Diabetes & Metabolic Syndrome: Clinical Research & Reviews 13 (2019) 1679–1683

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Review

Mechanistic effects of SGLT2 inhibition on blood pressure in diabetes

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ARTICLE INFO

Article history:
Received 25 February 2019
Accepted 14 March 2019

Keywords:
Sodium-glucose co-transporter inhibitors
Oxidative stress
Diabetes mellitus
Hypertension

ABSTRACT

Diabetes mellitus prevalence is increasing worldwide leading to increased morbidity and mortality through diabetes related microvascular and macrovascular disease. The treatment of hypertension has been shown to be a major therapeutic intervention for the prevention of cardiovascular events and other diabetes related complications in diabetes. Sodium-glucose co-transporter inhibitors (SGLT2i) are newly introduced anti-diabetes drugs that lower blood glucose by the inhibition of glucose reuptake and the induction of glycosuria. However, there is increasing evidence showing their cardiovascular benefit beyond the improvement of glycemic control. Here we review the latest findings on the effect of SGLT2i on blood pressure in diabetes.

1. Introduction

The global prevalence of diabetes mellitus (DM) is growing rapidly [1] with an increase in diabetes complications leading to increased morbidity and mortality [2,3]. DM imposes an increasing cost to health systems globally, necessitating therapeutic strategies to reduce diabetes complications [4,5]. Several large studies have indicated that the improvement in glycemic control is associated with a decrease in microvascular complications [4,6]. Addressing blood pressure directly is of benefit for both macrovascular and microvascular complications [7,8], and antihypertensive treatment is one of the pillars of diabetes therapy [8].

There are several classes of antidiabetic agents for the improvement of glycemic control that act though differing molecular mechanisms [9,10]. Some of these hypoglycemic agents may have additional beneficial actions being antioxidant and reducing inflammation in diabetes patients [4,9]. Data has accrued to show that sodium-glucose cotransporter inhibitors (SGLT2i's) may have an effect on blood pressure by a number of molecular mechanisms (Table 1) and in recent clinical trials, SGLT2i's have shown cardiovascular benefit (Table 2). This review specifically focuses on the hypertensive effects that these agent may have.

1.1. Sodium-glucose co-transporter inhibitors; novel anti-diabetic agents

SGLT2 inhibitors are a recently introduced class of anti-diabetes drugs that reduce blood glucose by inhibition of tubular glucose reabsorption leading to glycosuria [11,12]. This class of agents are independent of insulin secretion and are related to the serum level of glucose and therefore have a reduced risk of hypoglycemia compared to other agents [13]. Phlorizin was reported as the first SGLT2 inhibitor and subsequently more specific agents have been developed [13–16]. SGLTi's may have additional beneficial effects that contribute to the improvement of glycemic control such as the inhibition of gluconeogenesis, improvement of insulin sensitivity, enhancement of the glucagon response to hypoglycemia and the induction of insulin secretion from beta cells [17–20].

1.2. Diabetes mellitus classification

DM is classified into three main categories as type1; type2 and gestational diabetes [21]. Type 1 diabetes (T1DM) accounts for 5–10% of all diabetes subjects through beta-cell dysfunction and

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https://doi.org/10.1016/j.dsx.2019.03.031
1871-4021/

Table 1
Molecular mechanisms underlying the effects of SGLT2 inhibition on blood pressure.

Ref.	Antihypertensive Effects	Molecular Mechanisms	
[39–42]	Volume depletion via diuresis/natriuresis	Glycosuria and Diuretic Effects	SGLT2i and Hypertension
[47–49]	Modulating Autonomous Nervous System toward lower sympathetic rate	Autonomous Nervous System	
[37,38,57]	Weight reduction leading to lower risk for hypertension	Weight Loss	
[45,61–63]	Modulating nitric oxide synthesis and improvement in vascular relaxation	Nitric Oxide Homeostasis	
[8,9,67,68]	Improvement in renal function leading to better blood pressure control	Renal Function	
[71–76]	Prevent/improve oxidative stress leading to lower risk for hypertension	Oxidative Stress	

Table 2
Main clinical trials that evaluated the effects of SGLT2 inhibition on blood pressure.

Ref.	Effects on Blood Pressure	Used Drug (s)	Population of Study	Clinical Trial
[81]	Reduction in mean systolic pressure	Empagliflozin	823 patients with T2DM and hypertension	EMPA-REG OUTCOME
[80]	Reduction in systolic and diastolic blood pressure	Canagliflozin	1425 patients with T2DM	CANTATA-SU
[83]	Decline of blood pressure	Dapagliflozin	833 patients with T1DM	DEPICT-1
[84]	Improvement of systolic blood pressure at week 28	Dapagliflozin	695 patients with T2DM	DURATION-8 (NCT02229396)
[85]	Blood pressure reduction along with weight reduction	Empagliflozin	108 patients with T2DM	EMPA-REG EXTEND™ MONO
[86]	Reduction in blood pressure	Dapagliflozin	2360 patients with T2DM	A pooled analysis
[87]	Decrease in Systolic and diastolic blood pressures	Ipragliflozin	171 patients with T2DM	NCT01505426
[88]	Decline in systolic and diastolic blood pressures	Ipragliflozin	43 patients with T2DM	NCT01505426
[89]	Changes from baseline systolic and diastolic blood pressure at weeks 52 and 104	Empagliflozin	1549 patients with T2DM	NCT01167881
[90]	Reduced systolic blood pressure and body weight	Empagliflozin	899 patients with T2DM	NCT01289990
[91]	Reduced seated systolic and diastolic blood pressures	Dapagliflozin	801 patients with T2DM	NCT00660907
[92]	Change from baseline in systolic and diastolic blood pressures at week 24	Empagliflozin	224 patients with T2DM	NCT01177813
[93]	Reduction in standing systolic blood pressure	Ipragliflozin	165 patients with T2DM	NCT02794792
[94]	Reduction in diastolic and systolic blood pressures	Dapagliflozin	546 patients with T2DM	NCT00528879
[95]	Changes from baseline in systolic and diastolic blood pressure on Days 7 and 28	Empagliflozin	71 patients with T1DM	NCT02702011
[96]	No significant effects on blood pressure	Empagliflozin	2115 patients with T2DM	EMPA-REG OUTCOME
[97]	Reduction in mean seated blood pressure with no remarkable rise in orthostatic hypotension	Dapagliflozin	485 patients with T2DM	NCT00528372
[98]	Reduction in heart rate and blood pressure	Ipragliflozin	106 patients with T2DM	PRIME-V study (UMIN000015170, R000016861)

immune mediated destruction leading to lower insulin levels [21]. Type 2 diabetes (T2DM) is the most prevalent type of diabetes that accounts for about 90–95% of diabetic subjects and is mainly associated with an impaired cellular response to insulin and insulin resistance [21]. Gestational diabetes is the other type of DM that occurs in pregnant women mainly via hormonal induced insulin resistance in peripheral tissues [22]. However, another form of diabetes, "Latent Autoimmune Diabetes in Adults" or LADA has been introduced recently that is primarily considered as a subtype of TIDM [23].

1.3. Role of hypertension in diabetic complications

Diabetic nephropathy (DN), diabetic retinopathy (DR), stroke and diabetes-induced cardiovascular disorders are cloely linked to hypertension [24]. Evidence shows that hypertension can contribute directly as well as exacerbate the development and progression of diabetes related complications [24,25]. Grzeszczak et al., in 2013 reported that DN is accompanied with both systemic and intraglomerular hypertension [26].

Glomerular hyperfiltration is an independent risk factor for DN in both T1DM and T2DM patients and is exacerbated by hypertension [27,28]. Changes in blood pressure are associated with the development of atherosclerosis that markedly increases the risk of stroke and MI (myocardial infarction) in diabetic patients [29–31]. Similarly, other diabetes complications such as diabetic neuropathy and DR are affected by molecular pathways induced by hemodynamic changes and systemic hypertension [24,32,33].

1.4. Sodium-glucose co-transporter inhibitors and blood pressure

There is emerging evidence that SGLT2 inhibitors may reduce blood pressure [34,35]. All three FDA-approved forms of SGLT2i, namely canagliflozin, empagliflozin and dapagliflozin in T2DM patients reduce both diastolic and systolic blood pressure [36]. These hypoglycemic agents significantly modify the hemodynamic parameters and reduce blood pressure by at least six molecular pathways [36–38].

1.4.1. Sodium-glucose co-transporter inhibitors and natriuretic/diuretic effects

SGLT2 inhibition is associated with volume depletion due to higher glycosuria and possibly more natriuresis along with an extensive osmotic diuresis [36,39]. These effects are similar to cardiovascular drugs as such diuretics that are widely used in hypertensive patients to normalize blood pressure [39,40]. The hypovolemic effects of SGLT2i's can significantly reduce the shear stress and shear rate involved in hypertension by a reduction in both diastolic and systolic blood pressure [41,42].

1.4.2. Sodium-glucose co-transporter inhibitors and the autonomous nervous system

A higher level of activity in the sympathetic system is commonly observed in most cases of T2DM patients [43]. There is evidence that SGLT2 inhibition may modulate the autonomic nervous system and may readjust autonomic tone in vascular networks [44,45]. Cherney et al., in 2014 demonstrated that 8 weeks of empagliflozin

therapy ameliorated sympathetic nervous system activity and reduced vascular stiffness as well as blood pressure in T1DM patients [46]. In the EMPA-REG OUTCOME trial study in T2DM patients, the SGLT2i empagliflozin showed a lower rate of sympathetic nervous system activity and reduction of heart rate [47–49]. Matthews and colleagues in 2017 reported that SGLT2i by dapagliflozin decreased tyrosine hydroxylase and noradrenaline release in the heart and kidney of diabetic mice [50]. Thus, it may be hypothesized that SGLT2i reduce blood pressure via modulating autonomous nervous system activity [44]; however, the molecular links between SGLT2 inhibition and the autonomous nervous system have not been determined.

1.4.3. Sodium-glucose co-transporter inhibitors and weight loss

SGLT2i results in a net calorific loss due to glycosuria [51,52]. It is well known that obesity is one of the main risk factors for hypertension and weight reduction has been shown to normalize blood pressure in hypertensive subjects [53–55]. Pinto et al., in 2015 demonstrated that SGLT2 inhibition by canagliflozin reduced blood pressure in T2DM patients [56]. Also, Majewski and coworkers in 2015 found that SGLT2i's reduced blood pressure by lowering body weight in T2DM patients [37]. Consequently, this suggests that the reduction in the blood pressure seen with SGLT2i may be in part due to body weight reduction [37,38,57].

1.4.4. SGLT2i and nitric oxide synthesis

In hypertension, nitric oxide (NO) has been shown to be dysregulated [58,59]. NO is a key factor in normalizing vascular smooth muscles tone and impacts on physiological elasticity, relaxation of vasculature networks and normalizes blood pressure [59,60]. There is evidence indicating SGLT2i have direct effects on NO synthase activity; especially eNOS (endothelial NO synthase) and may modulate NO synthesis and can normalize vasculature network tonicity [45,61–63]. Modulation of NO synthesis is another possible mechanism by which SGLT2i may normalize blood pressure.

1.4.5. SGLT2i and renal function

Renal dysfunction and hypertension coexist in many hypertensive subjects [64,65]. Renal dysfunction is an important risk factor for the development of hypertension and improving renal function is commonly followed by better regulation of local and systemic blood pressure [65,66]. There is increasing evidence that SGLT2i therapy improves renal function via several molecular pathways [8,9,67]. Briasoulis and coworkers in 2018 reported that the renoprotective effects of SGLT2i can be beneficial for regulating blood pressure and normalizing hypertension [36]. Moreover, Kelly and coworkers in 2018 showed that SGLT2 inhibition in T2DM patents lowered blood pressure by improving renal sufficiency [68]. Therefore, the renoprotective effects of SGLT2 inhibitors are an additional mechanism by which these hypoglycemic agents may modulate blood pressure [68].

1.4.6. SGLT2i and oxidative stress

Free radical overload leading to the development of oxidative stress is an upstream event in many complications as well as hypertension [69–71]. It has been demonstrated that oxidative stress has a deleterious effect on endothelial function, vascular relaxation, autonomic tone and cardiac capability leading to an increased risk for atherosclerosis and higher blood pressure; the use of antioxidants may help reverse these pathophysiological mechanisms [71–74]. SGLT2 inhibitors can inhibit or suppress oxidative damage by lowering free radical generation via at least 7 molecular pathways, such as a decrease in pro-oxidant enzyme expression/activity; Lowering advanced glycation end product generation; lowering proinflammatory cytokine expression/release; improving insulin sensitivity; normalizing the hemodynamic state; improving mitochondrial function and amelioration of RAS (renin-angiotensin system) activity [11]. Moreover, they can inhibit oxidative damage by potentiating the antioxidant defense [75,76]. The effect of SGLT2i may therefore be through normalizing systemic blood pressure by attenuating systemic oxidative stress [75].

1.4.7. Other possible links between SGLT2i and hypertension

Additional effects of SGLT2i such as the prevention of glucotoxicity; anti-inflammatory and RAS suppression are also suggested to be related to normalizing hypertension [8,76,77]. Shin et al., in 2016 demonstrated that SGLT2 inhibition by dapagliflozin suppressed renal RAS activity in animal model of T2DM [76]. Oelze and coworkers in 2014 reported that the SGLT2 inhibitor empagliflozin ameliorated blood pressure by improving glucotoxicity in an animal model of T1DM [62]. There is also, evidences suggesting that treatment by SGLT2i ameliorates intrarenal and systemic inflammatory responses, which may be involved in the antihypertensive effect of these agents [78,79].

1.5. Clinical finding about antihypertensive roles of SGLT2i

Increasing clinical evidence supports the antihypertensive effects of SGLTi in diabetes [80–82]. In Table 2; we present the main clinical findings for the normotensive effects of SGLT2i.

2. Conclusion

SGLT2 inhibitors are recently introduced hypoglycemic agents that potentially lower blood glucose by glycosuria induction that may contribute to the improved cardiovascular outcomes seen in the clinical trials. This review has shown that SGLT2i can lower blood pressure by at least six separate pathways that include induction of glycosuria, modulating the autonomous nervous system, weight reduction, modulating NO synthesis, improving renal function and preventing oxidative stress. In addition, they may also have beneficial effects on inflammation, prevention of glucotoxicity and RAS activation that may also contribute to the reduction in blood pressure.

Conflicts of interest

The authors declare that they have no conflict of interest in this study.

Financial disclosure

No financial support was received in the writing of this paper.

Acknowledgment

The authors are thankful to the Clinical Research and Development Unit of the Baqiyatallah Hospital (Tehran, Iran).

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