EDITORIAL

Is there an actual link between vitamin D deficiency, cardiovascular disease, and glycemic control in patients with type 2 diabetes mellitus?

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Coronary artery disease (CAD) and acute myocardial infarction still represent the leading causes of mortality in developed countries. In fact, despite common utilization of primary percutaneous coronary intervention, the outcomes are still unsatisfactory in high-risk subgroups of patients, especially diabetic individuals.[1] Therefore, huge efforts have been made in the last decades to identify new risk factors for coronary atherosclerosis.[2,3] Special attention was given to vitamin D (VD), a secosteroid mainly involved in the homeostasis of calcium and bone tissue, but also displaying a broad spectrum of systemic hormonal effects, including modulation of the expression of about 3% of the human genome and "acute", non–genomic-dependent effects, mediated by the regulation of intracellular calcium.

In the current issue of *Polish Archives of Internal Medicine*, Kwiendacz et al[4] assessed the prevalence and cardiovascular impact of VD deficiency (VDD) among patients with type 2 diabetes mellitus (T2DM) from a single-center registry in the Upper Silesia region of Poland.

The authors observed that VDD (<20 ng/ml) occurred in 36% of the patients, and only a small group supplemented VD. Around one-third of the study population were diagnosed with cardiovascular disease (CVD), with no difference according to their VD status. Of note, VDD was more common among patients treated with sodium glucose co-transporter-2 inhibitors (SGLT-2is).

Indeed, as acknowledged by the authors, the study has a number of limitations, the main one being a small number of included patients. However, the outcomes were not significantly affected by the sample size, being in line with the results previously presented in the literature. In fact, the prevalence of VDD estimated in Europe is around 40%,[5] and comparable data were reported by our study group among patients with established CAD, where about one-third of the population displayed VD levels below 20 ng/ml, which was associated with an increased risk of major cardiovascular events.[6] In another registry,[7] diabetic patients displayed lower levels of VD and more severe CVD, although diabetic status did not emerge as an independent predictor of VDD, being more probably conferred by more advanced age or comorbidities, and especially chronic kidney disease.

Even though the Silesia Diabetes-Heart Project did not report any kind of follow-up allowing for evaluation of the prognostic impact of VDD, lower levels of VD have been consistently associated with an increased risk of CVD. Contrary to that, in the Polish study, the prevalence of atherosclerotic CVD was not affected by the levels of VD. However, the patients with VDD had a shorter duration of diabetes and were slightly younger, which indicated a shorter exposure to the proatherogenic conditions linked with DM (hyperglycemia, inflammation) and, potentially, a shorter duration of VDD.

In fact, the cardioprotective effects of VD, as well as the detrimental effects of its deficiency, are usually perceived over a long period of time, and therefore could still have gone unnoticed in the Polish study. Previous studies have suggested that childhood nutritional status of VD could be a major determinant of the development of CVD in adults.[8] Exposure duration has also been claimed as one of the reasons for failure of previous trials on VD supplementation.[9]

Another important factor to be considered in the relationship between VD and diabetes is glycemic control. Consistent data have demonstrated the impact of VD on promoting insulin sensitivity and improving metabolic status. In fact, VD

plays an important role in the regulation of pancreatic β-cells, modulating the secretion of insulin, stimulating the expression of insulin receptors, and reducing the production of cytokines associated with insulin resistance.[10]

In the study by Kwiendacz et al,[4] glycosylated hemoglobin was only slightly elevated in the VDD patients, and was accompanied by a modest increase in the use of insulin. However, the authors reported a significant association between lower levels of VD and the use of SGLT-2is.

Gliflozines are a novel type of hypoglycemic agents increasing glucose and sodium excretion with urine, which have demonstrated to improve the outcomes not only of DM treatment, but also in patients with CVD, heart failure, or renal failure.[11]

However, despite these positive results, limited economic resources resulted in severe restrictions concerning prescription of these agents in several countries, including Poland, where their reimbursement is warranted only for severely ill patients.[12] Therefore, it might be argued that the more common use of these drugs among patients with VDD could reflect a growth in the higher-risk polymorbid and fragile population, where VD levels tend to be lower.

Similar results have been previously reported in several studies with gliflozines, as a consequence of their mechanism of action. It has been hypothesized that inhibiting SGLT-2 could increase cellular sodium levels and cause another transporter to increase cellular uptake of phosphate, which could trigger body-wide signals to reduce VD levels in order to prevent calcium absorption in the gastrointestinal tract.

In the IMPROVE trial[13] in patients with T2DM and albuminuric kidney disease, dapagliflozin increased serum phosphate levels by 9% and parathormone by 16%, as compared with placebo, and thus induced calciuria. Similar results were also reported for other SGLT-2is.[14] However, 4 meta-analyses comparing the use of any SGLT-2i with placebo or other control treatments in tens of thousands of patients, including a Cochrane review in patients with diabetic kidney disease, did not confirm the relationship between SGLT-2i use and increased fracture risk.[15]

Indeed, very long-term data addressing the effects of gliflozines on mineral and bone metabolism are still missing. However, patients with DM, and especially with concomitant renal damage, already represent a population in which dysregulations in bone turnover and increased risk of fractures are common and need to be addressed. Thus, given the extremely large cardiorenal benefits of SGLT-2is, even a potential increase in bone side effects has to be weighed against the prognostic advantages. Nevertheless, while waiting for further data from randomized trials and real-world studies, VD levels and metabolism should be carefully considered in diabetic patients in order to establish an appropriate supplementation in the case of deficiency, especially in the presence of risk-enhancing conditions, such as renal failure, CVD, or the use of SGLT-2is.

ARTICLE INFORMATION

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