Relationship of vitamin D deficiency with cardiovascular disease and glycemic control in patients with type 2 diabetes mellitus

the Silesia Diabetes-Heart Project

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ORIGINAL ARTICLE

Relationship of vitamin D deficiency with cardiovascular disease and glycemic control in patients with type 2 diabetes mellitus: the Silesia Diabetes-Heart Project

Hanna Kwiendacz[1], Katarzyna Nabrdalik[1,2], Agata M. Wijata[3], Wojciech Bartman[4], Elżbieta Tabor[1], Anna Olejarz[5], Joanna Król[5], Julia Piaśnik[5], Jakub Nalepa[6], Tomasz Stompór[7], Janusz Gumprecht[1], Gregory Y. H. Lip[2,8]

1 Department of Internal Medicine, Diabetology and Nephrology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland
2 Liverpool Centre for Cardiovascular Science at University of Liverpool, Liverpool John Moores University and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom
3 Faculty of Biomedical Engineering, Silesian University of Technology, Zabrze, Poland
4 Department of Neurology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland
5 Students' Scientific Association at the Department of Internal Medicine, Diabetology and Nephrology in Zabrze, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland
6 Department of Algorithmics and Software, Silesian University of Technology, Gliwice, Poland
7 Department of Nephrology, Hypertensiology, and Internal Diseases, University of Warmia and Mazury, Olsztyn, Poland
8 Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

KEY WORDS

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EDITORIAL

by Verdoia and de Luca

Correspondence to:
Katarzyna Nabrdalik, MD, PhD, Department of Internal Medicine, Diabetology and Nephrology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland, ul. 3 Maja 13–15, 41-800 Zabrze, Poland, phone: +48 32 370 44 88, email: knabrdalik@sum.edu.pl
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ABSTRACT

INTRODUCTION Vitamin D (VD) has a pleiotropic effect on many health-related aspects, yet the results of studies regarding vitamin D deficiency (VDD) and both glycemic control and cardiovascular disease (CVD) are conflicting.

OBJECTIVES The aim of this work was to determine the prevalence of VDD and its associations with CVD and glycemic control among patients with type 2 diabetes mellitus (T2DM).

PATIENTS AND METHODS This was an observational study in T2DM patients recruited at the diabetology clinic in Zabrze, Poland (April–September 2019 and April–September 2020). The presence of CVD was determined based on medical records. Blood biochemical parameters, densitometry, and carotid artery ultrasound examination were performed. Control of diabetes was assessed based on glycated hemoglobin A_{1c} (HbA_{1c}) levels. A serum VD level below 20 ng/ml was considered as VDD.

RESULTS The prevalence of VDD in 197 patients was 36%. CVD was evident in 27% of the patients with VDD and in 33% of the patients with VD within the normal range (vitamin D sufficiency [VDS]) ($P = 0.34$). The difference between the groups regarding diabetes control was insignificant ($P = 0.05$), as for the VDD patients the median value (interquartile range) of HbA_{1c} was 7.5% (6.93%–7.9%), and for VDS patients it was 7.5% (6.56%–7.5%). The VDD patients were more often treated with sodium-glucose cotransporter-2 inhibitors (SGLT-2is) (44% vs 25%; $P = 0.01$).

CONCLUSIONS About one-third of the patients showed VDD. The VDD and VDS groups did not differ in terms of CVD occurrence and the difference in glycemic control was insignificant. The patients with VDD were more often treated with SGLT-2is, which requires further investigation.

INTRODUCTION According to the International Diabetes Federation, the number of adult (20–79 years old) patients with diabetes mellitus (DM) all over the world has tripled to 537 million since 2000, which accounts for more than 10% of the global adult population.[1] The patients with DM are at a high risk of developing micro- and macrovascular complications, which lead to

WHAT'S NEW?

There is no consistency in the literature between observational and interventional studies regarding vitamin D deficiency (VDD) and both cardiovascular disease (CVD) and glycemic control of diabetes. The outcomes of this observational study among Polish patients with type 2 diabetes revealed that 36% of the participants had VDD. We did not find any association between VDD and CVD, and the difference between the groups in glycemic control of diabetes was insignificant. However, we found out that the patients with VDD were more often treated with sodium-glucose cotransporter-2 inhibitors (SGLT-2is) than the patients with VD concentrations within the reference range, which is, to the best of our knowledge, a novel finding. This outcome is of high importance given the concerns that SGLT-2is may possibly affect the bone turnover through a negative influence on VD concentration.

deteriorated quality of life, increased medical expenditure, and premature death.[2,3]

People with DM now live much longer than decades ago, primarily thanks to the development of new drugs to treat DM and cardiovascular disease (CVD), as well as to the extensive use of interventional cardiology.[4] However, CVD is still the main cause of death in people with DM, and the diabetes control is satisfactory in no more than 50% of patients.[5]

Vitamin D (VD) is undoubtedly vital for proper bone structure[6] but through its pleiotropic actions, VD may influence CVD and metabolic control.[7] Vitamin D deficiency (VDD) occurs in almost half of the European and one-third of the North American population.[8-10] VD was first described in 1920,[11] and the interest in it has not waned since then.[12,13] The rationale for exploring its association with CVD was the discovery of VD receptor expression throughout the circulatory system,[14] including cardiomyocytes[15] and human coronary artery smooth cells.[16] It has been revealed in the experimental model with macrophages from obese patients with DM, hypertension, and VDD that VD supplementation (or, to be more precise, supplementation with its active form [1,25$(OH)_2D_3$]) leads to suppression of foam cell formation due to reduction of acetylated or oxidized low-density lipoprotein cholesterol uptake and promotion of the antiatherogenic monocyte / macrophage phenotype.[17,18] Therefore, VD concentrations could have an effect on CVD occurrence itself, and various studies have suggested that low VD concentrations may be associated with an increased risk of CVD.[19,20]

However, there is a lack of consistency between epidemiologic studies[21] and randomized controlled trials (RCTs),[22,23] as well as Mendelian randomization studies[24] with regard to VDD and CVD. Most epidemiologic studies indicate an association of VDD with increased CVD risk and with CVD risk factors, such as endothelial dysfunction, dyslipidemia, subclinical atherosclerosis, and arterial hypertension.[21] In contrast, RCTs[22,23] and Mendelian randomization studies[24] have failed to prove a significant and coherent effect of VD supplementation on either CVD occurrence or CVD risk.

Regarding the association of VD with glycemic control of DM, low VD concentration has been associated with insulin resistance, glucose metabolism disturbances, and increased risk of metabolic syndrome.[25] However, similarly to CVD events, VD supplementation assessed in RCTs does not improve glucose metabolism in type 2 diabetes mellitus (T2DM),[26,27] and has no role in T2DM prevention.[28]

Given that the results of epidemiologic studies and RCTs regarding VDD and both CVD and glycemic control in T2DM are conflicting, our aim was to determine VDD prevalence within a cohort of T2DM patients inhabiting the Upper Silesia region of Poland, and to establish its association with CVD and glycemic control.

PATIENTS AND METHODS We performed a single-center, observational study in a cohort of T2DM patients inhabiting the Upper Silesia region of Poland. We recruited consecutive patients attending a scheduled visit in the outpatient diabetology clinic in Zabrze, Poland, from April to September 2019, and from April to September 2020, in order to minimize the influence of seasonal sun exposure differences throughout the year. The inclusion criteria for the study were the age of at least 18 years and a diagnosis of T2DM. We excluded the patients with other types of diabetes, malignant neoplasms, estimated glomerular filtration rate (eGFR) below 60 ml/min/1.73 m^2, diagnosed with malabsorption syndrome, with active infection, liver disease, or primary hyperparathyroidism. All patients provided their written informed consent to participate in the study, and the study was approved by the Ethics Committee of the Medical University of Silesia (KNW/0022/KB1/10/17).

Once the informed consent had been obtained, the medical history of eligible patients was collected, including the data related to age, duration of DM, concomitant diseases, and medications, including VD supplementation. The presence of CVD was defined as at least 1 of the following: coronary angiography–confirmed coronary artery disease, prior myocardial infarction, percutaneous cardiac intervention or coronary artery bypass grafting, angiography-documented peripheral artery disease or prior vascular intervention, carotid artery atherosclerosis (stenosis >50%), and / or prior stroke or heart failure. Glycemic control was assessed by determining the glycated hemoglobin A_{1c} (HbA_{1c}) levels.

The patients who fulfilled the inclusion criteria to participate in the study had a visit scheduled to perform the following procedures: basic physical examination, drawing fasting blood samples, carotid ultrasound examination, and densitometry.

Basic physical examination included the measurement of height, waist, and hip circumference in meters, and body weight in kilograms. The body

mass index (BMI) was calculated through dividing the weight in kilograms by height in meters squared (kg/m^2), and waist-to-hip ratio (WHR) was obtained by dividing the waist circumference by the hip circumference. Blood pressure was measured 3 times (after 5 minutes of rest), in a sitting position using the Microlife BP AG1-20 sphygmomanometer (Microlife Corporation, Taipei, Taiwan), and the first measurement was discarded. The study was registered at ClinicalTrials.gov (NCT05626413) as a part of The Silesia Diabetes-Heart Project.

Laboratory parameters The following blood biochemical parameters were assessed: HbA_{1c}, total calcium, phosphates, total protein, and VD concentration. The patients included in the study had documented eGFR at least 60 ml/min/1.73 m^2 in the last month before the inclusion into the study.

HbA_{1c} levels were measured using high-performance liquid chromatography, and the results were expressed in the National Glycohemoglobin Standardization Program / Diabetes Control and Complications trial units.[29] Total calcium was determined by the photometric method (Roche, Penzber, Germany), phosphates and total protein by the colorimetric method (Roche), whereas VD concentrations [25(OH)D_3] were elaborated with the use of the electrochemiluminescence immunoassay (ECLIA, Roche).

Ultrasound examination of the carotid arteries was performed using high-resolution Doppler with double imaging and color coding of the flow (Color Doppler Duplex, CDD), with the Esaote MyLab60 ultrasound equipment (Esaote, Genoa, Italy) (variable frequency of 4–15 MHz) by the same certified neurologist. Bone mineral density (BMD) was assessed using a Hologic Explorer (Hologic Inc., Waltham, Massachusetts, United States; software version 13.0:3) densitometer.

The patients were split into 2 groups: VD deficient and those with VD within normal range (VD sufficient [VDS]). The VD level below 20 ng/ml was considered as VDD, and equal to or above 20 ng/ml as VDS.[30]

Statistical analysis GraphPad Prism 9.4.1 (GraphPad Software, Boston, Massachusetts, United States) and MATLAB R2022a (The MathWorks Inc., Natick, Massachusetts, United States) packages were used to perform the statistical analysis. In order to establish the distribution of quantitative variables, the Shapiro–Wilk normality test was used. For each continuous parameter, we report its mean (SD) for normally distributed variables, and median (IQR) for those variables that did not follow the normal distribution. The total number of ones and the percentage of ones are given for all binary variables. The χ^2, the unpaired-sample *t* test, or the Mann–Whitney test were performed for comparative analyses, depending on the data characteristics. In this study, the *P* values below 0.05 were considered significant.

RESULTS A total of 270 potentially eligible patients were invited to take part in this observational study, and 197 participants were finally enrolled (mean [SD] age, 61.51 (10.57) years; 50% women). The reasons for noncompletion are presented in FIGURE 1. The median duration of T2DM was 7 years (IQR, 3–11.25). Clinical characteristics of the patients are presented in TABLE 1. The data on blood biochemical parameters and blood pressure are shown in TABLE 2, and densitometry and carotid artery ultrasound examinations are summarized in TABLES 3 and 4.

VD status in the whole study group is shown in FIGURE 1. There were 71 patients (36% of all the participants) with VDD, of which 19 (27%) presented with CVD. Of 126 VDS patients (64% of the participants), 42 (33% of the VDS patients) presented with CVD. There was no difference in terms of CVD occurrence between the analyzed groups. The patients with VDD were more often treated with sodium-glucose cotransporter-2 inhibitors (SGLT-2is) than those who had VD within the reference range (44% vs 25%; $P = 0.01$; TABLE 1). The difference between the groups regarding diabetes control was insignificant ($P = 0.05$; TABLE 2), as in VDD patients the median HbA_{1c} value was 7.5% (IQR, 6.93%–7.9%), whereas for the VDS group it was 7.5% (IQR, 6.56%–7.5%).

In the VDD group, only 20% of the patients supplemented VD, while in the VDS group it was observed in 53% of the participants ($P < 0.001$). The supplementation lasted shorter in the VDD patients than in the VDS ones, with a median of 0 (IQR, 0–0) vs 1 (IQR, 0–8) month ($P = 0.001$), respectively.

We also compared the patients who did and did not use SGLT-2is, and found significant differences in terms of VD concentration, with a median of 20.57 ng/ml (IQR, 16.21–26.82) and 24.28 ng/ml (IQR, 18.32–30.61) ($P = 0.01$), the number of patients who supplemented VD (30% vs 46%; $P = 0.03$), median duration of VD supplementation 0 (IQR, 0–1) vs 0 (IQR, 0–7) months ($P = 0.04$), median HbA_{1c} value of 7.5% (IQR, 7.07%–8.65%) vs 7.5% (IQR, 6.43%–7.5%) ($P < 0.001$), and median intima-media thickness (IMT) of the left common carotid artery of 0.76 mm (IQR, 0.64–0.92) vs 0.71 mm (IQR, 0.6–0.79) ($P = 0.01$), respectively (TABLE 5).

DISCUSSION The key findings of our study are the following: the prevalence of VDD reached 36% of the studied population, and the VDD patients, as compared with the VDS patients, did not differ in terms of CVD occurrence but showed an insignificantly worse diabetes control. Additional analyses revealed that the patients with VDD were more often treated with SGLT-2is, had less frequent VD supplementation, and the VD supplementation period was shorter (TABLES 1 and 2).

The estimated prevalence of VDD (defined as VD concentration < 20 ng/ml) in Europe is about 40%,[8] and it is similar to the one presented in our study. The current prevalence is much lower than

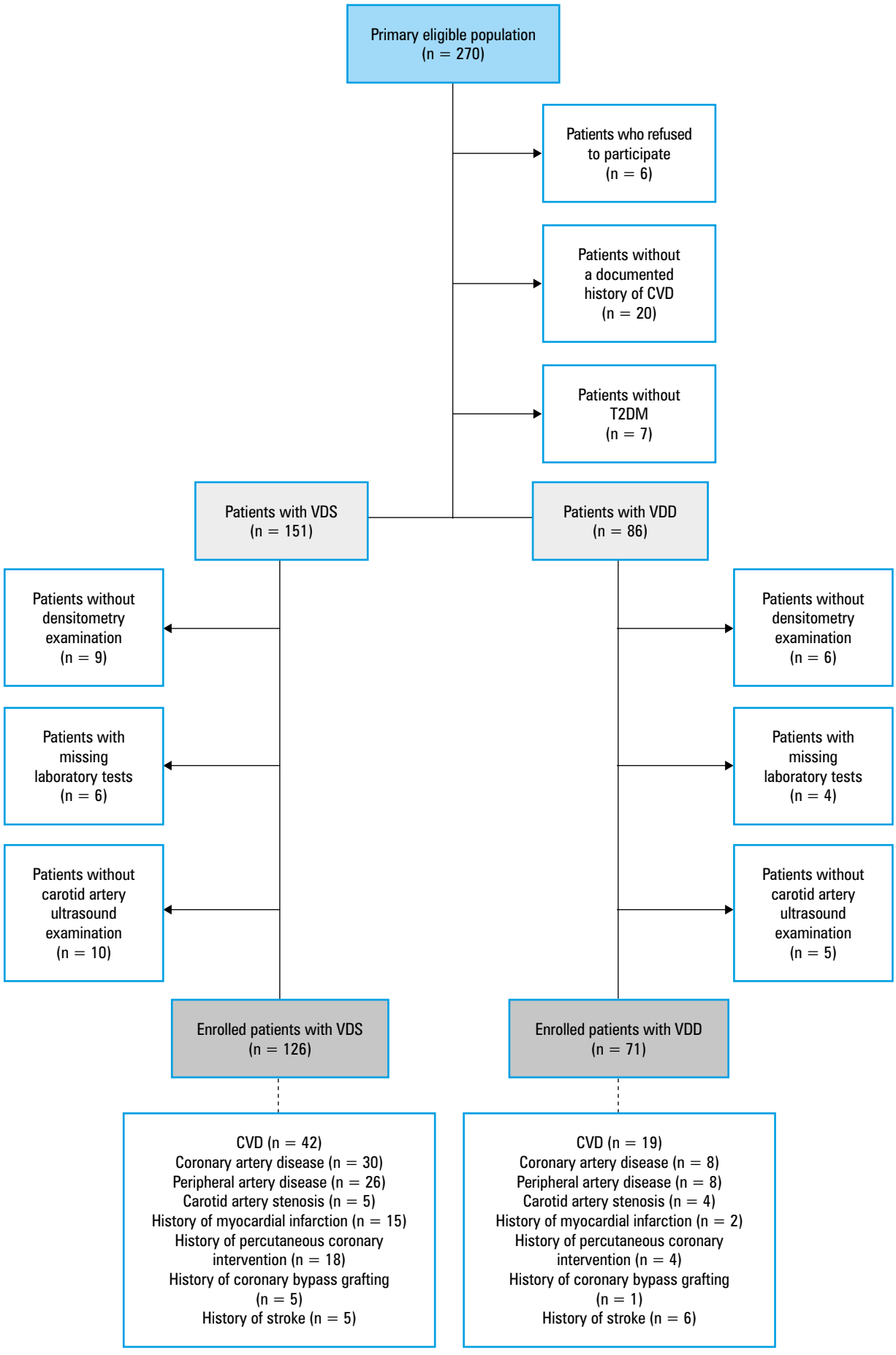

FIGURE 1 Enrollment of patients into our study from the primary eligible population
Abbreviations: CVD, cardiovascular disease; T2DM, type 2 diabetes mellitus; VDD, vitamin D deficiency; VDS, vitamin D sufficiency

the previous estimation from a sample of the Polish population in 2016, when it reached 66%.[9]

In general, there is no consistency between the observational and interventional studies regarding the links between VDD and CVD. Many observational works, unlike our study that failed to prove this association, suggested a relationship between VDD and CVD risk factor occurrence and CVD itself.[21] Still, VD supplementation assessed in RCTs seems not to have a significant beneficial effect on CVD.[22-24] In a meta-analysis of 83 000 patients in 21 RCTs,[23] VD supplementation (resulting in the increase in VD concentration) did not protect against CVD. This discrepancy is difficult to explain, and the incoherent results may be due to either various reference ranges of VDD or the possibility that VDD in patients with CVD might be just an epiphenomenon, as a correlation does not necessarily mean causation in this case.[31]

It is worth mentioning that the analyzed form of VD in the serum is its liver metabolite, $25(OH)D_3$, and not an active VD form, $1,25(OH)_2D_3$. The production of $1,25(OH)_2D_3$ in the kidneys is stimulated by 1α-hydroxylase, which is regulated by parathormone (PTH) as part of a feedback loop between the kidneys and parathyroid glands. Moreover $1,25(OH)_2D_3$ and phosphate stimulate fibroblast growth factor 23 secretion from bones, which in turn inhibits transcription of 1α-hydroxylase and promotes transcription of 24-hydroxylase (an enzyme responsible for VD catabolism).[32,33] The metabolism of $25(OH)D_3$ in the kidneys is still not fully elucidated, and there are gaps in our knowledge to be filled. The presented lack of association between VD concentration and CVD may be caused by the abovementioned hormonal interplay affecting the production of the active form of VD and further clinical outcomes.

For the majority of patients with T2DM, glycemic target expressed by HbA_{1c} levels is set at 7%; however, many individuals fail to achieve it.[5] It was already proven in some prior trials that patients with VDD present with a worse metabolic control of DM,[34,35] and the trend toward worse DM control has also been observed in our study. Nevertheless, there is no conclusive evidence that VD supplementation could be beneficial in terms of glycemic control.[36,37]

As suspected, there were significant differences between the patients with VDD and VDS with respect to the VD supplementation and its duration. In the VDD group, only 20% of the patients supplemented VD, while in the VDS group, this percentage reached 53%, and supplementation lasted for a shorter time in VDD patients. As many as 20% of the VDD patients supplemented VD, yet still had its concentration below 20 ng/ml, which might be explained by the lack of a proper dose (mean daily dose was 2678 IU) and/or a too short supplementation period.[38] In the trials designed and performed to establish the appropriate VD supplementation and to verify if an increase in the VD concentration can decrease the risk of developing DM, both the doses and duration of supplementation were higher and longer (4000 IU per day for 24 months,[28] 20 000 IU per week for 5 years,[39] or 28 000 IU per week for 24 weeks)[40], and even in the case of such high doses, the risk of DM did not decrease.

In addition, differences were found between SGLT-2i users and nonusers in relation to the VD status. The patients treated with SGLT-2is had a lower VD concentration, fewer of them supplemented VD, and the supplementation period was shorter than in the patients not treated with SGLT-2is. There have been concerns raised in the literature that SGLT-2is may affect bone status through a negative influence on VD concentrations.[41] Moreover, this class of drugs is increasingly often used due to its glucose-lowering and cardio- and nephroprotective benefits;[42] hence, its influence on VD concentrations and bone status seems important.[43] To the best of our knowledge, there are no trials designed solely to examine the associations between the SGLT-2i treatment and VD concentration, and the available results are acquired from trials assessing the SGLT-2i impact on bone health.

In an animal model, a long-term (25 weeks) inhibition of SGLT-2 did not modulate VD concentrations but it contributed to increased bone fragility.[44] In human studies, dapagliflozin did not affect VD concentration,[45] while canagliflozin decreased it (via a rapid increase in the serum phosphorus, fibroblast growth factor 23 and PTH levels, with a potentially negative impact on bone health),[41] and empagliflozin increased it slightly.[46] The effect of SGLT-2is on bone fractures and VD concentration remains controversial and requires further investigation.

Moreover, the individuals treated with SGLT-2is had better diabetes control expressed by HbA_{1c} levels (which is easy to explain as these agents have a strong glucose-lowering potential)[47] and larger IMT of the left carotid artery than those who did not use these drugs. IMT is an easy-to-obtain surrogate marker for atherosclerosis derived from ultrasound examination. It enables us to not only diagnose atherosclerosis at a subclinical stage but also to predict future cardiovascular events.[48] SGLT-2is are recognized as drugs with antiatherogenic potential that improve the outcome of patients already diagnosed with CVD or those at a high risk of developing atherosclerosis[49]; therefore, SGLT-2is might be more often offered to these groups of patients. The difference in IMT might be merely an accidental finding and it certainly requires further research. However, in our previous study, in which we exploited machine learning methods, we found that the plaque score of the right carotid artery, among others, can identify patients with metabolic-associated fatty liver disease and prevalent CVD.[50]

Limitations The main limitation of the presented study is a rather small number of patients. Also,

TABLE 1 Clinical characteristics of the study group

Parameter	Patients with VDD (n = 71)		Patients with VDS (n = 126)		*P* value
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	
Men, n (%)	39 (55)	–	60 (48)	–	0.32
Age, y	60.44 (10.45)	62 (55.25–67.75)	62.13 (10.63)	62 (54–70)	0.28
Duration of diabetes, y	7.65 (7.02)	6 (4–10)	9.02 (7.32)	8 (3–13)	0.20
BMI, kg/m^2	32.45 (5.06)	31.74 (29.54–34.43)	32.06 (5.14)	31.81 (28.73–35.16)	0.60
WHR	0.99 (0.12)	0.98 (0.92–1.04)	0.97 (0.09)	0.98 (0.91–1.03)	0.32
VD supplementation, n (%)	14 (20)	–	67 (53)	–	<0.001
VD dose, IU/day	2678.57 (1434.36)	2000 (2000–4000)	2285.71 (824.77)	2000 (2000–2750)	0.44
Duration of VD supplementation, mo	1.15 (3.44)	0 (0–0)	4.81 (9.06)	1 (0–8)	0.001
Cardiovascular disease, n (%)	19 (27)	–	42 (33)	–	0.34
Arterial hypertension, n (%)	57 (80)	–	103 (82)	–	0.80
Liver steatosis, n (%)	55 (77)	–	90 (71)	–	0.36
Chronic kidney disease, n (%)	3 (4)	–	5 (4)	–	0.93
ACEI/ARB, n (%)	43 (61)	–	74 (59)	–	0.80
β-Blocker, n (%)	31 (44)	–	64 (51)	–	0.34
Statin, n (%)	32 (45)	–	65 (52)	–	0.38
Fibrate, n (%)	10 (14)	–	8 (6)	–	0.07
Acetylsalicylic acid, n (%)	16 (23)	–	42 (33)	–	0.11
Metformin, n (%)	57 (80)	–	109 (86)	–	0.25
Insulin, n (%)	30 (42)	–	46 (37)	–	0.43
Sulfonylurea derivative, n (%)	13 (18)	–	22 (17)	–	0.88
SGLT-2 inhibitors, n (%)	31 (44)	–	32 (25)	–	0.01
GLP-1 analogues, n (%)	8 (11)	–	19 (15)	–	0.46
DPP-4 inhibitors, n (%)	2 (3)	–	2 (2)	–	0.56

For each continuous parameter, we report its mean (SD) and median with IQR, whereas for each binary parameter, the total number and percentage of patients are given.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT-2, sodium-glucose cotransporter-2; VD, vitamin D; WHR, waist-to-hip ratio; others, see **FIGURE 1**

TABLE 2 Blood biochemical parameters and blood pressure

Parameter	Patients with VDD (n = 71)		Patients with VDS (n = 126)		*P* value
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	
VD concentration, ng/ml	14.96 (3.19)	15.88 (12.8–16.74)	31.46 (11.12)	28.39 (23.44–36.61)	<0.001
HbA_{1c}, %	7.79 (1.85)	7.5 (6.93–7.9)	7.36 (1.2)	7.5 (6.56–7.5)	0.05
Systolic BP, mm Hg	133.63 (14.57)	130 (124.25–140)	132.24 (15.66)	130 (120–140)	0.54
Diastolic BP, mm Hg	80.72 (11.35)	80 (75–85)	80.41 (10.31)	80 (75–85)	0.85
Total calcium concentration, mmol/l	2.42 (0.19)	2.43 (2.37–2.51)	2.43 (0.09)	2.43 (2.37–2.49)	0.54
Phosphates concentration, mmol/l	1.12 (0.18)	1.13 (0.97–1.26)	1.13 (0.16)	1.15 (1.03–1.22)	0.74
Total protein, g/l	72.66 (4.6)	72.8 (70.7–75.23)	71.81 (3.73)	71.65 (69.5–74.4)	0.16

For each continuous parameter, we report its mean (SD) and median with IQR.

SI conversion factors: to convert plasma vitamin D to mmol/l, multiply by 42.496.

Abbreviations: BP, blood pressure; HbA_{1c}, hemoglobin A_{1c}; others, see **TABLE 1** and **FIGURE 1**

TABLE 3 Densitometry results

Parameter	Patients with VDD (n = 71)		Patients with VDS (n = 126)		*P* value
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	
FN BMD, g/cm^2	0.86 (0.14)	0.86 (0.77–0.94)	0.84 (0.15)	0.84 (0.72–0.93)	0.29
FN T-score	–0.21 (1.08)	–0.3 (–0.88 to 0.5)	–0.37 (1.07)	–0.3 (–1.2 to 0.3)	0.30
FN Z-score	0.8 (0.98)	0.7 (0.13–1.48)	0.82 (1.00)	0.8 (0.1–1.4)	0.90
TH BMD, g/cm^2	1.05 (0.16)	1.07 (0.97–1.14)	1.03 (0.14)	1.03 (0.94–1.12)	0.40
TH T-score	0.39 (1.2)	0.3 (–0.35 to 1.3)	0.3 (0.95)	0.3 (–0.3 to 0.9)	0.56
TH Z-score	1.04 (1.13)	1.1 (0.2–1.8)	1.16 (0.96)	1.1 (0.5–1.8)	0.41
L_1–L_4 BMD, g/cm^2	1.04 (0.16)	1.04 (0.93–1.13)	1.01 (0.19)	0.99 (0.89–1.11)	0.35
L_1–L_4 T-score	–0.32 (1.39)	–0.4 (–1.3 to 0.7)	–0.52 (1.67)	–0.8 (–1.7 to 0.4)	0.39
L_1–L_4 Z-score	0.57 (1.31)	0.5 (–0.38 to 1.5)	0.67 (1.73)	0.4 (–0.6 to 1.5)	0.69

For each quantitative parameter, we report its mean (SD) and median with IQR.

Abbreviations: BMD, bone mineral density; FN, femoral neck; L_1–L_4, lumbar vertebrae 1–4; TH, total hip; others, see **FIGURE 1**

TABLE 4 Carotid ultrasound examination results

Parameter	Patients with VDD (n = 71)		Patients with VDS (n = 126)		*P* value
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	
IMT mean of CCA, R	0.7 (0.15)	0.7 (0.57–0.82)	0.69 (0.16)	0.69 (0.59–0.77)	0.57
IMT mean of CCA, L	0.74 (0.18)	0.73 (0.63–0.84)	0.71 (0.15)	0.71 (0.61–0.79)	0.19
IMT max of CCA, R	0.84 (0.17)	0.84 (0.7–0.95)	0.83 (0.18)	0.8 (0.7–0.95)	0.79
IMT max of CCA, L	0.89 (0.22)	0.88 (0.74–1)	0.84 (0.17)	0.84 (0.71–0.9)	0.10
Plaque area, R	0.1 (0.33)	0 (0–0.13)	0.08 (0.15)	0.02 (0–0.12)	0.60
Plaque area, L	0.09 (0.17)	0.01 (0–0.14)	0.07 (0.14)	0 (0–0.09)	0.57
Plaque score, R	1.35 (1.66)	0 (0–2.2)	1.5 (1.8)	1.15 (0–2.3)	0.56
Plaque score, L	1.37 (1.67)	1 (0–2.2)	1.41 (1.74)	1.2 (0–2.2)	0.86

For each continuous parameter, we report its mean (SD) and median with IQR.

Abbreviations: CCA, common carotid artery; IMT, intima media thickness; L, left; R, right; others, see **FIGURE 1**

TABLE 5 Clinically and statistically significant differences in laboratory results and ultrasound examination between the users and nonusers of sodium-glucose cotransporter-2 inhibitors

Parameter	Patients treated with SGLT-2is (n = 63)		Patients not treated with SGLT-2is (n = 134)		*P* value
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	
VD concentration, ng/ml	22.21 (9.69)	20.57 (16.21–26.82)	27.07 (12.77)	24.28 (18.32–30.61)	0.01
VD supplementation, n (%)	19 (30)	–	62 (46)	–	0.03
Duration of VD supplementation, mo	3.43 (9.26)	0 (0–1)	3.52 (6.92)	0 (0–7)	0.04
HbA_{1c}, %	8.04 (1.66)	7.5 (7.07–8.65)	7.27 (1.33)	7.5 (6.43–7.5)	<0.001
Mean IMT of CCA, L	0.76 (0.17)	0.76 (0.64–0.92)	0.7 (0.16)	0.71 (0.6–0.79)	0.01

For each continuous parameter, we report its mean (SD) and median with IQR, whereas for each binary parameter, the total number and percentage of patients are given.

Abbreviations: see **TABLES 1** and **4**

we did not collect the information on the exact molecule of the SGLT-2is class, and the time of treatment with SGLT-2is. We did not determine the PTH concentration, as it is not performed routinely, yet we acknowledge this fact as a limitation of the study. Our paper describes associations, and does not imply causality. We recruited white European patients from a single center, and further studies in other ethnic groups and countries are needed to confirm our observations. Moreover, it should be noted that patients in the year 2020 were recruited during the COVID-19 pandemic, which could potentially limit the study participants to those who were the most committed

to continue their medical care and surveillance. Finally, as CVD might often go undetected as being asymptomatic, we might have underestimated its occurrence.

Conclusions The prevalence of VDD in the studied cohort was 36%. The analyzed groups did not differ in terms of CVD occurrence and the difference in glycemic control was insignificant. Moreover, the patients with VDD were more often treated with SGLT-2is. Finally, the patients treated with SGLT-2is had lower VD concentration, larger IMT, and lower HbA_{1c} levels than the patients who were treated otherwise.

ARTICLE INFORMATION

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