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REVIEW

Possible Preventative/Rehabilitative Role of Gliflozins in OSA and T2DM. A Systematic Literature Review-Based Hypothesis

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ABSTRACT

Obstructive sleep apnoea (OSA) is characterized by frequent apnoea episodes during sleep due to upper airway obstruction. The present review summarizes current knowledge on inter-relationships between OSA and type 2 diabetes mellitus (T2DM) and suggests the former as a possible target for sodium-glucose co-transporter-2 inhibitors (SGLT-2i). Based on pathophysiological mechanisms underlying OSA onset and renal SGLT-2 effects, we suggest that SGLT-2i indications might expand beyond current ones, including glucose, lipids, uric acid, blood pressure, and body weight control as well as chronic heart failure and kidney disease prevention.

Keywords: Obstructive sleep apnoea; SGLT-2i; Diabetes mellitus; Renal function; Vascular disease; Rehabilitation

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Key Summary Points
Obstructive sleep apnoea (OSA) is a syndrome often accompanying type 2 diabetes mellitus (T2DM) and precipitating severe cardiovascular events
The authors conducted a thorough, systematic literature search to analyze all interrelations known to date
This review summarizes current knowledge on inter-relationships between OSA and T2DM and on gliflozins (SGLT-2is), i.e., innovative glucose-lowering drugs increasingly extensively utilized in T2DM because of their inherent null hypoglycaemic risk
Gliflozins also prove effective against impaired cardiovascular and renal function, and one of them, at least, does so even in the absence of T2DM
Based on the underlying pharmacological mechanisms, gliflozins might also be promising as preventative, rehabilitative, and therapeutic tools against OSA

DIGITAL FEATURES

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INTRODUCTION

Frequent episodes of apnoea characterize obstructive sleep apnoea (OSA) during sleep due to upper airways obstruction [1–2]. Its diagnosis relies on an altered oxygen desaturation index (ODI) [3], apnoea/hypopnoea index (AHI), respiratory disturbance index (RDI) and respiratory effort-related arousals (RERAs) [4–6], polysomnography (PSG) [7], and especially the association of typical symptoms (e.g., unrefreshing sleep, daytime sleepiness, fatigue or insomnia, awakening with a gasping or choking sensation, loud snoring, or witnessed apnoeas) with an RDI $\geq$ 5 events per hour of sleep.

Despite being known for decades, OSA still has controversial clinical features, including unrefreshing sleep, daytime fatigue, and impaired concentration, requiring further investigation [8–10].

According to the so-called Chicago criteria [11], OSA's severity is given by the AHI value as follows: absent (< 5), mild (5–14), moderate (15–29), and severe ($\geq$ 30) [2].

Aim

The present review aims to summarize current knowledge on inter-relationships between OSA and type 2 diabetes mellitus (T2DM) and suggests the former as a possible target for sodium-glucose co-transporter-2 inhibitors (SGLT-2i). This way, SGLT-2i indications might expand further beyond current ones, including glucose, lipids, uric acid, blood pressure, and body weight control as well as chronic heart failure and kidney disease prevention.

METHODS

The information contained in the present review comes from a thorough analysis of the literature concerning T2DM, OSA, and SGLT2.is. Online databases (PubMed, Embase, Scopus, and Web of Science) were systematically searched for English-language publications dealing with any relationship between T2DM, related complications, or frequently associated diseases and OSA up to October 2020. The reference list of included papers also served as an additional source of information on the topic. A group of keywords was used in the systematic search, including: ("OSA" or "T2DM" or "T2DM complication") AND ("T2DM comorbidities" OR "cardiometabolic" OR glycaemia OR "insulin resistance" OR "inflammatory Cytokines" OR "obesity" OR "leptin" OR "SGLT2-1) AND (”trial“ OR ”randomization*“ OR ”control“ OR

"clinical" OR "meta-analysis"). Studies meeting the following criteria were excluded: < 2-week duration, non-randomized clinical trials, and cross-sectional studies.

Two independent reviewers (MM and SG) completed the data extraction process according to eligibility criteria. First, they evaluated paper quality by the bias assessment tool, according to the following domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias). Then, they classified each domain as: "low risk of bias", "high risk of bias", or "unclear risk of bias". Finally, based on the results obtained from the domains, they defined the overall quality of such studies as good (low risk for more than three domains), acceptable (low risk for three domains), and poor (low risk for less than three domains). This method allowed selecting 66 highly specific papers and 138 related publications.

No statistical analysis was possible or required as our paper is a review.

RESULTS

We systematized all the information collected from the literature under separate sections devoted to individual conditions and organ-specific pathologies.

Epidemiology

OSA has an estimated 3:1 to 5:1 male-to-female ratio [12] and is 2–3-fold more prevalent in older adults (> 65 years) [13–14]. Among middle-aged people, estimated symptomatic OSA's prevalence is about 4% in men and 2% in women [15], and asymptomatic OSA's prevalence is 20–30%, with a failed detection risk as high as 93% in women and 82% in men [16]. However, in the overall male adult population, it is even as high as 50% [17–18], with a continuously increasing trend within the developed countries, partly due to the parallel increase of the obesity rate [19].

Indeed, a major risk factor for OSA is visceral obesity [12, 20–22]. The higher the obesity degree, the more severe OSA is, with a close association with hypertension, coronary and cerebral vascular disease, and significantly increased all-cause mortality among people with untreated sleep disorders regardless of age, sex, and body mass index (BMI) [23]. In aged subjects, the ODI proved to be significantly associated with T2DM and three components of the metabolic syndrome, including hyperglycemia, hypertriglyceridemia, and essential arterial hypertension (EAH) [24].

OSA and T2DM

An extremely variable prevalence of OSA in T2DM has been reported [25–30], mostly ranging from 24% to 36% [31–32], and sometimes even 70% [12]. The risk for T2DM in patients with OSA, in turn, has been well known for decades. It ranges 30–71% and is higher for an AHI > 30 [31–34]. In addition, diabetes-related foot disease, insulin treatment, obesity, coronary heart disease (CHD), and depression are the most relevant risk factors for OSA in T2DM patients [35].

OSA and Autonomic Nervous System Dysfunction

The pathophysiological link between T2DM and OSA might be, at least in part, the activation of the sympathetic branch of the autonomic nervous system (ANS) by acute hypoxia occurring during sleep apnoea/hypopnoea episodes and consequent night respiratory effort-related arousals (RERAs) [36], eventually exacerbated by hypercapnia [37]. Consequential massive catecholamine release results in insulin resistance both directly and through increased cortisol output [38], contributing to a feed-forward cascade of adverse events generated by sleep loss, sleep fragmentation, hypoxia, and leading to weight gain, insulin resistance, and T2DM [39].

Moreover, aortic and carotid chemoreceptors, which regulate the SNS activity in response to changes in pH values, hypoxia, and hypercapnia, are activated, especially in patients with OSA and metabolic syndrome [40–41]. In normal sleep, despite eliciting increased central SNS outflow, hypoxic or hypercapnic chemoreflex activation triggers hyperventilation as well, which, in turn, inhibits SNS activity [40, 42–43]. Moreover, chemoreceptor-related SNS activation increases blood pressure (BP), which attenuates chemoreflex outputs through carotid arterial baroreceptors 43, i.e., the mechanism underlying the 10–20% nighttime, sleep stage-related BP lowering compared to waking hours observed in healthy subjects, known as "nocturnal BP dipping" [44–45].

Conversely, the peripheral chemoreflex triggered by apnoea-dependent hypoxia and hypercapnia without hyperventilation results in SNS-dependent vasoconstriction [40] and, when repeating over time, impairs carotid sinus and aortic baroreceptor sensitivity [46]. Consequently, any longstanding apnoea/hypopnoea syndrome may cause baroreceptors to "reset" at higher baseline BP levels throughout the day [40], thus precipitating chronic SNS activation [47–48] with increased BP and heart rate (HR). EAH and other adverse cardiovascular outcomes [40] will follow soon, thus suggesting to take the "non-dipping" phenomenon as a clinical marker of increased risk for OSA in hypertensive patients [40]. However, nighttime continuous positive airway pressure (CPAP) can counteract both chemoreceptor over-activation and baroreceptor hyporesponsiveness [49–52].

Therefore, OSA can exacerbate preexisting autonomic nervous system (ANS) dysfunction in T2DM patients. Indeed, patients with EAH + T2DM undergo more prominent peripheral SNS activation signs and insulin levels than those with either disease [53], which suggests that ANS dysfunction may be related to increased plasma insulin levels in those patients [53].

Moreover, in people with T2DM and cardiovascular autonomic neuropathy (CAN) an imbalance between SNS and parasympathetic vagus nerve (VN) activity was described due to either an absolute or a relative decrease in VN firing rate [54]. This may represent another self-sustained pathophysiological mechanism underlying SNS hyperactivity in the presence of OSA [12].

As opposed to what was observed in type 1 diabetes mellitus (T1DM), in patients with recent-onset T2DM, the decrease in cardiac VN activity and baroreflex sensitivity is strongly associated with hepatic steatosis, thus suggesting the latter to have a role in early hypoparasympathetic-type CAN in T2DM [55]. However, to describe this mechanism in greater detail, we have to outline that, despite insulin resistance contributing to early cardiovagal suppression in both DM types, the lower glucagon-stimulated insulin levels compensatorily increase parasympathetic tone in T1DM [56]. CAN has been reported to occur early in T2DM with a prevalence of 1.8%—or up to 15.3% when defined by the presence of at least two borderline and one pathological test, suggesting the need for ruling out CAN as early as possible in patients with T2DM [57].

According to some authors, OSA may induce resistance to body weight (BW)-lowering effects exerted by leptin [58] through β-3 lipolytic adipose tissue receptors [59]. The underlying mechanism seems to be SNS hyperactivity-related receptor downregulation with compensatory increased leptin concentrations [60] and consequent increased pro-inflammatory cytokine secretion [61–62]. Also, due to the selective nature of leptin-resistance, i.e., preserving cardiovascular effects [63], leptin-associated enhanced sympathetic nerve outflow [60] increases BP [64] and HR, thus paving the way to cardiovascular complications [65–66].

OSA and Diabetic Peripheral Neuropathy

A strong association also exists between OSA and diabetic peripheral neuropathy (DPN), being the rate of distal electroneurographically detected polyneuropathy twice as high in patients with newly diagnosed OSA as in controls (71% vs. 33%, respectively, $p < 0.01$) and improving significantly after nasal continuous positive airway pressure treatment (CPAP) [67–68].

DPN seems to have a 35.2% rate in mixed T1DM and T2DM [69] and to be significantly associated with OSA in T2DM patients [70]. Indeed, OSA occurs more frequently in T2DM patients with DPN [71], where it comes preferentially with lower intra-epidermal nerve fiber density, poly-adenosine-diphosphoribose polymerase (PARP) activation, and diabetic foot ulceration [72], most likely due to increased nitrosative/oxidative stress, and impaired microvascular regulation [70].

OSA and Diabetic Kidney Disease

OSA is also significantly associated with diabetic kidney disease (DKD)—even at its early stages—and any other diabetes-related complications in T2DM [73], probably as a result of AH [74].

Baseline OSA parameters, especially AHI, are independent predictors of future estimated glomerular filtration rate (eGFR) absolute value and change over time (i.e., 2.5 years on average). After controlling for multiple confounders, including OSA, the serum nitrotyrosine concentration emerges as an independent predictor of final eGFR and of eGFR change over time [75].

Also, CAN is an independent predictor of 9.6-year eGFR decline [76], with a significant association with CKD onset [77], thus suggesting that CAN can further exacerbate OSA-related damage to the kidney in patients with T2DM and OSA [75].

OSA was also associated with CKD in patients without diabetes in several cross-sectional and longitudinal observational studies, mainly depending on disease severity [78–82]. Moreover, patients with end-stage renal disease (ESRD) have a 50% to 60% prevalence of OSA [83–85] in favour of a two-way and mutual association between CKD and OSA [86].

OSA and Diabetic Retinopathy

Although the association between OSA and diabetic retinopathy (DR) has been a controversial issue in the past [87], a recent, large meta-analysis suggests OSA is significantly associated with increased DR risk in both DM types [88]. The association between DR (29% non-proliferative [NPDR] and 48% proliferative [PDR]) and sleep-disordered breathing (SDB) is robust [88–90]. Also, intermittent nocturnal hypoxia and related desaturation/reoxygenation phenomena are supposed to be the main underlying mechanisms [88–90], with intermittent nocturnal hypoxia and related desaturation/reoxygenation phenomena supposed to be the main underlying mechanisms [89–90] together with the nocturnal "non-dipping" phenomenon and daytime BP variability independently increasing the risk for cardiovascular diseases [91] and retinopathy in patients with T2DM [92]. Also, OSA is known to be an independent factor predicting progression to pre-proliferative/proliferative DR (OR, 5.2,95% CI 1.2–23.0, $p = 0.03$) [91], thus likely having a prominent role in the pathogenesis of severe sight-threatening clinical pictures [93].

Macrovascular Complications

OSA is associated with diabetic macrovascular complications, most often coronary heart disease (CHD) and stroke, atrial fibrillation (AF), and heart failure (HF) [94], and SDB acts as a predictor of incident CHD, AF, and HF [95].

Several data collected in obese patients with T2DM show the most severe AHI scores associated with an increased risk of major CV events [96–98]. For example, the cross-sectional, longitudinal adult-population-based Wisconsin Sleep Cohort Study showed that moderate to severe SDB (AHI > 20) was significantly associated with the prevalence of stroke over the next 4 years and might even contribute to the occurrence of such an event [99].

In the Sleep Heart Health Study (SHHS)—a multi-centre, prospective cohort study on cardiovascular consequences of OSA initiated in 1994—the association between OSA and stroke proved significant only in men after controlling for all possible covariates (OR 2.86, CI 1.10, 7.39) [100]. Also, after adjusting for multiple risk factors, OSA proved to be a significant predictor of incident CHD (myocardial infarction, revascularization procedure, or CHD death) only in men ≤ 70 years of age [101].

In conclusion, OSA seems to be associated with an increased risk for stroke rather than CHD.

Pathophysiology of T2DM Micro-macrovascular Complications in Patients with OSA

The bidirectional association between OSA and T2DM also involves microvascular and macrovascular complications [102–103]. Advanced glycation end product (AGE) accumulation along with increased protein kinase C, polyol, and hexosamine pathway activity could lead to the overexpression of reactive oxygen species (ROS) and pro-inflammatory cytokines, all of which have a role in diabetic complications [70, 104–108]. Indeed, some papers suggest an association between OSA and markedly increased intracellular ROS concentrations [including mainly superoxide ion (O^-), nitric oxide (NO), and hydrogen peroxide (H_2O_2)], which, by overwhelming antioxidant capacity, chemically modify lipidic, protidic, and DNA macromolecules [109–114].

Based on such mechanisms, chronic intermittent hypoxia (CIH) proves to induce overall pancreatic beta-cell dysfunction in mice through increased mitochondrial ROS concentrations, resulting in insulin resistance, defective proinsulin processing, and impaired glucose-stimulated insulin secretion. A mitochondrial ROS-scavenger treatment, in turn, can restore such changes [111].

Thus, referring to OSA-diabetes interactions, repeated nocturnal hypoxia/re-oxygenation episodes contribute to common pathogenic mechanisms of micro- and macro-vascular diabetic complications. This occurs essentially through apnoeic-dependent lower oxygen availability and subsequent reoxygenation-related ROS formation at breath resumption [102], further increasing oxidative stress-related systemic inflammation, endothelial cell dysfunction, SNS, and renin-angiotensin system activation in a self-sustained vicious cycle [102].

Indeed, exceptionally high levels of pro-inflammatory cytokines including tumor necrosis factor (TNF)-α, interleukin-6 (IL-6) and IL-8, and C-reactive protein—also widely recognized as significant cardiovascular risk markers—are in common in both OSA [115–118] and T2DM patients [119–121] and decrease after continuous positive airway pressure (C-PAP) treatment [122].

Also, AGE generation and tissue accrual resulting from covalent, non-enzymatic binding between glucides (endowed with reducing properties) and lipid, protein, or nucleic acid amine residues cause cell damage, eventually contributing to diabetic microvascular complications in people with T2DM and OSA [102]. However, CIH is known to induce elevated circulating AGE levels as a function of OSA severity in nondiabetic patients too [123–124] and, in that case, may play a crucial role in insulin resistance, thus entailing a high risk for T2DM onset [125].

Another pathophysiological link between OSA and diabetic micro-/macrovascular complications is the upregulation of RAS, which can be detrimental to renal function [86]. Indeed, several cross-sectional [126–127] and longitudinal studies [128–130] showed a CKD-to-OSA association even in patients without T2DM. For example, in a study carried out in China on 1259 critically ill patients (183 with a history of OSA), the incidence of acute kidney injury (AKI) in patients with OSA was higher compared with those without OSA (41 vs. 57%, $p < 0.001$) and, at multivariate analysis controlling for age, gender, race, and chronic and acute risk factors, an independent association was apparent between OSA and AKI (OR 1.53, 95% CI 1.04–2.24, $p = 0.031$) [131–132]. Such a detrimental effect of OSA on renal function may be attenuated by long-term C-PAP therapy [132] through improved insulin resistance, especially in the case of associated obesity [133].

In conclusion, C-PAP treatment of OSA may improve T2DM-related insulin resistance and inflammatory status, thus reducing the progression of micro-/macrovascular T2DM complications. However, the effects of other therapeutic interventions on patients with T2DM and OSA still await clarification.

Can Innovative Antihyperglycaemic Drugs Improve Both OSA and Its Clinical Consequences?

Besides exerting impressive antihyperglycaemic effects, SGLT-2is prove favourable at both the cardiovascular and renal levels [134–142]. The four currently available drugs from this class (canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin) ensure 90% active tubular resorption inhibition of glucose from glomerular filtrate [143–146], despite the remaining 10% being still reabsorbed through SGLT-1 receptors [147].

The already mentioned T2DM-related overactive SNS causes widespread kidney chemoreceptors and baroreceptors to send activating signals back to the brain, thus triggering a self-sustained mechanism involving RAS stimulation, increased systemic BP, and CKD progression [148]. Contrarily, SGLT-2is seem to reduce SNS overactivity at least partially through increased renal tubular glucose resorption [149], thus strongly contributing to observed lower cardiovascular risk and hospitalization rates [150–151].

Based on animal models of DKD [152–154], the mechanism behind favourable SGLT-2i renal effects seems to be the activation of the so-called tubule-glomerular feedback (TGF) as described below. TGF consists of the A1-adenosine receptor-mediated afferent glomerular arteriole vasoconstriction [155] in response to increased NaCl load to distal tubule [156–157]. Briefly, adenosine is known to act as a paracrine signal through three receptor types, i.e., A1, A2 (further classified into high-affinity A2a and low-affinity A2b subtypes), and A3 [157]. A2a and A2b receptor activation attenuates TGF response by inhibiting afferent glomerular arteriole vasoconstriction through adenylate cyclase-dependent cyclic adenose monophosphate (c-AMP) generation [158–159]. Contrarily, c-AMP production is inhibited by A1 receptor activation, while A3 receptor function is still unclear [158]. Such physiological mechanisms allow the kidney to contribute to BP regulation through renin release by the cells from the juxtaglomerular apparatus (JGA). These cells "interpret" increased NaCl load to the distal tubular region as a sign of extracellular fluid expansion, thus activating TGF and causing afferent glomerular arteriole vasoconstriction [160]. Therefore, it is conceivable that TGF activation is the physiological mechanism responsible for reduced SNS overactivation contributing to cardiovascular and renal SGLT-2i benefits as referred to OSA [150].

An additional favourable SGLT-2i effect on OSA, also resulting from the TGF activation mentioned above, may come from the recently identified evidence that, as opposed to T1DM patients [161], the glucose-dependent osmotic diuretic effect of SGLT-2i is not associated with increased RAS activity in T2DM patients [162]. Also, an experimental study performed in the T2DM animal model showed that the plasma renin activity or serum aldosterone level did not increase after dapagliflozin treatment [163].

Another possible favourable effect of SGLT-2is on clinical signs of OSA might come from increased hematocrit (Ht), which might further contribute to a reduced cardiovascular death (CD) rate [164]. Indeed, SGLT-i stimulation activates the adenosine-triphosphate (ATP)-dependent Na + -K + pump to actively export intracellular Na + into the blood vessels against a concentration gradient, thus depleting ATP and O_2 reserve [165]. The consequent pO_2 decrease determines functional exhaustion of renal tubular cells, thus inducing pro-inflammatory cytokine release, progressive interstitial injury, and subsequent fibrosis [166] through the transformation of fibroblasts into myofibroblasts [167], which, due to their lower erythropoietin secretory capacity, contribute to typical DKD-related anaemia [168]. Ht slowly increases within the first 2 months into SGLT-2i treatment independently of haemoconcentration and settles down after that [169]. Indeed, opposite to what was observed for the diuretic agent hydrochlorothiazide, erythropietin levels and reticulocyte count seem to increase in T2DM following dapagliflozin administration [170]. Indeed, opposite to what is observed for the diuretic agent hydrochlorothiazide, erythropietin levels and reticolocyte count seem to increase in T2DM following dapagliflozin administration [170]. Furthermore, increased erythropoietin levels (63%, $p = 0.0078$) were

found following empagliflozin treatment in patients with T2DM with preserved renal function (eGFR $\geq$ 60 ml·min^{-1}·1.73 m^{-2}) compared to control subjects [171].

Finally, SGLT-2i-related weight loss, due to visceral and subcutaneous adipose tissue reduction [172–174], may have a favourable effect on OSA. As shown in animal models of T2DM and metabolic syndrome, it depends on a sustained shift in energy substrates from carbohydrates to lipids with enhanced fatty-acid betaoxidation-related lipolysis [175–179], which proved to improve liver steatosis in T2DM patients and in T2DM animal models [180–184] and, as observed with canagliflozin, CHD-associated epicardial fat accumulation [185–187].

CONCLUSIONS AND FUTURE PERSPECTIVES

As already shown for HF and CKD, the pharmacological properties of SGLT-2is are suggestive of a potential role in the treatment of OSA independently of T2DM [136, 139, 141]. The most likely mechanisms involved in such beneficial effects of SGLT-2is on OSA are reported in Fig. 1 and can be summarized as follows: (1) sympathetic activity inhibiting effects [150, 188], expected to improve both associated CAN and cardiovascular and renal outcomes significantly [54]; (2) direct benefits on renal function [140–141], preventing associated CAN from further self-sustaining kidney function impairment [76–77, 86]; (3) Ht increasing effects, expected to reduce nighttime hypoxia [189–191].

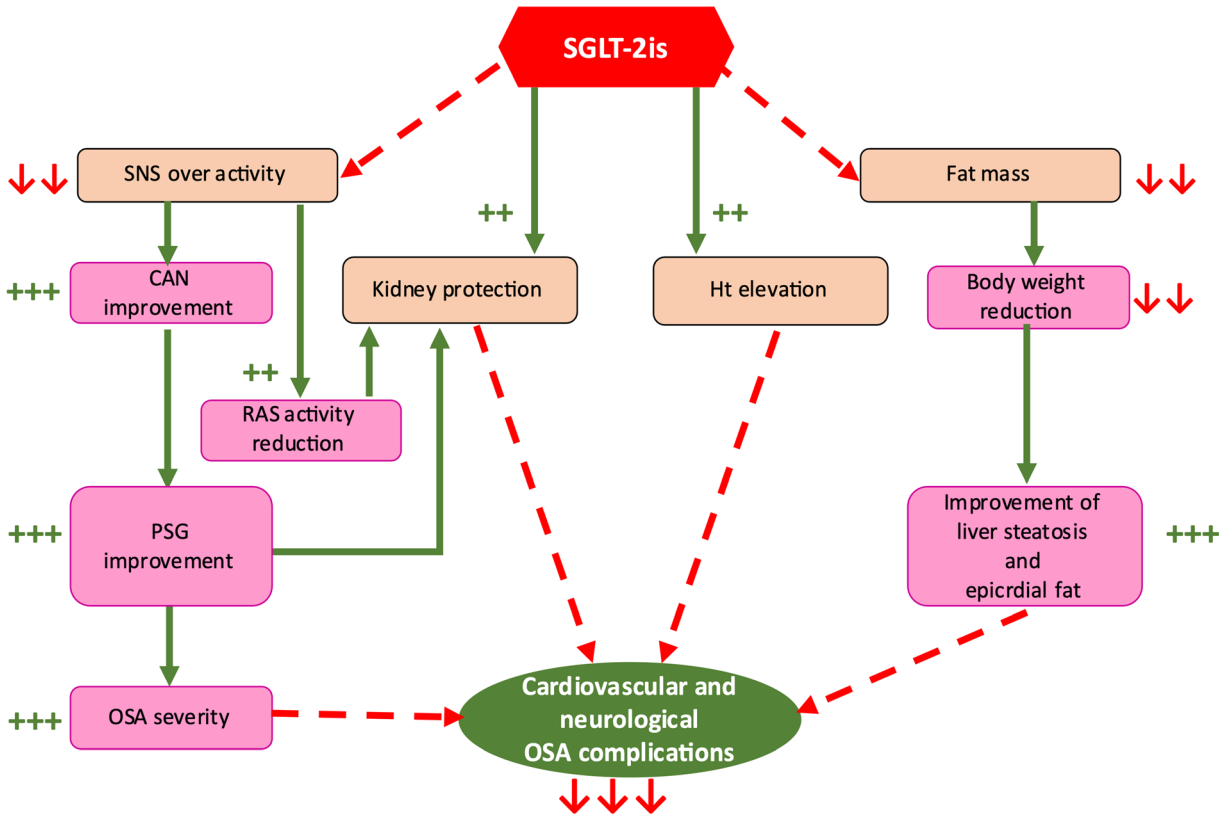

Fig. 1 The putative favourable effects of SGLT-2is on OSA. *CAN* cardiovascular autonomic neuropathy, *HT* haematocrit, *OSA* obstructive sleep apnoea, *PSG* polysomnography, *RAS* renin angiotensin system, *SGLT-2is* sodium/glucose co-transporter-2 inhibitors, *SNS* sympathetic nervous system. See text for details

Currently, only a few, yet promising, data are available on the effects of SGLT2-i in T2DM patients with OSAS, showing a marked decrease of AHI (31.9 ± 18.0 to 18.8 ± 11.5 events/h; $p = 0.003$), HbA1c, body weight, and BMI in the absence of any BP changes [192–193]. Also, in a metformin add-on study, differently from glimepiride, dapagliflozin significantly decreased the AHI and Epworth Somnolence Scale, triglycerides, and systolic and diastolic BP and increased oxygen saturation and high-density lipoprotein cholesterol (HDL-C) [161, 193–195].

Moreover, empagliflozin proved beneficial for cardiovascular and renal outcomes regardless of OSA but could also reduce the risk for OSA [196] by counteracting the hyperproduction and the hyperactivity of leptin [197], whose levels are elevated in OSA patients [65]. The latter hypothesis is still controversial [198]. However, based on a recent meta-analysis of ten randomized controlled trials, SGLT2i treatment is associated with decreased leptin and increased adiponectin levels in T2DM patients, eventually contributing to metabolic SGLT-2i benefits [199].

In conclusion, it is conceivable that the use of SGLT-2is will represent a promising preventative, rehabilitative, and therapeutic approach for OSA patients regardless of coexisting diabetes by also slowing CKD progression and managing CAN, both known to be closely associated with OSA and T2DM. Thus, these drugs might exert beneficial effects on CAN, and, as CAN is a very early diabetes and OSA complication [57], might be particularly indicated in the early stages of both diseases to reduce associated mortality risk [54, 188].

Indeed, expected OSA benefits might add to the already established cardiovascular and renal preventative effect of dapagliflozin in animal T2DM models [163], and in humans, even in the absence of T2DM as well [200].

Further clinical studies involving patients with and without diabetes are needed to confirm our hypothesis on SGLT-2is benefits in OSA rehabilitation and management and assess whether such benefits reflect a single drug or a whole class effect.

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Compliance with Ethical Guidelines. This study has been conducted in conformance with good clinical practice standards, is based on previously published studies and does not contain any studies with human participants or animals performed by any of the authors.

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Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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