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# Sodium-glucose cotransporter 2 inhibition as a potential treatment for idiopathic oedema

Kirin Rambaran[b], Lexley Pinto Pereira[a,b], Surujpal Teelucksingh[a,b,*]

[a] Faculty of Medical Sciences, The University of the West Indies, Eric Williams Medical Sciences Complex, Mount Hope, Trinidad and Tobago
[b] Department of Internal Medicine, Medical Associates Hospital, Corner of Albert and Abercromby Streets, St Joseph, Trinidad and Tobago

A B S T R A C T

Idiopathic oedema is a syndrome affecting primarily women that is characterized by frustrating intermittent fluid retention, with hallmarks of obesity, periodic oedema, anxiety, and a susceptibility to develop type 2 diabetes. Management is typically reassurance and weight control, with no known drug class proven to provide consistent relief. We hypothesise that sodium-glucose cotransporter 2 inhibition is a logical intervention in the treatment of idiopathic oedema, having effects on obesity, blood pressure, impaired glucose tolerance, sympathetic overdrive, and reduction in swelling – the most common and distressing complaint. Sodium-glucose cotransporter 2 inhibition by promoting greater electrolyte-free, but glucose driven, water clearance with preferential fluid clearance from the interstitial space, without compromising intravascular volume, may provide symptomatic relief of swelling and bloating. The consequent weight reduction secondary to caloric loss from renal glycosuria and decreased adiposity would prevent disease progression of type 2 diabetes or pre-diabetes. With diminished adrenergic output from central and peripheral autonomic influences, reduction of blood pressure occurs, and by similar mechanisms, anxiety may be reduced.

## Background

Idiopathic oedema also known as cyclic or periodic oedema is a poorly understood syndrome, almost exclusive to women [1]. It is characterized by frustrating intermittent fluid retention unrelated to the menstrual cycle. Intermittent non-specific protean symptoms often become chronic. Without any clear physical findings, recurrent generalized anxiety symptoms and a poly-symptomatic patient can incite frustration in the physician and perpetuates a vicious cycle of ambiguity [2].

First described in 1955 by Mach et al. [3], the aetiology of idiopathic oedema syndrome remains obscure. Some notable features have been identified, which include obesity, diurnal weight gain (more than 1 kg) without any secondary aetiology, abdominal bloating, swelling of the breasts and extremities (inclusive of the upper limbs), puffiness of the face, emotional lability (depression and neurotic symptoms), symptoms of generalised anxiety, type 2 diabetes mellitus, and occasionally hypothyroidism [4]. This cluster of clinical conditions is associated with vascular capillary hyper-permeability leading to retention of interstitial fluid manifesting as oedema [4]. Experimenting with $I^{125}$-labelled albumin, Edwards and Bayliss [2] put forward that an abnormally large leak of plasma fluid from circulation produces a considerable fall in plasma volume – which can result in postural hypotension, a not infrequent feature of the condition. In this multifactorial syndrome, the most consistent features are obesity, periodic oedema and anxiety, with a propensity to develop diabetes [4,5].

Idiopathic oedema presents a therapeutic challenge. Beyond reassurance and weight control, there is no known drug class that can provide consistent relief and as far as we are aware. A search of the PubMed and Scopus medical databases yields no definitive therapeutic approaches to patients with idiopathic oedema. Anecdotal reports cite the use of aminaphtone [6], low salt diet, aldosterone antagonists (spironolactone) and diuretics [7], and dopaminergic [8] or captopril [9] inhibition of the renin-angiotensin system. In terms of symptomatic treatment, periodic oedema remains the most frequent and distressing complaint for which diuretics offer no clinical benefit, but could indeed exacerbate postural hypotension.

## Hypothesis

We propose that sodium-glucose cotransporter 2 (SGLT2) inhibition offers a novel and logical intervention in the management of idiopathic oedema which may, at once, target oedema, weight loss and anxiety. Putative pleiotrophic effects of inhibition in this pathway on cardiovascular and renal physiology cause fluid and weight loss, diminished adrenergic output from central and peripheral autonomic influences with reduction of blood pressure and through the latter mechanism, ostensibly also reduced anxiety. The added benefit of weight loss may

* Corresponding author at: Department of Clinical Medical Sciences, Faculty of Medical Sciences, The University of the West Indies, Eric Williams Medical Sciences Complex, Trinidad and Tobago.
*E-mail address:* Surujpaul.Teelucksingh@sta.uwi.edu (S. Teelucksingh).

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reduce the tendency to type 2 diabetes known to be associated with the condition.

## Support for the hypothesis

### *SGLT2 inhibition as treatment for diabetes: Beyond the EMPA-REG outcome study*

Impressive results from the landmark EMPA-REG OUTCOME secondary prevention trial [10], on risk reduction of death from cardiovascular disease (38%), heart failure hospitalization (35%), and all-cause mortality (32%) in diabetic patients with high cardiovascular risk have not been seen before in any other cardiovascular outcome trial. These findings appear to be independent of the impressive reduction in hyperglycaemia per se, but rather due to additional mechanisms stemming from the pleiotropy of SGLT2 inhibition. The osmotic diuresis that ensues from SGLT2 inhibition leads to a reduction in preload and after load [11], triggering significant electrolyte-free water clearance, which depletes the interstitial fluid but not the vascular compartment. Hallow et al. [12] hypothesised that electrolyte-free water clearance consequent to SGLT2 inhibition causes a substantial two-fold reduction of interstitial fluid as compared with blood volume, which far exceeded the 78% reduction of blood volume after a loop diuretic. This preferential reduction of interstitial fluid seems unique to SGLT2 inhibition.

### *SGLT2 inhibition and weight and fluid loss*

Beyond the considerable impact of SGLT2 inhibition on glycaemic control, there are additional effects on body fluid distribution, natriuresis, blood pressure reduction, and weight loss. Improvements in cardiac and renal function occur through a complex interplay of osmotic, vascular, $Na^+/H^+$ exchange, hormonal and autonomic mechanisms [13]. Indeed the beneficial glucosuria and natriuresis have been reported in both diabetic and healthy subjects, with SGLT2 inhibitors setting a threshold for glucose spillage into urine well below normal fasting plasma glucose concentration [14].

Weight loss induced by SGLT2 inhibition does follow from caloric loss secondary to renal glycosuria, but in addition, ensues from decreased total body fat mass of both visceral and subcutaneous adiposity [15]. Interestingly SGLT2 inhibition has been associated with decreased levels of the leptin/adiponectin ratio [16] which is a recognised measure of insulin resistance and is strongly linked to visceral fat and features of the metabolic syndrome viz., hyperglycaemia, increased waist circumference, high systolic and diastolic blood pressure, hypertriglyceridemia, and low high-density lipoprotein cholesterol levels [17].

### *SGLT2 inhibition and renal function*

The pleiotropic effects of SGLT2 inhibition also involve the central and autonomic nervous systems, renal and systemic vascular tone, blood pressure, cardiac output and function. SGLT2 inhibition exploits the kidney to reduce extracellular volume expansion presumably mediated by decreased macula densa activity [18]. Sano [19] postulates that renal afferent nervous activity is reduced from central signalling of sympathetic outflow by SGLT2 inhibition providing additional cardiovascular protective effect.

### *SGLT2 inhibition and autonomic function*

Chronic sympathetic over-activity increases arterial stiffness and modifies renal sodium and water homeostasis to cause fluid retention and oedema. SGLT2 inhibition reduces arterial stiffness (an indicator of arterial noncompliance and thereby hypertension), improves blood pressure control and decreases risk of cardiovascular complications [20]. Clinical conditions such as ischemic heart disease, heart failure, hypertension, and type 2 diabetes mellitus (with or without the metabolic syndrome) are known risk factors for this pathophysiology. The hypotensive effect of SGLT2 inhibition being independent of increased chronotropy and other antihypertensive therapy, suggests sympathetic tone and injury from chronically elevated sympathetic activity are reduced. Studies of urinary epinephrine excretion link anxiety (a prominent feature of idiopathic oedema) with increased sympathoadrenal activity which is a possible biological gateway for cardiac disease [21].

## Evaluation of hypothesis

We propose to examine SGLT2 intervention in idiopathic oedema in a randomised, placebo controlled cross-over trial with intervention of empagliflozin or placebo. Since SGLT2 inhibitors excrete just 50–60% of the filtered glucose load in the diabetic and 35–40% in the normal glucose tolerant subject [22], we will use the lower dose of empagliflozin 10 mg. We will include female patients with complaints of ring tightness, shoe tightness/ankle swelling, bloating, anxiety/depression, irritability, panic attacks, breast pain, or a general anxiety disorder-7 (GAD-7) score of $\geq 5$. Patients receiving calcium channel blockers, renin-angiotensin-aldosterone system modulators, diuretics, and those suffering from hypertension and thyroid disorders will be excluded. Baseline HbA1c, diurnal weight, GAD-7 score and waist circumference at umbilicus will be recorded; and then weekly assessments will be made upon intervention. Patients will be encouraged to keep a journal of their symptomatic progress as well.

## Conclusion

Idiopathic oedema is associated with affective and somatic symptomatology, dysglycaemia and obesity which may antedate the diagnosis of type 2 diabetes. We propose SGLT2 inhibition will have effects on obesity, blood pressure, impaired glucose tolerance, sympathetic overdrive, and reduction in swelling – the most common and distressing complaint.

Our hypothesis is that the modest hemodynamic effect of SGLT2 inhibition promotes greater electrolyte-free, but glucose driven water clearance. The resultant benefit on the extracellular fluid compartment preferentially enhances fluid clearance from the interstitial fluid space, without compromising intravascular volume to provide symptomatic relief of the frequent distressing symptoms of swelling and bloating. The attendant weight reduction would prevent disease progression of type 2 diabetes or pre-diabetes which is often present in the obese subject with idiopathic oedema.

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None.

## Declaration of Competing Interest

The authors report no conflicts of interest.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2019.109270.

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