie na całym świecie obserwuje się wzrost zachorowalności na ostre zapalenie trzustki. W przypadku ostrego martwiczego zapalenia trzustki śmiertelność w większości szpitali osiąga 40%. Terapia jest skuteczna, jeśli metody odprowadzające obejmują kompleksową terapię tej choroby. Jedną z takich metod jest hemoperfuzja, tj. pozaustrojowa hemodializa krwi, szeroko stosowane w toksykologii. Autorzy artykułu zastosowali hemoperfuzję w kompleksowej terapii u pacjentów z ciężkim ostrym zapaleniem trzustki. Poniższe badania przedstawiają ocenę wyników hemoperfuzji stosowanej w kompleksowej terapii pacjentów z ostrym zapaleniem trzustki. **Materiał i metody.** W badaniu wzięło udział 38 pacjentów z ostrym, niezłośliwym i umiarkowanie ciężkim zapaleniem trzustki; leczonych w oddziale intensywnej opieki medycznej szpitala uniwersyteckiego na Ukrainie. Zgodnie z protokołem leczenia ostrego zapalenia trzustki leczono18 pacjentów. U 20 pacjentów leczenie to połączono dodatkowo z hemoperfuzją. Określono poziom amylazy, diastazy, prokalcytoniny, bilirubiny, dialdehydu malonowego i koniugatów dienowych w surowicy krwi oraz poziom leukocytów we krwi. **Wyniki.** Poziom prokalcytoniny, amylazy, bilirubiny, liczby leukocytów, dialdehydu malonowego i koniugatów dienowych były stabilizowane u pacjentów z obu grup, ale u tych pacjentów, u których włączono hemoperfuzję, wyniki były zdecydowanie lepsze. Przejawiały się one znacznie wyższym poziomem amylazy, bilirubiny, kreatyniny, mocznika, prokalcytoniny, dialdehydu malonowego i dienowych koniugatów u pacjentów, którym włączono hemoperfuzję hemoperfuzję ($p < 0,005$) niż w drugiej grupie poddawanej standardowej terapii lekowej. **Wnioski.** Hemoperfuzja może być stosowana jako skuteczna metoda w kompleksowym leczeniu pacjentów z ostrym zapaleniem trzustki.

Słowa kluczowe: ostre zapalenie trzustki, hemoperfuzja, amylaza, prokalcytonina

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Introduction

The number of patients with acute pancreatitis (AP) rises, and those with destructive forms amounts to 20-30% [1]. Even in big specialised hospitals, general and post-operative mortality does not fall, especially in case of infected forms of pancreonecrosis, which fall within 15 and 40%, or more [2]. According to the data, the research aimed at studying different methods of treatment of pancreonecrosis may have a significant practical value. The course of pancreonecrosis is frequently complicated with the development of severe sepsis. It is known that the usage of extracorporeal blood purification in the treatment of severe sepsis and septic shock, particularly hemofiltration and hemoperfusion is very successful [3, 4, 5, 6]. The research has demonstrated the effectiveness of this treatment, especially in patients with abdominal and gram-negative sepsis.

It was also found that there is some study on the successful usage of combination hemodialysis and hemoperfusion in treatment of AP, which was the complication of crush syndrome [7]. However, no fundamental research on its usage in the treatment of AP was found. The method of hemoperfusion is successfully used in a complex therapy of AP at the University Hospital of Ternopil State Medical University.

This research forwards the description of this treatment method. To our mind, this data are very essential as they prove that the hemoperfusion method can be used in the treatment of AP. It is vital and should be considered as the current methods of treatment do not ensure much effectiveness.

Material and methods

The study involved 38 patients with acute non-biliary moderately severe pancreatitis who were treated at the intensive care unit of Ternopil University Hospital in the years 2015-2016. The patients were in the early (within 1 week) phase of AP, characterised by transient organ failure, lasting less than 48 h. Alcohol pancreatitis was diagnosed in 7 patients, alimentary - in 16 patients, posttraumatic – in 15 patients. The diagnosis of AP was established by the presence of 2 of the 3 following criteria: abdominal pain, consistent with the disease, serum amylase greater than three times the upper limit of normal, and/or characteristic findings in abdominal imaging. Transabdominal ultrasound was performed in all patients. Contrast-enhanced computed tomography (CECT) of the pancreas was used in patients in whom the diagnosis was unclear or who failed to improve clinically within the first 48 – 72 hrs. after hospital admission or to evaluate complications. Traditional treatment was administered in all patients with AP. Aggressive hydration, defined as 250-500 ml per hour of isotonic crystalloid solution, was provided to all patients in the first 12 – 24 hrs. Lactated Ringer's solution was the preferred isotonic crystalloid replacement fluid. Antibiotics were given only for an extrapancreatic infection such as cholangitis, catheter-acquired infections, bacteremia, urinary tract infections or pneumonia. Enteral nutrition was initiated to prevent infectious complications. Parenteral nutrition was avoided unless the enteral route was not available or not tolerated. Nasojejunal delivery of enteral feeding was applied. All patients received synthetic octapeptide derivative of the natural hormone somatostatin - sandostatin, which has similar pharmacological effects, but much longer duration of action. The drug inhibits pathologically increased secretion of serotonin. The dose of sandostatin was 0,3 mg daily (8).

Patients were divided into 2 groups. The first group (18 patients) were treated following the protocol for the treatment of acute pancreatitis. In the other group (20 patients), this treatment was additionally combined with hemoperfusion. Hemoperfusion was implemented as a supplement to the general guideline principles on 1-3 day after the patients' hospitalisation in the intensive care unit. Hemoperfusion was done just after the rehydration of patients. This procedure was implemented by apparatus "Hemofenix" and sorbent SCN. The patients obtained from 1 to 5 seances of hemoperfusion with a break of 1-3 days between the seances. The following paper describes the results obtained after the 2nd séance of hemoperfusion (if patient obtained only 1 séance – the results were also described).

Since the distribution law for derived indices differed from the normal one, a non-parametric test was used. In this particular case, the test for dependent quantities should be used. Therefore, the Wilkinson test – a matched-pairs test, was applied. The marked asymmetry in the frequency distribution of indices having been obtained, the description of the median and quartile was found appropriate. The value of these indices is determined by their position in the system of the ranked value of indices and, regardless of the distribution law, serves as structural averages or variation indices. These indices are used for establishing one or another standard. The software "Statistica 10" was applied to do the computation.

The permission for research implementation was given by Bioethics commission of Ternopil State Medical University (protocol №29 from 20.05.2015).

Results and discussion

The described treatment caused better outcomes of the studied parameters in both patient groups. In contrast to standard treatment, there was a noticeable improvement when hemoperfusion was involved, and the results were significantly better. The results are presented in Table 1.

Table 1. Treatment of patients with non-biliary moderately-severe pancreatitis

Parameters	Data				
	Median	Minimum	Maximum	Lower quartile	Upper quartile
Body temperature in Celsius, before treatment	37.30	36.50	39.000	37.30	37.60
Body temperature in Celsius, standard treatment	37.30	36.80	37.800	37.00	37.50
Body temperature in Celsius, additional hemoperfusion	36.60*	36.00	38.000	36.20	36.60
Saturation, before treatment, %	92.00	91.00	96.000	92.00	93.00
Saturation, standard treatment, %	93.00	91.00	97.000	92.00	95.00
Saturation, additional hemoperfusion, %	97.00*	95.00	98.000	96.00	98.00
Leukocytes, before treatment, $\times 10^9$/L	14.45	5.50	27.600	11.70	16.00
Leukocytes, standard treatment, $\times 10^9$/L	12.40	10.60	13.400	12.00	13.20
Leukocytes, additional hemoperfusion $\times 10^9$/L	10.20*	6.10	16.000	8.80	11.60
Band neutrophils, before treatment, %	19.00	7.00	48.000	15.00	30.00
Band neutrophils, standard treatment, %	12.00	8.00	18.000	9.00	16.00
Band neutrophils, additional hemoperfusion, %	11.00*	7.00	16.000	9.00	14.00
Amylase, before treatment, U/L	976.50	453.00	3240.000	852.00	1982.00
Amylase, standard treatment, U/L	772.00*	664.00	999.000	732.00	882.00
Amylase, additional hemoperfusion, U/L	206.00* **	68.00	452.000	112.00	301.20
Bilirubin, before treatment, µmol/L	46.50	12.41	439.000	29.00	65.00
Bilirubin, standard treatment, µmol/L	36.00	24.00	59.000	29.00	38.90
Bilirubin, additional hemoperfusion, µmol/L	21.60* **	5.60	88.000	11.00	39.80
Creatinine, before treatment, µmol/L	110.00	39.00	510.000	89.00	179.00
Creatinine, standard treatment, µmol/L	85.00*	43.00	264.000	62.00	127.00
Creatinine, additional hemoperfusion, µmol/L	65.00* **	43.00	124.000	56.00	86.00
Urea, before treatment, mmol/L	18.00	2.49	46.370	12.82	22.00
Urea, standard treatment, mmol/L	15.17	6.50	22.840	10.12	17.50
Urea, additional hemoperfusion, mmol/L	6.85* **	2.60	31.200	4.30	10.00
Diastase, before treatment, U/L	996.50	70.46	9768.700	234.00	2543.00
Diastase, standard treatment, U/L	931.00	316.00	7863.000	516.00	1998.00
Diastase, additional hemoperfusion, U/L	239.00* **	51.50	989.000	186.00	517.20
Procalcitonin, before treatment, ng/mL	3.79	0.90	12.200	2.20	8.50
Procalcitonin, standard treatment, ng/mL	3.05*	0.22	6.200	2.10	3.60
Procalcitonin, additional hemoperfusion, ng/mL	1.40* **	0.14	6.400	0.50	3.11
Glasgow Coma Scale, before treatment, points	13.00	13.00	14.000	13.00	13.00
Glasgow Coma Scale, standard treatment, points	13.00	13.00	14.000	13.00	13.00
Glasgow Coma Scale, additional hemoperfusion, points	15.00*	14.00	15.000	15.00	15.00
Pulse, before treatment, beats/min	112.50	82.00	130.000	98.00	116.00
Pulse, standard treatment, beats/min	96.00*	78.00	102.000	86.00	98.00
Pulse, additional hemoperfusion, beats/min	84.00*	72.00	98.000	82.00	94.00
Malonic dialdehyde, before treatment, µmol/L	5.60	3.80	7.200	4.80	6.20
Malonic dialdehyde, standard treatment, µmol/L	3.80*	2.80	4.400	3.60	4.20
Malonic dialdehyde, additional hemoperfusion, µmol/L	1.60* **	1.40	2.100	1.50	1.80

Diene conjugates, before treatment, μmol/L	4.60	4.20	5.400	4.40	5.20
Diene conjugates, standard treatment, μmol/L	3.40	3.20	3.800	3.20	3.60
Diene conjugates, additional hemoperfusion, μmol/L	1.20* **	1.00	1.400	1.20	1.30

Note*- reliable index changes (P< 0.005) relative to the pre-treatment index;
** - reliable index changes (P< 0.005) relative to the index for the standard therapy group

The hemoperfusion group revealed reliable (P< 0.005) decrease of procalcitonin indices (2.18 times), leukocyte number (1.22 time), stab neutrophil number (1.73 time), amylase (4.74 times), diastase (3.9 times), and bilirubin (1.67 time), as compared to the results achieved with the drug therapy.

The increased level of lipid peroxidation markers, i.e. malonic dialdehyde and diene conjugate, was found in the patients. The increase is indicative of the adverse effect of lipid peroxidation in AP pathogenesis. In both groups, indices improved due to the treatment. However, the combined standard therapy and hemoperfusion resulted in reliable normalisation of the markers' level, as compared to the group of undergoing standard therapy. Presumably, hemoperfusion decreases the blood content of toxic products that had formed owing to an increased lipid peroxidation activity.

To our mind, one of the significant positive effects was the decrease of encephalopathy manifestation. In 5 patients, an expressed encephalopathy was observed with 11 points following the Glasgow Coma Scale. Despite the intensive treatment of AP, the positive changes in hemodynamics and laboratory indicators, the encephalopathy manifestation did not decrease. The usage of the 1st séance of hemoperfusion caused an increase in the Glasgow Coma Scale level up to 13 points, after the next hemoperfusion it equalled 15.

The term "hemoperfusion (in the post-Soviet countries – hemosorption) is a treatment method which relies on the transfer of patient's blood through the filter with sorbent – carbon resin or activated carbon [9, 10]. The filtered blood comes back to the patient's organism. Hemoperfusion is a good method of extracorporeal reduction of exogenous and endogenous toxins. The current adsorbents are the granules with membranous carbon, activated by cellulose or acryl hydrogel or non-ionic resin (XAD-2 and XAD-4). The activated carbon coating prevents the destruction of blood cells, especially thrombocytes and leukocytes. It is considered that this method is even more effective in toxicology than hemodialysis and peritoneal dialysis, especially when the toxic substances are fat-soluble. Besides, hemosorption, as an additional treatment method, can be used in patients with systemic lupus erythematosus, cold urticaria, psoriasis, food allergy, bronchial asthma and family hyperlipidemia.

In Ukraine, hemoperfusion (or hemosorption) is a widely spread method of efferent patients' treatment. The hemosorbents like carbon sorbents and ionic resins are used as they are produced in Ukraine. Carbon sorbents of SCN type (1К, SCN-2К) significantly decrease the level of toxins of low and average molecular weight and also protein-bound metabolites [8, 9, 11]. They remove toxic substances such as barbiturates, organophosphorus compounds, chlorinated hydrocarbons, myoglobin and do not influence K, Na, Mg, Ca concentrations. The effectiveness of carbon sorbents is also seen in case of acetaminophen and tricyclic antidepressants overdose, in terms of systemic inflammatory response syndrome (SIRS) as well.

The received data show a successful usage of hemoperfusion in AP treatment. The advantages of hemoperfusion compared to other methods of extracorporeal purification are high effectiveness and low cost. The cost of hemodialysis and ultra- and hemofiltration is comparatively higher.

Conclusions

The usage of hemoperfusion in patients with acute non-biliary moderately severe pancreatitis in addition to traditional drug therapy leads to a significant normalisation of amylase, diastase, procalcitonine, bilirubin and leukocytes levels compared to patients who were treated following only the standard protocol drug therapy.

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SOCIAL FUNCTIONING OF ELDERLY PEOPLE LIVING IN RURAL AREAS

FUNKCJONOWANIE SPOŁECZNE LUDZI STARSZYCH ZAMIESZKUJĄCYCH OBSZARY WIEJSKIE

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Wkład autorów:
A. Study design/planning
zaplanowanie badań
B. Data collection/entry
zebranie danych
C. Data analysis/statistics
dane – analiza i statystyki
D. Data interpretation
interpretacja danych
E. Preparation of manuscript
przygotowanie artykułu
F. Literature analysis/search
wyszukiwanie i analiza literatury
G. Funds collection
zebranie funduszy

Summary

Background. The aim of this work was to assess social functioning of elderly people living in rural areas.
Material and methods. The authors used own interview questionnaire to collect the data. The study was conducted in 504 citizens, older than 65 years, from eight villages.
Results. Women were more frequently widowed than men, had low educational level and lived alone. As most responses showed (51.98%), the received benefits did not cover the respondents' current needs and 5.95% of them claimed that they were insufficient. The remaining respondents, i.e. 42.06%, stated that the available resources fulfilled their needs. The respondents would also point to family's aid (n=411; 81.55%) or spouse's aid (n=147; 29.56%). Only 37 people benefited from social care (n=504; 7.34%), of which 24 (64.86%) claimed that the help provided by social care was insufficient.
Conclusions. Old women in rural areas tend to live alone more frequently, are widowed and have lower level of education than men. The received financial benefits do not fully cover current needs of older residents of rural areas regardless of sex. Among people of over 65 years living in rural areas, the majority (81.55%) would point to family support and only 2.18% indicated social care as a source of income.

Keywords: social functioning, seniors, rural areas

Streszczenie

Wprowadzenie. Celem pracy była ocena funkcjonowania społecznego osób w podeszłym wieku zamieszkujących obszary wiejskie.
Materiał i metody. Dane w badaniu zostały zebrane przy pomocy autorskiego kwestionariusza. Badania ankietowe przeprowadzono wśród 504 obywateli ośmiu wsi u osób powyżej 65 roku życia.
Wyniki. Kobiety były częściej wdowami niż mężczyźni, miały niski poziom wykształcenia i żyły samotnie. Zgodnie z większością odpowiedzi (51,98%), otrzymane świadczenia nie pokrywają bieżących potrzeb, 5,95% badanych stwierdziło, że zasoby były niewystarczające. Pozostała liczba respondentów 42,06% stwierdziła, że zasoby zaspokajają ich potrzeby. Najczęściej wskazywano na pomoc rodziny (n = 411; 81,55%) lub współmałżonka (n = 147, 29,56%). Tylko 37 osób korzystało z pomocy społecznej (n = 504; 7,34%), spośród których 24 osoby (64,86%) twierdziły, że pomoc zapewniona przez opiekę społeczną jest niewystarczająca.
Wnioski. Starsze kobiety żyjące na obszarach wiejskich częściej mieszkają samotnie, są wdowami i mają niższe wykształcenie niż mężczyźni. Wszystkie otrzymywane korzyści finansowe nie w pełni pokrywają bieżące potrzeby starszych mieszkańców obszarów wiejskich bez względu na płeć. Wśród osób powyżej 65 roku życia mieszkających na obszarach wiejskich większość (81,55%) wskazała pomoc rodzinną, a 2,18% wskazało opiekę społeczną jako źródło wsparcia.

Słowa kluczowe: funkcjonowanie społeczne, seniorzy, obszary wiejskie

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Introduction

The situation of seniors living in rural areas is determined by various factors, including family and housing conditions, material security, health condition, possible access to social care and medical services [1]. According to Iwański, seniors in rural areas create a specific social stratum, mostly consisting of poor, scattered around people, often without social care or other state aid [2]. The author draws attention to the difference between the highest pension paid by Social Insurance Company (ZUS) and Farmer's Social Security Fund (KRUS), which in 2009 totalled 765 PLN, which indicates that retirees in rural areas have much lower financial resource [2]. The disabled elderly living in rural areas experience various barriers and limitations [2-4], generally resulting from inappropriate infrastructure, personal social care and difficult financial situation [5, 6]. The scattered location of the housing causes that seniors living in rural areas experience troubles with shopping and access to cultural assets [2, 6]. Moreover, housing infrastructure of seniors in rural areas is worse than in urban ones. Many seniors reside in non-renovated and expensive to maintain houses, without water, sewer and gas installations, telephone and other devices providing comfortable living [2, 7]. Older residents of rural areas have more difficult access to support offered by psychologists or guided self-help [8]. Moreover, it is much more challenging to provide institutionalised aid as it is not accepted and considered to be humiliating. Additionally, the problem with financial aid is related to the income obtained from comparative fiscal hectare [1]. The work aimed to assess the social functioning of the elderly living in rural areas.

Material and methods

The research data for socio-demographic, financial and social support were collected using the authors' interview questionnaire. This study was carried out in 504 citizens, older than 65 years, from eight villages of Podkarpacie Province. The statistical analysis was completed using STATISTICA 6.0 PL software. The level of significance was set up at $p<0.05$. The Kendall rank correlation coefficient, Kolmogorov-Smirnoff, Pearson's chi-squared ($\chi 2$) tests and Kruskal-Wallis one-way analysis of variance followed by Dunn's test were used.

Results

The proportional ratio of men and women for every age category was similar. The most significant differences were among men and women between 66 and 70 years of age ($p<0.05$) (fig. 1).

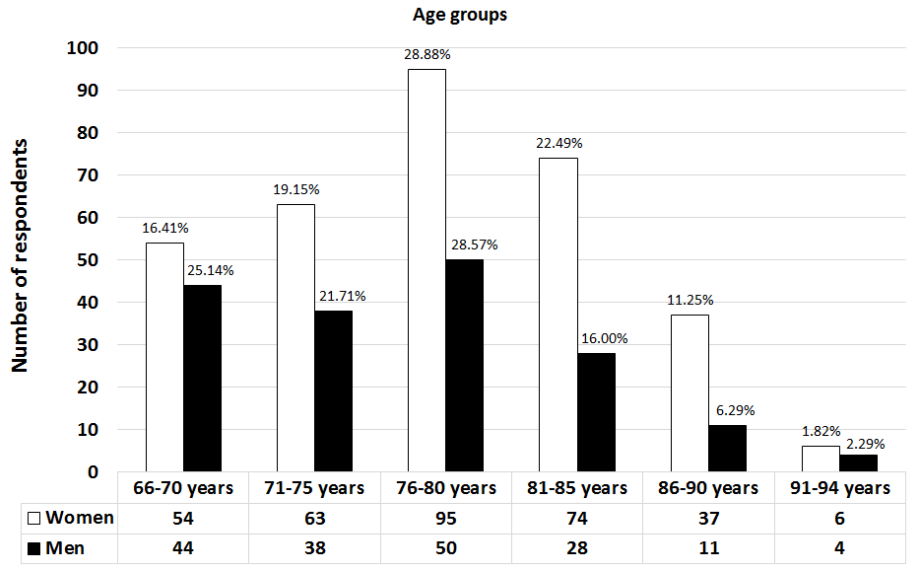

Figure 1. Age vs. sex of the test groups (N=504)

The age of women was significantly higher than that of men (p<0.001) (fig. 2).

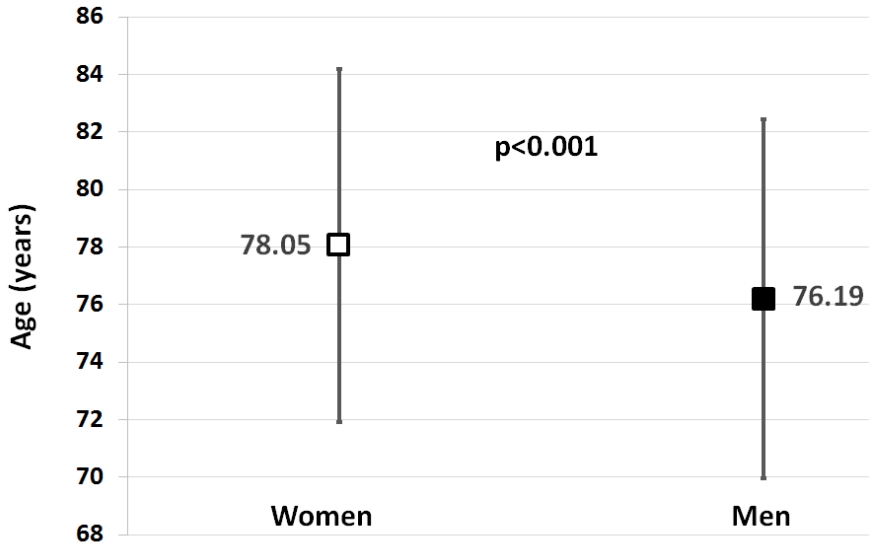

Figure 2. Sex vs. mean average and standard deviation of age (N=504)

The differentiation of marital status between women and men was observed within the investigated population. Men would more often be married than women (n=141; 80.57% vs. n=118; 35.87%), and single (n=6; 3.43% vs. n=3; 0.91%). On the other hand, women more often declared being widowed (n=206; 62.61% vs. n=27; 15.43%). Significant differences were observed between married men (p<0.001), and widowed women (p<0.001) (fig. 3).

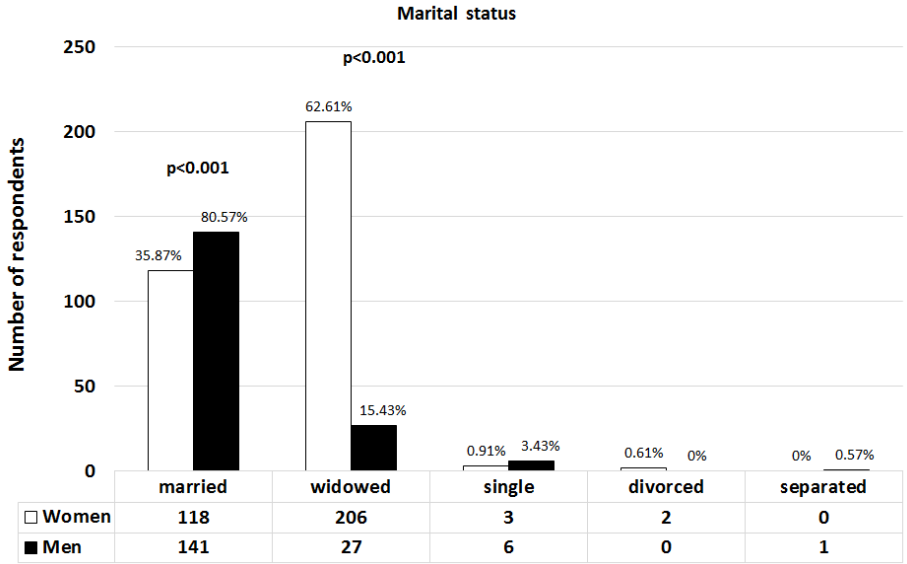

Figure 3. Marital status vs. sex (N=504)

On average, the widowed and single respondents were the oldest (79.36 and 79.00 respectively), followed by those who were divorced (75.55), and in separation (70.00). The average age of the married persons was 75.63 years. The age difference in the married, widowed and singles categories was significant at p<0.01 (fig. 3).

As regards the educational level, women would significantly more often than men declare incomplete primary education and would rarely have a vocational education (p<0.001) (fig. 4).

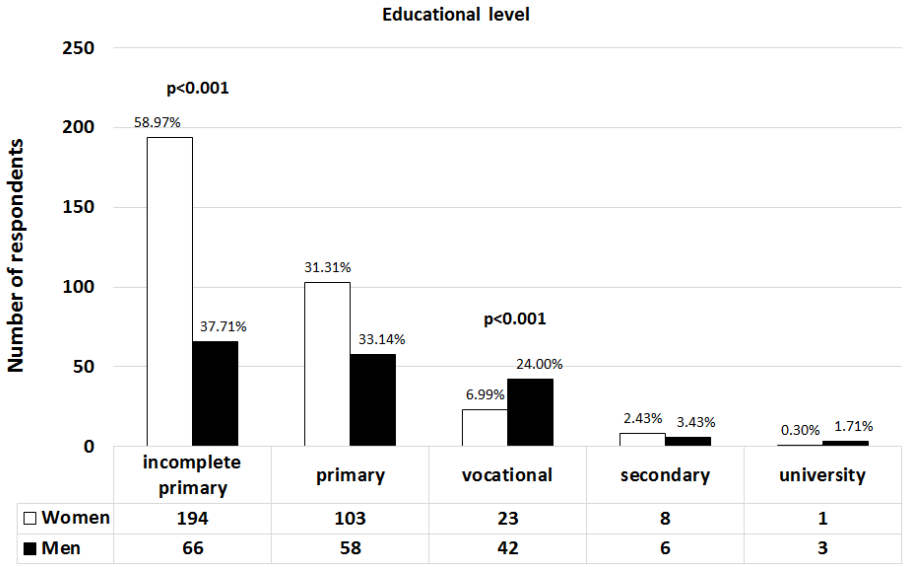

Figure 4. Education level of the tested groups vs. sex (N=504)

While analysing the age of the examined people with regard to their educational level, it was found that the respondents with incomplete primary education (average 79.74) and primary education (77.00) were older than people with secondary education (72.14) and a university degree (72.25). The youngest group consisted of the persons with vocational education (70.54) (fig. 4). The Kendall rank correlation coefficient test revealed a relationship between age and the level of education of the tested respondents (τ = - 0.3498; p<0.001). Younger people had higher educational level than the older ones.

For the vast majority of respondents (n=486; 96.43%), the pension was the primary source of income and for the remaining ones (n=18; 3.57%) – illness benefits. Only one person (0.20%) admitted to receiving additional employment income in the whole group of the respondents. Differences between women and men concerning the source of income were not statistically significant (p>0.10).

As most frequently given responses (51.98%) show, the received benefits did not cover the respondents' current needs, and only 5.95% assured that the resources were insufficient. The remaining respondents (42.06%) stated that resources fulfilled their needs. The received benefits were insufficient to cover current needs for a large number of men (n=84; 48.0%) and women (n=178; 54.1%), and for 6.38% (n=21) women and 5.14% (n=9) men, they were completely insufficient. The received benefits fully covered the needs of 39.51% (n=130) women and 46.86% (n=82) men. No significant differences were observed between women and men with regard to the received benefits which covered current needs (p>0.10).

The study rated the housing conditions using a four-grade scale. 28.17% (n=142) of the surveyed persons rated them as "very good", 46.43% (n=234) of the respondents would classify them as "good". The "average" category was pointed to by 23.61% (n=119) of the interviewees, and 1.79% (n=9) stated that they resided in "bad" housing conditions. No significant differences between men and women as for housing conditions were observed (p>0.10). Both women and men frequently pointed to "good" housing conditions (nearly 50% of indications).

A vast majority of the respondents (n=329; 65.28%) lived with their families, 23.21% (n=117) lived with their spouses, 11.31 % (n=57) lived alone and only 0.20% (n=1) lived with people who were not related. Although women lived with their family more frequently than men, the difference was not statistically significant. A significant difference was observed in women who more often lived alone than men (p<0.001), and rarely with spouses (p<0.001) (fig. 5).

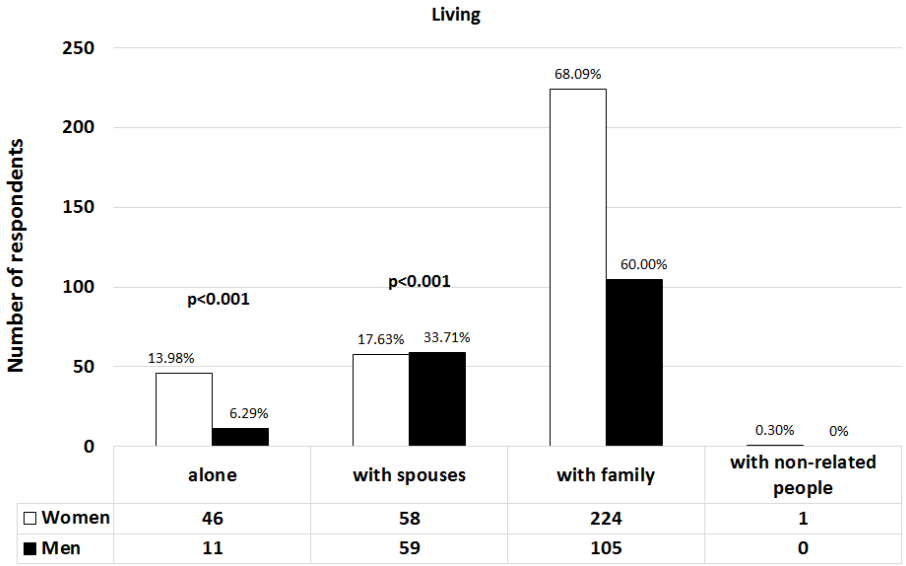

Figure 5. Living conditions of the examined respondents (N=504)

The respondents living with spouses were the youngest (average 76.40). They were followed by those who were older and living with family (77.43), those living alone (79.28), and with non-related people (81.00), respectively. The Kruskal-Wallis one-way analysis of variance indicated the existence of statistically significant age difference related to the living condition of the test group (the analysis excluded one person living with non-related people) - H (2, N = 503)=5.35; p<0.05). The Dunn's post-hoc test showed that all differences were statistically significant (p<0.01).

When asked whom they turn to to receive financial support if needed, the respondents most frequently indicated family (n=411; 81.55%) or spouse (n=147; 29.56%). One out of ten indicated neighbours (n=49; 9.72%), very few would use social care (n=11, 2.18 %), or other people or institutions (n=3; 0.60%). Among those who indicated spouses as persons providing support, 73 individuals (14.88%) would not mark any other option. It is noteworthy that 37 people took advantage of social care (7.34% of the test group). 32 persons in the test group (86.39% who used social care aid) used only one form of support, 4 (10.81%) used two forms and 1 (2.70%) would benefit from three forms of support. The interviewees most frequently got financial aid (n=26; 70.27%) or non-financial aid (n=14; 37.84%). Care services were used by 1 person (2.70%) and meal sponsoring by 2 respondents (5.41%). Additionally, 24 people (64.86%) claimed that the social care aid was insufficient, 10 people thought it to be sufficient (27.03%), and 3 people (8.11%) refrained from answering the question.

It was shown that women, more frequently than men, pointed to the aid received from family (p<0.001). Men would more frequently indicate that their wives were a source of aid (p<0.001) (fig. 6).

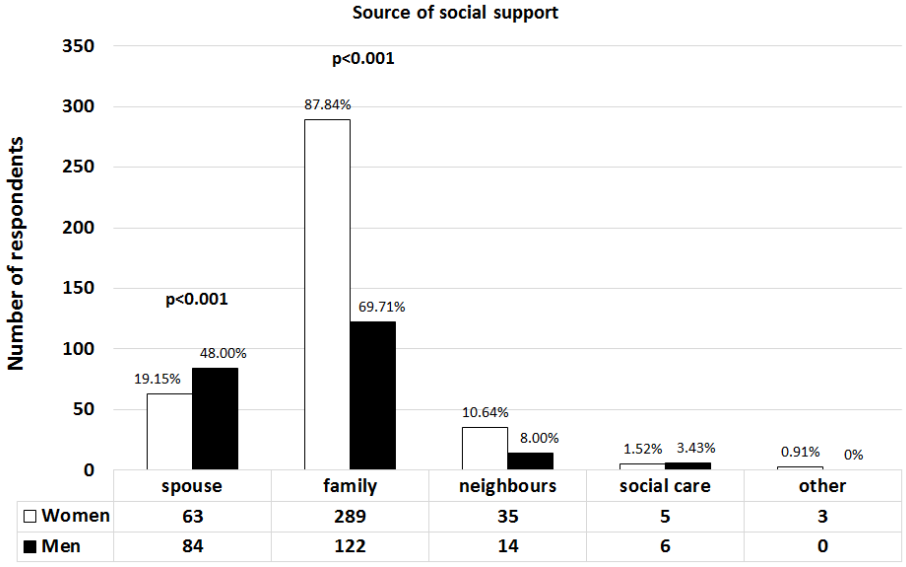

Figure 6. Source of social support vs. sex of respondents (N=504)

While comparing various sources of aid, it was shown that women would more frequently take advantage of one ($p<0.05$), and men – of two ($p<0.05$) sources of support. As for the respondents using social services, there were 19 women (51.35%) and 18 men (48.65%). They constituted appropriately 5.78% of the total number of women and 10.29% of men in the test group. The way both sexes used the social support was not statistically significant ($p<0.10$).

Further, the interviewees who indicated that their spouses were the persons who provided support were younger (average age 75.64) than other respondents and this difference was statistically significant ($p<0.001$). Those who used family's support (mean age 77.63 years) were a little older. So were those who relied on social services (77.82 years) and neighbours (78.04 years). These differences, however, were not statistically significant. The highest age mean was visible in persons who used one source of support (77.64). The higher the number of sources of support, the lower the mean age of the interviewees – up to 73.00 (4 sources of support); nonetheless, the observed differences were not statistically significant ($p>0.10$).

The age of the respondents using social care services was in the range of 66 to 92 (mean age 77.03, SD=6.83; Median=78). No age differences were observed in the respondents benefiting from social care services (n=37), and the rest of the investigated group (n=467) ($p>0.10$). As for the state of family relationships, the answers were provided by the most respondents (n=336; 66.67%), who would see them as "good". 97 interviewees (19.25%) would rate them as "very good". 60 respondents (11.90%) would see their relationships with families as "neutral" and 11 people (2.18%) – as "bad". No correlation between sex and the state of family relationships was observed ($p>0.10$). There was also no correlation between the state of the relationship and age variables ($p>0.10$).

Discussion

A number of demographic studies conducted by various authors have shown that both in Poland and other countries in the world the number of women in older age groups is significantly growing [9, 5, 10]. Following the statistical data, women more often live alone and assess their health condition as worse. Also, the financial benefits they receive are lower than those of men [10].

This tendency of ageing process was also confirmed in our study. In the older age categories, women were dominant, their age was significantly higher than the age of men. Women were also more often widowed and lived alone. However, the analysis of the financial situation and needs satisfied by the provided benefits showed no significant differences between women and men. Both women (54.10%) and men (48.00%) claimed that the received benefits did not fully cover their current needs. This may be a consequence of very low pensions and illness benefits in agriculture both for women and men, which, regardless of sex, put seniors residing in rural areas in disadvantageous financial condition.

The housing environment of seniors significantly influences the ageing process. Lack of appropriate adaptations to the needs of seniors, discrimination, lack of or inappropriate support contribute to pathological ageing and disability. By contrast, friendly environment, proper relationships, bonds and support lead to better functional efficiency of seniors, a slower ageing process and reduction of the risk of disability [11]. It is believed that people, regardless of their age, meet most important needs within their family. For older persons, family is the primary source of support and care and the main living activity, where family relationships are a vital source of satisfaction [12].

A number of studies by various authors showed that the elderly residing in rural areas mostly live with their families positively assess the resulting research data family relationships, and seek support and aid mainly from their family [12- 16]. This study confirmed these observations because as it was shown that merely 11.31% of seniors residing in rural areas lived alone. The remaining ones lived with family (65.28%) or spouses (23.21%). A vast majority assessed the family relationship as good (66.67%) or very good (19.25%). Only 11.90% of the respondents acknowledged that the relationships were neutral or bad (2.18%). Similarly, most people indicated that support can be obtained most frequently in family (81.55%) or provided by a spouse (29.17%).

It is believed that the decisive factors influencing the independent functioning of seniors is due to the housing conditions, which provide safety and independence [17]. In the presented study, most respondents rated their housing conditions as good (46.43%) or very good (28.17%), 23.61% of them saw their housing conditions as average, and only 1.79% claimed they were bad. It was noticed that people rating own housing conditions as bad and average were older than those assessing them as very good and good.

Based on the research carried out in the multicenter European project COPE, one can say that the care of disabled seniors in their home environment relies mainly on family care [18]. Following the Polish Central Statistical Office (GUS) forecast for years 2008-2035, the size of households will be decreasing (from 2.64 to 2.42

people per household), the percentage of single households will increase (from 26.9% to 32.5%), two-person households (from 26.5% to 28.7%) and childless households (from 65.6% to 75.8%). All this will impact family care capabilities negatively and the simultaneously forecasted increase in the number of seniors incapable of independent living will cause that support and help of others will be required [19]. Such circumstances enforce and will enforce a different approach to the elderly in future. Healthcare systems and social care units will have to take care of seniors; thus, causing that new guidelines on seniors' care will have to be compiled and issued [20]. It is of utmost importance that social care provided to seniors should be preceded by detailed identification of their needs and aimed at fulfilling these needs [21].

Previously, the study by Makara-Studzińska [22], based on the research of 250 seniors living in rural areas, revealed that rural areas generally lacked on rehabilitation, treatment and prevention centres in close vicinity to old peoples' homes. The health-related education, promotion of healthy lifestyles and social security are insufficient in rural areas [22]. In our study, we found that as few as 37 respondents (7.34%) used benefits of social services and the most frequently mentioned ones included: financial aid (26; 70.27% of all the respondents using social aid) or non-financial aid (14; 37.84%). Only one person (2.70%) took advantage of special care services, and two persons (5.41%) had their meal sponsored. Moreover, 24 people (64.86 %) claimed that social care aid was insufficient. Unfortunately, the data provided no correlation of age to sex and social care benefits in the tested groups.

Generally, it may be stated that rural environment is a very specific environment where apart from various advantages, including positive influence of natural environment and good family relationships, there are numerous impediments, namely low financial benefits and limited access to social services. Therefore, the planning of seniors' care in rural areas must necessarily take into account the specificity of living in the agricultural environment. The results suggest there should be better access to social care for seniors residing in rural areas (the most of all the special care services) and such aid should be synchronised with geriatric health care services. All this would enable rational provision of social care support regarding necessary demand.

Conclusions

1. Older women living in rural areas more frequently live alone, are widowed and have lower educational level than men.
2. All financial benefits do not fully cover current needs of older residents in rural areas.
3. In people of over 65 years living in rural areas, the majority (81.55%) indicated the family support and only 2.18% indicated the social care as the source of support.

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REVIEW OF RESEARCH ON ALCOHOL DEPENDENCE IN A MODEL OF MICE SELECTED FOR HIGH AND LOW STRESS-INDUCED ANALGESIA

PRZEGLĄD BADAŃ NAD UZALEŻNIENIEM OD ALKOHOLU W MODELU MYSZY SELEKCJONOWANYCH W KIERUNKU WYSOKIEJ I NISKIEJ ANALGEZJI POSTRESOWEJ

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A. Study design/planning
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B. Data collection/entry
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Summary

Decades of studies on alcohol dependence showed that it is a very complex and multifactorial disorder. Several receptor systems are involved in development and susceptibility to alcohol abuse; however, there are some which play a crucial role in its pathogenesis, e.g. dopaminergic or opioid system. In this paper, an effort is made to explain the role of endogenous opioid system activity in alcohol dependence. To achieve the goal, we use a unique model is used which shows mice lines that are divergently selected for high (HA) and low (LA) stress-induced analgesia. This process allowed for selecting individuals characterised by hyperactive (HA) or hypoactive (LA) opioid system. Basing on the performed experiments, we proved that delta opioid receptors play a critical role in the development of addiction. The most notable achievement is an unspecific reaction of mice with the hyperactive opioid system to naloxone – an unspecific opioid system antagonist, which is currently approved in the pharmacotherapy of dependent patients.

Keywords: alcohol abuse, selected mouse lines, opioid system

Streszczenie

Uzależnienie od alkoholu jest chorobą wieloczynnikową, za której etiologię odpowiedzialnych jest kilka mechanizmów. Wieloletnie badania pozwoliły na zidentyfikowanie kilku układów receptorowych, które są zaangażowane w rozwój oraz podatność do uzależnienia od alkoholu, jednakże niektóre z nich odgrywają krytyczną rolę w jego patogenezie np. układ dopaminergiczny lub opioidowy. W niniejszym artykule przedstawiamy wyniki badań, których celem było określenie roli endogennej aktywności układu opioidowego w uzależnieniu od alkoholu. Do realizacji tego celu wykorzystano unikalny model myszy selekcjonowanych w kierunku wysokiej (HA) oraz niskiej (LA) analgezji postresowej. Proces selekcji pozwolił na wybranie osobników charakteryzujących się wysoką (HA) oraz niską (LA) aktywnością układu opioidowego. Na podstawie przeprowadzonych eksperymentów, udowodniliśmy krytyczną rolę receptorów opioidowych typu delta w rozwoju uzależnienia od alkoholu. Godnym uwagi osiągnięciem było wykazanie niespecyficznej reakcji myszy o wysokiej aktywności układu opioidowego na nalokson – niespecyficznego antagonistę receptorów opioidowych, który jest aktualnie używany w farmakoterapii uzależnionych pacjentów.

Słowa kluczowe: uzależnienie od alkoholu, selekcjonowane linie myszy, układ opioidowy

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Introduction

Alcohol dependence is a multi-stage relapsing disorder, whose etiology is not fully understood. It is believed that several mechanisms are engaged in the development and course of alcohol illness. The complexity of this disorder manifests itself by the involvement of several receptor systems (glutaminergic, GABAergic, opioid, cannabinoid, dopaminergic, cholinergic, serotonergic) in mediating the rewarding and reinforcing effects of ethanol [1,2,3]. The abovementioned stages of which alcohol abuse consists of are: I – initiation of ethanol

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consumption, II – maintenance of consumption, III – craving and IV – relapse. It is environmental factors (i.e. stress) that are mainly responsible for the first phase of alcohol dependence. The further stage is caused by genetic factors (i.e. polymorphisms in alcohol metabolism genes) or genetic-environmental factors interactions. Craving or reinstatement of reward results from neuroadaptations, mainly in glutaminergic and GABAergic transmission, occurring during chronic ethanol ingestion [4,5,6]. As there is no effective pharmacotherapy of dependent patients, most of them return to alcohol drinking within three-years after the therapy [7].

The impact of the opioid system neurotransmission on the development and course of alcohol dependence is well-documented, hence experiments in which mouse characterised by high and low endogenous opioid system activity are used may help in better understanding of its role in the addiction process or trying to develop some new pharmacotherapies [3,8]. This model is well documented in the subjects with alcohol dependence [9,10,11], effects of chronic mild stress (CMS) [12], melanoma growth [13,14], and morphine efficacy [15]. It was developed on the basis of differences in the level of stress-induced analgesia (SSIA) resulting from the opioid system activity [16]. Thence two contrary lines were established: high-analgesia (HA), characterised by very high phenomenon of SSIA and low-analgesia (LA). Despite different endogenous opioid system activity, both lines have distinct blood-brain barrier (BBB) permeability [17]. Opposing to LA mice, HA mice have a very low selectivity of the BBB, which is the effect of lower expression of cell adhesion proteins – claudins and occludins [18].

To this date, over 90 generations of HA and LA were bred and selection is still maintained according to the protocol outlined in the Institute of Genetic of Animal Breeding of Polish Academy of Sciences [16,19]. In this paper, current findings on alcohol dependence in this unique model are presented. Secondly, the issue of morphine tolerance is discussed.

Aim of the work

The goal of this paper is to show current findings on alcohol dependence in this unique model of mice.

Alcohol dependence in HA and LA mice

As it was mentioned above after many years of research, it is well-documented that opioid system plays a critical role in the development of ethanol dependence and further ethanol consumption [3,20]. Activation of specific types of opioid receptors, after alcohol administration, may result in producing rewarding (delta and mu opioid receptors activation) or aversive (kappa opioid receptors activation) effects [21,22]. Due to high differences in endogenous opioid system activity, HA and LA mice were proposed as a good model to study the effect of this receptor system in ethanol dependence [9]. However, these lines cannot be considered as alcohol preferring and non-preferring lines, because of aversion to 8% alcohol and low difference of ethanol preference between them; approximately 25% preference in LA and 10% in HA mice in normal conditions [9]. Additionally, metabolism of alcohol is on the same level in both lines, which was assessed by measuring blood ethanol concentration (BEC) [10].

The first study performed on HA and LA lines on ethanol dependence proved that the congenital difference in endogenous opioid system activity causes differences in ethanol intake. In normal conditions, hyperactivity of this receptor system slightly decreases the daily consumed amount of ethanol [9]. Applying chronic mild stress (CMS) conditions causes that the LA mice are more likely to drink ethanol – almost 5 times more than in normal conditions, while there was no change of preference in the HA strain. Therefore, it has been postulated that CMS reveals a hidden phenotype, where a low endogenous activity of the opioid system plays a critical role in the predisposition to the development of alcohol dependence [9]. Further studies showed that a chronic stress stimulus leads to the development of depressive-like behaviour only in the mice characterised by a high endogenous activity of the opioid system, which was assessed in a tail-suspension test (TST). Moreover, the hot-plate test (HP) revealed that stressful conditions are responsible for a slight increase of nociception in the HA mice, whereas there was no such effect in the LA mice. Ingestion of small doses of ethanol by the high analgesia mice caused an attenuation of CMS-induced depressive-like behaviour and pain perception [12].

Sequencing the *Oprd1* gene, which codes delta opioid receptors, revealed an interesting transition C320T resulting in an A107V substitution, present in the colony of HA and LA mice [10]. In both lines, individuals with the CT genotype demonstrate an increased ethanol intake and preference, both in normal and CMS conditions, but the genotype effect is more significant in the mice with the endogenously hypoactive opioid system. Similarly to the previous studies, the development of depressive-like behaviour was defined by TST. After ingestion of ethanol under normal conditions, immobility time during TST remained unchanged in both genotypes of HA and LA mice. However, under stressful conditions, the presence of C320T transition results in a lower anti-

depressive effect of ethanol in the HA mice. Surprisingly, in the CT LA mice, ethanol caused pro-depressive effect despite a small effect of CMS [10].

The latest study performed on these divergently selected mouse lines focused on determining the role of endogenous opioid system activity and the subtypes of opioid receptors in the development of alcohol dependence [11]. Non-selective pharmacological antagonism of the opioid system by intraperitoneal administration of naloxone (NLX) resulted in a drastic increase of ethanol intake and preference in mice with a hyperactive opioid system. The development of depressive-like and anxiety-like behaviour, assessed in the TST and elevated-plus maze test (EPM), was observed during NLX therapy in HA mice, which may be a possible mechanism responsible for their high increase of ethanol consumption parameters. Ethanol ingestion had an anti-depressive and anxiolytic effect making individuals feel better and leading to uncontrolled ethanol consumption. This result is very interesting, as it points to a danger of using other non-selective antagonist of the opioid system – naltrexone, which is FDA approved drug in the therapy of alcohol-dependent patients [11]. However, stimulation of this receptor system by morphine caused slight attenuation of ethanol self-administration in both lines, but in the HA mice, the effect was more pronounced [Unpublished data].

An administration of a selective DOR antagonist – naltrindole (NTI), resulted in a very high increase of ethanol intake and preference – almost 90% preference for ethanol in HA mice, while no effect of DOR blockade was observed in LA mice. Results from other studies on DOR impact on ethanol consumption are not consistent. Some studies point out that the blockage of DOR or knock out of DOR gene induces ethanol intake [23,24,25]. However, there are also many studies reporting that treatment by DOR specific antagonists causes attenuation of ethanol drinking parameters [26,27,28,29]. Differences may result from different animal models used in the experiments but also because of the presence of $delta_1$ and $delta_2$, which have an opposing effect on ethanol consumption [30]. Moreover, the administration of NTI to CT heterozygotes of both lines caused no effect, despite their higher basal ethanol preference. It has been proven that C320T transition causes dysfunction of the DOR, resulting in the absence of NTI effect on ethanol consumption [10,11]. While comparing the studies by Sacharczuk et al. and Poznanski et al., different degree in response to congenital dysfunction and pharmacological blockage between HA and LA mice is explained by the possibility of compensation of delta opioid receptors dysfunction by mu opioid receptors in HA individuals with C320T transition, hence the genetic effect is more significant in LA mice. Additionally, pharmacological antagonism is 'artificial' at a specific point in time, thus there is no compensation mechanism established, and effect of the pharmacological blockade is more significant in HA mice [10,11].

Using cyprodime (CYP) – a selective MOR antagonist, induced an effect in the same manner as DOR blockage but with lower efficiency. This result is not consistent with other studies considering MOR blockage or MOR KO mice [31,32,33]. It has been proposed that difference may be a result of the development of the compensatory mechanism, which may neutralise the lack of rewarding the effect of endogenous opioids [11].

The antagonism of third opioid receptor subtype – KOR, by nor-Binaltorphinine slightly brought down ethanol intake and preference [11]. A number of pharmacological and knock-out studies indicate that impairment of dynorphin/kappa opioid receptor system causes attenuation of voluntary ethanol consumption [34,35,36,37,38]. Morales et al. observed that nor-Binaltorphimine attenuated a voluntary ethanol intake in female adults. They concluded that it might be related to sex differences in response to stressful situations (e.g. isolate-housing) [38]. Another publication reported that a systemic administration of nor-Binaltorphimine causes attenuation of ethanol consumption only in ethanol-dependent animals, while there was no effect in nondependent individuals [36]. Also, mice lacking kappa opioid receptors or preprodynorphin displayed a lower ethanol intake than their wild-type counterparts [34,35].

To this date, studies on alcohol dependence performed on HA and LA mice confirmed that the opioid system plays an essential role in the risk of occurrence and course of alcohol dependence. They also showed that the role of the interaction between genetic risk factors (low endogenous opioid system activity) and environmental factors (chronic mild stress) is critical in the development of ethanol dependence [9,10,11,12,39]. Also, it has been proven that DOR plays a major role in the development and course of alcohol illness [10,11]. The results obtained from these dependence studies may also lead to the explanation of the low therapeutic effect of nonselective antagonists of the opioid system in the pharmacotherapy of addicts. Ineffectiveness of this drug has been explained by blockage of all subtypes of opioid receptors, which have a different influence on ethanol intake [11]. Summarising, alcohol dependence is a very complex disorder and its pharmacotherapy should be personalised to avoid severe consequences as it was shown by using the non-selective opioid antagonist.

Morphine tolerance in HA and LA mice

Another issue related to dependence studied in HA and LA mice was the phenomenon of tolerance. Both lines were examined for tolerance to morphine-, stress-induced analgesia and cross-tolerance between them. Panocka et al. showed that an approximately 2-week period of everyday swimming can cause tolerance to stress-induced analgesia in mice. By applying more severe procedure of chronic stress (swimming every 2h for 2 days), it is possible to produce cross-tolerance to analgesic effect of morphine. They explained this phenomenon by continuous ligand binding to opioid receptors which causes their desensitisation during harsher stress procedure [15]. Repeated injections of morphine also produced tolerance, resulting in decreased analgesia effect of this drug. HA mice are more sensitive to morphine-induced analgesia approximately 4-fold, despite that there were no differences in the degree of tolerance to morphine between HA and LA mice [40]. Further studies, in which a nonclassical model of dependence was used, showed that despite genetic differences between both lines, there were no differences in the degree of morphine dependence [41].

Conclusions

We concluded that due to very unique characteristics of HA and LA mice such as a different endogenous opioid system activity and differences in blood-brain barrier structure, they can be used in a broad spectrum of medical studies such as alcohol dependence, pain or melanoma studies. Studies on our model showed that the naloxone, an FDA approved the drug, can be very dangerous in the therapy of people with enhanced opioid system activity. Also, our results indicate that pharmacotherapy of alcohol-dependent patients is very complicated due to individual traits in patients. Accordingly, it should be personalised in the most cases.

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IMPORTANCE OF CANNABINOIDS IN THE FUNCTIONING OF THE CENTRAL NERVOUS SYSTEM

ZNACZENIE KANNABINOIDÓW W FUNKCJONOWANIU OŚRODKOWEGO UKŁADU NERWOWEGO

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C. Data analysis/statistics
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D. Data interpretation
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Summary

At present, there is a great emphasis of public opinion on the legalisation of medical marijuana, i.e. the top parts of the cannabis plants rich in tetrahydrocannabinol (THC). Nevertheless, in the cannabis plants, there are many various cannabinoids, including cannabidiol (CBD). Scientific reports to-date indicate the possibility for using pharmacologically active cannabinoids in the treatment of such diseases/symptoms as: anorexia, vomiting, neuropathic pain, inflammatory diseases, multiple sclerosis, degenerative diseases of the central nervous system (Parkinson's disease, Huntington's disease, Alzheimer's disease, Tourette's syndrome), epilepsy, schizophrenia, and obesity. The article presents up-to-date information on the results of experimental studies concerning the effectiveness of cannabinoids, with particular consideration of diseases related with the central nervous system, including epilepsy, neuropathic pain, mental disorders, as well as obesity and anorexia.

Keywords: cannabinoids, central nervous system, brain diseases

Streszczenie

Aktualnie obserwuje się duży nacisk opinii społecznej na legalizację medycznej marihuany, czyli szczytowych części roślin konopi indyjskich bogatych w tetrahydrokannabinol (THC). Tymczasem, w konopiach jest wiele różnych kannabinoidów, między innymi kannabidiol (CBD). Aktualne doniesienia naukowe wskazują na możliwość wykorzystania farmakologicznej aktywności kannabinoidów w obszarze leczenia takich chorób/ objawów jak: anoreksja, wymioty, ból neurogenny, choroby zapalne, stwardnienie rozsiane, choroby degeneracyjne ośrodkowego układu nerwowego (choroba Parkinsona, Huntingtona, Alzheimera oraz zespół Tourette'a), padaczka, schizofrenia, otyłość. W pracy przedstawiono aktualne informacje na temat wyników prowadzonych dotychczas badań nad skutecznością kannabinoidów, ze szczególnym uwzględnieniem chorób związanych z ośrodkowym układem nerwowym, w tym: padaczką, bólem neuropatycznym, chorobami psychicznymi oraz otyłością i anoreksją.

Słowa kluczowe: kannabinoidy, ośrodkowy układ nerwowy, choroby mózgu

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Introduction

In the *Cannabis sativa* plants there occur more than 400 various substances belonging to more than a dozen chemical groups: carbohydrates, terpenes, fatty acids, steroids, heterocyclic compounds containing nitrogen, and cannabinoids, i.e. tricyclic benzopyran derivatives containing 21 carbon atoms.

Cannabinoids are a group of more than 100 organic compounds exerting an effect on cannabinoid receptors (CB). For the first time, these compounds were isolated from the herbaceous plant in the *Cannabis* genus. At present, this group includes cannabinoids known as phytocannabinoids (including Δ9–tetrahydroxycannabidiol (THC), Δ8–THC, tetrahydrocannabivarin, cannabinol, cannabidiolic acid, cannabidiol, cannabigerol, and cannabichromene), cannabinoids naturally occurring in plants and animals organisms, including humans – so-called endocannabinoids (i.e., N-arachidonoylethanolamine AEA = anandamide, 2-arachidonyloglycerol = 2-AG), and synthetic cannabinoids made in laboratories (including, marinol, nabilone, and rimonabant applied in medical treatment) [1].

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The content of cannabinoids in the plant varies according to the phase of the life cycle. In the vegetative phase dominate: cannabinol (CBN), cannabidiolic acid (CBDA), and tetrahydroxycannabidiolic acid (THCA). In the vegetative phase, in the flowering period, THC prevails, which is converted into cannabidiol (CBD) and cannabigerol (CBG) [2].

Natural cannabinoids are chemical compounds which show pharmacological activity [3]. THC is famous for psychoactive properties [4], while CBD is not psychoactive; however, shows anti-inflammatory properties, protects neurons against damage or degeneration, decreases anxiety, alleviates drug hunger, and has anti-psychotic properties. Current scientific reports indicate the possibility of use of pharmacologically active cannabinoids in the treatment of such diseases/symptoms as anorexia, vomiting, neuropathic pain, inflammatory diseases, multiple sclerosis, degenerative diseases of the central nervous system (Parkinson's disease, Huntington's disease, Tourette's syndrome, Alzheimer's disease), epilepsy, schizophrenia, cancer, obesity, and selected metabolic diseases [5,6].

Aim of the work

The following work aims to present the potential of cannabinoids in the treatment of diseases associated with the central nervous system.

Cannabinoid receptors

Until today, the presence of two sub-types of cannabinoid receptors (CB1 and CB2) has been confirmed, which belong to the group of metabotropic receptors linked with G protein [7].

The studies conducted to-date allowed determination of the structure of CB receptors, their localisation and changes in pharmacological effects related to their selectivity and affinity. Acting on the CB1 receptor (constructed of 472 amino acids, 7 transmembrane domains) is combined with the multi-directional activation of metabolic paths. These receptors are located presynaptically on the surface of the neurons of the central and peripheral nervous system, adipose tissue, gastrointestinal tract, muscles, heart, lungs, liver, kidneys, testicles, ovaries, prostate, as well as cells of the immune system and in the placenta [8,9]. Expression of these receptors was also confirmed in the eye, astrocytes, glial cells, and in the anterior lobe of the pituitary gland [10]. In the brain, there also occurs the sub-type CB1A receptors [11]. The structure of CB2 receptor is similar to that of CB1 receptor (constructed of 360 amino acids and 7 transmembrane domains). These receptors are located on haematopoietic cells, keratocytes, the immune system, NK cells (Natural Killers), B lymphocytes, T lymphocytes, monocytes, macrophages, mast cells, and in the spleen and tonsils [12,13,14]. Onaivi [15] has reported the discovery and functional presence of CB2 cannabinoid receptors in the mammalian brain that may be involved in depression and drug abuse [15]. The stimulation of CB2 receptors leads to a decrease in the sensation of pain and alleviation of inflammatory states. Compounds which show affinity to CB1 and CB2 receptors may be classified into natural cannabinoids present in extracts from *Cannabis*, synthetic cannabinoids, and endocannabinoids, which are synthesised in the body of mammals. Considering their structure, CB1 and CB2 receptors show 44% homology [16]. There is evidence indicating the presence of the cannabinoid CBx receptor in the brain [17].

Analgesic effect

The cannabinoid system plays an essential role in the process of antinociception (blocking pain sensation). Cannabinoids reduce acute and chronic pain of various aetiology (post-operative, cancer, migraine, neuropathic, rheumatic). The main problem is their psychotropic action. Therefore, the perspective to use selective CB2 receptor agonists is promising, which also have analgesic effect and, at the same time, are free from central undesirable effects [18]. It was observed that the mixture of THC and CBD has the capability of blocking platelet release of serotonin which occurs in the attacks of migraine [19]. In the treatment of neuropathic pain, a better effect was observed for the mixture of THC and CBD, than for the THC alone [20]. The applied mixture was well tolerated and also effective in reducing difficulty in falling asleep [21].

Regulation of food intake

The effect of cannabinoids in the treatment of obesity, anorexia and inhibition of vomiting is associated with antagonism of cannabinoid CB1 receptor, which is ascribed to participation in the possibility of controlling the satiety centre in the hypothalamus, regulation of metabolism and, in consequence, body weight control [22,23]. Probably, the cannabinoid system controls two types of food intake. In the limbic system, there exists a

regulation of intake of tasty food, which is a source of pleasure. In the hypothalamus, the regulation of appetite 'on demand' is a direct response to short-term starvation. Leptin decreases the activity of the cannabinoid system in the hypothalamus. An increase in the concentration of anandamide in the hypothalamus was observed in animals with the defect of leptin receptor. Leptin applied in genetically obese mice caused a decrease in the concentration of endocannabinoids in the hypothalamus [24]. This confirms the relationship between the activity of leptin and the endocannabinoid system [25]. The cannabinoid system creates the orexigenic path, which is probably an alternative to the classical path, controlled via the neuropeptide Y. This may explain the increase in appetite, especially for sweets, observed in hashish and marijuana smokers. The cannabinoid path, similar to the classical, remains under the negative control of leptin [18]. In the regulation of appetite, the main role is ascribed to CB1 receptors present in large numbers in the hypothalamic regions controlling the process of food intake: in the lateral hypothalamus, para-ventricular nucleus, and arcuate nucleus. Their expression was observed on the crucial for this process peptidergic neurons that secrete corticotropin releasing hormone (CRH) in para-ventricular nucleus, and melanin-concentrating hormone (MCH) [26]. A high density of CB1 receptors was additionally observed in the mesolimbic system, which also regulates appetite, participating in the motivational processes and processes of behavioural activation in response to the rewarding agents. This is probably the key point of capture because many data show that cannabinoids increase appetite by enhancing the positively strengthening (rewarding) effect of food. This effect results from the intensification of dopaminergic transmission in the mesolimbic system and may be partly conditioned by interaction with the opioid system [27]. The possibility of an intensification of hedonistic response caused by food is supported by the observation that products activating endocannabinoids, e.g. chocolate, are known for their rewarding properties [28]. Since the beginning of the 1970s, many clinical studies have been conducted concerning the use of cannabis and CB1 receptor agonists in the state of decreased appetite. The result of these studies is the indication for the use of Dronabinol® and nabilone (Cesamet®) in the treatment of anorexia in patients with cancer or AIDS [29]. Apart from the effect on the hedonist aspect of eating, they have anti-vomiting action and regulate the motility of the gastrointestinal tract. In patients with cancer, while applying chemotherapy and the treatment of cachexia syndrome in the course of AIDS, these properties have become a basis for the administration of dronabinol, and its synthetic derivative — nabilone [30].

At present, the possibility for using compounds blocking the CB1 receptor in the treatment of obesity evokes much hope. In various experimental models, including animals with genetically conditioned obesity, and obesity caused by high-caloric diet (i.e., diet-induced obesity), an anorectic effect of selective CB1 receptor antagonist SR141716A (Rimonabant®) was confirmed. Thus, the central action of cannabinoids seems to be the most frequent cause of obesity in humans. In rats and mice on diet-induced obesity, SR 141716A also corrected the concomitant hyperglycaemia, decreased insulin resistance, reduced the level of plasma insulin, and normalised lipid profile [31]. In 2001, Sanofi–Synthelabo presented the results of phase II clinical studies evaluating rimonabant. A considerable decrease was noted in the feeling of hunger, food intake, and body weight, with no effect on the sense of taste. The reduction of body weight did not achieve a plateau during 4–month administration, and the preparation was well tolerated. At present, rimonabant is at phase III clinical studies including also obese patients with concomitant diseases, such as type 2 diabetes and dyslipidaemia [32].

Mental disorders

Mood swings are clearly visible in hashish and marijuana smokers, THC produces euphoria, but there also occur the states of dysphoria, which may be accompanied by fear, or even panic attacks. Sometimes, a clear anxiolytic effect is observed. It is considered that the direction of mood swing depends on wellbeing at the moment of intake of THC, dose, and route of administration. Studies on animals confirm the engagement of the cannabinoid system in the control of emotional states. In mice, an enhancement of fear, aggression and anhedonia are observed. Paradoxically, CB1 receptor antagonist SR141716A exerts an anxiolytic effect, which may suggest the presence of another receptor controlling the fear response [33]. It is also probable that the antagonistic effect results from mechanisms which are independent of the cannabinoid system.

The CB1 receptors are present in many brain structures responsible for perception and expression of emotions: in the amygdala, septum, hippocampus, frontal and prefrontal cortex [34]. The result of their stimulation are changes in the concentrations of transmitters related in an antagonistic way with fear reaction. Cannabinoids inhibit the release of glutamic acid, which is a stimulating amino acid in the hippocampus, as well as in the amygdala [33]. However, on the other hand, cannabinoids produce effects which may induce fear: reduce the activity of GABAergic neurons in the amygdala and hippocampus, which leads to the disinhibition of glutamatergic and dopaminergic transmission in the frontal cortex and the amygdala, and also stimulate the hypothalamic-pituitary-adrenal axis responsible for neuroendocrine response in conditions of emotional stress

[35]. Based on these premises, in the group of CB1 receptor antagonists, potential neuroleptic drugs may be sought. The confirmation of this hypothesis is the anti-psychotic effect of cannabidiol [36].

CBD shows a wide range of therapeutic effects, including anxiolytic, anti-depressive and neuroprotective, within a wide scope of mental and neurodegenerative disorders [37,38]. Studies conducted based on neuroimaging showed that CBD affects the regions of the brain engaged in the neurobiology of psychiatric disorders [39].

Pre-clinical and clinical studies indicate that CBD is also potentially important in schizophrenia. CBD attenuates behavioural disorders related to schizophrenia [40,41]. Its effect is similar to that of atypical anti-psychotic drugs [42]. In humans, anti-psychotic properties of CBD were confirmed by the method of a double-blind clinical trial, where CBD reduced psychotic symptoms with effectiveness similar to that of an atypical anti-psychotic drug – amisulpride; however, with a considerably smaller number of side-effects [6]. Cannabidiol (CBD) has a wide range of beneficial effects in mental disorders [43]. CBD may modulate euphoric effects after taking THC, has a neuroprotective, anxiolytic effect, supporting the treatment of addiction to alcohol and nicotine [44]. Cannabidiol has anti-psychotic properties. Studies on animals [45] showed that CBD has a pharmacological profile similar to that of atypical anti-psychotic drugs. This includes neurochemical action and an effect on the patient's behaviour. Examinations performed using magnetic resonance imaging indicated that the effect of this compound takes place in the area of the striatum and temporal cortex. However, the mechanism of action has not been fully recognised. In 2014, it was confirmed that CBD exerts also a beneficial effect in the states of anxiety and depression [46]. The application of cannabinoids in bipolar disease caused the limitation in patients of the episodes of depression and persecution mania [47].

Neuroprotection is an essential mechanism of the effect of psychiatric drugs, protecting the structure and function of the nerve cells, promoting and protecting against oxidative stress, or an inflammatory process [48].

Motor disorders, spasticity

Natural and synthetic cannabinoids have a clear effect on motor functions. In small doses, they produce stimulation, whereas in high doses – motor depression or even catalepsy. This is conditioned by a high density of CB1 receptors in the cerebral cortex and the cerebellum, where the superior motor structures are located, and in the basal ganglia which are very significant in the processes of activation of voluntary movements, as well as in the mechanisms of maintaining skeletal muscle tone. Cannabinoids interfere in glutamatergic, GABAergic and dopaminergic neuronal paths, which may have important consequences for the therapy of Parkinson's disease, Huntington's disease, Tourette's syndrome, dystonia and spasticity occurring in multiple sclerosis (MS) and spinal cord injury [27,49].

The effect of cannabinoids has been best examined in multiple sclerosis. THC and nabilone result in the regression or alleviation of spasticity, night pain in legs, tremors, nycturia, paraesthesia, equilibrium disorders and memory. In the experimental MS model on animals, both CB1 and CB2 receptor agonists show a therapeutic effect, while their effect is eliminated by the selective antagonists of these receptors. In an experimental model of MS in mice, an increase in the concentration of AEA and 2–AG was observed in the brain and spinal cord, and elimination of spasticity under the effect of reuptake inhibitor. In turn, CB1 receptor antagonist enhances pathological symptoms. This may suggest that an increase in the concentration of endocannabinoids is the compensatory mechanism, activated in the course of MS [50]. Alleviation of spasticity may be explained by intensification of GABAergic transmission resulting from the inhibition of glutamate release [49].

The potential of cannabinoids in the treatment of Parkinson's disease is attributed to their neuroprotective effect against 6-hydroxydopamine, which has been confirmed in studies *in vitro* and *in vivo* [51]. CB receptors antagonists and agonists are said to effect the change in the symptoms of Parkinsonism, such as levodopa-induced dyskinesia, and the reduction of dystonia. The role of cannabinoids in the treatment of Huntington's disease is associated with the agonist effect of cannabinoid compounds on CB1 receptors leading to the reduction of hyperactivity [52]. In patients with Tourette's syndrome, after the administration of THC, the reduction of ticks was observed, without causing acute and long-lasting cognitive deficits [53].

Epilepsy

The history of the use of cannabis for therapeutic and industrial purposes goes back to 2000 BC. In 1851, in the United States Pharmacopeia marijuana was classified as a legal medical agent, and many physicians supported its use in the treatment of epilepsy, chronic migraine and pain [54]. Reports by neurologists of the Victorian Epoch concerning the use of cannabis in the treatment of epilepsy were promising [55]. However, when phenobarbital and phenytoin were introduced to the market, the use of products based on marijuana decreased [56].

Epilepsy is a disease difficult to treat and, in this case, the drug containing cannabidiol has already started to be applied. In the United States, Epidiolex® containing CBD was developed which has the status of an orphan drug. Studies conducted in both adults and children indicate that CBD may improve the state of health and life comfort of patients with epilepsy [57]. It is postulated that the mechanism of action is related to the inhibition of glutamate release. The regulation of glutamatergic transmission may decrease the excitability of neurons, and consequently, reduce the frequency of seizure episodes. At the present stage of studies, it seems that a drug containing cannabidiol is a safe one. Studies of cannabinoids are a step towards the replacement of drugs with strong undesirable effects with drugs with a wide range of safe use [58].

According to up-to-date data, there are 65 million people suffering from epilepsy worldwide, and the incidence is 20–70 new cases per 10,000 population. The frequency of occurrence of epilepsy in children is 41–187/100,000 [59]. In 30% of patients, epilepsy remains drug-resistant despite the adequate pharmacological treatment applied. The first information in the media concerning the treatment with cannabinoids of children with Dravet syndrome occurred in 2013. A girl, Charlotte Figi, was administered a special oil (containing a high amount of CBD and low of THC, i.e. ratio 16:1) produced from the cannabis strain named Charlott's web [60]. Experimental studies indicate the possible anti-epileptic effect of cannabinoids, especially CBD. While evaluating the effectiveness of treatment with CBD, in the clinical studies, attention is usually paid to the reduction of the number of seizures easy to document, such as tonic seizures, atonic, and tonic-clonic seizures. The group of patients participating in double-blind, placebo-controlled trials covered a total of 48 patients, including 29, who received CBD. The dose of CBD was 200–300 mg/daily [61-64]. Except for one study, in which 2 out of 4 patients were free from seizures, in the remaining cases no satisfactory effects of treatment with CBD as add-on therapy were observed, and no significant differences were noted compared to the group of patients who received placebo [61,64]. The most frequently reported undesirable symptoms included: fatigue and sleepiness; diarrhoea and eating disorders. In a prospective clinical study, 9 out of 23 patients experienced more than 50% reduction in the frequency of seizures [65]. The mean reduction in the number of seizures was 32% at the dose of Epidiolex of 25 mg/kg/daily [65]. Moreover, Geffrey et al. [66] in 13 patients with drug-resistant epilepsy evaluated the effect of simultaneous administration of CBD and an antiepileptic drug – clobazam. A decrease in the concentration of CBD was an indication for decreasing the dose of clobazam. As a result of the administration of CBD, a 50–55% reduction of seizures was observed in 11/13 patients, while in 2/13 – an increased number of seizures [66]. Based on the results of studies, the use of CBD seems to be mainly valuable in the treatment of drug-resistant epilepsy in children [67]. In a retrospective study of 75 children and adolescents with epilepsy, who were administered extracts from cannabis, 57% of parents observed some improvement in the frequency of seizures by 33% - 50%. The parents have also noted an increase in the child's motility and behaviour; however, undesirable effects occurred such as sleepiness (12%) and gastrointestinal disorders (11%) [68].

Conclusions

Cannabinoids, mainly of plant origin (phytocannabinoids), seems to be very interesting biologically active compounds with many potential therapeutic properties. They are characterised by high safety considering the toxicity of compounds, while undesirable effects remain within the adopted standards. Studies concerning the therapeutic effect of cannabinoids are more common than at any time previously in history. There is an increasing number of studies indicating that the cannabis plant or single cannabinoids may have therapeutic properties for selected neurological diseases in specified conditions.

Conflict of interests

The authors state that there is no conflict of interests.

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- Tytuł (w j. polskim i j. angielskim)
- Słowa kluczowe (z Medical Subject Headings [MeSH], katalog Index Medicus; w j. polskim i j. angielskim)
- Streszczenie (150-250 słów, w j. polskim i j. angielskim, podzielone na części)
- Wprowadzenie
- Materiał i metody
- Wyniki
- Dyskusja
- Wnioski
- Ujawnienia i uznania
- Bibliografia

Studia przypadków powinny zawierać następujące elementy:

- Tytuł (w j. polskim i j. angielskim)

- Słowa kluczowe (z Medical Subject Headings [MeSH], katalog Index Medicus; w j. polskim i j. angielskim)
- Streszczenie (150-200 słów, w j. polskim i w j. angielskim, podzielone na części)
- Wstęp
- Opis przypadku
- Wnioski
- Bibliografia

Artykuły przeglądowe powinny zawierać następujące elementy:

- Tytuł (w j. polskim i j. angielskim)
- Słowa kluczowe (z Medical Subject Headings [MeSH], katalog Index Medicus; w j. polskim i j. angielskim)
- Streszczenie (150-250 słów, w j. polskim i j. angielskim)
- Wstęp
- Cel pracy
- Krótki opis stanu wiedzy
- Wnioski
- Bibliografia

Tabele

Tabele powinny być ponumerowane zgodnie z ich kolejnością w tekście. Tekst powinien zawierać odniesienia do tabel.

Każda tabela powinna być przesłana w osobnym pliku.

Ilustracje

Każdy rysunek powinien być wysłany w osobnym pliku, nie zawartym w tekście.

Obrazki najlepiej przesłać w formacie TIF lub EPS. Format JPG jest także dozwolony.

Wszystkie obrazki, zarówno fotografie, wykresy, jak i diagramy, powinny być ponumerowane kolejno, zgodnie z pojawieniem się w tekście.

Cytaty i bibliografia

Pozycje literatury powinny być cytowane w nawiasach kwadratowych w kolejności cytowania.

Bibliografia powinna być ułożona w kolejności cytowania w tekście. Jeżeli liczba autorów przekracza 6, po 6 nazwisku należy dopisać „et al.".

Cytowanie czasopisma:

Tomao P, Ciceroni L, D'Ovidio MC, De Rosa M, Vonesch N, Iavicoli S, et al. Prevalence and incidence of antibodies to Borrelia burgdorferi and to tick-borne encephalitis virus in agricultural and forestry workers from Tuscany, Italy. Eur J Clin Microbiol Infect Dis. 2005; 24(7): 457–463.

Czasopismo – suplement:

Zajkowska J. Lyme borreliosis – guidelines of treatment and expectations of patients. Przegl Epidemiol. 2008; 62(Suppl.1): 142–151 (po polsku).

Tom czasopisma z numerem części:

Abend SM, Kulish N. The psychoanalytic method from an epistemological viewpoint. Int J Psychoanal. 2002;83(Pt 2):491-5.

Cytat z czasopisma online:

Zhang M, Holman CD, Price SD, Sanfilippo FM, Preen DB, Bulsara MK. Comorbidity and repeat admission to hospital for adverse drug reactions in older adults: retrospective cohort study. BMJ. 2009 Jan 7;338:a2752. doi: 10.1136/bmj.a2752.

Publikacja elektroniczna przed drukowaną:

Yu WM, Hawley TS, Hawley RG, Qu CK. Immortalization of yolk sac-derived precursor cells. Blood. 2002 Nov 15;100(10):3828-31. Epub 2002 Jul 5.

Książka:

Biernat E. Aktywność fizyczna mieszkańców Warszawy. Na przykładzie wybranych grup zawodowych. Warszawa: Oficyna Wydawnicza SGH; 2011 (in Polish).

Rozdział z książki:

Piątkowska M. Uczestnictwo Polaków w aktywności fizycznej w porównaniu do innych krajów Unii Europejskiej. In: Buśko K, Charzewska J, Kaczanowski K., editors. Współczesne metody badań aktywności, sprawności i wydolności fizycznej człowieka. Warszawa: Akademia Wychowania Fizycznego w Warszawie; 2010. p. 38-57 (in Polish).

Zapowiedzi/w druku:

Tian D, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. Proc Natl Acad Sci U S A. Forthcoming 2002.

Materiały opublikowane online nieposiadające numeru DOI:

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [Internet]. 2002 Jun [cited 2002 Aug 12]; 102(6): [about 1 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htmArticle

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Zarejestrowane manuskrypty są przesyłane do 2-3 niezależnych ekspertów do oceny naukowej. Przesłane artykuły są akceptowane do publikacji po otrzymaniu pozytywnej opinii niezależnych recenzentów. „Health Problems of Civilization" prowadzi proces recenzji „double-blind", w którym autorzy nie znają tożsamości recenzentów, a recenzenci – tożsamości autorów. Proces oceny zajmuje zazwyczaj 2-4 miesiące.

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