The Anti-aging Properties of Metformin, Flozins, and GLP-1 Receptor Agonists: A Mini Review

Tymoteusz Miłuch[1,2,A,C,D,F]
ORCID: 0000-0002-9433-6407

Mateusz Mucha[3,D]
ORCID: 0009-0009-5617-6500

Zuzanna Roszkowska[3,D]
ORCID: 0009-0008-8923-9689

Grzegorz Krupiński[1,E]
ORCID: 0009-0002-5112-8015

Michał Lis[1,4,E,F]
ORCID: 0000-0001-7675-398X

[1] Department of Internal Medicine, Endocrinology and Diabetology, Czerniakowski Hospital, Warsaw, Poland;
[2] Faculty of Medicine, Cardinal Stefan Wyszynski University, Warsaw, Poland;
[3] Faculty of Medicine, Medical University of Warsaw, Warsaw, Poland;
[4] Faculty of Medicine, Lazarski University, Warsaw, Poland

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ABSTRACT

The Anti-aging Properties of Metformin, Flozins, and GLP-1 Receptor Agonists: A Mini Review

Miłuch T.[1,2], Mucha M.[3], Roszkowska Z.[3], Krupiński G.[1], Lis M.[1,4]

[1] Department of Internal Medicine, Endocrinology and Diabetology, Czerniakowski Hospital, Warsaw, Poland; [2] Faculty of Medicine, Cardinal Stefan Wyszynski University, Warsaw, Poland; [3] Faculty of Medicine, Medical University of Warsaw, Warsaw, Poland; [4] Faculty of Medicine, Lazarski University, Warsaw, Poland

Obesity, insulin resistance, and type 2 diabetes mellitus (T2DM) are emerging health-care problems around the globe. The disturbances caused by these conditions are well-known factors leading to the acceleration of the aging process. The introduction of flozins and GLP-1 agonists has revolutionised therapeutic approaches and the efficient treatment of these disorders. Their cardio- and renoprotective properties have significantly reduced the occurrence of complications secondary to T2DM and premature deaths. In this review, we present the anti-aging mechanisms through which metformin, flozins, and GLP-1 receptor agonists act. They reverse changes in adipose tissue (such as its redistribution and reduction of brown adipose tissue), decrease inflammation, reduce oxidative stress, enhance cognition, and alleviate the symptoms of Parkinson's disease. Hence, we provide evidence that they promote 'healthy aging' and possibly lengthen life expectancy without an increase in disability. We identify the existing knowledge gaps and highlight the necessity for further research.

Keywords: *metformin, flozins (SGLT2i), GLP-1 analogs (GLP-1RA), antidiabetic drugs, aging*

STRESZCZENIE

Przeciwstarzeniowe działanie metforminy, flozyn oraz agonistów receptora GLP-1: Przegląd literatury

Miłuch T.[1,2], Mucha M.[3], Roszkowska Z.[3], Krupiński G.[1], Lis M.[1,4]

[1] Oddział Chorób Wewnętrznych, Endokrynologii, Diabetologii, Nefrologii, Szpital Czerniakowski, Warszawa; [2] Collegium Medicum, Uniwersytet Kardynała Stefana Wyszyńskiego, Warszawa; [3] Wydział Lekarski, Warszawski Uniwersytet Medyczny, Warszawa; [4] Wydział Medyczny, Uczelnia Łazarskiego, Warszawa

Otyłość, insulinooporność oraz cukrzyca typu 2 stają się coraz bardziej poważnymi problemami zdrowotnymi na świecie. Zmiany w ustroju wywołane przez te choroby są powiązane z komórkowymi mechanizmami starzenia. Pojawienie się na rynku inhibitorów SGLT2 (flozyn) oraz agonistów glukagonopodobnego peptydu 1 zrewolucjonizowało leczenie zarówno cukrzycy typu 2, jak i otyłości. Ich działanie kardio- i nefroprotekcyjne pozwoliło na skuteczne obniżenie ryzyka rozwoju powikłań i przedwczesnej śmierci pacjentów. W tej pracy przeglądowej przedstawiamy mechanizmy, w których metformina, flozyny oraz analogi GLP-1 mogą wykazać działanie spowalniające starzenie. Badania pokazują, że leki te mogą cofać zmiany zachodzące w tkance tłuszczowej spowodowane starzeniem. Redukują również nasilenie stanu zapalnego, stres oksydacyjny, poprawiają sprawność umysłową oraz w świetle nowych badań pomagają w redukcji objawów w przebiegu choroby Parkinsona. Dzięki temu promują „zdrowe starzenie" i być może mogą wydłużyć długość życia.

Słowa kluczowe: *metformina, flozyny (SGLT2i), analogi GLP-1 (GLP-1RA), leki przeciwcukrzycowe, starzenie*

Abbreviations: T2DM – type 2 diabetes mellitus; GLP-1RA – glucagon-like peptide 1 receptor agonist; IR – insulin resistance; SGLT2i – sodium–glucose co-transporter 2 inhibitors; UCP-1 – uncoupling protein 1/thermogenin; BAT – brown adipose tissue; APSCs – adipose progenitor stem cells; mTOR – mammalian target of rapamycin; ERK – extracellular signal--regulated kinase; SASP – senescence-associated secretory phenotype; IL – interleukin; TGF-β – transforming growth factor β; VEGF – vascular endothelial growth factor; AMPK – 5'AMP-activated protein kinase; NF-κB – factor kappa-light-chain-enhancer of activated B cells; CD – cluster of differentiation; TNF-α – tumor necrosis factor α; MCP-1 – monocyte chemoattractant protein 1; COX-2 – cyclooxygenase-2; ROS – reactive oxygen species; Nrf2 – nuclear factor erythroid 2-related factor 2; HO-1 – heme oxygenase-1; IFN-γ – Interferon γ; AD – Alzheimer's disease; PD – Parkinson's disease; CRP – C-reactive protein; Drp1 – dynamin-related protein 1; RNS – reactive nitrogen species; PCOS – polycystic ovary syndrome

1. Introduction

Insulin resistance (IR), obesity, and type 2 diabetes mellitus (T2DM) are known to accelerate the aging process. They influence metabolism and cause disturbances that have been associated with aging, such as dysfunction of adipose tissue, inflammation, and oxidative stress [1,2]. Recent years have brought a breakthrough in the management of T2DM. Sodium–glucose co-transporter 2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor analogues (GLP-1RA) have revolutionized treatment outcomes. Both flozins and GLP-1RA have been found effective in prolonging lifespan by reducing cardiovascular risk and providing protective action on kidneys. As some antidiabetic drugs address the causes accelerating aging, this review will focus on their potential role in promoting 'healthy aging' within individuals.

Metformin is an essential medication used as a first-line treatment for T2DM. Its 'off-label' indications include polycystic ovary syndrome, weight gain induced by antipsychotic medications, and prevention of T2DM. Metformin decreases gluconeogenesis in the liver and improves insulin sensitivity. In terms of aging, it has been shown to reverse some aging-associated changes in the body [3]. Metformin positively influences the redistribution and dysfunction of adipose tissue, decreases inflammation, improves mitochondrial function, and restores cells' antioxidative potential.

SGLT2 inhibitors (dapagliflozin, empagliflozin, tofogliflozin, and canagliflozin), also known as flozins, limit the reabsorption of glucose in the proximal tubule of the kidney, which results in glucosuria and underlies its hypoglycemic mechanism of action. SGLT2 inhibitors show cardio- and nephroprotective effects, and therefore prolong the lifespan of patients with T2DM [4]. Moreover, flozins exhibit anti-inflammatory properties, enhance mitochondrial functions, and limit DNA damage. These effects may constitute their anti-aging properties.

GLP-1RA (liraglutide, dulaglutide, semaglutide) stimulate insulin secretion when glucose levels reach supra-basal levels and inhibit glucagon release, complementing the insulinotropic effect. Moreover, they suppress appetite and promote weight loss, making them effective anti-obesity drugs [5]. GLP-1RA reduce cardiovascular incidents and show anti-inflammatory properties. GLP-1RA are also neuroprotective – they reduce neuroinflammation, enhance cognition, and limit the progression of Parkinson's and Alzheimer's diseases [6].

2. Metformin

Obesity is one of the causes of insulin resistance (IR) and type 2 diabetes. Metformin is one of the oldest drugs used to effectively address both of these disorders. As obesity is known to accelerate aging and IR increases with age, this section will focus on the role of metformin in age-related changes occurring in the body. These include dysfunction of adipose tissue, inflammaging, and oxidative str.

During aging, adipose tissue undergoes redistribution. The mass of subcutaneous fat decreases, while the reservoir of visceral fat increases. It is estimated that the mass of visceral adipose tissue increases twofold in women and fourfold in men between the 3rd and 7th decade of life [7]. This process results in IR, a higher risk of cardiovascular diseases, diabetes, and the acceleration of systemic aging. Tokubuchi et al. demonstrated that rats treated with metformin had a smaller volume of visceral adipose tissue than non-treated controls [8]. The same effect was observed in humans after 12 months of metformin therapy [9].

Brown and beige adipose tissues maintain body temperature by non-shivering thermogenesis. Their deposits decline with age, which results in disturbed energy utilization and prompts the development of obesity. Uncoupling protein 1 (UCP-1) expression decreases with age as well as the mass of brown adipose tissue (BAT) [10]. Metformin has been shown to increase UCP-1 mRNA expression in BAT. Moreover, metformin effectively reduces the expression of white adipose tissue-related genes in both the liver and visceral fat [11]. It also promotes the proliferation and differentiation of brown adipocytes, which results in an increase in BAT mass [12].

Adipose progenitor stem cells (APSCs) provide mature adipocytes, constituting the functional plasticity of adipose tissue. The proliferation and differentiation rate of APSCs decline with age, impairing lipid homeostasis in the body. Obesity is another factor prompting the dysfunction of APSCs. As a result, the liver and other tissues are exposed to greater amounts of lipotoxic free fatty acids, leading to the development of metabolic syndrome. A recent study has shown that metformin can improve the preservation of adipose stem cells by reducing their rate of proliferation and differentiation into mature adipocytes. This effect is dependent on the reduction of mTOR and ERK signaling pathways and the promotion of autophagy [13].

The accumulation of senescent cells is another component of adipose tissue aging. A decrease in cell proliferation is a major cause of lowered tissue regeneration potential, leading to systemic aging. This state results in disturbed adipogenesis, inflammation, and IR. Senescent cells can develop a senescence-associated secretory phenotype (SASP), comprising proinflammatory cytokines (IL-1β, IL-6, TNF-α), growth factors (TGF-β, VEGF), and intercellular adhesion molecules [14,15]. These are believed to further suppress adipogenesis and aggravate the aging process [16]. Metformin has been shown to decrease senescence by alleviating oxidative stress and mitochondrial dysfunction in the adipose tissue of older women. This effect is mediated by the activation of 5'AMP-activated protein kinase (AMPK) [17]. Metformin can also work independently of AMPK – it has been shown that metformin blocks the expression of proinflammatory cytokines, which are mostly regulated by NF-κB, as it inhibits the phosphorylation of the IKKα/β kinase complex needed for NF-κB activation [18]. This leads to the suppression of SASP.

The decline in APSCs, the accumulation of senescent cells, and the shift to a SASP profile lead to the infiltration of immune cells within the white adipose tissue. Metformin has been shown to exhibit immunomodulatory and immunosuppressive properties. It slows down the proliferation of lymphocytes (CD3+, CD8+) [19] and down-regulates proinflammatory cytokine secretion (IL-6, TNF-α, MCP-1) [20]. Metformin also reduces the expression of COX-2, an enzyme playing a central role in the inflammatory process [19]. The suppression of immune cell proliferation, reduction of COX-2 synthesis, and decrease in proinflammatory cytokines by metformin lead to a reduction in the low-grade inflammation that characterizes both aging and obesity.

Oxidative stress is another component of aging and obesity, damaging proteins, cells, and DNA. Metformin inhibits complex 1 of the electron transport chain, thereby reducing the production of reactive oxygen species (ROS) in mitochondria [21]. Moreover, metformin has been found to activate antioxidant signaling pathway (Nrf2/HO-1) [22]. In clinical trials, Esteghamati et al. demonstrated that markers of oxidative stress were significantly lower among patients with diabetes treated with metformin [23]. By reducing the concentration of ROS, it also countered associated DNA damage, reducing the risk of cancer development [24]. Therefore, metformin restores the balance between ROS and antioxidants.

A meta-analysis conducted by Campbell et al. proved that metformin reduces the risk of diseases of aging and can extend the lifespan of individuals [25]. It acts through various mechanisms whose effects sum up to reverse aging-associated processes. Metformin improves the function of adipose tissue, reduces inflammation, restores the ROS-antioxidant balance, and protects proteins and DNA. It enhances insulin sensitivity in tissues and improves glucose metabolism. Gathered evidence suggests that metformin might be able to prolong lifespan and reverse the pro-aging reaction of the organism to obesity.

However, even though metformin has been shown to reduce body visceral fat among adolescents with obesity, this effect was not observed among women with polycystic ovary syndrome (PCOS) [26]. The heterogeneity of different study results reveals the need for conducting systematic reviews with meta-analyses on the subject to identify the patients who would benefit most from metformin treatment. The effect of up-regulating UCP-1 mRNA expression observed in animal models was not shown among women with PCOS either (1500 mg metformin per day for 60 days) [27]. The data on improving mitochondrial function is very promising, but still not entirely conclusive [28]. Future study protocols should include interventions on different subjects (both adolescents and adults diagnosed with simple obesity, PCOS, T2DM, or non-alcoholic fatty liver disease, as well as healthy patients) and testing at several time points to verify if metformin positively influences the mass of visceral fat and BAT activity.

3. Glucagon-like peptide-1 receptor analogs (GLP-1RA)

GLP-1RA constitute a relatively novel group of drugs used to treat T2DM. Not only do they effectively lower glycaemia, but they also decrease the risk of cardiovascular incidents and preserve renal function [29]. GLP-1RA also promote weight loss and exhibit anti-inflammatory activity in various organs.

Chronic kidney disease is common among the older population and is associated with T2DM [30,31]. This suggests that controlling glucose levels, especially in

diabetic patients, is beneficial for kidneys. GLP-1 analogues present renoprotective properties, particularly affecting macroalbuminuria, in patients with T2DM [32]. In a mouse model of diabetes, exenatide was found to reduce albuminuria, glomerular hypertrophy, type IV collagen, and lipid accumulation in kidneys. It also improved glomerular hyperfiltration, ameliorated oxidative stress, and reduced macrophage infiltration [33]. Moreover, Muskiet et al. found that exenatide acutely improved glomerular filtration rate (P=0.015), effective renal plasma flow (P=0.015), and glomerular pressure (P=0.015) in men with obesity [34]. A recent clinical trial conducted by Perkovic et al. proved semaglutide to reduce the risk of major kidney disease events (kidney failure, >50% reduction of estimated glomerular filtration rate, death) by 24% compared to placebo among patients with T2DM and chronic kidney disease [35]. Additionally, Mann et al. showed that monotherapy with semaglutide reduces the risk of kidney disease events as effectively as polytherapy with semaglutide and an SGLT2 inhibitor [36].

In a study from 2012, Cechin et al. found that exenatide reduced levels of IL-1β, IL-2, IL-5, IL-7, TNF-α, and IFN-γ in human pancreatic islet cultures. Furthermore, they observed that administering the drug to immunodeficient mice that received human islet transplantation upregulated serine proteinase inhibitor 9, which promotes apoptosis, thus preventing further islet degradation [37].

Hogan et al. demonstrated that GLP-1RA therapy reduces levels of inflammatory cytokines (TNF-α, IL-1β, IL-6) and increases the secretion of anti-inflammatory adiponectin in patients with T2DM, independently of weight loss and glycemic effects [38]. They also observed a decrease in the concentration of sCD163 (an inflammatory macrophage activator), which is known to increase with age and is associated with age-related diseases [39]. This indicates that GLP-1RA exhibit anti-aging properties by modulating inflammation and immune response.

Rakipovski et al. have demonstrated that liraglutide and semaglutide reduce atherosclerosis, even independently of their beneficial effect on cholesterol levels [40]. The mechanism is not fully understood yet, although it is hypothesized that the anti-inflammatory action of GLP-1RA might prevent plaque formation [40]. It was found that liraglutide suppresses foam cell formation by downregulating CD36, which results in a lower uptake of low-density lipoprotein by these cells [41]. These results are consistent with the outcome of a meta-analysis conducted by Kristensen et al., which proved the cardioprotective effect of GLP-1RA [42].

Inflammation is associated with many diseases related to aging, including Alzheimer's disease (AD), Parkinson's disease (PD), osteoarthritis, and more [43,44]. GLP-1RA therapy has also been found to exert neuroprotective effects in AD and PD animal models by attenuating neuroinflammation, which is associated with the progression of these diseases [45]. It reduces microglial activation in mice carrying genes for amyloid precursor protein and tau plaque formation. Moreover, they preserve dopaminergic neurons and alleviate brain inflammation in mice with a PD model induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, which degrades dopaminergic neurons [46]. Athauda et al. conducted a clinical trial that revealed that exenatide improved motor scores in patients with PD [47]. Exenatide was also found effective in alleviating PD symptoms in a systematic review and meta-analysis conducted by Wang et al. [48]. A Cochrane review conducted by Mulvaney et al. indicated that there is low-certainty evidence that exenatide improves motor impairment in patients with PD, although its effect on non-motor symptoms remained unclear [49].

Moreover, Meissner et al. have proved lixisenatide to limit the progression of early PD and even cause slight improvement. Participants in the control group received a placebo, and their symptoms worsened during the course of the study (12 months) [50].

Liraglutide enhanced synaptic plasticity (induced by a weak stimulation protocol) in the hippocampus of rats, although exenatide impaired it [51]. Moreover, Gejl et al. showed that liraglutide increases glucose transfer via the blood-brain barrier and net clearances of glucose in the brain in patients with AD. This resulted in an improvement of the total cognitive score in the participants [52]the transporters become a potential target of therapy. The incretin hormone GLP-1 prevents the decline of cerebral metabolic rate for glucose (CMRglc. Unfortunately, no positive impact was observed when exenatide was given to patients with AD in Mullins et al.'s research. However, it should be mentioned that their study was terminated early [53], and therefore is not entirely conclusive. A meta-analysis performed by Bi et al. included studies with patients diagnosed with AD, diabetes mellitus, or both, and taking exenatide or liraglutide. Treatment with GLP-1RA was found to improve cognitive functions when compared to placebo. As the authors mention, only five studies were included and the sample size was limited, so the results should be interpreted with caution [54].

Moreover, a meta-analysis of preclinical studies found GLP-1RA effective in the acute treatment of ischemic stroke by reducing inflammation, endothelial leakage, oxidative stress, and apoptosis [55]. The results of these studies are promising; however, more research on human subjects is needed.

Gathered data strongly suggest that GLP-1RA exhibit anti-aging properties. These drugs have been found to prolong lifespan by reducing cardiovascular diseases and protecting renal function. Moreover, they reduce inflammation, which is another factor associated with aging. Unexpectedly, GLP-1RA were also found to improve cognition and possibly limit the progression of PD and AD.

4. Flozins – SGLT2i

The most widely used flozins are dapagliflozin, empagliflozin, tofogliflozin, and canagliflozin. They have been widely used in the treatment of T2DM due to their ability to reduce glycated hemoglobin levels without inducing hypoglycemia. Moreover, they show additional benefits, such as weight loss, and improve several biochemical parameters including lipid profile, hyperuricemia, and blood pressure.

The increasing prevalence of diabetes mellitus has led to a rise in diseases based on vascular impairment, such as retinopathy, kidney dysfunction, and diabetic foot ailments. These can be caused by vascular impairments, which are a consequence of aging. This results in arterial stiffness and accelerated pulse wave transmission. Vascular aging usually starts at the molecular level and includes factors such as DNA damage and chronic inflammation.

Chronic inflammation can lead to endothelial dysfunction and exacerbate atherosclerosis [56]. Furthermore, higher levels of CRP and IL-6 are correlated with aortic sclerosis [57]. Empagliflozin and dapagliflozin can alleviate endothelial inflammation induced by TNFα in vitro [58], and therefore decrease CRP and IL-6 secretion. DNA damage can include several forms such as partial deletions, extrusions, or double-stranded breaks. It can modulate gene expression or lead to apoptosis due to escalating damage [59].

The loss of mitochondrial membrane potential and respiratory capacity generally occurs, usually associated with an increase in oxygen free radicals [60]. Interestingly, SGLT2i prescribed under pathological conditions have revealed beneficial effects in terms of mitochondrial dynamics. Empagliflozin, for instance, has shown the ability to delay microvascular endothelial cell senescence and improve angiogenesis. It works through the activation of AMPK and the consequent inhibition of mitochondrial fission via suppression of Drp1 mitochondrial recruitment [61]. In another study, the cardioprotective effects of SGLT2i were linked to an improvement in mitochondrial functionality via the normalization of mitochondrial membrane potential, Ca2+ homeostasis, decreased ROS and RNS (reactive nitrogen species) production, a recovered ADP/ATP ratio, and balance between fusion- and fission-related proteins [62].

Moreover, empagliflozin enhanced the expression of UCP1 (probably via AMPK signaling) in mice. This led to metabolic changes and weight loss. The effect is caused by the browning of white adipose tissue and counteracts the changes occurring during aging [63]. Furthermore, a systematic review with a meta-analysis of randomized controlled trials conducted by Wang et al. revealed that SGLT2i reduce the mass of visceral adipose tissue, subcutaneous adipose tissue, and ectopic liver fat more effectively than other antidiabetic drugs and placebo [64]. Therefore, they reverse adipose tissue redistribution, which characterizes aging. However, Rayeev et al. did not report a reduction in visceral and subcutaneous adipose tissue in patients taking dapagliflozin for 12 weeks. Nevertheless, liver fat decreased significantly in participants when compared to controls (on placebo). This may suggest that longer exposure to the drug is needed to observe a positive change in adipose tissue mass and distribution.

Moreover, flozins exhibit a neuroprotective effect. They have the ability to cross the blood-brain barrier and target SGLT1 and SGLT2 receptors that are also expressed in the central nervous system [65]. Due to their ability to reduce vascular inflammation and oxidative stress, flozins can decrease cardiovascular risk. Research conducted by Irace et al. showed that 3 months of therapy with flozins regressed complex intima-media thickness, which is a marker of early atherosclerosis [66]. Atherosclerosis impairs cerebral blood flow and contributes to developing neurological dysfunctions such as dementia [67]

A recent systematic review and meta-analysis conducted by Tang et al. in 2023 showed promising results that patients taking SGLT2i have a lower risk of developing all-cause dementia. The review included three observational studies with heterogeneous results, and therefore its outcome should be interpreted with caution. However, its findings should encourage further research, as dementia is associated with major disability and a low quality of life [68].

5. Discussion

Throughout this paper, we have demonstrated that metformin, flozins, and GLP-1RA may present anti-aging properties through various mechanisms of action. All of them were found to reduce inflammation. Moreover, metformin and SGLT2i enhance mitochondrial function and therefore reduce oxidative stress caused by ROS/antioxidant imbalance. Both flozins and GLP-1RA exhibit cardio- and renoprotective effects. Metformin counteracts adipose tissue redistri-

bution, increases the mass of brown adipose tissue, and reduces cell senescence. GLP-1RA can improve cognition and alleviate the symptoms of AD and PD. These effects reverse some of the changes occurring through the course of aging, making antidiabetic drugs an interesting topic for further investigation.

Data on the positive influence of GLP-1RA on neurodegenerative disorders is limited, and therefore even meta-analyses are not entirely conclusive on their role in preventing or managing these diseases. Even if the results are promising, more research is needed to determine their efficacy. Hopefully, ongoing clinical trials with liraglutide and semaglutide (NCT04777396, NCT04777409, NCT02953665, NCT03659682) will provide us with more answers.

Although research presents us with promising results on the anti-aging properties of the aforementioned drugs, there are still not enough studies focusing on aging itself. They do not cover the topic comprehensively. In order to establish the hypothesis of anti-aging effects, more studies need to be conducted. Fortunately, there are ongoing clinical trials that aim to address this statement. One of them (NCT04401904) focuses on age-related processes and the impact on them by using SGLT2 inhibitors [69]. Another one (NCT05302596) investigates the influence of semaglutide on age-related diseases and, importantly, muscle strength, which correlates with longer preservation of health and independence [70]. Moreover, even more studies are being conducted on the role of metformin in aging and age-related biomarkers[71–73].

Considering the previously cited research, some properties were studied only on rodent models, indicating that research on humans must be included in further approaches. Different results from preclinical and clinical studies may arise from varying concentrations of the drug; for example, relative doses of metformin range from 0.15-1 for clinical trials compared to 2-45 for in vivo trials [28,74]. It would also be beneficial to delve into the topic of synergistic effects of the mentioned drugs. Moreover, further research should determine the effects and safety profile of antidiabetic drug administration with no absolute indications but as a form of prevention, aimed at extending life expectancy. Even if all of the mentioned drug classes are successfully used together, possible drug interactions should also be taken into consideration.

References

1. Ou M.Y., Zhang H., Tan P.C. et al.: Adipose Tissue Aging: Mechanisms and Therapeutic Implications. Cell Death Dis 2022; 13(4): 300. doi:10.1038/s41419-022-04752-6.
2. Ferrucci L., Fabbri E.: Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nat Rev Cardiol 2018; 15(9): 505-522. doi:10.1038/s41569-018-0064-2.
3. Corcoran C., Jacobs T.F.: Metformin. In: StatPearls; StatPearls Publishing: Treasure Island (FL); 2023.
4. Padda I.S., Mahtani A.U., Parmar M.: Sodium-Glucose Transport Protein 2 (SGLT2) Inhibitors. In: StatPearls; StatPearls Publishing: Treasure Island (FL); 2023.
5. Logan C., Costello R.A.: Glucagon-Like Peptide-1 Receptor Agonists. In: StatPearls; StatPearls Publishing: Treasure Island (FL); 2024; https://www.ncbi.nlm.nih.gov/books/NBK551568/ (accessed 05.01.2024).
6. Kopp K.O., Glotfelty E.J., Li Y. et al.: Glucagon-like peptide-1 (GLP-1) receptor agonists and neuroinflammation: Implications for neurodegenerative disease treatment. Pharmacol Res 2022; 186: 106550. doi:10.1016/j.phrs.2022.:106550.
7. Hunter G.R., Gower B.A., Kane B.L.: Age Related Shift in Visceral Fat. Int J Body Compos Res 2010; 8(3): 103-108.
8. Tokubuchi I., Tajiri Y., Iwata S. et al.: Beneficial effects of metformin on energy metabolism and visceral fat volume through a possible mechanism of fatty acid oxidation in human subjects and rats. PLoS One 2017; 12(2): e0171293. doi:10.1371/journal.pone.0171293.
9. Tock L., Dâmaso A.R., de Piano A. et al.: Long-Term Effects of Metformin and Lifestyle Modification on Nonalcoholic Fatty Liver Disease Obese Adolescents. J Obes 2010; 2010: e831901. doi:10.1155/2010/831901.
10. Zoico E., Rubele S., De Caro A. et al.: Brown and Beige Adipose Tissue and Aging. Front Endocrinol (Lausanne) 2019; 10: 368. doi: 10.3389/fendo.2019.00368.
11. Kim E.K., Lee S.H., Jhun J.Y. et al.: Metformin Prevents Fatty Liver and Improves Balance of White/Brown Adipose in an Obesity Mouse Model by Inducing FGF21. Mediators Inflamm 2016; 2016: e5813030. doi:10.1155/2016/5813030.
12. Karise I., Bargut T.C., del Sol M. et al.: Metformin enhances mitochondrial biogenesis and thermogenesis in brown adipocytes of mice. Biomed Pharmacother 2019; 111: 1156-1165. doi:10.1016/j.biopha.2019.01.021.
13. Chinnapaka S., Yang K.S., Flowers Q. et al.: Metformin Improves Stemness of Human Adipose-Derived Stem Cells by Downmodulation of Mechanistic Target of Rapamycin (mTOR) and Extracellular Signal-Regulated Kinase (ERK) Signaling. Biomedicines 2021; 9(12): 1782. doi:10.3390/biomedicines9121782.
14. De Ycaza A.E.E., Søndergaard E., Morgan-Bathke M. et al.: Senescent cells in human adipose tissue: A cross-sectional study. Obesity (Silver Spring) 2021; 29(8): 1320-1327. doi:10.1002/oby.23202.
15. Frasca D., Blomberg B.B.: Adipose tissue, immune aging and cellular senescence. Semin Immunopathol 2020; 42(5): 573-587. doi:10.1007/s00281-020-00812-1.
16. Xu M., Palmer A.K., Ding H. et al.: Targeting senescent cells enhances adipogenesis and metabolic function in old age. Elife 2015; 4: e12997. doi:10.7554/eLife.12997.
17. Le Pelletier L., Mantecon M., Gorwood J. et al.: Metformin alleviates stress-induced cellular senescence of aging human adipose stromal cells and the ensuing adipocyte dysfunction. Elife 2021; 10: e62635. doi:10.7554/eLife.62635.
18. Moiseeva O., Deschênes-Simard X., St-Germain E. et al.: Metformin inhibits the senescence-associated secretory phenotype by interfering with IKK/NF-κB activation. Aging Cell 2013; 12(3): 489-498. doi:10.1111/acel.12075.
19. Bajetto A., Pattarozzi A., Sirito R. et al.: Metformin potentiates immunosuppressant activity and adipogenic differentiation of human umbilical cord-mesenchymal stem cells. Int Immunopharmacol 2023; 124(Pt B): 111078. doi:10.1016/j.intimp.2023.111078.
20. Cruciani S., Garroni G., Pala R. et al.: Metformin and Vitamin D Modulate Inflammation and Autophagy during Adipose-Derived Stem Cell Differentiation. Int J Mol Sci 2021; 22(13): 6686. doi:10.3390/ijms22136686.
21. Fontaine E.: Metformin-Induced Mitochondrial Complex I Inhibition: Facts, Uncertainties, and Consequences. Front Endocrinol (Lausanne) 2018; 9: 753. doi: 10.3389/fendo.2018.00753.
22. Li Y., Zhou T., Edwards P.A. et al.: Metformin inhibits oxidative stress and enhances anti-oxidative signaling pathway in human retinal vascular endothelial cells. Invest Ophthalmol Vis Sci 2018; 59(9): 5479.
23. Esteghamati A., Eskandari D., Mirmiranpour H. et al.: Effects of metformin on markers of oxidative stress and antioxidant reserve in patients with newly diagnosed type 2 diabetes: A randomized clinical trial. Clin Nutr 2013; 32(2): 179-185. doi:10.1016/j.clnu.2012.08.006.
24. Algire C., Moiseeva O., Deschênes-Simard X. et al.: Metformin Reduces Endogenous Reactive Oxygen Species and

Associated DNA Damage. Cancer Prev Res (Phila) 2012; 5(4): 536-543. doi:10.1158/1940-6207.CAPR-11-0536.
25. Campbell J.M., Bellman S.M., Stephenson M.D. et al.: Metformin Reduces All-Cause Mortality and Diseases of Ageing Independent of Its Effect on Diabetes Control: A Systematic Review and Meta-Analysis. Ageing Res Rev 2017; 40: 31-44. doi:10.1016/j.arr.2017.08.003.
26. Lord J., Thomas R., Fox B. et al.: The effect of metformin on fat distribution and the metabolic syndrome in women with polycystic ovary syndrome—a randomised, double-blind, placebo-controlled trial. BJOG Int J Obstet Gynaecol 2006; 113(7): 817-824. doi:10.1111/j.1471-0528.2006.00966.x.
27. Oliveira F.R., Mamede M., Bizzi M.F. et al.: Effects of Short Term Metformin Treatment on Brown Adipose Tissue Activity and Plasma Irisin Levels in Women with Polycystic Ovary Syndrome: A Randomized Controlled Trial. Horm Metab Res 2020; 52(10): 718-723. doi:10.1055/a-1157-0615.
28. Mohammed I., Hollenberg M.D., Ding H. et al.: A Critical Review of the Evidence That Metformin Is a Putative Anti-Aging Drug That Enhances Healthspan and Extends Lifespan. Front Endocrinol (Lausanne) 2021; 12: 718942. doi:10.3389/fendo.2021.718942.
29. Basalay M.V., Mastitskaya S., Mrochek A. et al.: Glucagon-like peptide-1 (GLP-1) mediates cardioprotection by remote ischaemic conditioning. Cardiovasc Res 2016; 112(3): 669-676. doi:10.1093/cvr/cvw216.
30. Levey A.S., Inker L.A., Coresh J.: Chronic Kidney Disease in Older People. JAMA 2015; 314(6): 557-558. doi:10.1001/jama.2015.6753.
31. Pyram R., Kansara A., Banerji M.A. et al: Chronic Kidney Disease and Diabetes. Maturitas 2012; 71: 94-103. doi:10.1016/j.maturitas.2011.11.009.
32. Vitale M., Haxhi J., Cirrito T. et al.: Renal protection with glucagon-like peptide-1 receptor agonists. Curr Opin Pharmacol 2020; 54: 91-101. doi:10.1016/j.coph.2020.08.018.
33. Filippatos T.D., Elisaf M.S.: Effects of glucagon-like peptide-1 receptor agonists on renal function. World J Diabetes 2013; 4(5): 190-201. doi:10.4239/wjd.v4.i5.190.
34. Muskiet M.H.A., Tonneijck L., Smits M.M. et al.: Acute renal haemodynamic effects of glucagon-like peptide-1 receptor agonist exenatide in healthy overweight men. Diabetes Obes Metab 2016; 18(2): 178-185. doi:10.1111/dom.12601.
35. Perkovic V., Tuttle K.R., Rossing P. et al.: Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes. N Engl J Med 2024; 3912): 109-121. doi:10.1056/NEJMoa2403347.
36. Mann J.F.E., Rossing P., Bakris G. et al.: Effects of semaglutide with and without concomitant SGLT2 inhibitor use in participants with type 2 diabetes and chronic kidney disease in the FLOW trial. Nat Med 2024; 1-1. doi:10.1038/s41591-024-03133-0.
37. Cechin S.R., Pérez-Álvarez I., Fenjves E. et al.: Anti-Inflammatory Properties of Exenatide in Human Pancreatic Islets. Cell Transplant 2012; 21(4): 633-648. doi:10.3727/096368911X576027.
38. Hogan A.E., Gaoatswe G., Lynch L. et al.: Glucagon-like peptide 1 analogue therapy directly modulates innate immune-mediated inflammation in individuals with type 2 diabetes mellitus. Diabetologia 2014; 57(4): 781-784. doi:10.1007/s00125-013-3145-0.
39. Martin G.E., Gouillou M., Hearps A.C. et al.: Age-Associated Changes in Monocyte and Innate Immune Activation Markers Occur More Rapidly in HIV Infected Women. PLoS One 2013; 8(1): e55279. doi:10.1371/journal.pone.0055279.
40. Rakipovski G., Rolin B., Nøhr J. et al.: The GLP-1 Analogs Liraglutide and Semaglutide Reduce Atherosclerosis in ApoE-/- and LDLr-/- Mice by a Mechanism That Includes Inflammatory Pathways. JACC Basic Transl Sci 2018; 3(6): 844-857. doi:10.1016/j.jacbts.2018.09.004.
41. Tashiro Y., Sato K., Watanabe T. et al.: A glucagon-like peptide-1 analog liraglutide suppresses macrophage foam cell formation and atherosclerosis. Peptides 2014; 54: 19-26. doi:10.1016/j.peptides.2013.12.015.
42. Kristensen S.L., Rørth R., Jhund P.S. et al.: Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet Diabetes Endocrinol 2019; 7(10): 776-785. doi:10.1016/S2213-8587(19)30249-9.
43. McGeer P.L., McGeer E.G.: Inflammation and the Degenerative Diseases of Aging. Ann N Y Acad Sci 2004; 1035: 104-116. doi:10.1196/annals.1332.007.
44. Fülöp T., Larbi A., Witkowski J.M.: Human Inflammaging. Gerontology 2019; 65(5): 495-504. doi:10.1159/000497375.
45. Batista A.F., Bodart-Santos V., De Felice F.G. et al.: Neuroprotective Actions of Glucagon-Like Peptide-1 (GLP-1) Analogues in Alzheimer's and Parkinson's Diseases. CNS Drugs 2019; 33(3): 209-223. doi:10.1007/s40263-018-0593-6.
46. Feng P., Zhang X., Li D. et al.: Two novel dual GLP-1/GIP receptor agonists are neuroprotective in the MPTP mouse model of Parkinson's disease. Neuropharmacology 2018; 133: 385-394. doi:10.1016/j.neuropharm.2018.02.012.
47. Athauda D., Maclagan K., Skene S.S. et al.: Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo-controlled trial. Lancet 2017; 390(10103): 1664-1675. doi:10.1016/S0140-6736(17)31585-4.
48. Wang S.Y., Wu S.L., Chen T.C. et al.: Antidiabetic Agents for Treatment of Parkinson's Disease: A Meta-Analysis. Int J Environ Res Public Health 2020; 17(13): 4805. doi:10.3390/ijerph17134805.
49. Mulvaney C.A., Duarte G.S., Handley J. et al.: GLP-1 Receptor Agonists for Parkinson's Disease. Cochrane Database Syst Rev 2020; 7(7): CD012990. doi:10.1002/14651858.CD012990.pub2.
50. Meissner W.G., Remy P., Giordana C. et al.: Trial of Lixisenatide in Early Parkinson's Disease. N Engl J Med 2024; 390(13): 1176-1185. doi:10.1056/NEJMoa2312323.
51. McClean P.L., Gault V.A., Harriott P. et al.: Glucagon-like peptide-1 analogues enhance synaptic plasticity in the brain: A link between diabetes and Alzheimer's disease. Eur J Pharmacol 2010; 630(1-3): 158-162. doi:10.1016/j.ejphar.2009.12.023.
52. Gejl M., Brock B., Egefjord L. et al.: Blood-Brain Glucose Transfer in Alzheimer's Disease: Effect of GLP-1 Analog Treatment. Sci Rep 2017; 7(1): 17490. doi:10.1038/s41598-017-17718-y.
53. Mullins R.J., Mustapic M., Chia C.W. et al.: A Pilot Study of Exenatide Actions in Alzheimer's Disease. Curr Alzheimer Res 2019; 16(8): 741-752. doi:10.2174/1567205016666190913155950.
54. Bi Z., Wang L., Wang W.: Evaluating the effects of glucagon-like peptide-1 receptor agonists on cognitive function in Alzheimer's disease: A systematic review and meta-analysis. Adv Clin Exp Med 2023; 32(11): 1223-1231. doi:10.17219/acem/161734.
55. Marlet I.R., Ölmestig J.N.E., Vilsbøll T. et al.: Neuroprotective Mechanisms of Glucagon-like Peptide-1-Based Therapies in Ischaemic Stroke: A Systematic Review Based on Pre-Clinical Studies. Basic Clin Pharmacol Toxicol 2018; 122(6): 559-569. doi:10.1111/bcpt.12974.
56. Chao J., Guo Y., Chao L.: Protective Role of Endogenous Kallistatin in Vascular Injury and Senescence by Inhibiting Oxidative Stress and Inflammation. Oxid Med Cell Longev 2018; 2018: 4138560. doi:10.1155/2018/4138560.
57. Donato A.J., Machin D.R., Lesniewski L.A.: Mechanisms of Dysfunction in the Aging Vasculature and Role in Age-Related Disease. Circ Res 2018; 123(7): 825-848. doi:10.1161/CIRCRESAHA.118.312563.
58. Uthman L., Homayr A., Juni R.P. et al.: Empagliflozin and Dapagliflozin Reduce ROS Generation and Restore NO Bioavailability in Tumor Necrosis Factor α-Stimulated Human Coronary Arterial Endothelial Cells. Cell Physiol Biochem Int J Exp Cell Physiol Biochem Pharmacol 2019; 53(5): 865-886. doi:10.33594/000000178.
59. Martinet W., Knaapen M.W.M., De Meyer G.R.Y. et al.: Elevated Levels of Oxidative DNA Damage and DNA Repair Enzymes in Human Atherosclerotic Plaques. Circulation 2002; 106(8): 927-932. doi:10.1161/01.cir.0000026393.47805.21.
60. López-Otín C., Blasco M.A., Partridge L. et al.: The Hallmarks of Aging. Cell 2013; 153(6): 1194-1217. doi:10.1016/j.cell.2013.05.039.
61. Zhou H., Wang S., Zhu P. et al.: Empagliflozin rescues diabetic myocardial microvascular injury via AMPK-mediated inhibition of mitochondrial fission. Redox Biol 2018; 15: 335-346. doi:10.1016/j.redox.2017.12.019.
62. Durak A., Olgar Y., Degirmenci S. et al.: A SGLT2 inhibitor dapagliflozin suppresses prolonged ventricular-repolarization through augmentation of mitochondrial function in insulin-resistant metabolic syndrome rats. Cardiovasc Diabetol 2018; 17(1): 144. doi:10.1186/s12933-018-0790-0.
63. Xu L., Xu C., Liu X. et al.: Empagliflozin Induces White Adipocyte Browning and Modulates Mitochondrial Dynamics

in KK Cg-Ay/J Mice and Mouse Adipocytes. Front Physiol 2021; 12: 745058. doi:10.3389/fphys.2021.: 745058.
64. Wang X., Wu N., Sun C. et al.: Effects of SGLT-2 inhibitors on adipose tissue distribution in patients with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. Diabetol Metab Syndr 2023; 15(1): 113. doi:10.1186/s13098-023-01085-y.
65. Tahara A., Takasu T., Yokono M. et al.: Characterization and comparison of sodium-glucose cotransporter 2 inhibitors in pharmacokinetics, pharmacodynamics, and pharmacologic effects. J Pharmacol Sci 2016; 130(3): 159-169. doi:10.1016/j.jphs.2016.02.003.
66. Irace C., Casciaro F., Scavelli F.B. et al.: Empagliflozin influences blood viscosity and wall shear stress in subjects with type 2 diabetes mellitus compared with incretin-based therapy. Cardiovasc Diabetol 2018; 17: 52. doi:10.1186/s12933-018-0695-y.
67. Shabir O., Berwick J., Francis S.E.: Neurovascular dysfunction in vascular dementia, Alzheimer's and atherosclerosis. BMC Neurosci 2018; 19: 62. doi:10.1186/s12868-018-0465-5.
68. Tang H., Shao H., Shaaban C.E. et al.: Newer glucose-lowering drugs and risk of dementia: a systematic review and meta-analysis of observational studies. J Am Geriatr Soc 2023; 71(7): 2096-2106. doi:10.1111/jgs.18306.
69. Study Details: SGLT2 Inhibition in Older Obese Adults with Pre-Diabetes. ClinicalTrials.gov; https://clinicaltrials.gov/study/NCT04401904?term=Aging&intr=SGLT2%20inhibitor&rank=2 (accessed 03.01.2024).
70. Study Details: Semaglutide Use in Elderly Obese Patients. ClinicalTrials.gov; https://clinicaltrials.gov/study/NCT05302596?term=Aging&intr=GLP1%20receptor%20agonist&rank=1 (accessed 03.01.2024).
71. Study Details: Antecedent Metabolic Health and Metformin Aging Study. ClinicalTrials.gov; https://clinicaltrials.gov/study/NCT04264897?term=Aging&intr=Metformin&rank=1 (accessed 03.01.2024).
72. Study Details: Metformin in Longevity Study (MILES). ClinicalTrials.gov; https://clinicaltrials.gov/study/NCT02432287?term=Aging&intr=Metformin&rank=2 (accessed 03.01.2024).
73. Study Details: Effect of Metformin on Frailty in 12 Subjects. ClinicalTrials.gov; https://clinicaltrials.gov/study/NCT03451006?term=Aging&intr=Metformin&rank=3 (accessed 03.01.2024).
74. Badrick E., Renehan A.G.: Diabetes and cancer: 5 years into the recent controversy. Eur J Cancer 2014; 50(12): 2119-2125. doi:10.1016/j.ejca.2014.04.032.

Conflict of interest

Michał Lis reports receiving lecture fees from Novo Nordisk, AstraZeneca, Sanofi, Boehringer Ingelheim International. Tymoteusz Miłuch, Mateusz Mucha, Zuzanna Roszkowska and Grzegorz Krupiński declare no conflict of interest.

Correspondence address:

Tymoteusz Miłuch
Czerniakowski Hospital in Warsaw
Internal Medicine Department with Endocrinology and Diabetology Subdepartment and Nephrology Subdepartment with Dialysis Station
Stępińska 19/25 St.
00-739 Warsaw, Poland
e-mail:
tymoteusz.miluch@szpitalczerniakowski.waw.pl