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editorial-office@sciformat.ca

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A LITERATURE REVIEW OF SGLT2 INHIBITORS IMPACT ON MAJOR NEURODEGENERATIVE DISORDERS INCLUDING ALZHEIMER AND PARKINSON DISEASE

Jakub Jucha
Jagiellonian University Medical College, Kraków, Poland
ORCID ID: 0009-0001-4189-6750

Dominik Zając *(Corresponding Author, Email: dominik.zajac.science@gmail.com)*
Central Clinical Hospital of UCC WUM, Warszawa, Poland
ORCID ID: 0009-0004-0415-5322

Dominika Darasz
Medical University of Warsaw, Warszawa, Poland
ORCID ID: 0009-0009-5576-9697

Artur Łukawski
Central Clinical Hospital of UCC WUM, Warszawa, Poland
ORCID ID: 0009-0006-6252-1655

Lesia Slobozheniuk
Central Clinical Hospital of UCC WUM, Warszawa, Poland
ORCID ID: 0009-0006-8432-568X

Magdalena Bieniak
Praski Hospital of the Transfiguration of Our Lord, Warszawa, Poland
ORCID ID: 0009-0000-1472-7532

Marta Kaczorek
Institute of Psychiatry and Neurology, Warszawa, Poland
ORCID ID: 0009-0007-1406-2076

Krzysztof Machnik
Stefan Żeromski Specialist Hospital in Kraków, Kraków, Poland
ORCID ID: 0009-0000-3345-8593

Oliwia Dziewięcka
A. Falkiewicz Specialist Hospital in Wrocław, Poland
ORCID ID: 0009-0008-7784-1680

Wojciech Ziębka
A. Falkiewicz Specialist Hospital in Wrocław, Poland
ORCID ID: 0009-0000-6835-6773

ABSTRACT

SGLT2i (sodium-glucose cotransporter 2 inhibitors), also called flozins or gliflozins, are a group of hypoglycemic agents that have revolutionized the approach in treatment of T2DM (type 2 diabetes mellitus). Recent years have witnessed a rise in number of neurological conditions, which requires novel approaches to be examined to provide neuroprotection in these patients. Some studies suggest that presence of SGLT2 receptors in the central nervous system can provide possible neuroprotective properties in Alzheimer and Parkinson disease with the use of SGLT2i. We aimed in this review to summarize current evidence of SGLT2i impact on the central nervous system (CNS), as well to define their potential role in the comprehensive management of patients with neurologic disorders.

Methods and materials: A qualitative synthesis of the data focusing on SGLT2 inhibitors, Alzheimer and Parkinson disease was performed. This literature review of SGLT2 inhibitors effect on neuroprotection in neurodegenerative disorders included recent publications, primarily from the past 10 years, and was conducted from November 2023 to May 2026 using the PubMed database.

We performed a systematic search using specific keywords and medical subject headings (MeSH terms) related to SGLT2 inhibitors, Alzheimer and Parkinson disease. The primary search terms were: “SGLT2 inhibitors”, “sodium-glucose cotransporter 2 inhibitors”, “Alzheimer disease”, “Parkinson disease”, “neuroprotection”, “mild cognitive impairment”, and “flozins”. The criteria for inclusion of articles were as follows: published before May 2026, written in English, peer-reviewed original research articles. Exclusion criteria included publications not available in full text, articles in languages other than English. Editorials, commentaries, and conference abstracts without full data were also excluded. Titles and abstracts of the retrieved articles were screened to determine eligibility based on the inclusion and exclusion criteria.

KEYWORDS

SGLT2, Sodium-Glucose Cotransporter-2 Inhibitors, Alzheimer Disease, Parkinson Disease

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Introduction.

Glucose is a vital fuel for the body's energy production and is essential for many metabolic processes. To transport glucose effectively, the body uses several different transporter proteins, one of which is sodium-glucose linked transporter 2 (SGLT2), also known as the sodium-glucose cotransporter. SGLT2 is a member of the SGLT protein family and is responsible for reabsorbing almost all of the 180 g of glucose that is filtered by the kidneys each day. In people with type 2 diabetes, SGLT2 may be overactive, leading to elevated levels of glucose in the blood. SGLT2 inhibitors are a class of medications widely used in type 2 diabetes treatment. They work by inhibiting the activity of a SGLT2 which helps the body remove excess glucose from the blood and reduce its high blood levels.

SGLT2 inhibitors are usually taken orally and are often used in combination with other anti-diabetic medications, such as metformin or insulin. They are generally well tolerated and have been shown to be effective at lowering blood sugar levels and reducing the risk of complications in people with type 2 diabetes. Common side effects of SGLT2i may include genital infections, urinary tract infections, and increased risk of bone fractures. SGLT2i should not be used by people with certain medical conditions, such as severe kidney disease, and in people at risk for low blood pressure or dehydration.

In addition to being used to treat type 2 diabetes, SGLT2i may also be used to treat other conditions. A large body of research has suggested that SGLT2i may have potential benefits for people with heart failure, as they may help reduce the risk of hospitalization and improve quality of life in people with this condition. SGLT2i may also be used off-label to treat other conditions, such as diabetic nephropathy and nonalcoholic fatty liver disease. Finally, there were reports suggesting that SGLT2i may have neuroprotective effects. Some

research has found that SGLT2i may help reduce the risk of cognitive decline in people with type 2 diabetes and may also have protective effects against certain neurological conditions, such as Parkinson's disease and multiple sclerosis. In our work we want to better assess the potential role of SGLT2i in the neurological field. The information of the SGLT2i impact on the nervous system and certain neurological conditions from accessible literature was collected and properly analyzed to provide better comprehension in this area.

1. SGLT2 inhibitors.

SGLT2i (sodium-glucose cotransport 2 inhibitors) are revolutionary oral hypoglycemic agents that have just been positioned in the management of treatment of type 2 diabetes mellitus (T2DM) and due to their many pleiotropic effects such as cardiovascular benefits (significant blood pressure reduction) and neuroprotective potential (anti-inflammatory and anti-atherosclerotic action; oxidative stress reduction) [1], [2], they greatly improve the quality of life and reduce patients' medical expenses [3]. However, clinical trials performed on patients with type 1 diabetes mellitus (T1DM), showed that SGLT2i apart from improving HbA1c, reducing body weight and improving blood pressure, increase the risk of diabetic ketoacidosis (DKA). For this reason, SGLT2i are still being evaluated for use in patients with T1DM [4]. SGLT2i, also called flozins or gliflozins, such as Dapagliflozin, Canagliflozin, Empagliflozin and Ertugliflozin are approved by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) to clinical use [2]. It is also worth mentioning that Sotagliflozin, dual inhibitor of both types of SGLTs (SGLT1 and SGLT2) [5], [6], has been recently approved for treatment in both diabetes mellitus type 1 and type 2 [6]. Although, main affinity of SGLT2 inhibitors is apical SGLT2 protein, there have been observed differences in selectivity profiles between SGLT2i [7].

SGLT2 blockers are high-affinity, competitive [8] inhibitors which preferentially bind to the external surface of the SGLTs in the luminal membrane of the epithelial cells in the proximal tubule of kidney [1], [8], [9]. The binding is possible only in the presence of Na^+ [8], [9] and results in locking the transporter in an outward-facing conformation [8] and blocking glucose reabsorption from the urine by 40-50%. Therefore, their main physiological action is lowering blood glucose levels by reducing glucose reabsorption to approximately 100-130 g/day and greater urinary glucose excretion (UGE) up to 50-80 g/day [1], [2], [8]. Excretion of 50-80g glucose (which corresponds to 200-320 kcal of energy) induces weight loss, which may lead to sarcopenia in elderly patients [10]. Thus, SGLT2i have glycosuric and natriuretic properties, which by lowering pathological hyperfiltration, may have beneficial effect on renal protection [6]. The induction of the diuresis by SGLT2i is related to elevation of urine pH and small increase in bicarbonate excretion but its mechanism is unclear. Natriuretic properties of flozins may be associated with the suppression of the Na^+/H^+ exchanger 3 (NHE3) [6], [11]. The mechanisms of SGLT2 inhibition by flozins are presented in **Fig. 1**.

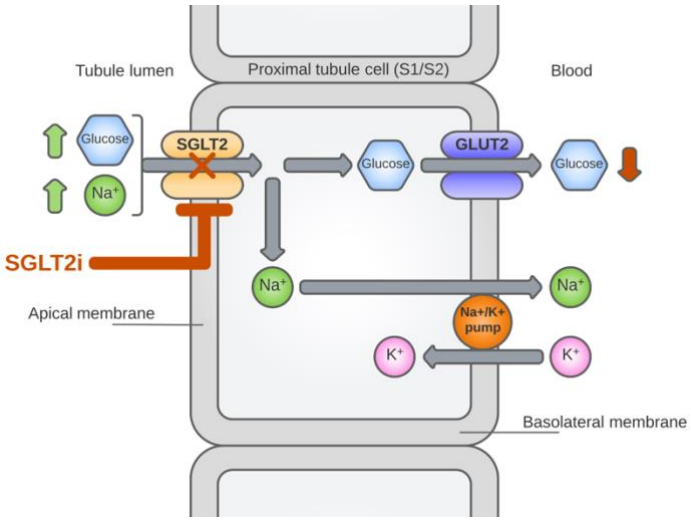

Fig. 1. *Main effects of SGLT2 inhibition in kidneys. SGLT2 – sodium-glucose cotransporter 2; SGLT2i – sodium-glucose cotransporter 2 inhibitors; GLUT2 – glucose transporter 2; ↑ – increase; ↓ – decrease; X – inhibition.*

2. Distribution of SGLT receptors in the central nervous system.

SGLT2i are believed to have neuroprotective properties and to positively impact cognitive functions due to their ability to cross blood-brain barrier (BBB). Many studies state that significant expression of SGLT2 can be found, beyond the blood-brain barrier endothelial cells, in various areas of the brain, including the hippocampus and cerebellum, as well as the choroid plexus epithelium, ependymal cells, amygdala, hypothalamus, periaqueductal grey (PAG), nucleus of the solitary tract (NTS) and microvessels in human brain (shown on **Fig. 2**) [1], [12], [13]. It is interesting to note that the presence of SGLT2 in choroid plexus epithelial cells and ependymal cells may affect the composition of cerebrospinal fluid (CSF) [1], [14]. SGLT1, which is significantly more prevalent, has been found in cortical pyramidal cells, hippocampus pyramidal and granular cells, as well as in the cerebellar Purkinje cells, microvessels and ventromedial hypothalamus nuclei [1], [13], [15].

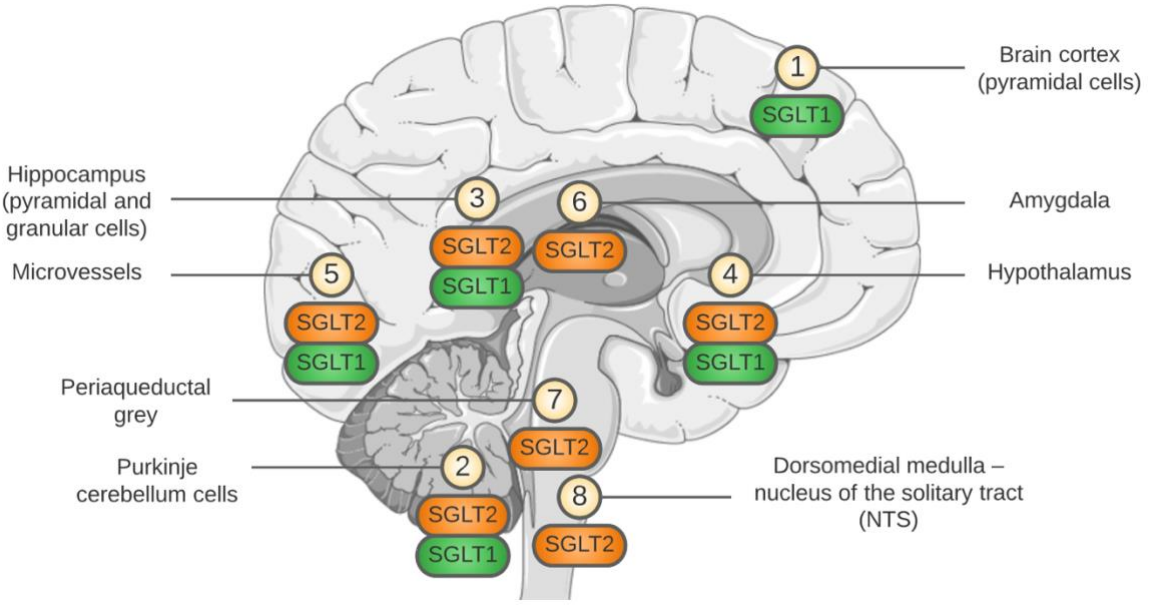

Fig. 2. *Distribution of SGLT receptors in the central nervous system (CNS): 1 – Pyramidal cells of brain cortex; 2 – Purkinje cerebellum cells; 3 – Hippocampus pyramidal and granular cells; 4 – Hypothalamus; 5 – Microvessels; 6 – Amygdala cells; 7 – Periaqueductal grey (PAG); 8 – Dorsomedial medulla, nucleus of the solitary tract (NTS). Figure modified with text based on References [1], [13], [15], [16] after adaptation of "Brain" from Servier Medical Art by Servier, licensed under a Creative Commons Attribution 3.0 Unported License [17].*

SGLT2 inhibitors are lipid-soluble and able to cross BBB, reaching the brain:serum ratio from 0.3 to 0.5 [1]. That passage is even enhanced in brain pathologies causing disruption of the BBB [18]. Thus, SGLT2i may exert their effect on central nervous system both in direct and indirect way, and this is by binding to the SGLT proteins in brain and by lowering plasma glucose levels, respectively. Also, significant upregulation of SGLT has been described after traumatic brain injury, and this might be responsible for increased glucose uptake by brain after trauma [19]. SGLT1 protein expression rose significantly 52h after injury and peaked at 72h, whereas SGLT2 increased 52h and 72h post injury. According to the authors, taking advantage of that phenomenon may be used in forensic practice to determine whether traumatic brain injury occurred and time of the injury.

Alzheimer disease (AD) and mild cognitive impairment (MCI).

MCI is a neurocognitive disorder where cognitive impairments are beyond those expected by the person age, but they are not severe enough to classify them as dementia. MCI in common in T2D patients – the combined prevalence of MCI in T2D patients estimated to be 45.0% (95% CI=36.0, 54.0) [20].

Alzheimer disease is an irreversible neurodegenerative disease and global leading cause of dementia. It accounts for 60-80% of all causes of dementia [21]. In Europe, the prevalence of Alzheimer's disease was estimated at 5.05% (95% CI, 4.73-5.39) in patients above 65 years old, whereas the incidence was 11.08 per

1000 person-years (95% CI, 10.30-11.89) [22]. Clinically, AD is associated with progressive and irreversible neuron loss especially in cortical areas, which leads to a memory and other cognitive function loss, but also personality and behavioral changes. Disease eventually leads to disability and premature death and its progress cannot be stopped, though it can be delayed.

Although the age is undoubtedly the most important risk factor for development of the Alzheimer disease [23], T2D and glucose metabolism deregulation also seems to hold huge significance. The study performed by Juliette Janson et al. showed that diabetes or glucose intolerance might be present in up to 80% patients with AD [24]. Geert Jan Biessels et al. showed in their epidemiological study that T2D increases the risk of development of AD 1.5-2 times. In fact, mechanism of diabetes mellitus like insulin resistance and IGF signaling disruption tend to overlap with pathogenesis of AD to that extend, that the Alzheimer disease is frequently called “Type 3 diabetes” by many authors [22], [25], [26]. Diabetes mellitus may also accelerate transition from MCI to dementia, and it might be associated with other neuropsychiatric conditions, such as depression, anxiety. Thus, good diabetes control may reduce the mental health complications in patients with psychiatric conditions [26].

Several pathophysiological and metabolic abnormalities have been associated with AD. Those are chronic inflammation, impaired insulin and IGF signalization, increased permeability of BBB that could be a complication of inflammation process, amyloid extracellular deposition called amyloid plaques, forming of neurofibrillary tangles containing hyperphosphorylated Tau protein intracellularly, mitochondrial dysfunction and oxidative stress. SGLT2i may ameliorate AD symptoms and slow down disease progress by influencing those processes in different ways [27], [28], [29], [30].

First, SGLT2i, such as Empagliflozin can reduce insulin levels, increase glucagon levels and increase serum beta-hydroxybutyrate (BHB) and non-esterified fatty acids (NEFAs) – that was shown by Avgerinos et al. in patients without diabetics [31]. Similar effect was presented by Kullmann et al. in patients with prediabetes – they showed that Empagliflozin treatment can improve and restore insulin sensitivity in hypothalamus in those patients. In that experiment, conducted by using fMRI measurement of cerebral blood flow (CBF) and performing nasal insulin administration to the brain researchers showed significant ($p=0.019$) change in hypothalamic sensitivity in Empagliflozin-treated group in comparison to placebo group, so as significant ($p=0.04$) change in Empagliflozin group before and after 8 weeks treatment [32]. They also suggest that Empagliflozin should be positioned as the first pharmacological approach to reverse the brain insulin resistance. The brain was long thought to be an insulin independent organ, as its glucose use does not depend on insulin. However, in recent years an abundance of insulin receptors was identified in the brain, and it was appreciated that insulin signaling can influence variety of brain functions, affecting both cognitive and metabolic outcomes [33]. That insulin sensitivity restoring effect is particularly important in inhibiting advancement of AD because, as mentioned before, many scientists associate AD development and progression with insulin resistance [30], [34], [35].

Elevated BHB levels were observed after chronic and acute administration of Empagliflozin in non-diabetic population. This might be important because accumulating evidence signifies that ketones are efficient alternative for glucose to the cerebral tissue and could be used in chronic neurodegenerative disorders where there is altered glucose utilization by the brain [46], [35]. Furthermore, blood ketone bodies like BHB can modulate NLRP3 inflammasome-IL1β signaling [36], a pathologic pathway that is thought to be especially important in AD [37]. The NOD-, LRR- and pyrin domain containing protein 3 (NLRP3) inflammasome is a critical component of the innate immune system that mediates caspase-1 activation and secretion of proinflammatory cytokines IL-1β and IL-18 in response to infection or cellular damage [38]. Aberration of that signaling pathway has been found in many diseases with inflammatory background like AD. BHB can inhibit that pathway and thus can reduce chronic inflammation observed in AD. According to that phenomenon increasing levels of ketone bodies, such as BHB can be beneficial to patients with AD and other neurodegenerative diseases.

What is more, the study found that Empagliflozin may decrease potentially harmful excitatory neurotransmission by decreasing levels of glutamine and glutamate [39] – the latter is well known for its effect called “excitotoxicity”, where too strong and prolonged stimulation of neuron by excitatory glutamate results in metabolic dysregulation of neurons and eventually cell death [40]. That effect may be induced trough elevation of BHB levels – BHB has been shown to decrease glutamate levels in vitro, probably due to reduced accessibility of reduced nicotinamide adenine dinucleotide (NADH) for cytosolic malate dehydrogenase which resulted in inhibition of malate-aspartate shuttle activity, that in turn is hypothesized to have an obligatory involvement for glutamate formation [41].

Solitary administration of Empagliflozin was also associated with increased levels phosphorylated insulin-like growth factor-1 receptor (pIGF-1R) phosphorylated insulin receptor (pIR), phosphorylated-in-tyrosine insulin receptor substrate-1 (pY-IRS-1), and phosphorylated protein kinase B or AKT (pAKT) in extracellular vesicles enriched for neuronal origin (NEVs). That effect holds significant relevance, because AD and its progression was associated with these NEV biomarkers abnormalities [53], [42]. However, elevated levels of those factors were observed only after first administration of Empagliflozin but not after 14 days [39]. Whether this effect can be sustained requires further investigation.

The pathogenesis and progress of AD has been also associated with unrestrained chronic mTOR pathway activation [43], [44]. The mammalian target of rapamycin (mTOR) signaling pathway seems to be a key determinant in sensing of the nutrients and regulating cell growth and autophagy [45], [46]. Generally, mTOR is responsible for docking into the lysosomal surface and regulating lysosomal acidification and protein breakdown. High levels of nutrients and growth factors activate mTOR, permitting it to dock to the lysosomal surface, allowing it to stop protein degradation and driving anabolic intracellular signaling. Overactivity of mTOR, driven for example by glucose excess, can lead to inhibition of amyloid precursor protein (APP) degradation, leading to accumulation of APP in lysosomes. That can ultimately cause disruption of lysosomes integrity and leak of the cathepsins into the cytoplasm, resulting in cellular death [60], [47]. Physiologically, mTOR in the central nervous system is involved in variety of processes, such as synaptic plasticity (especially in hippocampus), memory preservation and neuronal recovery. Dysregulation of beforementioned pathway is emerging as an important factor in many human diseases, inter alios AD [45]. That chronic activation of mTOR pathway may result in sustaining metabolic and mitochondrial dysfunction, breakdown of the BBB by endothelial dysfunction, and also driving hyperphosphorylation of tau and formation of amyloid plaques in brain [61], [48]. SGLT2i can mediate mTOR inhibition indirectly, via continuous loss of glucose in the urine. Thus, by restoring appropriate mTOR signaling SGLT2i can prevent the progression of AD [49].

Administration of Empagliflozin was also associated with amelioration of cerebral oxidative stress and increased levels of brain-derived neurotrophic factor (BDNF) in rats [50]. Lin et al. showed that Empagliflozin treatment reduced cerebral superoxide and 8-OHdG (8-hydroxy-deoxyguanosine), which aligned with reduction of cerebral NADPH oxidase subunit. That effect combined with elevation of BDNF levels was supposedly responsible for prevention of cognitive function impairment in tested rats. Chronic oxidative stress is also a widely discussed factor considered in Alzheimer pathogenesis and progression [27], [51], partially because brain is more vulnerable than other organs to oxidative stress and many components of neurons can be oxidized. Oxidative stress can promote amyloid deposition and tau hyperphosphorylation which are key components of AD, and that can further cause cell damage and death [52]. Moreover, BDNF plasma levels tends to be decreased in patients with T2D, so as BDNF output from human brain is also inhibited when glucose levels are elevated [53]. Also, disruption in BDNF biosynthesis and signaling is associated with AD [54], [55]. Thus, mitigating oxidative stress and elevating BDNF levels may be beneficial for patients suffering from AD.

Another possible mechanism of SGLT2i influence on the AD is direct interaction with brain acetylcholinesterase (AChE). AChE is a serine protease, that hydrolyses neurotransmitter acetylcholine into acetate and choline, thus prevents it from binding with postsynaptic receptors and neurotransmission [56]. Brain AChE is primary target of most prevalent anti-AD drugs, such as donepezil, rivastigmine and galantamine. They inhibit AChE and in result increase the concentration of acetylcholine in brain, which concentration is thought to be decreased in the CNS of patients with AD [57]. It has been shown that Dapagliflozin interacts with 19 AChE amino acids residues, which residues plays important role in substrate binding, hence Dapagliflozin may directly inhibit AChE [58]. Arafa et al. showed an improvement in behavioral tests in scopolamine-induced memory impairment in rats after administration of Canaglizflozin, and this could be due to an improvement in memory mediated by AChE inhibition. What study also found was significant increase in hippocampus M1 AChE receptor, what as well may be associated with cognitive improvement [59].

Parkinson's disease (PD).

Parkinson's disease is the second most common neurodegenerative disease, with global prevalence doubling from 1990 to 2015 and reaching 6 million people worldwide. It is estimated that the number of patients suffering from PD will double again reaching the number of 12 million by 2040. Considering other factors, like increasing longevity, industrialization and decreased smoking rates that number can raise to over 17 million. According to that, some scientists coined a term "Parkinson pandemic" [60] to emphasize its increasing prevalence.

PD clinically presents with motor symptoms, characterized by bradykinesia – slowness of movement and decrease in its amplitude, rest tremor and abnormalities in posture and gait [61]. Those motor disturbances cause progressive disability and increasing reduction in quality of patient's life. Motor changes are linked to degeneration of substantia nigra (especially pars compacta) and depletion of dopamine transmission to other parts of the brain, most notably to striatum [62]. Although the disease is primarily defined as movement disorder, other symptoms are also prominent and becoming increasingly significant as the disease progresses. Especially important are neuropsychiatric symptoms, such as depression, anxiety, cognitive function loss, apathy and others. Those symptoms are among the most common non-motor features of PD [63]. Other symptoms include hyposmia, constipation, reduced gastric emptying, erectile dysfunction and much more. They are linked to various pathological mechanisms, such as autonomic and more generally peripheral nervous system disfunction [64].

Although the disease is considered as uncurable, there are treatments available to relieve symptoms, improve quality of life and generally inhibit the disease progression. The most effective medication available for treating motor symptoms is levodopa [65]. The evidence regarding SGLT2i usefulness in PD patients is limited, however some trials have been performed.

Throughout the years growing evidence was gathered regarding connections between PD and diabetes mellitus. As it turns out, diabetes is not only associated with higher risk of developing PD but also with its quicker progression, faster advancing disability and worse answer for treatment – generally worse PD phenotype [66], [67], [68]. Additionally, 50-80% of patients with PD may have abnormal glucose tolerance [69]. PD and T2D share common pathogenetic features, such as disruption of insulin signaling that can lead to insulin dysregulation, mitochondrial dysfunction, oxidative stress, inflammation in CNS and finally degeneration of neurons [70]. Thus, SGLT2i, by lowering glucose levels, can protect and improve mitochondrial function and reduce oxidative stress generated by those organs, and in consequence improve the course of PD.

Mousa et al. showed that Empagliflozin can improve motor and histopathological changes caused by subcutaneous injection of rotenone (ROT-induced parkinsonism) in mice [71]. Rotenone is a pesticide that inhibits mitochondrial complex I and is widely used to induce parkinsonism in rats. The improvement was probably mediated through antioxidative, anti-inflammatory and neuroprotective effects in dose dependent manner. Improvement in neuroplasticity was observed indicated by elevation in BDNF, cAMP response element-binding protein (CREB) and neuronal PAS domain Protein 4. Motawi et al. performed similar experiment, whereas they showed a restorative effect of Empagliflozin on biochemical alterations seen after subcutaneous injection of rotenone and improved motor functions. In the histopathological examination, they showed increased intact neuron count and reduced astrogliosis and microgliosis in comparison to untreated group [72]. Empagliflozin worked by moderating the GRP78/PERK/eIF2α/CHOP endoplasmic reticulum (ER) stress pathway, downregulating miR-211-5p, which was predicted to target CHOP, a downstream effector in the ER stress pathway. That resulted in reduction of oxidative stress, decreasing astrocyte and microglial activation and inflammation alongside with augmenting the autophagy. Similar experiment was performed by Arab et al., however they administered Dapagliflozin instead of Empagliflozin in rats after rotenone induction of parkinsonism. As in previous cases, they observed attenuation of PD motor disfunction and diminished histopathologic alterations. Apart from that they acknowledged significant alleviation in neuronal oxidative stress via lowering lipid peroxides and restoration of previously disrupted DJ-1/Nrf2 pathway. Dapagliflozin also suppressed inflammation, probably by curbing activation of NF-κB pathway and decreasing TNF-α levels [73].

Discussion and conclusions.

The pleiotropic properties of SGLT2 inhibitors have been previously demonstrated in the fields of cardiology and nephrology, where they have been found to have cardioprotective and nephroprotective effects [74], [75], [76], [77], [78], [79]. The use of SGLT2 inhibitors in medicine is expanding, with ongoing research into new areas of application [80], [81]. Our study showed that SGLT2 inhibitors may have an impact on the nervous system through direct or indirect pathways [82]. One potential area of use for these inhibitors is in the management of certain neurological conditions.

The most obvious benefit of these inhibitors is their ability to reduce elevated glucose levels. These medications were specifically designed to lower blood glucose in individuals with diabetes mellitus through renal excretion, and their effectiveness for this purpose has been well documented [83], [84], [85]. Lowering blood glucose levels appears to be beneficial for neurons on its own, however SGLT2 inhibitors also have pleiotropic effects on the nervous system. These inhibitors interact with various molecular targets and affect different proteins, demonstrating multifaceted effects on neural health. There is also a growing understanding of the association between diabetes mellitus and neurological disorders [86], [87], [88], [89].

Pugazhenthi et al. noted that chronic neuroinflammation can occur as a result of diabetes mellitus. It is believed that this neuroinflammation in the diabetic brain results from peripheral inflammation, with cytokines produced by macrophages playing a role in its development due to their ability to cross the blood-brain barrier [90]. The direct effects of saturated fatty acids and advanced glycation end products on astrocytes and microglial cells may also contribute to the process [90].

Neuroinflammation is thought to be a key factor in the pathogenesis of neurodegeneration in Alzheimer's disease [91], [92], [93], [94]. Simultaneously there is a growing body of evidence indicating a connection between Alzheimer's disease and diabetes mellitus, with chronic diabetes having a significant impact on brain function [95], [96], [97]. Pugazhenthi et al. observed that diabetes management often focuses on traditional complications such as diabetic retinopathy, peripheral neuropathy, nephropathy, and cardiovascular diseases [90]. For that reason, the available guidelines for diabetes management were analyzed in order to examine current therapeutic approaches for addressing cognitive sequelae in diabetes treatment [98]. The National Institute for Health and Excellence (NICE) guidelines, which were updated in 2022, do not provide much information on preventing cognitive damage among diabetes complications [99].

However, the guidelines do state that SGLT2 inhibitors should be considered for all patients with type 2 diabetes and should be offered to those individuals with higher cardiovascular risk, or whose cardiovascular risk increases over time, or for patients with an albumin-to-creatinine ratio over 30 mg/mmol. In turn, the American Diabetes Association (ADA) shares a similar point of view with NICE regarding the use of SGLT2 inhibitors in managing diabetes-related conditions such as atherosclerotic cardiovascular disease, indicators of high cardiovascular risk, heart failure, or chronic kidney disease [100].

Both ADA and European Association for the Study of Diabetes (EASD) highlighted that older patients with diabetes are at a greater risk of depression and cognitive disorders. It is recommended to screen for mild cognitive impairment or dementia in adults aged 65 or older. In the case of cognitive impairment, the diabetes treatment regimen should be simplified as much as possible and tailored to minimize the risk of hypoglycemia and these patients should be referred for additional support.

The ADA guidelines also refer to the increased prevalence of Alzheimer's disease among diabetic patients but note that clinical trials with cholinesterase inhibitors and glutamatergic antagonists have not shown positive therapeutic benefits in maintaining or significantly improving cognitive function. Intranasal insulin therapy as well as metformin therapy were found to be potentially beneficial in a pilot study, providing insight for future clinical trials and mechanistic studies.

The guidelines acknowledge the connection between diabetes and cognitive impairment, but there is a lack of information about the potential prevention of cognitive disorders or any cognitive improvement management. Additionally, SGLT2 inhibitors have not been considered in this field. The guidelines state that further research on the pathophysiology and intervention for diabetic cognitive decline is needed, as it is a challenging but high-reward area. Up to date there are several clinical trials being conducted that hopefully dispel any doubts and potentially demonstrate the efficacy of SGLT2i [101].

As the rest neurological disorders are lesser connected to the diabetes mellitus like Parkinson’s disease, naturally the guidelines have not referred to management of these conditions. Also presented research about benefits of SGLT2i treatment on major depression disorders, autism spectrum disorders or other neurological conditions including Huntington disease are promising but should be further verified due to limited

investigations The neurological conditions in our comprehension should be considered as an integral part of metabolic disorders in diabetes mellitus.

In this review we summarized current evidence of SGLT2i impact on the central nervous system (CNS), as well their potential role in the comprehensive management of patients with neurologic disorders. Although the use of SGLT2i in neurodegenerative disorders is promising, the further research is needed to determine which patients will benefit the most from that therapeutical approach.

All authors have read and agreed with the published version of the manuscript.

Authors' contribution:

Conceptualization: Jakub Jucha
Methodology: Jakub Jucha, Dominik Zając, Dominika Darasz
Software: Artur Łukawski, Wojciech Ziębka
Check: Dominika Darasz, Lesia Slobozheniuk, Magdalena Bieniak
Formal analysis: Jakub Jucha, Krzysztof Machnik
Investigation: Artur Łukawski, Magdalena Bieniak, Wojciech Ziębka
Resources: Krzysztof Machnik, Dominika Darasz
Data curation: Lesia Slobozheniuk, Oliwia Dziewięcka
Writing-rough preparation: Dominik Zając, Marta Kaczorek
Writing-review and editing: Dominik Zając, Oliwia Dziewięcka
Supervision: Dominik Zając, Marta Kaczorek
Project administration: Jakub Jucha

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