

## Stiff, numb hands

(JUNE 2013)

**TO THE EDITOR:** Regarding the case of tetany presented by Drs. Shaheen and Merugu in the June 2013 issue of *Cleveland Clinic Journal of Medicine* (pages 360–362), their clinical discussion was right on, but they did not mention the clinical use of and need for ionized calcium levels in a case like this and the follow-up to confirm this was not a patient with latent hypoparathyroidism.

There is often a major discrepancy between the total calcium (no matter how it is “corrected”) and the free (ionized) calcium value, and the need to follow it during the correction phase of both hypercalcemia and hypocalcemia is critical.

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**IN REPLY:** Generally, it is preferable to measure the ionized calcium directly, particularly if there is uncertainty about whether the corrected serum calcium is reflective of the ionized calcium, if the patient’s symptoms are atypical, or if a reliable laboratory is available to measure ionized calcium.

Direct measurement of the ionized calcium concentration could be favored compared with measuring the corrected calcium in patients with symptoms of hypocalcemia in the setting of a normal total calcium concentration. Symptomatic hypocalcemia with normal total calcium but low ionized calcium can occasionally occur in patients with acute respiratory alkalosis due to increased binding of calcium to albumin. Thus, respiratory alkalosis may cause an acute decrease in ionized calcium. Furthermore, the ionized fraction can change without an alteration in the total serum calcium concentration, as with hyperparathyroidism, which increases the ionized calcium at the expense of that bound to albumin, and hyperphosphatemia, which increases the fraction bound to inorganic anions, decreasing ionized calcium. In patients

who have chronic kidney disease and a low serum bicarbonate or a low serum albumin, or both, measuring the ionized calcium is preferable to measuring the total calcium in order to diagnose hypocalcemia or hypercalcemia.

The patient was given oral magnesium, potassium, calcium, and vitamin D to continue at home. In addition, she was advised to avoid excessive alcohol consumption, and she was followed by her primary care doctor. All the laboratory values normalized within 1 month of abstinence from alcohol, and she has been well since. We agree regarding the importance of checking on the ionized calcium to confirm the hypocalcemia and normalization after treatment as stated above. Ionized calcium was never checked during the hospital stay or during the follow-up after the discharge.

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## Canagliflozin

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**TO THE EDITOR:** We found Dr. Vouyiouklis’s article about the recently approved sodium-glucose cotransport 2 (SGLT) inhibitor canagliflozin very useful. However, we strongly believe there are some issues that should be addressed.

In discussing the canagliflozin trials, Dr. Vouyiouklis did not mention a phase III randomized, double-blind, double-arm study, in which canagliflozin (100 and 300 mg) in addition to metformin was compared with placebo and sitagliptin (100 mg) in patients with type 2 diabetes.<sup>1</sup> This study recruited 1,284 participants in 22 countries. At week 52, hemoglobin A<sub>1c</sub> levels had declined by 0.73% in the sitagliptin group, 0.73% in the canagliflozin 100 mg group, and 0.88%

in the canagliflozin 300 mg group. Thus, canagliflozin 100 mg demonstrated noninferiority, and canagliflozin 300 mg demonstrated superiority. In addition, as previously described by other trials, a significant statistical reduction was observed in weight and blood pressure with modest elevations in LDL cholesterol and the incidence of mycotic urinary infections.

Current guidelines and recommendations give a wide variety of therapeutic options as the second step if lifestyle interventions and metformin fail to achieve glycemic control.<sup>2</sup> The best combination regimen is still debated and, because of their excellent side-effect profile, dipeptidyl peptidase-4 inhibitors (gliptins) are one of the most used therapeutic classes. We believe this study adds important evidence that could help with decision-making in routine clinical practice.

Also, canagliflozin's favorable effects on weight and blood pressure inevitably lead to the question, Are the weight loss and decreased systolic blood pressure due to osmotic diuresis or to lean or body fat weight loss? The mechanism of action of SGLT2 inhibitors, per se, favors osmotic diuresis, and several trials have demonstrated this same effect, as well as postural dizziness and orthostatic hypotension.<sup>3,4</sup> Until now, the exact cause of this weight loss has not been elucidated, and no trial has demonstrated with precision a reduction in lean or fat body weight as a direct effect of SGLT2 inhibitors. This, in addition to LDL elevation, could have important clinical implications, as diuretic osmosis will subsequently activate the renin-angiotensin-aldosterone system. This might initially blunt this blood pressure reduction and promote parasympathetic inhibition, sympathetic activation, and myocardial and vascular fibrosis that can potentially lead in the long term to adverse cardiovascular outcomes.<sup>5</sup>

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**TO THE EDITOR:** In a recent *CCJM* review of canagliflozin,<sup>1</sup> this novel antihyperglycemic medication was noted to be associated with a dose-dependent increase in low-density lipoprotein (LDL) cholesterol, with an increase in LDL of 8.3 mg/dL (0.215 mmol/L) seen with the 300-mg/day dose of canagliflozin.

The Cholesterol Treatment Trialists' (CTT) meta-analysis<sup>2</sup> showed a significant 21% proportional reduction in major vascular events per 1.0 mmol/L reduction in LDL cholesterol in people with diabetes treated with statins over an average of 4.3 years. If we assume that raising LDL cholesterol by 1.0 mmol/L has the opposite effect, then patients taking 300 mg per day of canagliflozin would be expected to suffer an increase in major vascular events of about 4.5% over 4.3 years. Put another way, for every 22 diabetic patients treated with canagliflozin over 4.3 years, one additional major vascular event

CONTINUED ON PAGE 90

CONTINUED FROM PAGE 88

would be expected on the basis of the associated increase in LDL cholesterol.

The CTT data also showed a significant 9% decrease in all-cause mortality for every 1.0 mmol/L decrease in LDL cholesterol. Again, assuming that raising LDL has the opposite effect of lowering it, then we should expect an additional death for each 52 diabetic patients treated with 300 mg/day of canagliflozin per day for 4.3 years.

The hypotensive side effect of canagliflozin might tend to mitigate some of the above adverse effects, as might its antihyperglycemic effect. Still, it would seem prudent to use this novel agent only as a second- or third-line choice, particularly in diabetic patients who have already suffered a major vascular event.

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**IN REPLY:** I would like to thank these readers very much for their response and comments.

Additional data provided from the study conducted by Lavallo-González et al evaluating the efficacy and safety of canagliflozin (100-mg and 300-mg doses) vs placebo and sitagliptin in patients with type 2 diabetes showed similar findings in weight and blood pressure reduction with slight LDL

elevation with the studies mentioned in my article.<sup>1</sup> At 52 weeks, as noted, canagliflozin 100 mg demonstrated noninferiority, and canagliflozin 300 mg showed a statistically significant superiority to sitagliptin in lowering hemoglobin A<sub>1c</sub> (a change of -0.73% with canagliflozin 100 mg, -0.88% with canagliflozin 300 mg, and -0.73% with sitagliptin), which may be considered in treatment decisions along with the other possible effects of this drug.<sup>1</sup>

The decision to use canagliflozin as second- or third-line therapy should be individualized after considering all of the patient's risk factors as well as the potential benefit vs side effects of this drug. Metformin remains my first-line choice in the management of type 2 diabetes. In my clinical practice, thus far, I have not used canagliflozin in patients with known coronary disease or a history of cardiovascular events. I have ensured that the LDL is certainly below goal before starting any patient on this drug, and I have followed the LDL closely, without hesitating to increase the statin drug to keep the LDL below goal. I agree that the slight increase of LDL is of concern, and certainly long-term studies are necessary to see whether there will be any increase in cardiovascular events from the use of canagliflozin.

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