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Stratification and Management of Cardiovascular Risk among Patients with Psoriasis

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Abstract

Older patients belong to the group with increased CVD risk, and one of the pillars of modern medicine is the stratification of risk and its reduction. Hence, physicians must approach the patient holistically and consider the multitude of factors that increase that risk. Recent reports suggest that, in addition to the classic cardiovascular risk factors, there is a group of lesser-known factors that also increases the incidence of CVD. One of them is psoriasis. This disease, known primarily for its cutaneous manifestation, actually impacts the whole body due to systemic inflammation. The challenge for physicians is to incorporate these new risk factors into the standard management of patients with psoriasis and to adjust treatment. Our work aims to analyse not only the association of psoriasis with increased CVD risk, but also what therapeutic options are available. This work also seeks to outline the actual risk in patients with psoriasis, which is higher than in the general population, as well as to highlight the problem that there are no tools that can unambiguously determine it.

Key words: *psoriasis, cardiovascular risk, risk assessment*

Introduction

Psoriasis (Ps) is an autoimmune disease associated with chronic inflammation [1]. The pathogenesis is very complex and still under investigation, but it seems that it is the activation of Th17 lymphocytes mediated by IL-23 [2, 3] which is crucial. Genetic factors are significant in the development of the disease; however, their role is probably greater in early-onset psoriasis rather than late-onset [3]. Psoriasis affects women and men equally, but more frequently white (especially Caucasian and Scandinavian) individuals [2]. According to the WHO Global report on psoriasis, about 100 million people worldwide are affected by the disease; however, scientists claim that the data may be underestimated [4]. Generally, the main manifestations of this condition are red, flaky plaques or patches on skin due to impaired keratosis and the inflammatory process [2].

Although inflammation is not only limited to skin, it has a systemic character. From a cardiovascular point of view, it is significant that it is localized in the vessel wall and for this reason it promotes atherosclerosis [3, 5, 6, 7].

We have analysed studies concerning different approaches to managing cardiovascular risk (CVR) in patients over 65 years old affected by different types of psoriasis. The aim of this review was to verify the current state of knowledge on the association between psoriasis and CVD, identify the different methods of CVR stratification of those patients and to compare the effectiveness and safety of the different therapeutic methods recently used.

Cardiovascular diseases (CVD) are the first cause of death in many countries. Between 1990 and 2015, most European states saw an increase in the number of new CVD cases, with a 100% increase in some countries. In 2015, there were just under 11.3 million new cases of CVD in Europe [8]. Detection and prevention is the basic and appropriate approach. Taking into account individual cardiovascular risk in the treatment process of psoriasis may have a beneficial influence not only for the patient, but potentially also for the health care system, thanks to the prevention of cardiovascular complications.

Correlation between psoriasis metabolic syndrome and cardiovascular risk

The incidence of metabolic syndrome (MS) in psoriasis patients is higher compared to the rest of the population [9]. Individual components of metabolic syndrome, such as increased waist circumference, elevated triglyceride levels, reduced HDL-C content, impaired fasting plasma glucose and arterial hypertension also occur more frequently in those patients in comparison to the global population. According to H. Radner et al., 18.5% of psoriasis patients had increased Total Cholesterol, 16. 9% increased LDL and 33.7% increased TG; 74.2% of men and of 16.9% women had low HDL, and 68.8% of men and 86.5% of women had increased waist circumference [10]. Statistically, per 1000 patients with psoriasis hypertension (range 68.2–79.8) is most common, followed by hyperlipidaemia (range 40.3–52.0), obesity (range 24.4–32.9) and diabetes (range 10.6–14.7) [10]. These findings are in accordance with other studies [12, 13, 14, 15]. However, there are inconsistencies when it comes to the impact of psoriasis on hypertension, hypercholesterolemia and hyperglycaemia. In one large cross-sectional study, psoriasis was positively associated with a higher Body Mass Index (BMI), waist circumference and hsCRP, with the corresponding increased incidence of overweight and metabolic syndrome. A positive link with diabetes, myocardial infarction and angina has also been proven, yet, in this study, there were no clear association between psoriasis and blood pressure, blood lipids or blood glucose levels [15]. This may be due to the fact that the investigator did not have any information on the use of lipid lowering drugs and could not rule out the possibility that this had an effect on the results. N. Curcó et al. tried to investigate the prevalence of metabolic syndrome and other cardiovascular risk factors in a group of patients with psoriasis and its association with the severity of skin lesions, patient characteristics and lifestyle [16]. CVR was assessed using systematic coronary risk assessment (SCORE) cards; CVR was considered high when values were ≥5%. Patients with severe psoriasis have been proved to have a higher risk of cardiovascular events than those with mild psoriasis. It is associated with the fact that the occurrence of diabetes

mellitus, baseline glycemia, insulin levels, and score risk was higher in patients with severe psoriasis. Insulin levels were associated with BMI and waist circumference, but not with Body Surface Area (BSA) and Psoriasis Area and Severity Index (PASI). In addition, when metabolic syndrome criteria were analysed independently, it was found that patients with severe psoriasis had lower levels of HDL-C than those with mild psoriasis. It is worth noting that the increased incidence of metabolic syndrome was observed especially in postmenopausal women (40%; 18/45). Metabolic syndrome accelerates the process of atherosclerosis, as it has been shown that patients with psoriasis show an increase in IMT (carotid artery intima-media thickness). Patients in the study group showed increased PWV (Pulse wave velocity), as well as increased IMT of the left part of the common carotid artery [12]. The increased risk of metabolic diseases applies not only to Ps and to Psoriatic arthritis (PsA) [17]. The same study showed that major adverse cardiovascular events (MACE) significantly increased in people with psoriasis. It is worth noting that adequate therapy has shown a reduction in risk. Patients on biological agents were less likely to have a PASI >10; however, patients on topical agents were 3.2 times more likely to have a PASI >10 [11]. No treatment led to an increase in CVD risk associated with increased BMI, blood pressure >140/90 or Waist to height ratio (WtHR) >0.5. This study showed that BMI and other CVD risk factors were not significantly increased in patients who were on biological agents. This suggests that the improvement in PASI may also correspond to an improvement in BMI and therefore other CVD risk factors. Psoriasis significantly increases not only the risk of psoriatic arthritis, but also of other diseases, such as non-specific inflammatory bowel diseases, uveitis, and psychological and psychiatric disorders [18]. Among psychiatric disorders, mainly depression, the incidence in psoriasis patients is about 20% [10]. It is believed that the onset of depression may increase the risk of developing cardiovascular disease. Of these, 47.2% had a moderate risk and 8.8% had a high risk of developing coronary artery disease within 10 years. Forty-five patients (28.3%) had a higher than expected risk score for same-sex individuals and ages. In addition to the significant prevalence of depression and regular alcohol consumption, there was also a link to smoking.

Psoriasis affects hormonal balance, although the mechanisms of the relationship between psoriasis and arterial hypertension are not conclusively established. As is well known, people with severe psoriasis have higher serum endothelin (ET-1) values compared to the general population [19]. Increased plasma renin activity, increased angiotensin converting enzyme activity and elevated ET-1 in psoriasis patients may contribute to poor blood pressure control. In addition, there is speculation that increased Angiotensin II levels may disturb the balance between the proliferation and differentiation of keratinocytes and have a proinflammatory effect [20].

Risk assessment

The Framingham Score (FRS) is the most commonly used theoretical regimen that shows a causal link with cardiovascular disease (CVD) and justifies adequate CVR stratification for future CVD. A Framingham score is calculated based on age, LDL and HDL cholesterol, blood pressure, diabetes and smoking in men and women. The sum of the points of each CVR factor for 10 years is estimated. In assessment of the risk of psoriasis patients, a certain study has proved the FRS was significantly higher in psoriasis patients than in the control group (8.36±5.75 vs. 6.61±4. 13; P<0.001) [9]. FRS was higher in men and in patients over 50 years of age. Depending on the severity of psoriasis, FRS increased from mild to moderate-severe (6.82±4.48 to 8.8±6.71; P=0.003). A close link between psoriasis and factors associated with a higher likelihood of cardiovascular disease has been shown [12]. Of the 159 patients, 38.4% had a moderate risk and 8.8% had a high risk of developing coronary artery disease within 10 years [10]. Such associations occur in patients with moderate to severe psoriasis and this risk is much greater than that reported in the general population. The risk of heart attack in psoriasis patients compared to the general HR population was 1.59 (95% CI: 1.26–2.02) in the early period and 1.60 (95% CI: 1.28–2.00) in the late period [21]. As the researchers point out, current guidelines recognize the increased risk of CVD among psoriatic patients and the need for early identification and better stratification [13]. However, predictive cardiovascular risk algorithms such as the Framingham risk scale

do not take into account systemic inflammatory activity as caused by psoriasis leading to an underestimation of actual risk. This might explain why some studies do not find a correlation between Ps and CVR. One study with patients over the age of 75 with acute coronary syndrome (ACS) and Ps did not show psoriasis being associated with a higher cardiovascular risk, but in this study the majority of psoriasis cases had a low PASI score. It is also worth mentioning that only three cases were treated systematically [22]. Similarly, about a quarter of psoriasis patients in the control group received certain systemic medications during their lifetime, while most of them received local treatment during the study. Therefore, anti-inflammatory treatment of psoriasis is unlikely to affect the cardiovascular system results because the inflammatory response is not significantly intensified during such a stage of the disease. Structural parameters such as the use of cardiac and vascular imaging and laboratory biomarkers can be used to improve the sensitivity of traditional risk stratification algorithms in psoriasis patients. Therefore, it is worth analysing another factor, namely Quality Intima Media Thickness (QIMT). It is another important parameter, responsible for identifying subclinical atherosclerotic disease in patients with or without risk factors. Elaine Abrahão-Machado and colleagues verified the thickening of the inner layer arteries, internal QIMT [23]. In group 1 of patients receiving TNF-α inhibitors (TNF-α-i), 56% of patients had thickening of the intima media layer of the carotid artery and 28% had developed cervical plaques. In group 2 taking MTX, 72% of patients had altered QIMT results and 20% had plaques on the carotid artery. There was no statistically significant difference between CVR (as measured by Framingham and QIMT) compared to the drug used in the group (MTX and TNF-α-i), so it is not possible to determine from the study which medicine is more effective. While it is noteworthy in this study that there is a moderate to strong positive association of QIMT values correlated with Framingham score values ($p<0,001$), it also indicates the possible use of QIMT as a screening test for cardiovascular risk assessment in Ps patients. In a similar study there were two groups of 25 patients each: one taking MTX for more than 6 months, the other taking either infliximab or adalimumab in the same time period [24]. Framingham-based CVR score risk results showed a reduction of risk: more than 60% presented low risk, with

a probability of less than 10% of developing a cardiovascular event in 10 years, with 56% in the MTX group and 72% in the biological group. The authors assume that drugs that remove inflammatory factors associated with the pathological process of psoriasis may reduce the risk of CV. Therefore, the assumed treatment of psoriasis should not only affect the reduction of skin plaques, but also the reduction of inflammation [24]. The last possible screening tool to discuss is Carotid Intima-Media Thickness (CIMT). In the study to determine the effect of psoriasis on CIMT, the mean age was 54 in all those diagnosed with psoriasis [25]. The mean CIMT measurement for the study sample was 0.7 (0.12) mm and increased CIMT was found in 6 patients (15.0%), of whom 2 had myocardial infarction. Moderately linear correlations were observed between CIMT and the 10-year risk of a cardiovascular incident predicted on the Framingham scale: (=0.55; P=0.002).

Treatment

Statins

Statins seem to be the best pharmacological option for controlling cardiovascular risk among psoriatic patients. In fact, it is especially their pleiotropic anti-inflammatory and immunomodulating effects which might play a key role in relieving inflammation [26]. Many studies have inspected the effectiveness of statin therapy as a part of their research (Table 1). Ports et al. evaluated results from three clinical trials (CARDS, TNT, IDEAL) relating to cardiovascular outcomes of statins administration in patients with psoriasis compared with non-psoriatic patients [27]. A statistically significant difference was noticed in HDL-C increase in the group with psoriasis – interestingly, the increase in this parameter was inversely proportional to the dose. On the other hand, reduction of unfavourable parameters for cardiovascular risk – for example, TC:HDL-C, LDL/HDL, ApoB:ApoA1 – was directly proportional to statin doses and the decline was greater in the psoriasis-free group. Psoriatic patients should be assessed for cardiovascular risk and, on this basis, a decision should be made whether they qualify for statin therapy. Currently available tools for

assessment of cardiovascular risk have a tendency to underestimate it in patients with chronic inflammatory diseases, such as psoriasis [28]. According to Masson et al., only patients with moderate/average CV risk should take statins. Eighteen-month therapy intense rosuvastatin treatment resulted in a statistically significant reduction of LDL-C level and some reduction in height of atherosclerotic plaques in carotid arteries (carotid plaques, CP) of patients with rheumatoid arthritis (RA), ankylosis spondylitis (AS) or PsA. The plaque height reduction effect was most expressed among the youngest group. It should be emphasized that patients were taking simultaneously at least one of the following drugs on a regular basis for their underlying disease: bDMARDs, sDMARDs (biological/synthetic disease modifying antirheumatic drugs), NSAIDs, a-HT (antihypertensive) medications, prednisolone. In the group taking bDMARDs, the reduction of CP height was much smaller compared to those taking sDMARDs, or those not taking DMARDs at all [29]. On top of that, this therapy significantly improved arterial stiffness parameters and lowered BP. Strong correlation between aPWV improvement and SBP reduction has been observed and it was independent from a-HT therapy patterns of individual patients [30]. Another study assessed the safety and efficacy of atorvastatin as a complementary treatment of mild-to-moderate chronic plaque psoriasis. Besides that, patients participating in that study were allowed to use beclomethasone valerate 0.1% ointment topically. After six months, PASI reduction was higher in the atorvastatin group compared to a placebo, but the difference was not statistically significant [31]. Researchers indicated atorvastatin has the strongest anti-inflammatory component among all statins, especially starting with a 40 mg/day dose. Interestingly, the hsCRP level in the atorvastatin group rose more than in the placebo group, although it was not a statistically significant increase. According to the scientists, the strategy of using atorvastatin routinely in psoriatic patients needs to be evaluated further [31].

TNF-α inhibitors and DMARDs

Eder et al. investigated how TNF-α-i therapy could affect subclinical atherosclerosis in patients with Ps and PsA [32]. Interestingly, TNF-α-i treatment

caused statistically significant inhibition of the forming of atherosclerotic plaques among men, while in women there was no association between using TNF-α-i and atherosclerosis progression. This anti-atherogenic effect was observed independently of the use of other systemic drugs. Despite some hypotheses, scientists failed to understand the reasons for the gender difference in response to TNF-α-i in plaque progression. After one year of follow-up in the group taking TNF-α-i, inflammation within the aortic wall significantly improved compared to the no treatment group. Surprisingly, in this study, DMARDs treatment in comparison with non-systemic treatment turned out to be less effective in stopping progression of atherosclerosis. According to the researchers, this may be due to the fact that patients treated only topically have generally less advanced disease and therefore a potentially lower baseline cardiovascular risk (including a tendency to build up atherosclerotic plaques). Sparks et al. analysed retrospectively a group of 985 patients with psoriasis taking DMARDs. All patients had a past medical history (PMH) of a CV event [33]. At baseline, most patients were taking csDMARDs (conventional synthetic DMARDs), such as methotrexate, hydroxychloroquine, sulfasalazine. Investigators state that dermatologists should advise their psoriasis patients not to quit DMARDs therapy after the initial CV event, which according to the authors is quite a common phenomenon. They point out that it is important to have in mind that psoriasis is an independent CV risk factor, and discontinuation of systemic therapy with DMARDs after an initial CV event was associated with higher risk of a subsequent CV event. The study involved patients with Ps, RA and PsA, but interestingly the discontinuation rate of prior treatment with DMARDs was the highest in the group with psoriasis. Taking into account another classic DMARD – methotrexate – its immunomodulatory component probably plays the main role in psoriasis relief. Warren et al. investigated the pros and cons of subcutaneous administration of methotrexate versus traditional per os treatment [34]. As advantages of s.c. administration they indicated: less time needed to achieve improvement; more stable long-term response (measured as improvement in PASI and sPGA [static physician global assessment]) and lower doses needed to gain the same effect. Moreover, patients are less likely to resign from subcutaneous MTX than from oral form.

Managing metabolic syndrome

Breaking down the link between psoriasis and the metabolic syndrome spectrum seems to be a critical strategy in reducing cardiovascular risk among these patients.

Researchers generally agree that treating metabolic syndrome significantly reduces cardiovascular risk and for this reason all patients with psoriasis should be actively screened and properly treated [36, 37]. Therapeutic strategies have to take into account complex pathogenesis of MS.

Dietary intervention should be one of the first steps in the psoriasis treatment process. Psoriatic patients have essential nutrient deficiency, which results in intensification of ROS (reactive oxygen species) production and therefore increased oxidative stress [37]. Many clinical trials have shown that diets rich in ω-3 PUFA are associated with relieving psoriasis symptoms. Reducing weight improves PASI in overweight and obese patients. Furthermore, patients with BMI >40 have a generally impaired response to any systemic treatment of psoriasis [37]. According to Peralta et al., ustekinumab (monoclonal antibody anti-IL-12 and IL-23) is a good option for inverse psoriasis. It is resistant to standard therapy and is also present in the group of patients with high BMI [37]. A good target of therapeutic intervention seems to be an adiponectin. Increasing its serum level might be key in preventing insulin-resistance [36]. Singh et al. observed effects of using pioglitazone and metformin in patients with mild to moderate psoriasis [3]. After 12 weeks, significant improvement of PASI, ESI and PGA was noticed in both groups compared to a placebo. In both the metformin and pioglitazone groups, significant improvement in fasting plasma glucose, total cholesterol and triglycerides was observed. In the metformin group, after 12 weeks a substantial reduction of weight, waist circumference and BMI was seen when compared to a placebo. On top of that, in the pioglitazone group there was a significant decrease in SBP and DBP. Pioglitazone and metformin in this study were equally effective in managing metabolic syndrome but due to the better weight reduction effect of metformin, it could be preferred [35].

Ascorbic acid

Reactive oxygen species (ROS) take part in the pathogenesis of inflammatory diseases such as psoriasis. Ascorbic acid (VIT C) is known for its antioxidant properties, thanks to which it is commonly used in cosmetics. The idea was put forward that VIT C could be used to treat psoriasis through its anti-inflammatory effects. However, the penetration of this drug into the affected skin had to be verified. N. Leveque et al. demonstrated that ascorbic acid concentrations in psoriatic lesional skin were statistically lower compared to those in healthy subjects [38]. Attempts have been made to use DDH-1, a derivative of VIT C with higher penetration into the skin. Findings are very promising: DDH-1 dose-dependently reduced the elevated mRNA expression of IL-1b and TNF-α in the skin lesions and 0.5% DDH-1 significantly inhibited their expression. DDH-1 administration also dose-dependently inhibited inflammatory cell infiltration into the skin lesions [39]. An interesting and promising target for future anti-psoriatic therapies might be LXR-α (Liver X Receptor-alpha) encoded by the NR1H3 gene. In the study performed using cultured keratinocytes derived from skin biopsies of psoriatic lesions, it turned out that the agonizing aforementioned receptor, or promoting its expression, could inhibit the proliferation of keratinocytes (observed decreased number of cells in S-phase of the cell cycle) [40]. Ascorbic acid and atorvastatin were used as LXR-α activators. In the group of cells treated with atorvastatin, an increase of 55% in LXR-α gene expression was observed compared to 24% in those treated with ascorbic acid.

Discussion

Patients suffering from psoriasis should be assessed for the risk of cardiovascular disease and their concomitant diseases should be actively treated. A study in Denmark used imaging and population studies to verify whether a longer duration of psoriasis could lead to increased vascular inflammation, which could in turn lead to serious cardiovascular complications due to longer exposure to chronic systemic inflammation observed in psoriasis [41].

This study is crucial, as it has shown that psoriasis duration is associated with increased vascular inflammation, a relationship which persists even when adjusting for traditional CV risk factors. On the basis of field studies, it has been shown that the risk of future CV events increases by 1% each year of the disease; that means psoriasis has the same effect as smoking, for example. Moreover, patients who had psoriasis for more than 10 years were more susceptible to hypertension, suggesting that certain factors in both the skin and cardiovascular system may be affected during the development of the disease [14]. It has been proven that mortality was significantly higher in the psoriasis group compared to the general population. In psoriasis patients, having two or more vascular risk factors was associated with higher mortality compared to having only one or no risk factors [13]. An increased incidence of MACE in inflammatory diseases, such as psoriasis is reported [15]. Researchers suggest the need to improve screening and management of traditional CV risk factors in patients with inflammatory diseases. Despite the well-established link between psoriasis and CVD risk factors, psoriasis patients are not necessarily aware of this relationship, which can affect their lifestyle and reduce risk management. The percentage of patients who correctly identified psoriasis as a CVD risk factor was 50.8% [11]. Patients should be advised of the risk by their clinicians.

Conclusion

The influence of psoriasis on cardiovascular risk is still an unexplored clinical aspect of this disease. The problem with the current risk stratification methods is the underestimation of the impact of this skin disease on the cardiovascular system. Undoubtedly, the group that could benefit from prophylactic pharmacology and screening methods are patients with advanced psoriasis, as well as patients with other concomitant factors of CVD. Better methods of cardiovascular risk stratification in patients with psoriasis should be sought.

It is also advisable to look for new therapeutic methods that will prevent complications of chronic inflammation accompanying psoriasis.

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Table 1. Summarizing the results of pharmacological studies in psoriasis

Article	Mean age of participants	Number of participants	Comorbidities of study population	Intervention in this study (dose min.-max.)	Tools for evaluating CV risk factors	Duration of study	Type of study
Rollefstad et al.	60.8 +/ – 8.5 yo	**86** (RA-55, AS-21, PsA-10)	HT, DM, CVDs, carotid artery plaques	Rosuvastatin (5–40 mg o.d.) patients >70 yo started with 5mg o.d.	LDL-C and measure of height of carotid artery plaques with USG (B-mode)	18 months	Retrospective analysis of RORA-AS study (NCT01389388)
Chua et al.	41.29 +/ – 11.38 yo	**28** (mild-to-moderate chronic plaque psoriasis [PASI<10]; 14 – atorvastatin group; 14 –placebo group) **Only 14 finished the study** (6 from atorvastatin group and 8 from placebo group)	No info	Atorvastatin (40 mg o.d.)	Lipid profile (TC, TG, LDL, HDL), hsCRP	6 months	Randomized, double-blinded clinical trial (NCT01389388)
Ikdahl et al.	No info	**89** (RA-55, AS-23, PsA-11)	HT, CVDs, DM, atherosclerotic plaques in carotid artery	Rosuvastatin (5–40 mg o.d.; average 30 mg o.d.)	Parameters of arterial stiffness (AIx, aPWV); SBP, DBP	18 months	Retrospective analysis of RORA-AS study
Lerman et al.	PS 50,4 +/- 12,6 yo Hiperlipidemic cohort 61,2+/- 3,5 yo	**105** – PS (plaque psoriasis; 50 underwent 1-year follow-up) 100 – hiperlipidemia without psoriasis and any other inflammatory diseases (eligible for statins therapy according to NCEP ATP III guidelines) 25 – healthy control group	hiperlipidemias	none	Assessing coronary plaque burden (TB and NCB) and HRP using CCTA; TC, HDL, LDL, hsCRP	No info	Observational study

Article	Mean age of participants	Number of participants	Comorbidities of study population	Intervention in this study (dose min.-max.)	Tools for evaluating CV risk factors	Duration of study	Type of study
Ports et al.	CARDS: 60.3+/-7,7 yo Pooled TNT/IDEAL: 61,6+/-8,7 yo	**52** – CARDS **49** – Pooled TNT/IDEAL	DM, MS, CVDs,	CARDS – 10 mg atorvastatin TNT – 8-week 10 mg atorvastatin next randomization 10 or 80 mg atorvastatin IDEAL – randomization to 20 mg simvastatin or 80 mg atorvastatin	TC, LDL, HDL, TGs, ApoB, ApoA1	Clinical trials conducted in years 1999–2001	Retrospective analysis of: CARDS (NCT00327418), TNT (NCT00327418), IDEAL (NCT00159835)
Eder et al.	Stage 1. 54.5 +/-11.5 yo Stage 2. 51.9 +/-10.5 yo	Stage 1. **319** patients with PS alone or PS + PsA Stage 2. **34** patients with PsA alone (only men)	DM, HT, dyslipidemias	TNFi – exact drugs and doses not specified Stage 1. 5 PS and 106 PS+PsA patients were receiving therapy	Stage 1. ultrasound assessment of carotid arteries plaques Stage 2. vascular inflammation assessed by FDG-PET/CT	No info	Prospective cohort and prospected nested cohort study

Legend: DM – diabetes mellitus, yo – years old, PS – psoriasis, MS – metabolic syndrome, HT – hypertension, CVD – cardiovascular disease, o.d. – once daily, SBP/DBP – systolic/diastolic blood pressure, aPWV – aortic pulse wave velocity, TNFi – TNF inhibitor, hsCRP – high sensitivity C-reactive protein, AIx – augmentation Index

Source: [27, 28, 29, 30, 41, 42].

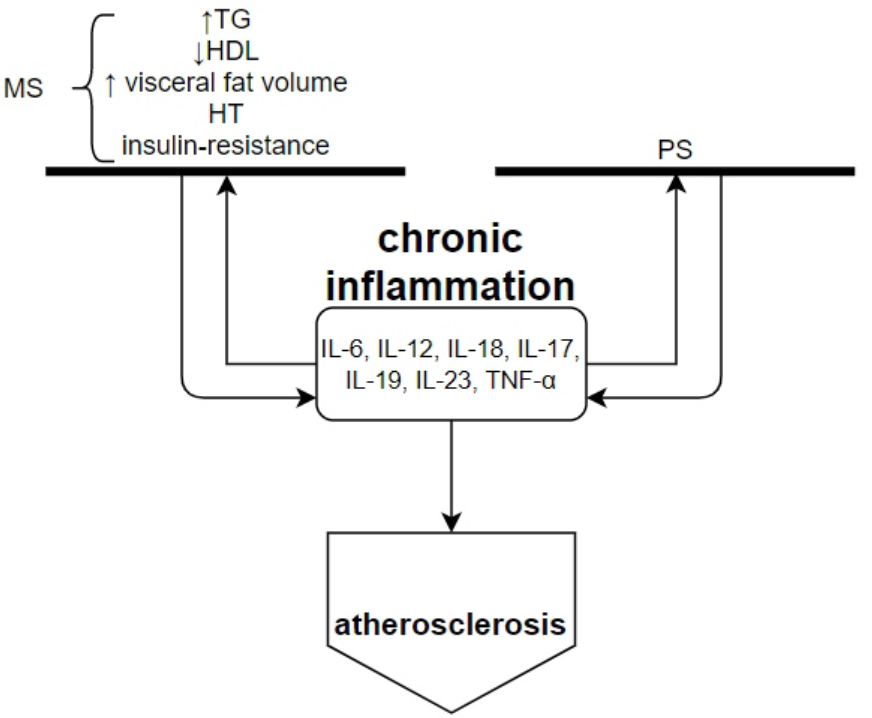

Figure 1. Linkage between psoriasis, metabolic syndrome and atherosclerosis

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Patients' Assessment of Medical Services Provided in Three Selected Chemotherapy Departments at Hospitals of Different Referral Level in Lodz Voivodeship

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Abstract

Introduction: *Growing competition in the field of medical services impels health centres to strive for better quality of care and greater satisfaction of patients. Providing high quality care and ensuring well-being of patients should always be a priority for health care institutions.*

Objectives: *The aim of the study was to present and compare patients' opinions on medical care provided and to determine the degree of their satisfaction as measured in three selected chemotherapy departments in hospitals of different referral level in Lodz voivodeship.*

Material and methods: *The study was conducted among 450 patients hospitalized in three selected chemotherapy departments in hospitals of different referral level in Lodz voivodeship in the second half of 2018. The research tool used was a self-designed questionnaire composed of 50 questions, divided into issue-related sections such as first contact with, and organization of, a given centre, treatment and care, and information on the patient.*

Results: *It was established that the possibility to get acquainted with hospital regulations and Patients' Rights Charter, adherence to timelines of diagnostic procedures and chemotherapy medication, access to pastoral care and psychological counselling, translates into patients' comfort and satisfaction, the appropriately measured mean level of which proved significantly different for each of the studied medical centres. Consequently, patients' opinions on health services provided in the selected chemotherapy departments of different referral levels varied.*

Conclusions: *Considering the empirical distribution of a synthesized SAT variable, especially its median computed for random patient samples from the compared medical centres, it can be concluded that best satisfied with services and treatment were patients of the NU-MED Diagnostic and Oncology Centre*

in Tomaszow Mazowiecki. The worst rated in this respect was the Voivodeship Copernicus Multi-Specialist Oncology and Traumatology Centre in Lodz.

Key words: *patients' satisfaction, health services, referral levels*

Introduction

In the 21st century, medical institutions whose priority is to expand medical services on the health-related market must compete for patients by offering services of higher and higher quality [1]. One of the elements of health services' quality assessment is the level of patient satisfaction [2]. Carrying out surveys of patients' satisfaction with health services plays a key role in gathering knowledge on the quality of provided medical care. The quality of the medical care has a bearing not only on patient health, experience of safety and confidence but may also be a matter of life itself [3]. Patients are the essential source of information which can lead to changes in areas needing modification and betterment [4]; thanks to their feedback the quality of services can be continually improved in order to better meet patients' expectations [5]. These expectations may of course vary from one patient to another, depending on their subjective criteria, psychological and emotional status, or previous experience with medical institutions. This survey concerned oncological patients where medical care and disease-related help is of the utmost importance since chemotherapy treatment greatly affects patients on many levels – physical, emotional, social – and has a limiting influence on their professional and home activities [6]. There are many factors affecting the level of satisfaction, including:

- access to information on health status
- duration of wait for service
- promptness of medical procedures
- empathy [7].

The patient who decides to avail himself or herself of a medical service expects, among other things, proper information and communication, the right of having a say in decision-making with regard to treatment modes, the positive effect of treatment, honesty, and psychological comfort during the course of treatment [8].

The patient dissatisfied with health services of a given medical centre can decide to seek help in another, and can communicate his negative opinion to other potential future patients. The satisfied patient, on the other hand,

will be less inclined to pay attention to possible deficiencies, e.g. in medical facilities or décor of a medical centre [9].

Thus, medical providers should be interested in monitoring changes in patients' preferences and implement improvements in the performance of their services [10]. Effective management of medical services should be based on coordinating and harmonizing multiple aspects of in-patient and out-patient care, including technical, economic and administrative angles [11]. Medical centres should focus not only on the clinical correctness of services but should endeavour also to secure patient satisfaction [12]. By understanding patients' needs for an empathetic and respectful approach they will be able to meet patients' expectations and achieve better patient management [13]. Many other works, e.g. the work by P. Francois et al., emphasize that the evaluation of hospital management activity, as perceived by hospital staff and as identified through patient satisfaction surveys and an analysis of patient complaints, contributes to defining priorities and designing strategies to solve problems and implement continuous quality improvement in hospital departments [14].

Material and methods

The authors obtained permission from the Bioethical Committee at the Medical University of Lodz to conduct the study as well as each patient's consent to participate in it. This study consists of a comparative analysis of patients' opinions on health services provided to them at three chemotherapy departments in hospitals of different referral level in Lodz voivodeship, and of defining their level of satisfaction [15]. The medical centres studied were:

- → The Voivodeship Copernicus Multi-Specialist Oncology and Traumatology Centre in Lodz (referral level III);
- → The Poddebice Health Centre (referral level I);
- → The NU-MED Diagnostic and Oncology Centre in Tomaszow Mazowiecki (specialist level – oncology).

The study was conducted in the period of June-November 2018 among 450 patients undergoing chemotherapy treatment. In each hospital 150 face-to-face questionnaire interviews were conducted. Every patient was allowed

only one interview during their whole course of treatment, and participation was optional. The study sample was randomized, i.e. patients were included in the study according to the simple independent sampling scheme on the basis of patients ID lists presented by a given hospital.

The questionnaire consists of 50 questions. The first part of the questionnaire referred to information on hospital regulations and patients' rights, structure and topography of the department, types of treatment, and availability of pastoral care or psychological counselling. Further questions concerned issues such as cleanliness of wards, rooms and bathrooms, equipment and facilities, quality of meals, quality of nursing and doctoral care. Final questions gathered information on the patient: gender, age and level of education. The obtained data were statistically analysed with the programmes MS Excel, Gretl and Statistica statistical package version 12. The results are presented by means of simple statistical tools such as boxplots, analysis of the SAT variable (see definition of the SAT variable below), the Kruskal–Wallis test and the multiple comparisons method.

Results

The study comprised 450 patients, including 227 women (50.44%) and 223 men (49.55%). Most of the respondents were aged 65–74 years (38%), followed by the group aged 55–64 years (31.11%). One hundred and sixty patients (35.56%) had secondary vocational education, whilst 20 patients with bachelor's degree constituted the smallest group (4.44%). With regard to the distance from place of residence to the medical centre where patients received treatment, the largest group consisted of patients with 11–50 km to cover (42.22%), and the smallest, with over 200 km – 1.33%. With respect to diagnosis established according to ICD-10, the greatest group of 130 patients (28.89%) were treated for large bowel cancer, 95 (21.11%) for lung cancer, and only 7 (1.56%) for urinary bladder neoplasm. With regard to the chemotherapy treatment patients were undergoing when interviewed, the greatest number of patients – 151 (33.56%) – were receiving their first course, and 95 (21.11%) had undergone 7 or more courses of chemotherapy.

The smallest group, undergoing their fourth course of chemotherapy, consisted of 19 patients (4.22%).

Admission to hospital

Data analysis shows that the **possibility of getting acquainted with hospital regulations** is rated highest by patients of the Voivodeship Copernicus Multi-Specialist Oncology and Traumatology Centre in Lodz (91.33% of respondents). Second in positive ranking with regard to this criterion (86.67% of respondents) was NU-MED Diagnostic and Oncology Centre in Tomaszow Mazowiecki. The poorest assessment (77.33% of respondents) was granted to the Poddebice Health Centre.

Regarding **the possibility of getting acquainted with the Patients' Rights Charter** the centre rated highest by respondents was the Voivodeship Copernicus Multi-Specialist Oncology and Traumatology Centre in Lodz (90.67% of approving responses), followed by the NU-MED Diagnostic and Oncology Centre in Tomaszow Mazowiecki (87.33% of positive marks); third was the Poddebice Health Centre (76.67%). It is worth noting that for the Oncology Therapy Department in Tomaszow Mazowiecki none of the interviewed respondents gave a negative answer concerning this aspect.

Treatment

Analysing the opinions of patients with regard to **adherence to timelines of diagnostic procedures,** the most favourably appraised was the Poddebice Health Centre (97.33%). The hospital in Tomaszow Mazowiecki received positive opinions from 90% of respondents, and the hospital in Lodz, 88%.

Concerning the question on **timeliness of planned chemotherapy (cytostatics) treatment implementation**, 80% of patients at the hospital in Tomaszow Mazowiecki stated that the treatment started as scheduled. For the hospital in Lodz it was 73.33%, and for the centre in Poddebice, 67.33%.

Patient evaluation of access to pastoral and psychological care

Information on the **availability of pastoral care** was best provided by the NU-MED Diagnostic and Oncology Centre in Tomaszow Mazowiecki, according to 74.67% of questionnaire respondents, and least by the Poddebice Health Centre – 68%. Quite a few patients, about 30% of each of the three institutions, commented they were not fully informed that such services were accessible to them. Therefore, this aspect of hospital care needs improvement in that the information should be clearer and easier to access.

The highest rating with regard to information on the **availability of psychological care** was for the NU-MED Diagnostic and Oncology Centre in Tomaszow Mazowiecki (78% positive opinions); it was 62% for the Voivodeship Copernicus Multi-Specialist Oncology and Traumatology Centre in Lodz, whilst the lowest was for the Poddebice Health Centre where only 46.67% of respondents were informed they could seek psychological help.

Statistical analysis

For the purpose of the study, a synthesized SAT measure was designed to globally assess the level of patients' satisfaction in each of the three hospitals. To facilitate the interpretation of this variable, it was normalized to range <-2, 2>, where the right end of the range denotes a maximally positive opinion, 0 denotes a neutral attitude of the patient, and the left end signifies a maximally negative opinion.

Definition of the SAT variable

The construction of the SAT variable which defines the patient's general satisfaction with the course of hospitalization is as follows:

- → at stage 1, it contains sub-indicators: X1 – satisfaction with cleanliness of the ward, room and bathroom (the mean of responses to questions 36–38), X2 – satisfaction with room facilities (question 39), X3 – satisfaction with meals (question 40);

X4 – satisfaction with hospital staff (the mean of responses to questions 41–44);
X5 – satisfaction with quality of provided health services (question 45);

→ at stage 2 the variables were re-scaled to adopt values from the range {-2, -1, 0, 1, 2}, with value 0 denoting a patient's neutral attitude, 2 maximally positive, and – 2 maximally negative;
→ at stage 3 a synthesized SAT index was established which constitutes the arithmetic mean of variables indicators: X1, X2, X3, X4 and X5.

Evaluation of the SAT variable distribution for three studied medical centres

A comparison of the SAT variable distribution among the whole population of the three assessed hospitals was done with the non-parametric Kruskal–Wallis test [16] (see Table 1). The ANOVA [17] – analysis of variance to analyse the differences among means – was not used, particularly because the assumptions on the normality of SAT variable distribution, as well as equality of the variation of this characteristic among the hospital patients, were not met (they were respectively modified with Shapiro–Wilk's [18] and Bartlett's tests [19]).

The Kruskal–Wallis test confirmed that the distributions of the SAT variable among the hospitalized patients are significantly different when compared between the hospitals. To be more exact: p-value close to null, as computed on the basis of the sample results, speaks for rejection of the null hypothesis suggesting lack of differences between these distributions. This is further confirmed by boxplots set for all hospitals, which display the most typical values of the SAT characteristic among the total of patients of these hospitals (areas quartile 1 – quartile 3) (see Figure 1). The so-called boxes on these graphs do not group on the same horizontal line. Nonparametric tests for multiple comparisons [20] which then compared the distribution of the SAT variable among the patients of a given hospital with the distribution of an analogous distribution from each of the other two hospitals (pairwise comparisons) showed statistically significant differences in the

distribution of the SAT characteristic among patients of any of the hospital pair (see Table 2). Red colour marks statistically significant differences with the level of significance set at 5%. Therefore, there are statistically significant differences between the studied hospitals with respect to the distribution of the SAT variable.

Table 1. Kruskal–Wallis test for comparison of the SAT variable distribution in three analysed hospitals

Variable: SAT	Kruskal–Wallis test (ANOVA) Grouping variable: hospital H (2, N=450) =154, 7843 p=0,000			
	Code	Number of observations	Sum of ranges	Mean rank
Poddebice	1	150	31,788.50	211.9233
Lodz	2	150	20,971.50	139.8100
Tomaszow Maz.	3	150	48,715.00	324.7667

SAT variable – synthesized measure assessing globally the level of patient satisfaction with hospitalization in a given hospital

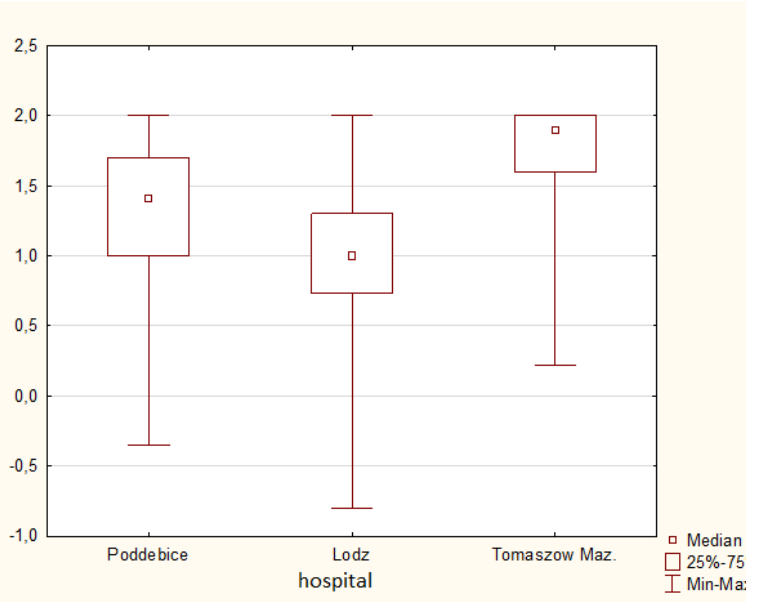

Figure 1. Boxplot graphs for the SAT variable distribution in three analysed hospitals

Table 2. Multiple comparisons for analysis of the SAT variable distribution in three analysed hospitals

Variable: SAT	Multiple comparisons: p- values (*)		
	Poddebice R:211,92	Lodz R:139,81	Tomaszow Maz. R:324,77
Poddebice		0.000005	0.00
Lodz	0.000005		0.00
Tomaszow Maz.	0.000000	0.000000	

(*) Red colour marks statistically significant differences

Source: own study.

Discussion

The obtained results, presented in Table 1, Table 2 and Figure 1 clearly show that the hospitals described in this study differ with regard to the level of patients' satisfaction with health services provided there. Considering the level of the synthesized SAT variable, it can be concluded that patients who were most satisfied with the care level of hospitalization were those of the hospital in Tomaszow Mazowiecki. The worst ranking was for the hospital in Lodz. Since the study was based on a randomized sample of patients and on the Kruskal–Wallis significance test, the above mentioned conclusion can be generalized, i.e. it does not refer only to the studied sample of patients but is general in nature and comprises the whole population of hospitalized beneficiaries of health services. Similar analyses of assessment of patients' satisfaction can be found in works of other authors [21, 22, 23]; however, they focus on the evaluation of a given patient's satisfaction with particular aspects of hospitalization such as medical staff, nursing staff, facilities, quality of meals, etc., separately, whereas the added value in this work is the proposal and analysis of own, original SAT variable which analyses the satisfaction factor in a synthesized and global way, i.e. takes into account all the considered as considered aspects simultaneously. Such an approach has special practical significance where a prompt, unequivocal assessment of a hospital is needed since one figure expresses it better than a set of figures that may

be potentially ambiguous and confusing in the assessment and thus make the choice of hospital more difficult.

Conclusions

It is to be hoped that the results and recommendations stemming from published works will be taken into consideration and brought to health-related practice by relevant authorities. The main author of the article intends to continue her work by incorporating more hospitals in the study and by enlarging study samples, using the methodology presented herein, including the SAT variable.

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Use of Antidiabetic Drugs in Prevention of Dementia among Elderly

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Abstract

Cognitive impairment, including memory problems or pathologies related to thought processes, can be caused by mental, neurodegenerative, and somatic diseases. Parkinson's disease, Alzheimer's disease and vascular disease are common in elderly people who are burdened with chronic diseases such as diabetes and can contribute to the deterioration of cognitive functions. Research indicates a possible neuroprotective effect of antidiabetic drugs used in the treatment of type 2 diabetes. Therefore, the use of incretin drugs and fluids in order to improve cognitive functions seems to be very promising.

Key words: *Alzheimer's disease (AD), Parkinson's disease (PD), Neuroinflammation, Glucagon-like peptide-1 (GLP-1), DPP-4 inhibitors*

Cognitive functions in elderly – introduction

Cognitive functions are activities that serve a person in obtaining spatial orientation, information about themselves and their own body, analyzing the situation, formulating conclusions, making appropriate decisions and acting [1]. These include perceptual, attention, memory, thought, language, learning, and executive functions [1].

The quality of cognitive functions declines with age. It manifests itself through deterioration of memory, reaction, focus, reasoning, and accidents from structural changes, and aging [2]. According to some authors [3], the deterioration of cognitive functions contributes to the increased risk of Alzheimer's disease.

The incidence of dementia increases with age: in people aged 60–64 it is 1–2%, aged 75–79 years – 6–8%, over 90 years – over 35% [4]. Also, earlier occurrence of mild cognitive impairment (MDI; cognitive impairment that is greater than expected for a given age but does not significantly affect daily functioning) increases the risk of future dementia [5].

Many mechanisms can lead to the development of cognitive dysfunction. J. Dzierzewski et al. [2] mention, among others, deposition of amyloid-β and Tau protein, increased neurodegenerative processes, hypoxia, vascular changes, low physical activity, and sleep problems.

One of the risk factors of cognitive impairment is type 2 diabetes (T2D) [12]. It is associated with an increased risk of mild dementia, compared to the general population [13], and a faster transition of MDI to dementia [14]. In diabetic patients, the aging process begins earlier and progresses faster – this also applies to cognitive functions [1]. People over 60 years of age, 4 years after the diagnosis of diabetes, showed a significant deterioration of cognitive functions compared to healthy people. At the same time, it occurs more often than in people of the same age without disturbances in carbohydrate metabolism [1]. In a meta-analysis involving over a million patients, the risk of dementia in people with diabetes was almost twice as high as in people without diabetes. It concerned both Alzheimer's disease and vascular dementia [15].

This disease is associated with an increased risk of vascular pathologies in a more significant way than with atherosclerosis and neurofibrillary tangles characteristic of Alzheimer's disease [16]. Endocrine system disorders may cause degenerative-atrophic changes in the CNS [1]. Also, episodes of hypoglycemia occurring in the course of diabetes increase the risk of developing dementia [14].

Cognitive impairment in patients with diabetes mellitus is associated with worse self-control, glycemic control, and greater incidence of hospitalizations, episodes of severe hypoglycemia, and cardiovascular events [14].

Although the subject is not new, the question of the influence of diabetes on cognitive functions has not been well researched [1]. The society gets older, that is why the problem of dementia is current and we found the possibility of stopping it using antidiabetic drugs very interesting. The life expectancy prolongs, and it is important to provide a good quality of the life for the elderly people. Antidiabetic drugs, which connection with cognitive functions we researched, are supposed to be a good prophylaxis of dementia in elderly patients.

Influence of incretin drugs on cognitive functions in Alzheimer's Disease:

Alzheimer's disease (AD) is a neurodegenerative disease that is the most common cause of dementia in the world [17]. Most often it appears after the age of 65, while in the case of a genetically determined form, the disease emerges around the age of 45 [17]. The disease affects about 3% of people aged 65–75, 17% aged 75–84 and 32% of people over 84 years of age. This number is expected to increase to 13.8 million by 2050 [34].

The background of the disease includes deposition of β-amyloid (Aβ) plaques as well as hyperphosphorylated tau protein in neurofibrillary neuron tangles (NFT), which results in decreased function or loss of synapses and neurodegeneration [17, 34]. The lesions attack the areas of the cerebral cortex and the hippocampus, most often starting from the frontal and temporal lobes, where senile plaques and neurofibrillary tangles are initially detected [17, 18].

Aβ is a natural product of the cleavage of amyloid precursor protein (APP) into peptides of different lengths in healthy individuals, Aβ is rapidly broken

down. In patients with AD, the main aggregation is the Aβ42 isoform with amyloidogenic properties, which increases the plasma Aβ42/ Aβ40 isoform ratio. Abnormal amyloid plaque (Aβ) contributes to the hyperphosphorylation of the tau protein, which spreads to neighboring neurons causing their death [18]. Dysfunction of the APO-E gene on chromosome 19, which encodes the apolipoprotein E (APOE) protein involved in the catabolism of lipoproteins, also contributes to the development of the disease [17, 18]. APOE exists in 3 isoforms: APOE2, APOE3 and APOE4. Studies have shown that APOE4 is associated with an increased risk of AD and a reduced risk of developing the disease associated with APOE2 [17].

AD proceeds from cognitive and functional deterioration [34]. Episodic memory disorders, i.e. the ability to encode new information and create memories, occur in the early stages of the disease [18, 19]. Then there are topographic difficulties, problems with multitasking and loss of self-confidence. As the disease progresses, the disorders worsen and become more and more burdensome in everyday life. Later in the disease, cognitive disorders may be accompanied by behavioral changes, impaired mobility, hallucinations and convulsions [35].

One of the risk factors for AD in addition to age is diabetes mellitus (DM). Evidence suggests a 2-fold higher risk of AD in people with DM compared to healthy people [28]. One of the common features of both AD and DM is the presence of aberrant insulin signaling [29]. Research has shown that insulin signaling influences neuronal function, the disturbance of which leads to Alzheimer's disease. Additionally, in diabetics, disturbances in insulin signaling may contribute to the progression of AD [36]. Chronic peripheral hyperglycemia is responsible for cognitive impairment in DM, additionally, patients suffer from chronic peripheral hyperinsulinemia and insulin resistance [24]. Hyperinsulinemia can cause insulin resistance in the nerve tissues that build the brain, which interferes with the activity of the insulin receptor and results in defective transport to the brain [25]. In the brains of AD patients, decreased insulin sensitivity was observed despite the lack of concomitant diabetes [24, 25]. The presence of insulin resistance reduced Aβ degradation by the insulin-degrading enzyme (IDE), while the resulting amyloid plaque

accumulation caused the destruction of insulin receptors from the cell surface. Additionally, a decrease in insulin signaling results in an increase in the activity of glycogen synthase 3 kinase (GSK-3β) and leads to abnormal phosphorylation of the tau protein [27]. Impairment of insulin signaling may affect cognitive functions in both DM and AD [19–21]. Both in the course of DM and PD, mitochondrial function disorders, increased inflammation, amyloid plaque deposition and excessive oxidative stress also occur [26].

Glucagon-1-like peptide (GLP-1) is a hormone secreted in the small intestine in response to the food it receives, but it can also be synthesized in the central nervous system by cells of the solitary nucleus (NTS) [32]. A study using a GLP-1 receptor agonist showed increased proliferation and decreased degradation of pancreatic β cells, decreased gluconeogenesis, and increased insulin production, and may also provide protection against oxidative damage [33, 34]. Liraglutide and exenatide, which are GLP-1 agonists, inhibit AD progression and neurodegenerative processes, reducing the level of Aβ [34]. GLP-1, after crossing the blood-brain barrier, binds to its receptor, which results in the activation of signaling pathways, facilitating insulin signaling. Additionally, GLP-1 may act as a growth factor in the brain, causing synaptogenesis and neurogenesis [34].

Dipeptidyl peptidase-4 (DPP-4) inhibitors are currently used in the treatment of type II diabetes (T2DM). Studies show their possible effectiveness in the treatment of AD [26]. Linagliptin and sitagliptin belong to the group of DPP-4 inhibitors [26]. Linagliptin enhances insulin signaling, thereby reducing tau protein hyperphosphorylation by preventing GSK3β activation [26, 27]. In a mouse study on the use of Linagliptin in AD, a reduction in the Aβ42/Aβ40 ratio was also noticed, which resulted in reduced formation of senile plaques in the extracellular space and reduced NFT deposition, which in turn improved cognitive functions [27].

Research confirms that sitagliptin also reduces the accumulation of Aβ in the brain structures by about 60%, which may be related to the stromal cell-derived factor 1α (SDF-1α) [31]. DPP-4 inhibitors inhibit DPP-4, which reduces the activity of the SDF-1α/CXCR4 axis. The probable cause of CNS neurogenesis in adults may be the proliferation of neuronal stem cells (NSCs)

and hemopoietic stem cells (HSCs) stimulated by the SDF-1α/CXCR4 Axis and the migration of NSCs and HSCs to pathologically altered areas [30]. Blocking DPP-4 with DDP-4 inhibitors enables the action of the SDF-1α/CXCR4 axis and thus promotes neurogenesis also that the SDF-1α/CXCR4 axis regulates synaptic transmission, neuron excitability, which promotes the regeneration of lost neurons in the diseased brain. Neurogenesis, on the other hand, influences learning and memory processes that are disturbed in AD [30]. It has been proven that signal propagation in glial networks and reduces Aβ accumulation (Bezzi et al., 2001, Wang et al., 2012b). CXCL12/CXCR4 signaling promotes synaptic integration and reduces beta amyloid deposition through astrocyte-mediated glutamate release in CA1 [14]. Additionally, DPP-4 inhibitors slow down the enzymatic degradation of GLP-1, extending its half-life in the blood and enhancing its effect [30, 31]. Moreover, sitagliptin reduces the level of markers of inflammation and oxidative stress and improves cognitive functions in the elderly [31].

Influence on the course of Parkinson's disease

Parkinson's disease (PD) is one of the most common neurodegenerative disorders in which there is a loss of dopaminergic (DA) neurons in the substantia nigra of the midbrain [37]. PD is characterized by the presence of the Lewy bodies, formed by fibril proteins, mainly α-synuclein [37]. A-synuclein is a protein involved in inter-vesicular transport. Its erroneous folding leads to a change in the conformation into a β-sheet and aggregation into larger structures that may have neurotoxic effects, e.g. by impaired axonal transport or synaptic dysfunction [37]. Neurological deficits are visible in the area of motor functions (e.g. ataxia), but there are also problems with memory, unexplained pain, mood and sleep disturbances [38].

In the aging global population, we can observe an increase in the incidence of Parkinson's disease [39]. According to data from 2017, about 1 million people are struggling with this disease, most often they are elderly people around the age of 60, although the disease is more and more often diagnosed in much younger patients, even around the age of 40 [40]. It is

estimated that by 2030 the number of people with PD will increase by over 50% [41]. Metabolic diseases are one of the risk factors for neurodegenerative disorders [42], therefore diabetics are approximately twice as likely to develop dementia [43].

Diabetic patients are more prone to PD [44]. It is associated with the participation of insulin resistance and chronic microglial inflammation in the pathogenesis of PD [44]. The study shows [45] that α-synuclein reduces the activity of the insulin signaling pathway by abnormal activation of P13 K, AKT, mTORC1 pathways, and also due to activation of JNK [45]. This causes, for instance reduction of tissue sensitivity to insulin and loss of homeostasis [45]. Insulin resistance, initiated by aggregation of alpha-synuclein, enhances its accumulation, which is the self-propelling mechanism of PD [46].

Incretin drugs used in the treatment of diabetes, i.e. glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), can find their application in the treatment of Parkinson's disease by influencing the mechanisms causing it [47]. The positive effect of incretin drugs in patients with PD is indicated by a study [48] involving 45 patients with non-coexisting diabetes who were administered exendin-4 for 12 months, a significant improvement in physical activity and cognitive parameters was observed by an average of 2.7 points on the MDS-UPDRS. Moreover, 12 months after the end of drug administration, these parameters did not change. Phase II double-blind studies confirmed the previous findings [48]. GLP-1 may help not only in the treatment of Parkinson's disease, but also in other neurodegenerative diseases due to its positive effect on cognitive-motor function [49]. Stimulation of the GLP-1 receptor increases the expression of complex I, formed in the basal cytoplasm from cytochrome c and the Apaf-1 protein, and Bcl-2, and also reduces the activation of caspase-3, which allows the maintenance of mitochondrial function in dopaminergic neurons and translates into improved levels of striatal dopamine in diabetics with PD [50].

GLP-1 analogs are capable of crossing the blood-brain barrier. They show neuroprotective effects of GLP-1 receptor stimulation and improvement in both motor and non-motor disorders [51]. A study conducted with the use of a GLP-1 receptor agonist showed increased proliferation and decreased

degradation of pancreatic β cells, decreased gluconeogenesis and increased insulin production [52]. Exendin-4 protects pancreatic β cells by improving mitochondrial function and inactivating FOX01. Reversal of biochemical and behavioral deficits after the use of GLP-1 analogues has also been reported [52].

The same is true of the sister hormone GIP, which as a growth hormone is important in resuming the body's use of energy (this drops significantly with PD). GIP analogues reduce the inflammation of cells of the immune system. Improvement in motor activities and exploratory behavior was also noted [53]. It is very important for the function of nerve cells and the connections between them that both hormones are growth hormones – thus the number of synapses is maintained [54].

After many studies showing the positive effect of incretin drugs on the course of PD, other therapies have been explored. Rosiglitazone, a thiazolidinedione drug, lowers glucose levels by improving the insulin sensitivity of cells. Its main task is to regulate the formation of new cells that build adipose tissue together with glucose and metabolism [55]. In the experiment from 2016, the degeneration of dopaminergic cells in rodents was achieved (so that, similarly to Parkinson's disease, cytoplasmic Lewy bodies, oxidative stress and characteristic stiffness were produced). Thanks to these actions, it has been proven that therapy with a drug from the thiazolidinedione group responds to inflammation in the body, with the weakening of the activity of central nervous system cells, with pro-inflammatory cytokines, oxidative stress and astrocytic gliosis. Additionally, it inhibits a very important enzyme in the metabolism of dopamine [45].

The data from the United Kingdom Clinical Practice Research Datalink (CPRD) database on the incidence of PD in diabetics depending on the medications taken was also analyzed. In people taking rosiglitazone, the incidence of PD was 28% lower than in people taking other drugs for diabetes [21].

Influence on vascular diseases of central nervous system

Worldwide, stroke is the second leading cause of death and the third leading cause of disability [56]. Currently, early reperfusion is the only FDA-approved

therapy proven to be highly effective and to reduce disability in patients undergoing intravenous thrombolysis (IVT) and endovascular thrombectomy (EVT) [58–60].

Due to the high number of deaths, more and more researchers are trying to develop complementary treatment strategies that would reduce damage to nerve cells or even help renew them. Drugs used in the treatment of diabetes mellitus type 2 (DM2) are also of great interest, especially GLP-1 analogs (glucagon like peptide-1), with liraglutide being a representative of which. Many data suggest that it may have neuroprotective effects [59]. Liraglutide is widely used in the treatment of diabetes mellitus type 2, administered subcutaneously once a day and in obesity [61]. The mechanism of action leads to binding GLP-1 to the glucagon-like peptide-1 receptor (GLP-1R) and secrete insulin in a glucose-dependent manner, and cause lowers of glucose level. Activation of GLP-1R also leads to the induction of proliferation and increased resistance to apoptosis of beta cells. It exerts glucoregulatory effect via slowing of gastric emptying and glucose-dependent inhibition of glucagon secretion [62]. For potentially and neurological benefits, it is important that it crosses the blood brain barrier (BBB) [63] and it is also dipeptidyl peptidase-IV (DPP-4) resistant analogues of human GLP-1 [64].

The result of ischemia, in particular late reperfusion, is the production of reactive oxygen metabolite, which in turn contribute to the activation of processes leading to cell death [65]. Clinical research suggests that liraglutide is a neuroprotective agent, it may prevent apoptosis and reduce oxidative stress [66] and also has antioxidant effects and increases the level of vascular endothelial growth factor (VEGF). On the report of Steven P Marso et al. [67] liraglutide reduced the rate of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke among patients with type 2 diabetes mellitus. According to Zhu et al. [68] liraglutide reduced infarct volume caused by the occlusion of middle cerebral artery occlusion (MCAO), decreased neurological deficits and decreased stress-induced hyperglycemia. Liraglutide inhibited cell apoptosis by reducing reactive oxygen stages (ROS) as well, increased the expression level of the anti-apoptotic Bcl-2 and Bcl-xl proteins, while it decreased the expression

level of the pro-apoptotic Bax and Bad proteins. As stated by Briyal S et al. [69] the administration of liraglutide for 14 days before induction of MCAO markedly attenuated infarct volumes, neurological deficit and the reduction of oxidative stress markers. Terminal deoxynucleotidyl transferase (TdT) dUTP Nick-End Labeling (TUNEL) assay has been designed to detect apoptotic cells that undergo extensive DNA degradation during the late stages of apoptosis [70]. As a result of the TUNEL analysis of cells, the number of TUNEL-positive cells was significantly reduced. In many publications based on preclinical studies, GLP-1 mimetics influence the acute inflammatory response secondary to ischemia by reducing the release of proinflammatory cytokines and biomarkers of oxidative stress [71] Jin et al. [72] introduced that exenatide significantly reduced the expression of hypoxia-inducible factor-1α (HIF-1α), which stimulates the expression of inflammatory cytokines, influencing cell apoptosis after ischemic stroke [74]. High doses of exenatide (50 μg/kg) delivered 1.5 and 3 hours after the ischemic episode has shown neuroprotective effects, but the effect disappeared when the drug was administered later [75]. Experimental studies by Basalay et al. [76] compared the effects of two GLP-1 analogues, liraglutide and semaglutide. The functional neuroprotective effects of liraglutide in a rat model of acute ischemic stroke have been shown to be dose-dependent, and both drugs reduce infarct size. It should be noted that this effect was observed when liraglutide was administered 90 minutes of middle cerebral artery occlusion (MCAO), but not in the 120 and 180 minutes ischaemia. It is related to the difference in infarct progression in the brain of rats vs. humans [77, 78]. Therefore, more research is needed in order to draw conclusions about the effectiveness of liraglutide in acute cerebral ischemia of humans.

Conclusion

Cognitive functions deteriorate among older people [2]. Some factors of these processes are unknown [3], others relate to DM [12]. As DM is connected with higher risk of Alzheimer's disease [28] and Parkinson's disease [44], the more important is appropriate treatment. This article shows the

results of the research, which suggest positive role of anti-diabetic drugs in the therapy of neurological diseases [26, 47, 60], not only DM. Some results also indicate the influence of GLP-1 on neurogenesis [34], what can mean that these medicines have improving effect on the cognitive function also among patients without DM but suffering from dementia. The use of anti-diabetic drugs can be a base for the new way of dementia treatment, but further research is needed.

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The Effect of Alcohol Consumption on Demographics, Population Health and Social Wellbeing in Poland

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Abstract

Alcohol consumption in Poland has almost doubled between 2002 and 2018 from 6.5 to 11.7 litres of alcohol per adult inhabitant. Such rises have resulted in an epidemic of alcohol-related diseases which have thereby become one of the main factors affecting average life expectancy; this actually rose during 2013–2017 but then fell in 2018. A study undertaken on 52 OECD countries, (Organisation for Economic Co-operation and Development), projected a 1.6 year decrease in life expectancy in Poland due to alcohol-related disease and injury by 2050. Health-related alcohol abuse is influenced by alcohol's widespread availability and relatively low price, and the ineffectual enforcement of legal regulations for the sale of alcohol to minors. An increased availability of alcohol also fuels demand for alcoholic beverages, which in turn increases the risk of numerous injuries, accidents, aggressive behaviour, domestic violence and criminal or suicidal tendencies. An increased burden is now being placed on the state health care system due to the absence of an appropriate national policy regarding the harmful effects of drinking alcohol. Such policies should therefore be re-targeted on decreasing the availability of alcohol in order reduce harmful drinking behaviour that adversely and directly impact on health and society.

Key words: *alcohol consumption, demography, population health, social well-being, mortality*

Introduction

Statistics show that consumption of alcoholic drinks has varied over the last dozen years in Poland depending on the socio-economic climate prevailing during this time. An almost twofold increase in consumption was observed over 2002–2018 for every adult inhabitant, which has resulted in Poland being one of the league leaders in the total volume of alcohol consumed in Europe [1, 2].

This has led to an outbreak of alcohol-related diseases and injuries that are one of the principal factors for declining life expectancy in Poland [3–5]. An OECD on 52 counties has estimated that average life expectancy in Poland will fall by 1.6 years in 2050 [2]. The amount of alcohol drunk is not the only determinant of harm to health and social interaction; the structured ways and patterns that alcohol is drunk also need to be considered. Indeed, the WHO has defined the following aspects that lead to harmful alcohol consumption: the amount of alcohol drunk, frequency of drinking, grades of drinking patterns (occasional, regular, heavy episodic drinking [HED]) and social context, particularly if adversely affecting life in society [6].

Study Aim

To investigate and discuss the effect of alcohol in Poland on its demographics, population health and society.

Current knowledge

Alcohol drinking patterns in Poland

Alcohol consumption has been estimated at 3.7 litres of pure alcohol per person per year prior to the outbreak of World War I [7]. During the inter-war period, alcohol consumption in Poland did not exceed the limits of 2 litres of pure alcohol per capita. There was a clear downward trend observed at these times up until 1933 which was the culmination point of the grave economic

crises of the 1930s. As the national economy became steadily more stable in 1935–1939, a slight increase in alcohol consumption of beverages was noted followed by a clear upward trend during World War II [7]. After the war, economic and social changes in the population were accompanied by increasing demands for all kinds of manufactured products, mainly industrial, including those of the alcohol-spirits manufacturing industry. Alcohol consumption continued to rise further after World War II [3], where a rate of 2.5 litres of pure alcohol per inhabitant was seen in 1947; however, rates were found to be constant between 1954 and 1957, hovering around 3.1–3.2 litres, and then slowing down at the turn of 1957/1958. In 1958, alcohol consumption stood at 3.7 litres, which remained unchanged until 1964 when it rose to 3.9 litres [7, 8]; this resulted from anti-alcohol government policies, such as reducing the number of alcohol retailers and placing restrictions on times of sale as implemented by local government under 1959 legislation, which also importantly introduced an alcohol pricing policy. A successive rise in alcohol consumption was observed, which reached 9.2 litres per adult inhabitant in 1978, despite there being a slowdown between 1970 and 1974 due to increased alcohol prices. At the beginning of the 1980s, rates decreased to 8.4 litres of pure alcohol and continued to fall to 6.3 litres in 1984 which was related to the rationing of alcoholic beverages at that time. Annual alcohol consumption rates increased to 7.5 litres in 1985, but then fluctuated at 6–7 litres per capita during 1985–2002; this being at a moderate European level [9, 10]. After 2002, excise duty on spirits was reduced by 30% and advertising of alcoholic drinks was permitted; indeed, TV adverts on beer had in fact been allowed since 2001 [11]. An almost twofold jump was recorded from 6.5 litres in 2002 to 10 litres in per capita in 2017 arising from the widespread availability and the relatively low price of alcoholic drinks [1, 2]. The latest report from the Organization for Economic Cooperation and Development (OECD) showed that in 2018 the average consumption of pure alcohol per adult inhabitant was 11.3 litres; however, this was higher in Poland at 11.7 litres of pure alcohol [2], being equivalent to more than 2.4 bottles of wine or 4.5 litres of beer per week per person over the age of 15 years. Nevertheless, the average volume of alcohol consumption per capita is

underestimated because of the unofficially recorded alcohol consumption of home-produced products, leading to a higher figure of consumption estimated to actually oscillate around 15 litres.

An increase of 0.23 litres was however noted by the Polish Central Statistical Office in 2019, thereby achieving an all-time record [10], mainly due to the sale of vodka in small 100 ml and 200 ml bottles, commonly known as 'monkeys'. According to a Synergion study, such 'monkeys' were daily bought by 3 million Poles in 2019 [12], but this fell by one third in the first half of 2021 when the so-called 'sugar-tax' was introduced to encourage the choosing of healthy foodstuff products and beverages. Nonetheless, this doesn't mean that alcoholic drinks were not selected. Indeed, larger bottles of alcohol were purchased to compensate, since they were not liable to this additional taxation (Figure 1).

Adult attitudes shape how adolescents become introduced to alcohol. Studies have shown that parents, as well as adolescent peers, mostly determine a teenager's decision on drinking and whether they do so before the age of 18 years. A clear association has been found with the lifestyle of the parents [13]. An OECD report from 2019 shows that over 60% of teenagers aged over 15 years drink alcohol in Poland, and one in five reported actually being drunk twice. Moreover, one in five teenagers under 15 years get drunk at least once a month [2]. A ESPAD survey in 2019 showed that 11% of students aged 15–16 and 19% of students aged 17–18 had been drunk at least once in the 30 day period prior to the study, to such an extent that they couldn't walk straight, had slurred speech and suffered from memory loss of previous events [14]. The term 'binge drinking' is hereby referred to as consuming on any one occasion over 5 or more drinks (each equivalent to 70 g of ethanol) for men and 4 or more for women, whilst the term 'being drunk' refers to when such binge drinking is repeated [15, 16]. An early start to drinking alcohol inhibits the normal development of the body. Furthermore, heavy and frequent drinking during adolescence adversely affects the growth and integrity of certain brain structures. Alcohol use during adolescence is associated with accelerated decreases in grey matter and attenuated increases in white matter volume, and aberrant neural activity during

executive functioning, attentional control, and reward sensitivity tasks, when compared to non-drinking adolescents [17]. The most frequently consumed adolescent drinks are: beer – 74%, vodka – 62% and wine – 43% [2].

The toxic effect of alcohol differs with respect to gender, as it manifests itself differently among women drinkers than among men. In 1993, the level of alcohol consumption differed most strongly in terms of gender. Men drank over five times more than women. Over time, we perceive another disturbing phenomenon. Since then, CBOS studies have worryingly shown that the highest rate of drinking was found in women aged 25–34 years (93%), whilst the lowest was for those women aged 65 years and over, at 63%. Furthermore, studies showed that men aged 45–54 years predominately drink alcohol most often at a rate of 99%, but less frequently when older (>83% when aged over 65 years). At younger ages below 35 years, rates of drinking are similar for both males and females; however, there is a significant gender difference in the oldest age group of 20%. Today's 18–24 year-olds differ significantly from their peers of 10 years ago. At that time, 98% of such males drank alcohol, whilst this fell to 90% in 2019. Women's rates for this age group however rose to 89% (a 10% increase) [18]. ESPAD studies have shown that differences between boys and girls drinking have become blurred over the last eight years. Girls had demonstrated slightly higher rates of drinking than boys during the last 30 days prior to the studies; this being also observed in other Polish studies [2]. An OECD report for 2018 showed that Polish women drink 5.6 litres of pure alcohol per capita annually, whilst men drink 18.4 litres [9]. Women are physiologically more susceptible to the harmful effects of alcohol than men, which is associated with a greater amount of adipose tissue and less fluid in their bodies resulting in higher concentrations of alcohol in the blood. Moreover, the female body contains approximately 70–80% less alcohol dehydrogenase compared to men, which is an enzyme responsible for metabolising ethanol [19]. Even though women drink considerably less spirits than men, the number of women and girls excessively consuming alcohol has been increasing in recent years with levels approaching those in men. Studies have suggested that women, more so than men, experience cerebral dysfunction, (including anxiety and depressive mood disorders),

hormonal dysfunction, fractures and injuries caused by road accidents and acts of violence. Drinking alcohol during pregnancy is especially dangerous with estimated rates varying between 25% and even 50%. Such behaviour is detrimental to foetal development, frequently causing premature births and spontaneous abortions. The most serious complication is the so-called Foetal Alcohol Syndrome (FAS), which is manifested by slower in-uterine growth and growth after birth, craniofacial defects (e.g. flat face, divergent strabismus, lack of a labrum, thin upper lip), and mental retardation [20].

Alcohol preferences depend on socio-demographic factors. Men mostly drink beer (56%), whilst women mostly drink wine (45%). Interestingly, high-grade alcohol, such as cognac or whiskey, is most frequently chosen by 11% of both men and women. Beer definitely outclasses other beverages in the youngest group of respondents (18–24 years olds), with rates of 63%, whereas the following age group (25–34 years) chose beer much less frequently (39%), then followed by wine (31%). Around every one in three respondents aged over 45 years declared that beer was their favoured drink; moreover, vodka consumption was also increasing, by more than one in five (22%) for respondents aged 55–64 years and more than one in four (26%) of those aged over 65 years [18].

The effect of drinking alcohol on Polish demographics

Life expectancy has decreased in part due to the rapid increase in the consumption of alcoholic beverages. After the end of World War II, life expectancy for both sexes was gradually increasing, which at the beginning of the 20th century had stood only at 40 years. Between 1960 and 1990, life expectancy improved slightly, especially for men; in the 1990s, it became 66.2 years for men and 75.2 years for women. It then improved further by 4 years for men and 3 years for women. However, the 21st century witnessed the first decline in premature mortality amongst young people and middle-aged adults in 2003, which coincided with a sharp increase in alcohol consumption in Poland. Average life expectancy in Poland increased by about 5% in women and 7% in men during 1991–2002, followed by 0.1% yearly increases during

2003–2007. It then increased by 0.3% in women and 0.6% in men throughout 2008–2013 and further increased during 2013–2017. However, in 2018 the average life expectancy fell in Poland [5, 19]. It can be presumed that this was due to the nearly twofold increase in alcohol consumption recorded in 2002–2019. In 2019, average life expectancy for men was 81.8 years and 74.1 years for women (Figure 2). Studies undertaken in 52 OECD countries demonstrate that life expectancy by 2050 will drop by 0.9 years, where the biggest drops are forecast in the countries of Central and Eastern Europe [2]; life expectancy in Poland will become reduced by 1.6 years due to disease and injuries caused by alcohol consumption. These estimates are based on women having one drink a day and 1.5 drinks for men.

The effect of drinking alcohol on health and social wellbeing in Poland

The body's biological susceptibility to alcohol can be influenced by genetic factors, health, gender and age. American studies on genetic mechanisms found that this susceptibility may be influenced by changes in some of the genes responsible for coding the enzymes involved in alcohol metabolism and in those genes that shape the brain's responses that are responsible for encoding receptors in neurons [20]. The adverse impact of excessive alcohol consumption, leading to addiction, is a hereditary, genetically determined trait [21].

The effect of alcohol on the human body depends on the dose, intensity, type of alcohol consumed and inter-individual variability [22–24]. Numerous pathological changes are caused by the toxic effects of ethyl alcohol and its metabolites, particularly acetaldehyde. The body's absorption of alcohol already begins in the mouth. Alcohol then reaches the stomach, duodenum and intestines, and from there the cerebral cortex which is responsible for processing signals governing human behaviour. By such ways, changes to the digestive system occur when directly exposed to alcohol, such as chronic inflammation of the mucous membranes, mouth, oesophagus, stomach, duodenum, pancreas and liver, as well as disrupted intestinal peristalsis. Such changes lead to the development of neoplastic disease, including in the oesophagus, mouth, pharynx, colon and rectum [21, 25].

The first effects of alcohol that become apparent are however neurotoxic which are noticeable within the peripheral and central nervous system (CNS). Initially, degeneration occurs in the frontal and temporal lobes, and further increases in alcohol intoxication lead to disruptions to the centres responsible for visual-motor coordination in the cerebral cortex. Ultimately, the functions of the cerebellum may become damaged causing problems in maintaining the body's balance [26]. The risk of dementia is increased by heavy alcohol consumption as demonstrated by a study on 30 million hospitalised patients in France. Over 50% of all diagnosed dementia in patients under the age of 65 was due to alcohol abuse. Other studies show a close relationship between alcohol, the risk of dementia, and the presence of apolipoprotein E4 (APOE E4). This gene is associated with an increased risk of Alzheimer's disease in people aged over 65 years [27].

The prevalence of alcoholism per a given population increases or decreases according to increases or decreases in alcohol consumption by that population. The rapid increase in drunkenness caused a sudden deterioration in public health during the first half of the nineteenth century and thus restrictions were placed on vodka production [8]. The liver is the body's most vulnerable organ to alcohol due to its detoxification function, achieved by enzymatic processes whereby the main transformations of alcohol take place. The first stage of the pathology is alcoholic liver disease, which then leads onto the following: steatosis, inflammation, fibrosis, cirrhosis and cancer. There was a sharp increase in the consumption of alcohol in Poland during 2003–2017, which has contributed, *inter alia,* to an increase in mortality due to alcoholic cirrhosis by 630% in women and 260% in men [3]. Long-term and intensive alcohol consumption is associated with the development of cardiovascular diseases, such as hypertension, arrhythmia, alcoholic cardiomyopathy, (a degenerative change in myocardial fibres), steatosis, and cardiac enlargement [28–30]. Strokes deserve special attention, being the second most common cause of death in the world among adults and the fourth most common cause of disease burden. Heavy alcohol use is also associated with an increased risk of ischaemic and haemorrhagic stroke. It is estimated that as countries around the world become richer, alcohol consumption will

increase, and thus the number of deaths from stroke will continue to rise. Without efforts to increase effective alcohol control measures, the number of deaths from stroke, especially in economically developing countries, will increase by 1.3 million, reaching 7.8 million by 2030 [31, 32].

Chronic alcohol abuse leads to mental malfunctioning, causing stress-induced emotional disturbances, insomnia, depression, and anxiety. The result of the above may be such diseases as: Korsakoff's psychosis or Wernicke-Korsakoff's syndrome, alcoholic dementia, alcoholic delirium, alcoholic hallucinosis, alcoholic epilepsy [33].

The WHO has defined a strategy to reduce harmful alcohol consumption, setting priority areas for global action in order to deal with the ever-increasing burden of alcohol-related disease [34]. The health consequences of alcohol abuse are influenced by its widespread availability, relatively low price, advertising campaigns for promoting alcohol consumption, especially beer, and ineffective enforcement of legal regulations on the sale of alcohol to minors. Increasing the availability of alcohol leads to a greater demand for alcoholic drinks, which in turn increases the risk of numerous injuries occurring, of accidents, aggression, domestic violence as well as criminal or even suicidal behaviour. A causal relationship has been demonstrated in a large body of literature between drinking alcohol and all types of inadvertent trauma and suicide attempts. Alcohol increases the risk of problems in the family and society, which accounts for 40–60% of deaths and injuries, which has been intensely observed in Poland [35].

Conclusions

The burden placed upon the state health care system due to the harmful consequences of drinking alcohol stems from the lack of having an appropriate national policy on alcohol. Such policies should thus be re-focused on reducing the availability of alcohol, so as to limit hazardous and harmful drinking, which is a direct cause of ill-health and societal problems.

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Figure 1. Average annual consumption of alcoholic beverages per capita in liters per 100% alcohol

Source: State Agency for Solving Alcohol Problems [www.parpa.pl/index.php/badania-i-informacje-statystyczne/statystyki].

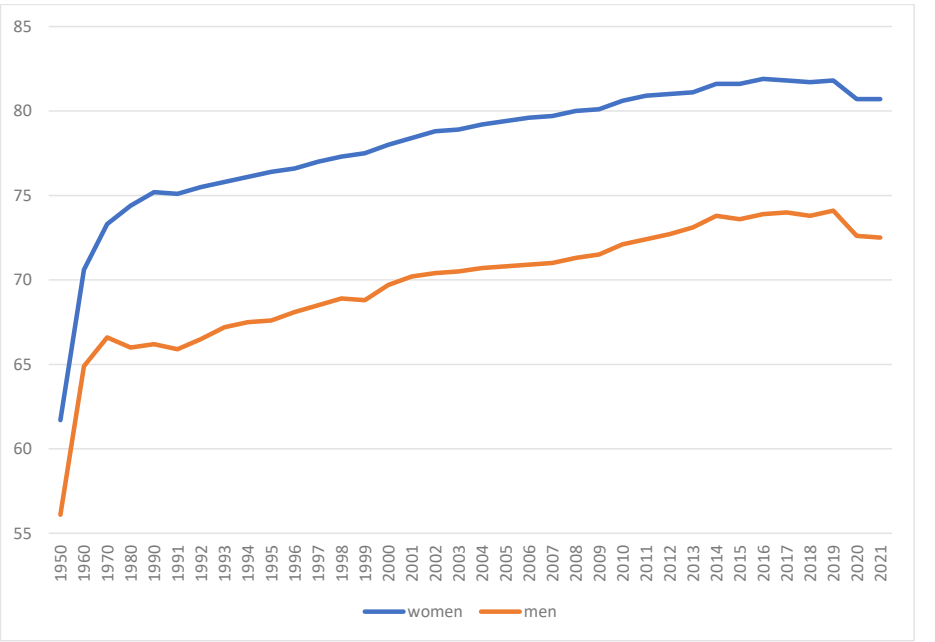

Figure 2. Life expectancy of women and men in 1950–2021

Source: [https://stat.gov.pl/obszary-tematyczne/ludnosc/trwanie-zycia].

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The Effect of a Plant-based Diets on the Cardiovascular System in Geriatric Patients – Review

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Abstract

Cardiovascular disease is one of the most common causes of death in developed countries and its incidence increases with age. The group of cardiovascular diseases includes different disease entities. Most of them are associated with the atherosclerotic process in the blood vessels. One of the most important methods of preventing atherosclerosis and its complications is proper nutrition, rich in polyunsaturated vegetable oils and low in saturated fatty acids. Many research results confirm the positive effect of a plant-based diet on the circulatory system. A well-balanced diet based on plant-based products reduces the risk of hypertension, heart disease, prevents type 2 diabetes, lowers cholesterol and helps to reduce blood pressure. Vegetarian eating patterns can reduce cardiovascular disease mortality by 30%. In addition, the plant-based diet is the only dietary pattern that has shown cessation and reversal of atherosclerotic plaque. Today, plant-based diets are becoming more popular and are increasingly used as a means of preventing and treating cardio-metabolic diseases.

Key words: *plant-based diet, cardiovascular disease, geriatric patient*

Introduction

Cardiovascular diseases (CVD) have been ones of the main causes of disability and mortality in the world population for years. CVDs are group of disorders whose development is most often based on atherosclerosis. It leads to reduction in the patency of blood vessels and even their complete closure. As a result of these pathological changes, blood flow to the brain or heart becomes obstructed. The development of atherosclerosis is especially dangerous because it can lead to ischemic heart cells. CVDs are chronic diseases that develop asymptomatically over a long period of time. Symptoms usually appear only in the advanced stage of the disease [1].

The frequency of their occurrence is influenced by many different factors. Modifiable risk factors are those that can be influenced by changing bad habits. These include smoking, obesity high blood cholesterol physical inactivity and hypertension. Non-modifiable risk factors are those that cannot be changed. These include gender, age and genetic burden. The dominant risk factors for CVD are advanced age and an improperly balanced diet, in which products are rich in saturated fat predominate [2, 3]. Currently, plant-based diets are gaining popularity and are increasingly used to prevent and treat cardio-metabolic diseases [4].

Definition and epidemiology

CVDs are a group of disorders relating to pathology of heart and blood vessels. According to the World Health Organization, this group includes coronary heart disease, cerebrovascular disease, congenital heart disease, peripheral arterial disease, rheumatic heart disease, deep vein thrombosis and pulmonary embolism. The most common cause of acute cases , including heart attack and stroke, is a blockage in the form of fatty deposits in the blood vessels. These deposits prevent the free flow of blood to the heart or brain [5].

CVDs are the most common causes of death among elderly people. It is estimated that by 2030, 20% of the population will be over the age of

65 years old [6]. The aging of the organism is the main, non-modifiable risk factor for these diseases. The latest research shows that in Europe 45% of deaths are caused by cardiovascular diseases. The epidemiological structure of these diseases is changing, but coronary heart disease is still the dominant one. Cerebrovascular disease is another serious and life-threatening disorder.

These two diseases are the most common causes of death from CVDs. They account for 20 and 11% of deaths, respectively [7]. Death rates from stroke and coronary heart disease are higher in Eastern and Central Europe than in Western, Northern and Southern Europe [8]. The percentage of deaths due to cardiovascular diseases is higher in women (49% of all deaths) than in men (40% of all deaths) [7].

Etiology of cardiovascular diseases

The most common cause of development for cardiovascular diseases is atherosclerosis. Even in the early years of the 20th century, atherosclerosis was perceived as an integral part of human aging [9]. Today, there is awareness, that the initiation and development of atherosclerosis depends on the lifestyle. Epidemiological studies have shown that the incidence of cardiovascular diseases and the number of deaths due to them are directly related to the risk factors of atherosclerosis [10]. The previously mentioned modifiable risk factors are responsible for 90% of the cardiac risk of the population and are independent of the region of the world, race, sex or age [11, 12]. These include smoking, dyslipidemia, hypertension, diabetes, visceral obesity, psychosocial factors, diet, alcohol consumption and physical activity.

Atherosclerosis is a chronic inflammatory disease of the arteries which consists of 1) endothelial dysfunction, 2) lipid storage in the endothelium, 3) accumulation of leukocytes and smooth muscle cells in the vessel wall, 4 formation of foam cells and 5) deposition of cell matrix fibers [11]. The undisputed cardiovascular risk factor is hypercholesterolaemia [13]. The risk of coronary artery disease is twice as high in a person with elevated levels of total cholesterol (240 mg/dl) than in a person with a concentration of 200 mg/dl. There is evidence that high plasma concentration of LDL cholesterol is the

cause of the onset and progression of atherosclerosis, and lowering the concentration reduces the risk of cardiovascular events [11]. Other abnormalities leading to the development of atherosclerosis are increased levels of very low density lipoproteins (VLDL), residual lipoproteins, lipoprotein [a] or decreased HDL levels [13]. The significance of elevated triglycerides as a risk factor for atherosclerosis is still unknown [10].

Pharmacotherapy of atherosclerosis

As part of the primary prevention of cardiovascular diseases, changes in lifestyle and, if necessary, pharmacological treatment should be pursued in the first place [14]. People with an existing disease, should eliminate or modified conventional risk and should implement pharmacotherapy. European Cardiac Society identifies 3 groups of drugs that improve the prognosis of coronary artery disease: anti-aggregation drugs, statins and angiotensin converting enzyme inhibitors.

Antiplatelet drugs significantly reduce the risk of vascular thrombosis. The most common standard is acetylsalicylic acid (ASA, acetylsalicylic acid) at a dose of 75–150 mg per day [15]. In some cases, the inhibitory purinergic P2Y receptor (P2Y12, an adenosine diphosphate receptor expressed by platelets) is also used in combination with aspirin [16].

The use of statins in patients has been shown to reduce the number of CVD events. The main benefits of using this group of drugs are the reduction of LDL cholesterol by up to half, depending on the type and dose of statin used [16]. This slows down and inhibits the development of atherosclerosis, and sometimes even leads to the regression of existing changes. Their additional advantage is improving the functioning of the endothelium, because of anti-inflammatory and anticoagulant activity [15].

Angiotensin converting enzyme (ACEI) inhibitors are being improved in patients with atherosclerosis and concomitant hypertension, diabetes or after a heart attack. This class of drugs blocks the conversion of angiotensin I to II. They have a beneficial effect on cell remodeling, as well as anti-arrhythmic and stabilizing effect on atherosclerotic plaque [15].

The impact of a plant-based diet on the cardiovascular system

Plant-based diets are characterized by the reduction or complete elimination of animal products. They are usually based on the consumption of vegetables, fruits, grains, nuts and legumes. Numerous studies have shown that following a diet rich in high-quality plant foods is associated with a reduced risk of cardiovascular complications in the elderly. Moreover, a vegetarian diet is the only dietary pattern that has shown resolution and reversal of atherosclerotic plaque in clinical trials [17, 18].

A well-balanced plant-based diet allows to lower abnormal lipid levels, helps to normalize blood pressure, fibrinogen levels and reduce overweight [19].

There are several biological mechanisms that may explain the beneficial cardiometabolic effects of this kind of diets. These are: lower calorie intake, decreased consumption of saturated fat and cholesterol, increased consumption of fiber, increased consumption of antioxidants and micronutrients, higher consumption of poly – and monounsaturated fatty acids, higher consumption of plant sterols [17, 20].

Plant-based diet and lipids

The lipidogram determines the concentration of triglycerides, total cholesterol, and low and high-density lipoproteins (LDL and HDL, respectively). The analysis of these indicators provides information on the state of lipid metabolism and metabolic disorders. As a result, it is possible to determine the risk of developing atherosclerosis and cardiovascular complications.

Clinical studies have shown that for every 1% decrease in LDL cholesterol, the risk of a serious cardiac event is reduced by approximately 1%. Diet modification and increased physical activity may lower LDL cholesterol up to 40%.

Consumption of saturated fat increases plasma LDL cholesterol, which is one of the major risk factors for coronary heart disease. Research shows that modification of eating habits and introducing a diet rich in polyunsaturated vegetable oils can reduce the risk of cardiovascular disease by improving the

lipid profile by up to 30%. The incidence of cardiovascular disease would decrease with a change of diet.

Moreover, recent studies have shown that dietary cholesterol increases the concentration of total and LDL cholesterol in the serum. Dietary cholesterol comes from animal products (meat, eggs, dairy). The use of a vegan diet can significantly reduce total and LDL cholesterol levels, which is directly related to a reduced risk of heart disease [17, 21, 22].

Plant-based diet and blood pressure

Systolic hypertension is an independent, well-documented risk factor for cardiovascular complications. It has also been proven that the amount of systolic blood pressure is a stronger prognostic indicator than the amount of diastolic pressure. Systolic hypertension increases cardiac mortality 3 times, stroke frequency 4 times and heart disease incidence 2,5 times [23].

A high intake of animal protein, especially meat, increases blood pressure. On the other hand, high potassium intake effectively lowers them, among people with hypertension. Plant-based diets are usually characterized by low fat intakes and high fiber and potassium intakes. Observational studies showed that people on plant-based diets had on average lower systolic blood pressure by 6.9 mm Hg, and diastolic blood pressure was lower by 4.7 mm Hg. It should be mentioned that the reduction took place independently of the use of non-pharmacological preventive methods, such as reducing salt intake, reducing the weight of patients, and increasing their physical activity [17]. A cross-sectional study of 11,004 British men and women by EPIC (European Prospective Investigation into Cancer) and Nutrition-Oxford found that among of 4 types of diets (carnivorous, pescatarian, vegetarian and vegan), veganism promotes the rarest occurrence of hypertension among patients. The mechanism by which plant-based diets lower blood pressure is not fully understood, but there are several hypotheses. These include 1) better vasodilation, 2) greater supply of antioxidants from the diet, 3) greater anti-inflammatory effect, 4) increased insulin sensitivity, 5) decreased blood viscosity, 6) changes in the RAA system and 7) sympathetic nervous system. It is also

possible that 8) modifications in the intestinal microbiota caused by plant diets are important [24]. Observational studies have shown correlations between the lower occurrence of hypertension in people with eating habits avoiding the consumption of animal products [25].

Overall, meta-analyzes, clinical and cross-sectional studies have shown strong evidence and benefits of a plant-based diet for hypertension.

Plant-based diet and glycemic control:

Type 2 diabetes has already gained the name of a civilization disease, rising all over the world, and has even gained the name of an epidemic of the 21st century. It affects people of all ages, and in Poland alone in 2018 the number of patients according to the NHF was 2.6 million [26]. Currently, there are approximately 415 million people with diabetes worldwide, and this number is expected to rise to 642 million by 2040 [27].

Plant diets are helpful in supporting the therapy of type 2 diabetes. Studies have shown reductions in drug use as well as significant improvement in performance in people who have adopted a plant-based diet and exercise. In type 2 diabetes, this allows to better control your blood glucose, even without exercise. This is due to factors such as weight loss as well as low blood lipids. Long-term studies also show that patients stay on a low-fat vegan diet longer than on a conventional caloric deficit diet [17, 28].

Observations have shown an association between inadequate blood glucose control and cardiovascular risk. Plant-based diets lower HbA1c (glycosylated hemoglobin) by 0.4 percentage points compared to conventional diets. This change alone reduces cardiovascular risk by approximately 6% [16, 17].

An additional mechanism that may affect better glycemic control are gastrointestinal hormones, especially incretins, whose action in type 2 diabetes is weakened. Plant-based diets can improve the release of these hormones [17]. Switching to a plant-based diet promotes greater consumption of products that reduce the risk of diabetes (e.g. grain fiber). It also excludes from the diet products that may contribute to the development of insulin resistance, like red meat [29]. In a 24-week randomized, controlled trial, patients on a vegetarian diet had better insulin sensitivity than patients on a conventional diabetic diet [30]. In addition, animal proteins have a greater effect on the

hemodynamics of the kidneys than plant proteins. Using only plant-based proteins in the diet may theoretically reduce the risk of developing kidney failure by reducing renal hyperfiltration and proteinuria [31].

In conclusion, a plant-based diet will not cure patients with type 2 diabetes but may have a beneficial effect on its control and prevention of associated cardiovascular events.

Discussion

According to epidemiological studies, one of the significant risk factors for the development of CVDs is advanced age, so with the aging of the world population, the incidence of these diseases is expected to increase [32]. Studies show that eating using a diet rich in high-quality plant products is associated with a reduction in CVD mortality and overall mortality [33, 34]. According to the latest publications, vegetarians have better cardiovascular outcomes compared to those on omnivorous diets, including a reduced risk of morbidity and mortality from ischemic heart disease, a reduced risk of developing type 2 diabetes, reduced cancer incidence and a reduced risk of metabolic syndrome [35, 36, 37]. Studies show that change of the eating habits and introducing a vegetarian diet is associated with an improvement in the lipid profile, including a reduction in total cholesterol, low-density lipoprotein cholesterol, and triglycerides [38, 39]. A well-balanced plant-based diet may be used as an effective therapeutic method to treat hypercholesterolaemia, hypertension and other CVDs risk factors, while reducing overall drug intake [40].

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