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PHARMACOLOGIC TREATMENT OF TYPE 2 DIABETES (HE LEBOVITZ AND G BAHTIYAR, SECTION EDITORS)

Type 2 Diabetes Mellitus, Insulin Resistance, and Vitamin D

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Abstract

Purpose of Review There is a growing, largely inconsistent, literature on the role of vitamin D in association with type 2 diabetes, insulin resistance/insulin secretion, glycemic indices, and complications of type 2 diabetes. Pathophysiologic, bystander, preventive, and treatment roles of vitamin D have all been proposed. In this focused review, we attempt to organize and clarify our current information in this area.

Recent Findings Clinical study interpretation is difficult because of variability in dosage, dosage form, study duration, and populations studied, as well as recently reported normal human polymorphisms in vitamin D synthesis and catabolism, vitamin D-binding protein, and vitamin D receptors in addition to a host of potential epigenetic confounders. Low vitamin D status appears to be associated with type 2 diabetes and most other insulin resistance disorders reported to date. The extraskeletal benefits of supplementation/repletion in these disorders in our species, with a few highlighted exceptions, remain to be established.

Summary This focused review attempts to summarize our current knowledge in this burgeoning area through a review of key meta-analyses, observational studies, randomized control trials, and Mendelian randomization studies and will hopefully serve as a guide to indicate future research directions and current best practice.

Keywords Vitamin D status · T2DM · Insulin resistance · Diabetes complications · Vitamin D deficiency · Metabolic syndrome

Introduction

There is considerable interest in vitamin D's role in type 2 diabetes (T2DM) and insulin resistance beyond its role in bone/calcium metabolism. A recent review summarized reports showing significant positive correlation between serum 1,25-OH-vitamin D (the active form) and both insulin sensitivity and secretion, a negative association between vitamin D deficiency and glycemic control, and a positive association of vitamin D deficiency with T2DM [1••]. Randomized control trials (RCTs) of supplementation in healthy people, those with prediabetes and those with T2DM, yielded varied results. Small glycemic benefits from supplementation are reported mostly with baseline vitamin D deficiency. Most meta-analyses of interventional RCTs show inconsistent benefits on glycemic control in T2DM.

Vitamin D—Insulin Sensitivity/Insulin Secretion

Gulseth studied supplementation's effects on insulin sensitivity and secretion in people with T2DM with replete baseline serum 25-OH-vitamin D (25OHD) (38.0 + 12.6 nmol/L) [2••].

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Despite raising the mean serum 25OHD to 96.9 ± 18.3 at 4 weeks and 53.7 ± 9.2 after 6 months, there was no significant change in insulin sensitivity/secretion, or glycemic control, possibly because patients were replete at baseline.

One study reported that vitamin D_3 10,000 IU/day × 8 weeks was associated with a significant decrease in acute insulin response to glucose ($P = 0.011$) and a significant increase in insulin sensitivity ($P = 0.012$) in 8 people with prediabetes [3]. From these studies, it appears that vitamin D supplementation may improve insulin sensitivity in patients at increased risk for T2DM with baseline low vitamin D status.

Vitamin D—Type 2 Diabetes Prevention

This subject was reviewed by Angellotti and Pittas [4•]. Despite evidence for prevention from mechanistic and observational studies, a definitive answer is impossible because the possibility of reverse causation cannot be eliminated. Serum 25OHD is not only a marker of vitamin D status, but of overall health, confounding interpretation. Small studies and post hoc analyses in people with normal glucose tolerance do not support a preventive role for vitamin D in normals; however, a preventive possibility exists in high-risk populations, e.g., those with prediabetes and pending adequately powered RCTs, such as the recently completed D2d trial [5]. The just released results of this pivotal trial will be discussed later in this article. It should be noted that there is no consensus on what treatment doses of vitamin D are appropriate in intervention trials, given the variety of preparations available, the baseline vitamin D status, and individual variability in vitamin D absorption [5]. The Institute of Medicine recommends most adults take 400 IU/day of vitamin D and 800 IU for those 71 years old and older. The D2d study used 4000 IU daily based on studies showing that for most adults, this will achieve a sustained serum 25OHD of 30–50 nmol/L There is consensus that serum 25-OH-vitamin D levels < 20 nmol/L are deficient, while those > 20 < 30 are insufficient [5]. The rationale for and limitations of these definitions are discussed later.

In Forouhi's study, baseline serum 25OHD correlated inversely with serum glucose and insulin 10 years later [6]. This study is strengthened by its community, prospective design, and controlling for confounders (physical activity, obesity), but is limited by sample size ($n = 524$) and 50% dropout.

A study of 25 postmenopausal women taking 2000 IU vitamin D_3/day reported no effect on insulin resistance or glycemia [7].

In post hoc analysis from a trial studying skeletal outcomes using 700 IU vitamin D_3 + calcium/day, a significant decrease in homeostasis model assessment of insulin resistance (HOMA-IR) was noted in patients with prediabetes, but not in those with normal glucose tolerance [8]. The beneficial effect apparent in this study, as contrasted with the previous study, despite a considerably lower daily dose of vitamin D, may be related to the fact that the patients in this trial were at higher risk for T2DM. The foregoing studies suggest that vitamin D supplementation may reduce the risk of developing T2DM in those with low baseline vitamin D status and at high risk of developing T2DM. Results of intervention trials are summarized in Table 1. Mendelian randomization studies, discussed later in this article, also yield somewhat conflicting results on the role of vitamin D in prevention of T2DM. For now, the role of vitamin D in T2DM prevention remains unclear.

Vitamin D—Glycemic Control in Type 2 Diabetes

Santos systematically reviewed literature on vitamin D status and glycemic control [9••]. An inverse relationship between serum 25OHD and indices of glucose metabolism, e.g., HOMA-IR, was confirmed. Most studies showed no supplementation benefit on glycemic control or insulin sensitivity indicators such as A1c, HOMA-IR, or quantitative insulin sensitivity check index (QUICKI). While better glycemic control is associated with higher vitamin D status in people with T2DM, the reviewed studies did not show any clear glycemic benefit from vitamin D supplementation/repletion.

Vitamin D—Diabetic Peripheral Neuropathy

Qu reported an association between vitamin D deficiency/insufficiency and diabetic peripheral neuropathy in a meta-analysis [10••]. A significant difference in mean serum 25OHD between people with diabetes with/without neuropathy was seen in people of white and Asian background. The reviewed studies did not discuss preventive or therapeutic effects of vitamin D repletion/supplementation. Low vitamin D status is associated with diabetic peripheral neuropathy; causality is not confirmed.

Vitamin D—Diabetic Autonomic Neuropathy

Hansen reported a U-shaped association of both low and high serum 25OHD with cardiac neuropathy. Linear regression models demonstrated that a rise in serum 25OHD from 25 to 50 paralleled a 3.9% (95% CI 0.1–7.9) rise in heart rate

Table 1 Effects of vitamin D interventions in T2DM, its complications, polymorphism of vitamin D receptor gene (VDR) and vitamin D-binding protein (VDBP), and Mendelian randomization studies of single nucleotide polymorphisms (SNPs) involved in determination of serum 25OHD concentrations

Concern	Intervention	Effects observed
Glycemic control in people with T2DM	Vitamin D (various preparations and doses)	No clear benefit on indicators of glycemic control.
Diabetic nephropathy	Vitamin D (various preparations and doses)	Pooled data of meta-analysis did not show any significant change in UACR (urine albumin/creatinine ratio).
	1,25-OH2-vitamin D_3 and its analogs	Achieved significant improvement of renal function in people with diabetic kidney disease, especially when combined with RAAS inhibitors.
All-cause mortality in people with T2DM	Vitamin D (various preparations and doses)	Unknown whether vitamin D supplementation decreases risk of all-cause mortality.
Surrogate inflammatory risk factors in macrovascular disease	Vitamin $D_3 \leq$ 4000 IU daily × 12 weeks	Significantly lowers hs-CRP in people with T2DM and has no significant effect on TNF alpha and IL-6.
NAFLD	Vitamin D (various doses)	Inconsistent findings to assess effects of oral vitamin D supplementation in patients with NAFLD and NASH.
Metabolic profile of people with T2DM	2000 IU vitamin D_3 daily for a year Polymorphisms of VDR and VDBP Fok-I CC *a* Taq-I GG *b* Bsm-I TT *c*	*a* Lowest increment in 25OHD. *b* Significant improvement in serum triglycerides, LDL and total cholesterol, insulin, HbA1C, and HOMA-IR. *c* Significant improvement in serum triglycerides, insulin, and HOMA-IR.
Mendelian randomization studies of T2DM prevention with vitamin D	SNPs affecting 25OHD synthesis, transport, and catabolism	Vitamin D did not prevent T2DM in European people at high risk.
	SNPs affecting only vitamin D synthesis	Vitamin D could be inferred to prevent T2DM in European and Chinese people at high risk.
D2d study	4000 IU vitamin D_3 daily × 4 years to prevent T2DM in people with prediabetes	No significant preventive effect of vitamin D supplementation on incident T2DM in people with prediabetes, not preselected for vitamin D deficiency.

RAAS renin-angiotensin-aldosterone system, *hs-CRP* highly sensitive C-reactive protein, *TNF alpha* tumor necrosis factor alpha, *IL-6* interleukin 6, *NAFLD* nonalcoholic fatty liver disease, *NASH* nonalcoholic steatohepatitis, *SNP* single nucleotide polymorphism

response to deep breathing (E/I ratio) and 4.8% (95% CI 4.7–9.3) to standing (30/15 ratio). A rise from 125 to 150 in serum 25OHD was associated with decreases of 2.6% (95% CI − 5.8–0.1) and 4.1% (95% CI − 5.8 to − 0.5), respectively [11••]. Kedar studied relationships between vitamin D status and gastric emptying time in idiopathic gastroparesis ($n = 42$) and diabetic gastroparesis ($n = 17$) [12]. Increasing serum 25OHD was associated with reduced gastric emptying time throughout the study period in people with idiopathic gastroparesis. There was significant association at hour 2 ($P = 0.069$) and for total test period ($P = 0.046$). At hours 1 and 4, correlation was particularly strong ($P = 0.034$ and 0.076, respectively). No associations were observed between diabetic gastroparesis and vitamin D status.

High and low vitamin D levels were associated with cardiovascular autonomic neuropathy in people with diabetes. There is no association of gastric emptying time with vitamin D status in people with diabetic gastroparesis. No intervention studies have been reported as yet.

Vitamin D—Erectile Dysfunction in Type 2 Diabetes

Erectile dysfunction (ED) is concerning, not only with regard to quality of life but also because it is a "red flag" for generalized atherosclerosis and future cardiovascular events. Basat studied this in 98 people with T2DM, age 18–80, using the International Index of Erectile Function (IIEF-5) questionnaire. Patients were stratified into three groups of IIEF-5 scores: 5–10—severe ED ($n = 32$), 11–20—moderate ED ($n = 45$), and 21–25—without ED ($n = 21$). Serum 25OHD was lower in groups 5–10. There was a positive correlation between IIED% score and serum 25OHD ($r = 0.21$, $P =$

0.038) [13••]. Low vitamin D status is associated with ED; the effects of repletion/supplementation on prevention or treatment of ED in people with T2DM are not yet known.

Vitamin D—Diabetic Retinopathy

Currently, there is insufficient evidence showing whether vitamin D deficiency is related to diabetic retinopathy, and the determination of this relationship has rarely been studied. Luo conducted a meta-analysis on vitamin D status/diabetic retinopathy association using a systematic literature search, including 15 observational studies involving 17,664 people with T2DM [14••]. People with vitamin D deficiency had a significantly increased risk of diabetic retinopathy (OR = 2.03, 95% CI 1.07–3.86), and a decrease of 1.7 nmol/L (95% CI − 2.72–0.66) in serum 25OHD was found in diabetic retinopathy. Sensitivity analysis showed that exclusion of any single study did not materially change outcome, confirming the association between vitamin D deficiency and increased risk of diabetic retinopathy. In summary, low vitamin D status is associated with diabetic retinopathy. The effects of vitamin D repletion/supplementation on prevention and treatment of diabetic retinopathy are not currently known; considering the high prevalence of vitamin D deficiency and the burden of diabetic retinopathy, screening people with type 2 diabetes, who are at risk for vitamin D deficiency, should be considered.

Vitamin D—Diabetic Nephropathy

Derakhshanian's meta-analysis of vitamin D status/diabetic nephropathy associations and repletion effects systematically searched articles published 2009–2014 [15]. The pooled OR from cross-sectional studies was 1.80 (95% CI 1.25–2.59; P = 0.002), demonstrating negative serum 25OHD/diabetic nephropathy risk association. Pooled data of urine albumin-to-creatinine ratios (UACR) in vitamin D supplementation trials demonstrated no significant change (17.98; 95% CI − 35.35–71.32; P = 0.51), supporting higher diabetic nephropathy risk in vitamin D deficiency. In summary, low vitamin D status is associated with higher risk for nephropathy in patients with T2DM. Pooling the results of available clinical trials after vitamin D supplementation did not support causality in this association.

Chokhandre performed a meta-analysis on supplementation of vitamin D or its analogs in chronic kidney disease [16]. Inflammation and oxidative stress participate in diabetic nephropathy pathogenesis. Both are believed to be regulated via nuclear receptors including vitamin D receptors. They summarized data on vitamin D's possible role in diabetic nephropathy, searching databases for relevant trials. Trials assessing renal functions including UACR, albuminuria, and estimated glomerular filtration rate (eGFR) were reviewed. Quality and risk of bias assessments were conducted. Effects on 25OHD, calcium, and HbA1c were assessed. The mean or its percent change along with their standard deviation was used for result reporting. Six studies assessed effects of cholecalciferol, calcitriol, and paricalcitol, respectively, in diabetic nephropathy. Trial designs differed (3 randomized, 1 nonrandomized, 2 uncontrolled studies) with differing degrees of quality and bias risks. Analogs achieved significant renal function improvement in 2 RCTs (perhaps because they eliminate the need for a renally dependent 1-α-hydroxylation step). No study reported significant hypercalcemia incidence. Larger, longer RCTs, comparing efficacy/safety of vitamin D/analogs, are needed.

Li reviewed associations of vitamin D/diabetic nephropathy, reinforcing awareness that diabetic nephropathy is the leading diabetic renal complication and a major cause of renal failure [17]. The renin-angiotensin-aldosterone system (RAAS) is a principal cause of progressive kidney damage. RAAS antagonists are the major diabetic nephropathy pharmacotherapy. Limiting their efficacy is a compensatory increase in renin via interference with renin feedback inhibition. Vitamin D renoprotectively downregulates the RAAS through suppression of renin expression. Vitamin D receptor-null mice demonstrate worse diabetic nephropathy, likely due to impaired downregulation of RAAS activation. Combinations using RAAS inhibition + vitamin D analogs dramatically decreased renal injuries via analog inhibition of compensatory renin increase. Recent data suggest vitamin D and its analogs are renoprotective in diabetic nephropathy. In summary, low vitamin D status appears to be associated with worse renal function in people with T2DM-associated CKD. Supplementation with analogs of the active form of vitamin D, particularly when combined with RAAS inhibitors, appears to improve renal function in this demographic.

Vitamin D—Type 2 Diabetes Macrovascular/Microvascular Complications

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study examined relationships between vitamin D status and macrovascular/microvascular complications [18]. Associations between baseline vitamin D status and macrovascular/microvascular disease incidences were analyzed using the Cox proportional hazards models and logistic regression in a 5-year observational study; 50% had vitamin D deficiency/insufficiency. Participants with serum 25OHD < 50 nmol/L had a greater cumulative incidence of macrovascular/microvascular occurrences than those with levels ≥ 50 nmol/L. Treatment-stratified multivariate analysis, adjusted for potential confounders, found that vitamin D status was an independent macrovascular outcome predictor. A

50 nmol/L difference in serum 25OHD was associated with a 23% ($P = 0.007$) change in macrovascular event risk. Relevant adjustments did not affect outcomes. Unadjusted risk for microvascular complications was 18% ($P = 0.006$) higher during the study, although excess risk fell to 11–14% and lost statistical significance after adjustments. In summary, lower vitamin D status was associated with greater macrovascular/microvascular occurrence risk; causality was not established.

Yu's meta-analysis of 13 RCTs assessed vitamin D supplementation effects on macrovascular inflammatory risk factors [19••]. Supplementation significantly decreased hs-CRP level by 0.45 μg/mL, but did not affect TNF-α or IL-6. Subgroup analysis demonstrated that supplementation significantly lowered hs-CRP by 0.34 μg/mL in trials with daily dose ≤ 4000 IU and by 0.31 μg/mL among trials lasting > 12 weeks.

Norman and Powell summarized research on vitamin D and cardiovascular disease [20]. Vitamin D metabolites function extraskeletally, where 1-α-hydroxylation affects regulatory pathways via paracrine and autocrine actions. The active metabolite binds to vitamin D receptors, affecting gene expression in processes likely relevant to cardiovascular disease. Vitamin D receptors exist in all important cardiovascular cell types. Studies confirm a role for vitamin D metabolites in pathways integral to cardiovascular function and disease. Clinical studies mostly show independent associations between vitamin D deficiency and various cardiovascular disease expressions. Supplementation's role in cardiovascular disease is uncertain.

Few studies have investigated the association between vitamin D and peripheral arterial disease (PAD) in patients with T2DM. Li studied associations of PAD with vitamin D status in 1028 people with T2DM [21••]. PAD was defined as an ankle-brachial index (ABI) < 0.9. Known surrogate PAD markers (blood pressure, HbA1c, lipids, comorbidities, carotid intima-media thickness, and vitamin D status) were measured. PAD prevalence was higher in participants with decreased (23.9%) than in those with normal (15.6%) 25OHD (≥ 30 nmol/L, $P < 0.01$). Low vitamin D status was associated with increased risk of PAD (OR = 1.69, 95% CI 1.17–2.44, $P < 0.001$), and PAD was significantly more likely to occur in participants ≥ 65 years of age (OR = 2.56, 95% CI 1.51–4.48 vs. 1.21, 95% CI 0.80–1.83). After adjusting for known cardiovascular risk factors and potential confounding variables, the association of decreased 25(OH)D and PAD remained significant in patients < 65 years of age (OR = 1.55; 95% CI 1.14–2.12, $P = 0.006$). In conclusion, low vitamin D levels were associated with a decreased ABI and increased prevalence of PAD in patients with T2DM. Vitamin D deficiency might be an independent risk factor for PAD in patients with T2DM < 65 years of age. Whether vitamin D supplementation could significantly improve vascular outcomes remains unclear.

Vitamin D—Type 2 Diabetes Mortality

Joergensen studied associations between vitamin D status and mortality in a longitudinal observational follow-up study of 289 people with T2DM (normoalbuminuria ($n = 172$), microalbuminuria ($n = 73$), macroalbuminuria ($n = 44$) at baseline) who they followed for a median (range) of 15.0 (0.2–23.0) years [22]. Median plasma 25OHD = 35.7 (5–136.7) nmol/L. Vitamin D status was unassociated with age, sex, eGFR, UACR, or HbA1C at baseline. Vitamin D deficiency was weakly associated with high systolic blood pressure ($r = 0.13$, $P = 0.03$). During the study, 196 (68%) patients expired. All-cause mortality was higher with severe vitamin D deficiency (HR = 1.96; 95% CI 1.29–2.98) and remained significant following adjustment for UACR, A1C, T2DM duration, and classical cardiovascular risk factors (OR = 2.03). Profound vitamin D deficiency was associated with excess cardiovascular mortality (OR = 1.95) and remained significant following adjustment (OR = 1.90). Profound baseline vitamin D deficiency failed to predict development of micro/macroalbuminuria but predicted increased rates of all-cause/cardiovascular mortality, independently of UACR and traditional risk factors. In summary, low vitamin D status is independently associated with increased cardiovascular and overall mortality risk in people with T2DM; it is unknown whether supplementation/repletion can reduce this risk.

Vitamin D—Nonalcoholic Fatty Liver Disease (NAFLD)

Barchetta studied associations between vitamin D deficiency and nonalcoholic fatty liver disease (NAFLD) and repletion trials [23••]. Epidemiological studies generally found associations between vitamin D deficiency and NAFLD/steatohepatitis (NASH), after adjustment for confounders. Several reported antifibrotic, antiinflammatory, and insulin-sensitizing vitamin D effects on the liver, yet results from interventional studies are inconsistent. The number of interventional RCTs in NAFLD/NASH is small. Promising data came from recent trials using newer dosing regimens. Further, well-designed studies are needed to robustly recommend optimizing Vitamin D status as a preventive and/or treatment strategy.

Vitamin D—Other Disorders Associated with Insulin Resistance

Polycystic ovarian syndrome, classic and nonclassic adrenal hyperplasia, and gout are all, like T2DM, associated with insulin resistance, which play a role in their pathophysiologies and are frequent comorbidities of T2DM. Insulin-sensitizing interventions, including vitamin D repletion/supplementation,

have been reported to ameliorate these conditions; however, detailed discussion of these topics is beyond the scope and space allowance of this article. Interested readers may refer to references [24–81, 82••, 83–85, 86••].

Please see Table 2 summarizing vitamin D associations with T2DM complications.

Conclusions

While there is considerable preclinical evidence that low vitamin D status contributes to the pathogenesis of insulin resistance and T2DM and that repletion improves glycemic control in some species, vitamin D's role in the pathogenesis, prevention, and treatment of insulin resistance T2DM in humans remains unclear. There is widespread agreement from epidemiologic studies that hypovitaminosis D is prevalent in people with these disorders [87, 88]. Most people with T2DM have low serum 25OHD, while high vitamin D status is associated with lower incident diabetes risk [89, 90]. Sipahi studied the relationship of VDS with parameters including glycemic control, serum uric acid, and microalbuminuria in T2DM and chronic kidney disease. They reported that higher HbA1c predicted lower vitamin D status S [82]. Despite consensus that serum 25OHD < 30 nmol/L indicates suboptimal vitamin D status, one must recognize that many factors contribute to whether a given serum concentration is adequate.

Inverse correlations between obesity indicators and vitamin D status have been frequently reported [24–26, 29, 34, 38]. Since vitamin D is fat soluble, a greater percentage of it is sequestered in fat in overweight and obese subjects, reducing serum concentrations. Overweight and obese people also have a greater volume of distribution, potentially diluting serum 25OHD concentrations.

Polymorphisms in vitamin D-binding protein (VDBP) affect serum 25OHD [86••, 91]. Binding affinity differences among these VDBP forms affect serum-free 25OHD and the amount convertible to 1,25-OH-vitamin D.

Selection of 30 nmol/L as the lower limit of sufficiency is based on the observation that most people will not have an elevated serum parathyroid hormone (PTH) with a serum 25OHD > 30 nmol/L, resulting in less net bone loss; however, this says nothing about what concentration(s) are sufficient to obtain purported nonskeletal benefits.

There are also vitamin D receptor polymorphisms determining whether a given serum 25OHD concentration is adequate and possibly predicting the metabolic response to supplementation in people with T2DM [92, 93••, 94, 95••].

Table 2 Vitamin D deficiency and its associations with various complications in patients with T2DM

Vitamin D deficiency in T2DM	Findings of vitamin D deficiency and its related complications in T2DM
Diabetic peripheral neuropathy	Significant difference in mean serum vitamin D levels between diabetic patients with and without neuropathy was seen in both white and Asian patients
Cardiac autonomic neuropathy	U-shaped association seen both with low and high serum vitamin D levels with cardiac autonomic neuropathy in patients with both T2DM and T1DM
Erectile dysfunction	Significant negative correlation between VDS and severe ED questionnaire group in T2DM
Diabetic retinopathy	Significantly increased risk of diabetic retinopathy in patients withT2DM
Diabetic nephropathy	A significant negative association between serum vitamin D concentration and nephropathy risk in patients with diabetes
NASH	Presence of association between hypovitaminosis D and NASH, NAFLD
Micro- and macrovascular outcomes	Lower serum 25-OH-vitamin D concentrations are associated with a greater risk for macrovascular/microvascular disease occurrences in people with T2DM
PAD	Significant association of low serum vitamin D and PAD, age > 65 years
All-cause mortality	Profound hypovitaminosis D predicted an increased rate of both all-cause and cardiovascular mortalities, independently of UAER (urinary albumin excretion rate) and traditional cardiovascular risk factors

As stated by Al-Dahgri et al., there is inconsistent evidence of benefit of supplementation on metabolic profile in T2DM, possibly due to vitamin D receptor variants [93••]. They investigated the metabolic effects of 1 year of supplementation in people with T2DM according to their vitamin D receptor polymorphisms. A total of 204 patients took 2000 IU vitamin D_3 daily. Serum 25OHD and metabolic profiles were determined at entry and at 1 year. Vitamin D receptor polymorphisms (Taq-I, Bsm-I, Apa-I, and Fok-I) were identified using TaqMan genotyping assays. Supplementation was significantly associated with increased HOMA β-cell function ($P = 0.003$) and significantly decreased triglycerides and total and LDL cholesterol ($P < 0.001$). The lowest increment in 25OHD levels was found in Fok-I CC genotypes ($P < 0.0001$). With supplementation, Taq-I GG genotype carriers experienced significant improvements in triglycerides and LDL and total cholesterol, insulin, HbA1c, and HOMA-IR ($P < 0.005$, 0.01, < 0.001, < 0.005, 0.03, and 0.01, respectively). Bsm-I TT genotype carriers experienced significant improvements in triglycerides ($P = 0.01$), insulin, and HOMA-IR (P values < 0.05). Improvements in metabolic profile associated with supplementation are affected by VDR polymorphisms, specifically for Taq-I GG and Bsm-I TT genotypes.

Polymorphisms in the 1-α-hydroxylase gene as well as renal function variation may affect available serum 1,25-OH-vitamin D [94, 95••]. Such potentially confounding polymorphisms and epigenetic differences in vitamin D expression are the norm in humans and are less likely to be an issue in preclinical studies, which often have genetically identical (or nearly so) subjects. This may explain some discrepancies between human and animal studies, where vitamin D's role in the pathogenesis, prevention, and treatment of IR and T2DM seems clearer.

Mendelian randomization studies have used single nucleotide polymorphisms (SNPs) associated with serum 25OHD concentrations, identified via genome wide association studies, to assess causality of vitamin D status in incident T2DM [96, 97]. When SNPs involved in vitamin D synthesis as well as its transport and catabolism were considered, causality could not be inferred in a European population. When only SNPs involved in vitamin D synthesis with no known pleiotropic effects were considered, excluding those involved in vitamin D transport and catabolism, a causally protective effect of higher vitamin D status in T2DM prevention could be inferred in both Chinese and European populations; however, the results of meta-analyses of ongoing trials in high-risk populations using higher vitamin D doses, such as the D2d trial, will be necessary to answer the question of causality more definitively [5]. Following the initial submission of this manuscript, the results of the D2d study were simultaneously presented at the annual scientific meeting of the American Diabetes Association and published online [98••]. A total of 2423 participants who met the previously described eligibility criteria, 80% of whom were vitamin D replete at baseline, were randomized to receive either placebo or 4000 IU cholecalciferol/day. At 2 years after randomization, mean serum 25-hydroxyvitamin D level in the vitamin D group was 54.3 ng/mL (from 27.7 ng per/mL at baseline) vs. 28.8 ng/mL in the placebo group (from 28.2 ng/mL at baseline). After a median follow-up of 2.5 years, the difference in incident T2DM between the 2 groups of people with 2 indicators for prediabetes at baseline was not statistically significant; the hazard ratio for vitamin D supplementation vs. placebo was 0.88 (95% CI 0.75–1.04; $P = 0.12$). In subgroup analysis, those individuals with hypovitaminosis D at baseline appeared to have a lower risk of developing T2DM with supplementation. While D2d is the largest intervention trial to date and shows that relatively high dose vitamin D supplementation in people at high risk for T2DM (having 2 indicators for pre-DM) was not protective against incident T2DM over a median follow-up period of 2.5 years, it leaves a number of important questions unanswered. If, for example, at study end, the highest and lowest quintiles of serum 25OHD had been compared for incident T2DM, would a significant difference have emerged? Had the eligibility criteria specified that subjects have vitamin D deficiency at baseline, might repletion/supplementation been proven to be effective in reducing incident T2DM? Could it be that interventions such as vitamin D supplementation are timing-dependent, e.g., would intervention earlier in the continuum from normal glucose tolerance to T2DM have resulted in a different outcome? Would significant benefit be demonstrated given a longer study duration? Might vitamin D reduce incident T2DM when combined with another lifestyle or pharmacologic intervention? Finally, might it be that any reduction in incident T2DM with vitamin D is dependent upon one or more polymorphisms in vitamin D-binding protein, vitamin D receptor, 1-α-hydroxylase, vitamin D synthesis, transport, or catabolism? To be effective in T2DM prevention should vitamin D treatment be as genetically targeted as biologic and chemotherapeutic cancer treatments are becoming?

The role of vitamin D status in the pathogenesis, prevention, and treatment of T2DM complications is unclear, though promising [45, 99–103]. As noted, there is a significant association between low vitamin D status and diabetic peripheral neuropathy. Both low and high vitamin D status are associated with diabetic cardiac neuropathy. There was no association between vitamin D status and gastric emptying time in people with diabetic gastroparesis, while in idiopathic gastroparesis, rising vitamin D concentrations were associated with shorter gastric emptying time.

No studies surfaced in our search concerning vitamin D and other diabetic autonomic neuropathies, mononeuropathy, or amyotrophy; however, Basat and colleagues found that the lowest vitamin D status was in men with T2DM with the most severe ED. Their findings are hard to interpret because ED results from a complex interplay of neurologic, vascular, hormonal, pharmacologic, toxicological, and psychologic factors.

The association of low vitamin D status with increased diabetic retinopathy risk in people with T2DM appears to be well

established as does the association of low vitamin D status with increased diabetic nephropathy risk. Interventional studies suggest that vitamin D analogs potentiate the renoprotective effects of RAAS inhibitors.

Low vitamin D status is consistently associated with poor macrovascular outcomes in people with T2DM. Vitamin D deficiency appears to be independently associated with PAD risk in people with T2DM. It is unclear whether repletion reduces the risk of incident T2DM macrovascular complications or their severity.

Low vitamin D status is associated with systolic hypertension, and the HR for all-cause mortality in people with T2DM was almost doubled that in those with VDD, even after correction for confounders. There is a similar increase in excess cardiovascular mortality with severe VDD. The effect of repletion on overall and cardiovascular mortality in people with T2DM is unknown.

Most studies show an association between low vitamin D status and NAFLD in T2DM. There is scarce, inconsistent data on the effects of supplementation on prevention or treatment.

Remaining confusion concerning vitamin D's association with T2DM arises because low vitamin D status is seen in many chronic and acute illnesses, and it is unknown whether it plays a causative role or is simply a bystander and general health indicator. Further confusion results because many apparently healthy people have vitamin D deficiency/insufficiency, and there is considerable heterogeneity in humans in vitamin D status due to polymorphisms in vitamin D synthesis, transport, 1-α-hydroxylation, transport/VDBP, catabolism, VDR, and in other epigenetic factors. It seems prudent to suggest that people at increased risk for T2DM, as well as those with T2DM, periodically have their vitamin D status monitored and maintain it in the mid-reference range.

Learning points

- Low vitamin D status is highly associated with insulin resistance, impaired insulin secretion, and increased risk of incident T2DM, particularly in people already at high risk for incident T2DM.
- In some other species, the association of low vitamin D status with risk of incident T2DM appears to be causal.
- Causality of low vitamin D status in incident T2DM in humans is not yet established due to conflicting results of interventional studies and Mendelian randomization studies on both incidence and glycemic markers. Intervention studies have varied much in terms of dosages and forms of vitamin D used, duration of intervention, and study populations. The just completed D2d study does not support a preventive role for vitamin D in people with 2 markers for prediabetes, not selected for baseline vitamin D deficiency.
- Low vitamin D status is highly associated with a number of microvascular and macrovascular complications of T2DM including peripheral neuropathy, erectile dysfunction, retinopathy, diabetic kidney disease, and overall mortality. It does not appear to be associated with diabetic gastroparesis. The relationship between vitamin D status and diabetic cardiac neuropathy is U-shaped.
- Intervention studies in people with T2DM and chronic kidney disease have shown significant therapeutic benefit when vitamin D analogs have been combined with RAAS inhibitors. Causality of low vitamin D status in T2DM complications, with the exception of renal complications, is not established.

Authors' Contributions AS is the corresponding author and reviewed about 65% of the articles cited. PD reviewed about 35% of the articles cited, chiefly those on gout, insulin resistance, and vitamin D, and she also prepared the 1st and 2nd drafts of the summary tables. GB, PD, VL, and AS all reviewed and edited the final presubmission draft.

Compliance with Ethical Standards

Conflict of Interest Alan Sacerdote, Paulomi Dave, Vladimir Lokshin, and Gül Bahtiyar declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national institutional guidelines).

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- • Of importance
- •• Of major importance

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