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Review

SGLT2 inhibitors-induced electrolyte abnormalities: An analysis of the associated mechanisms

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ABSTRACT

Aims: Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a new class of antidiabetic drugs that affect serum electrolytes levels. The aim of this review is the detailed presentation of the associated mechanisms of the SGLT2 inhibitors-induced electrolyte abnormalities.
Materials and methods: Eligible trials and relevant articles published in PubMed (last search in July 2017) are included in the review.
Results: SGLT2 inhibitors induce small increases in serum concentrations of magnesium, potassium and phosphate. The small increase in serum phosphate concentration may result in reduced bone density and increased risk of bone fractures, mainly seen with canagliflozin, but recent meta-analyses did not show increased risk of bone fractures with SGLT2 inhibitors.
Conclusion: The increases in serum electrolytes levels may play a role in the cardiovascular protection that has been recently reported with empagliflozin and canagliflozin.

Contents

1. Introduction

Changes in serum electrolyte parameters, namely small increases in serum magnesium, potassium and phosphate levels, have been repeatedly reported with sodium-glucose co-transporter 2 (SGLT2) inhibitors administration [1–3]. SGLT2 inhibitors lower blood pressure levels; thus, these drugs have been regarded as unique "diuretics" not associated with electrolytes depletion commonly encountered with the use of conventional diuretics [2]. However, the underlying pathophysiological mechanisms of these electrolyte changes are not well defined. Aim of the present review is the analysis of the putative mechanisms of the SGLT2 inhibitors-associated changes in serum electrolytes.

2. Methods

We searched for eligible trials published in PubMed (last search in July 2017) by using the following search algorithm:

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(Sodium-Glucose co-transporter 2 OR empagliflozin OR canagliflozin OR dapagliflozin OR ipragliflozin) AND (electrolytes OR magnesium OR potassium OR phosphorus OR sodium)

The search was limited by the following criteria:

- Published in the English language
- Published as clinical trial, meta-analysis, case report, comparative study, observational study, evaluation study, or validation study.

The initial search identified 258 articles in Pubmed, which were scrutinized for relevance. Further articles were retrieved from Pubmed and Scopus by searching relevant review articles.

3. Effects on electrolytes

3.1. SGLT2 inhibitors and magnesium homeostasis

A meta-analysis of 18 randomized controlled trials including 15,309 patients with four SGLT2 inhibitors (canagliflozin, empagliflozin, dapagliflozin and ipragliflozin) showed that these drugs can increase serum magnesium levels by approximately 0.08–0.2 mEq/L in individuals without chronic kidney disease. Interestingly, canagliflozin increased serum magnesium in a linear dose-dependent manner (Table 1) [4]. This finding is also confirmed by another analysis showing dose-dependent increases in serum magnesium levels along with increases in serum potassium and phosphate levels with canagliflozin administration, which were greater in individuals with decreased renal function (Table 2) [5]. Additionally, a post-hoc analysis of randomized controlled trials showed that both doses of canagliflozin were associated with normalization of serum magnesium levels in patients with type 2 diabetes [6]. It should be mentioned that this even small increase in serum magnesium concentration may have contributed to the cardiovascular benefits of empagliflozin in the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes trial (EMPA-REG OUTCOME) trial [7]. In fact, the increase in serum magnesium along with an increase in serum potassium concentrations may decrease the risk of cardiac arrhythmias, a possible beneficial effect explaining, at least in part, the cardiovascular event reduction in the EMPA-REG OUTCOME and Canagliflozin Cardiovascular Assessment Study (CANVAS) trials [8,9].

Many mechanisms are implicated in the SGLT2 inhibitors-induced serum magnesium concentration increase (Fig. 1). It is well known that renal magnesium wasting-induced hypomagnesemia is associated with diabetes mellitus and its complications [10]. This magnesiuria is possibly due to reduced transient receptor potential ion channel 6 (TRPM6) activity in the distal convoluted tubules and may be related to insulin resistance [11,12]. In fact, a down-regulation of TRPM6 channels was observed in obese type 2 diabetic rats resulting in hypermagnesiuric hypomagnesemia [13].

Table 1
Effects of SGLT2 inhibitors on magnesium homeostasis: Results of a meta-analysis of 18 randomized controlled trials (n = 15,309 patients with eGFR > 60 ml/min/1.73 m^2) [4].

	Dosage	Change in serum magnesium
Canagliflozin	100 mg/d	+0.12 mEq/L
	300 mg/d	+0.18 mEq/L
Dapagliflozin	10 mg/d	+0.2 mEq/L
Empagliflozin	10 mg/d	+0.08 mEq/L
	25 mg/d	+0.14 mEq/L

SGLT2 = sodium-glucose co-transporter 2; eGFR = estimated glomerular filtration rate.

Table 2
Percent increases in serum electrolytes after canagliflozin administration: the role of drug dose and baseline renal function [5].

	GFR > 60 ml/min/1.73 m^2		GFR 45–60 ml/min/1.73 m^2	
	100 mg	300 mg	100 mg	300 mg
Potassium	0.6%	1%	1.7%	2.8%
Magnesium	8.1%	9.3%	8.8%	12.6%
Phosphate	3.5%	5.2%	2.9%	4.7%

GFR = glomerular filtration rate.

Thus, the improvement of insulin resistance observed after SGLT2 inhibitors administration is possibly associated with a reduced magnesium excretion through TRPM6 [14–16]. Furthermore, the natriuresis and osmotic diuresis-induced extracellular volume depletion can lead to a small increase in serum magnesium due to hemoconcentration [4]. Additionally, the increased glucagon concentrations commonly observed during SGLT2 inhibitors administration [14–17] can also affect magnesium homeostasis, since glucagon is associated with increased magnesium reabsorption in the distal renal tubules [18]. It should also be mentioned that insulin induces a shift of magnesium from the plasma to the intracellular space [19]. Thus, the reduced serum insulin levels noticed after these drugs administration [20] is followed by a redistribution of magnesium out of the cells to the extracellular space.

On the other hand, SGLT2 inhibitors can increase aldosterone concentrations [1] due to natriuresis and osmotic diuresis-induced hypovolemia and it is well known that aldosterone may have a direct effect on magnesium transport [21] leading to increased magnesium excretion. In fact, spironolactone, an aldosterone inhibitor, can decrease renal magnesium wasting [22,23]. Thus, it seems that the aforementioned mechanisms that lead to elevation of serum magnesium concentrations can counterbalance the increased magnesium excretion due to increased aldosterone concentrations, ultimately leading to a small increase in serum magnesium levels (Fig. 1).

3.2. SGLT2 inhibitors and potassium homeostasis

SGLT2 inhibitors administration, mainly canagliflozin, is associated with small increases in serum potassium concentration especially in patients with reduced renal function (Table 2) as well as in patients consuming drugs that affect potassium homeostasis, such as inhibitors of the renin-angiotensin system [5]. It should be mentioned that changes in serum potassium concentration are not observed in all studies with SGLT2 inhibitors. No change in serum potassium levels was found with empagliflozin in the EMPA-REG trial [8] (Table 3) or in patients with type 2 diabetes mellitus (T2DM) and stage 2/3 chronic kidney disease (estimated glomerular filtration rate (eGFR) ≥60 ml/min/1.73 m^2 and between 30 and 60 ml/min/1.73 m^2, respectively) [24]. Additionally, dapagliflozin was not associated with serum potassium changes in patients with moderate renal impairment (eGFR 30–59 ml/min/1.7 3m^2) [25]. This was also confirmed in a pooled analysis of 14 randomized trials, which showed that dapagliflozin was not related with an increased risk of hyperkalemia even in patients with baseline eGFR ≤60 ml/min/1.73 m^2 [26].

The associated mechanisms leading to a small serum potassium levels increase with SGLT2 inhibitors are shown in Fig. 2. SGLT2 inhibition-induced natriuresis and osmotic diuresis is expected to increase renal potassium excretion due to i) increased tubular flow rate to the distal convoluted and collecting tubules (in this case, potassium is excreted through the “max big” potassium channels)

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