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The role of vitamin D in the metabolic homeostasis of diabetic bone

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Abstract

Most studies across a variety of geographic locations suggest that vitamin D insufficiency is more common in individuals with type 1 diabetes (T1D) compared to the general population. In type 2 diabetes (T2D), while obesity is commonplace and lower vitamin D levels are present in obese adolescents and adults, the association between vitamin D insufficiency and T2D is less clear. Studies suggest that the relationship between T2D and vitamin D may be concurrently influenced by ethnicity, geography, BMI and age. None-the-less, diabetic osteopathy is a significant co-morbidity of both forms of diabetes, and is characterized by micro-architectural changes that decrease bone quality leading to an increased risk for bone fracture in both disorders. The question remains, however, to what degree vitamin D homeostasis contributes to or exacerbates skeletal pathology in diabetes. Proposed mechanisms for vitamin D deficiency in diabetes include: 1) genetic predisposition (T1D); 2) increased BMI (T2D); 3) concurrent albuminuria (T1D or T2D); or 4) exaggerated renal excretion of vitamin D metabolites or vitamin D binding protein (T1D, T2D, animal models). The specific effects of vitamin D treatment on diabetic osteoporosis have been examined in rodents, and demonstrate skeletal improvements even in the face of untreated diabetes. However, human clinical trial data examining whether vitamin D status can be directly related to or is predictive of bone quality and fracture risk in those with diabetes is still needed. Herein, we provide a review of the literature linking vitamin D, diabetes and skeletal health.

Keywords

type 1 diabetes; type 2 diabetes; diabetic osteoporosis; diabetic fracture; vitamin D binding protein; vitamin D receptor

Introduction

Diabetic osteopathy is a significant co-morbidity of both type 1 diabetes (T1D) and type 2 diabetes (T2D), characterized by micro-architectural changes that increase the brittleness of bone¹ leading to an increased risk for bone fracture.² In fact, recent data suggests that diabetes may be the strongest independent risk factor for osteoporotic hip fracture in *non-elderly* patients^{3–4}. Chronic hyperglycemia, hypoinsulinemia or insulin resistance, hypercalciuria, osteoblast dysfunction, inflammation, disruption of the growth hormone (GH): IGF-I: IGFBP system and diabetes pharmacotherapy may all contribute to this skeletal fragility.² Interestingly, an increased prevalence of vitamin D deficiency and/or insufficiency in patients with either T1D or T2D has also been reported across the world^{5–9}, though the role of vitamin D in the metabolic homeostasis of *diabetic* bone remains unclear.

Herein, we will review the available literature linking vitamin D, diabetes and skeletal health.

Vitamin D physiology

In humans, two sources contribute to vitamin D availability, endogenous synthesis in the skin, and exogenous consumption in foods and supplements.¹⁰ Most circulating vitamin D derives from photochemical and thermal conversion of 7-dehydrocholesterol to vitamin D₃ by ultraviolet B radiation exposure of the skin. Additionally, ingestion of vitamin D as D₂ (ergocalciferol, plant derived) or D₃ (cholecalciferol, animal derived) can occur from natural food sources (oily fishes, organ meats, mushrooms), vitamin D-fortified foods (milk, orange juice) or commercial vitamin supplements, though diet contributes to <10% of one's vitamin D supply¹¹. Within the circulation, vitamin D complexes with vitamin D binding protein (DBP), the major transport protein for vitamin D metabolites in plasma. It is subsequently converted by hepatic 25-hydroxylase to 25-hydroxyvitamin D (25OHD), with ~88% of 25OHD in the circulation again bound to DBP¹². The DBP + 25OHD complex is freely filtered across the glomerulus allowing transport to the renal proximal tubule (PT). In the PT, reabsorption of the DBP + 25OHD complex facilitates the generation of 1, 25-dihydroxy vitamin D via 1 α -hydroxylase activity in PT epithelial cells (Figure 1A)^{13–14}. Many other tissues also possess the 1-hydroxylase enzyme, allowing for localized production of 1,25(OH)₂D as well. 1,25(OH)₂D can then bind to vitamin D nuclear receptors present in numerous tissues, initiating the activation of >200 genes.¹⁵ Nutritional rickets in children and osteomalacia in adults are undisputed consequences of vitamin D deficiency; more recently, however, vitamin D insufficiency has also been implicated in other health concerns, including cardiovascular disease, immune disorders and certain cancers.¹⁶

Defining the problem

Vitamin D levels in T1D

Several studies have examined the prevalence of vitamin D deficiency among individuals with T1D, both in childhood and adulthood and in a variety of geographic locations. A case-control survey of 170 Qatari youth with T1D and 170 age-, gender- and ethnicity-matched controls demonstrated a significant increase in the prevalence of vitamin D deficiency (25OHD <30 ng/ml) in the T1D subjects (90.6%), in a country in which vitamin D deficiency in non-diabetic children was also high (85.3%), likely due to culturally limited sunlight exposure.¹⁷ In this analysis, the incidence of fractures and a family history of vitamin D deficiency were also significantly higher in diabetic children. A prospective study of 129 Swiss children and adolescents with T1D also reported a high prevalence of vitamin D deficiency (25OHD <50 nmol/L) in these patients (60.5%), possibly attributed to the absence of vitamin D supplementation in many Swiss foods¹⁸. Vitamin D levels in T1D participants maintained a seasonal fluctuation, but were not correlated with duration of disease (mean 4.9 years). Unfortunately, a control group comparison was not available. An older, but larger study of young adults in Sweden demonstrated lower levels of vitamin D in participants with T1D compared with age- and sex-matched controls, both at the time of diagnosis and when assessed 8 years later, particularly in diabetic men⁹. Interestingly, they noted a positive correlation between 25OHD concentrations at diagnosis and at 8-year follow-up, but no correlation with HbA1c, suggesting perhaps an inherent individual propensity toward deficiency. Consistent with data from the northern hemisphere, a study of 47 adolescents with T1D from Brisbane, Australia compared with gender and age-matched historical control data also reported a significantly lower mean 25OHD level in T1D participants (54.7 nmol/L vs. 64.6 nmol/L)¹⁹; moreover, adolescents with T1D were three times more likely to have vitamin D deficiency (< 50 nmol/L). Again, vitamin D levels did not correlate with duration of disease (mean 4.7 years).

Vitamin D insufficiency was also reported as common in a study of pediatric patients with T1D in the northeastern United States; 25OHD levels <30 ng/ml were present in 76% of subjects and 25OHD concentration correlated negatively with age.⁵ And, in our own investigation of T1D subjects (14–40 years of age) in a southern US location, we found that 25OHD concentrations were lower in participants with T1D (n=115) and 53% of T1D participants were vitamin D insufficient (< 30 ng/ml) while only 38% of age-matched healthy control participants (n=55) were vitamin D insufficient.²⁰ The relative risk for vitamin D insufficiency/deficiency in T1D in this cohort was 2.29 (95% CI: 1.06, 4.92). Finally, a recent comparison of 25OHD concentrations measured in 720 T1D plasma samples and 2610 control plasma samples available in the United Kingdom also confirmed that both male and female T1D subjects had lower circulating levels of 25OHD compared with the general population.²¹

In contrast to these studies, Bierschenk *et al.*, demonstrated that median 25OHD levels were comparable between established T1D subjects, new-onset T1D subjects and control subjects (including first-degree relatives of T1D subjects), when studied in individuals residing in a solar rich environment in the US²². Interestingly, however, in this study vitamin D levels in *all* groups were suboptimal, with 76.1% of new-onset T1D, 68.5% of established T1D, and 70.1% of control subjects having 25OHD levels < 30 ng/ml.²² By comparison, in a recent study of 57 adolescent subjects with T1D recruited from the Diabetes Center at Vanderbilt Medical Center, the authors report that serum 25OHD levels were comparable to a general adolescent population, as reported by the National Health and Nutrition Examination Survey (NHANES 2001–2004)²³; moreover, when comparing the T1D subjects with HbA1c values > 9% (n=27) to those with HbA1c values < 9% (n=30), they found no difference in 25OHD status or bone mineral density (BMD) between groups²⁴. In this study, however, only 43% of T1D females and 40% of T1D males had 25OHD levels < 30 ng/ml.

Hence, while a modest increase in the prevalence of vitamin D insufficiency in T1D was a common finding in most but not all studies, vitamin D insufficiency was also frequent in comparably studied non-diabetic individuals.

Vitamin D levels in T2D

Lower vitamin D levels are present both in obese adolescents and obese adults^{25–26}; also, an inverse correlation between vitamin D and body mass index (BMI) has been established^{27–28}, attributable in part to increased vitamin D storage in adipose tissue.²⁹ Because obesity is a primary risk factor for T2D, lower vitamin D levels in T2D would be anticipated. In addition, some studies have demonstrated an association between lower vitamin D levels and either metabolic syndrome or carbohydrate intolerance.³⁰ Despite this, studies examining vitamin D levels in patients with established T2D provide inconsistent results.

Cross-sectional studies in adults comparing T2D with geographic controls have demonstrated: 1) a higher prevalence of vitamin D deficiency (<50 nmol/L) in South Asians with T2D living in the United Kingdom³¹; 2) a lower prevalence of *severe* vitamin D deficiency (<12.5 nmol/L) in Saudi Arabians with T2D³² and yet; 3) a similar prevalence of deficiency in elderly patients with T2D in Indonesia (<50 nmol/L).³³ A study of 581 Japanese patients with T2D compared with 51 non-diabetic subjects also reported very similar mean vitamin D levels (17.0 vs. 17.5 ng/ml) in these two groups.

In African Americans, a concurrent racial disparity characterized by *both* lower serum 25OHD levels^{25–26} and a higher prevalence of T2D, compared with European Americans, would predict an overlap of vitamin D deficiency and T2D in this group. Studies directly examining the prevalence of vitamin D deficiency among African Americans with T2D are

limited; however, an analysis of serum 25OHD concentrations, diabetes and ethnicity from the National Health and Nutrition Examination Survey, years 1988–1994 (NHANES III), failed to confirm an association between serum 25OHD quartile and diabetes relative risk in non-Hispanic blacks, though the expected inverse correlation was seen in non-Hispanic whites and in Mexican-Americans.²⁵ In contrast, a study of 133 adults with diabetes (116 with T2D, 17 with T1D) evaluated at a US academic medical center confirmed a high combined prevalence of vitamin D deficiency (51.1%; 20 ng/mL) in this cohort, *and* reported relatively lower 25OHD levels in African Americans.

Studies directly comparing vitamin D deficiency in T1D and T2D are also imperfect. A study by Di Cesar, *et al* reported that 63.5% of adult type 2 diabetics (n=50) were vitamin D deficient (<20 ng/ml) compared with only 36% of type 1 diabetics (n=63), though their T1D cohort was significantly younger (49 vs. 61 years) and had a lower BMI (26 vs. 34 kg/m²). Taken together, these studies suggest that the relationship between T2D and vitamin D is multifactorial and concurrently influenced, at minimum, by ethnicity, geography, BMI and age.

Studies have also examined vitamin D levels as they relate to the relative risk of T2D, though this type of analysis does not directly address the prevalence of vitamin D deficiency in individuals with T2D. Never-the-less, a meta-analysis of 28 studies, including 99,745 adult participants demonstrated that higher levels of vitamin D in middle-aged and elderly individuals were associated with a 55% reduction in relative risk of T2D.³⁴ Another meta-analysis reviewing all MEDLINE observational studies reported through January, 2007 combined data from those studies that reported an association between 25OHD level and prevalent T2D³⁵. When data from non-Hispanic blacks was excluded, they found a significant inverse association between 25OHD concentration and T2D (OR=0.36; 95% CI: 0.16, 0.80). These authors also examined case-control studies from the same time period, and noted that of 13 studies published from 1979–2006, 10 studies reported lower serum 25OHD levels in patients with T2D or glucose intolerance, compared with non-diabetic controls.³⁵ An examination of 3983 adults participating in the NHANES Survey for years 2001–2002 and 2003–2004 also suggested that 25OHD levels were negatively associated with the prevalence of diabetes.³⁶ In contrast, a population-based longitudinal assessment over 11 years of follow-up in Norway demonstrated that while individuals in the lowest quartile for serum 25OHD concentration had an increased hazard ratio for T2D (RR = 1.89), adjustment for BMI eliminated this as a significant risk association.³⁷

Studies have also examined prospectively, whether low serum 25OHD levels impact, prospectively, the development of T2D at some time in the future. A recent population-based prospective study of 5200 Australian men and women in which serum 25OHD levels were assessed at baseline, demonstrated that during a 5-year follow-up period, each 25 nmol/L increment in serum 25OHD was associated with a 24% reduced risk of subsequently being diagnosed with T2D³⁸. Similarly, a retrospective analysis of pooled data available from two nested case-control studies collected between 1973 and 1980 in Finland, demonstrated that during a 22-year follow-up period, men (free of diabetes at baseline) with baseline serum 25OHD levels in the highest quartile had a significantly reduced risk of incident diabetes.^{39–40} One of these two studies, however, demonstrated that participants in the highest serum 25OHD quartile also had lower BMIs⁴¹, reinforcing the hypothesis that obesity is a common risk factor for both vitamin D deficiency and future T2D. A study examining 524 non-diabetic European-origin adults (40–69 years at baseline) found that baseline 25OHD levels were significantly inversely associated with 10-year risk of hyperglycemia and insulin resistance, even after adjusting for BMI.⁴² And, in a very recent study of 489 Canadian adults considered at risk for T2D (mean age, 50±10 years), a higher

baseline 25OHD level independently predicted better β -cell function and glucose homeostasis 3 years later.⁴³

Vitamin D and diabetes; Cause or effect?

The question remains, therefore, whether lower levels of vitamin D contribute pathologically to the development of T1D or T2D, coexist as a consequence of diabetes, coexist due to a common confounding variable, or perhaps genetically co-segregate within individuals. When measured *at the time of T1D diagnosis* and compared with age-matched non-diabetic participants, lower levels of vitamin D have been reported in children in North India⁴⁴ and Italy⁴⁵, as well among young adults in Sweden.⁹ However, this dysregulation has been partially attributed, by some, to concurrent ketoacidosis.⁴⁶ Lower levels of vitamin D have also been reported in New Zealand adults *newly diagnosed with T2D*⁴⁷ suggesting that vitamin deficiency in either condition may predate disease onset. Additionally, as detailed above, prospective analyses suggest that lower serum 25OHD levels might not only predate T2D onset, but influence disease risk. Consistent with this concept, data exist to support a role for vitamin D in pancreatic β -cell function in T2D⁴⁸. Details of these studies are reviewed below.

Vitamin D and insulin secretion

Pancreatic β -cells manufacture the 1α -hydroxylase enzyme, allowing for localized production of physiologically active 1,25-dihydroxyvitamin D [$1,25(\text{OH})_2\text{D}$] from 25OHD.⁴⁹ They also possess nuclear vitamin D receptors (VDR)^{50–51} and vitamin D-dependent calcium binding proteins have been identified in pancreatic islets. Additionally, pancreatic islets exhibit $1,25(\text{OH})_2\text{D}$ -mediated rapid insulinotropic responses to treatment via non-genomic signal transduction pathways.^{52–53} Together these features provide the site-specific machinery for intra-pancreatic vitamin D-mediated insulin secretion⁵⁴. Consistent with this, a detrimental effect of vitamin D deficiency or genetic inactivation of the vitamin D receptor gene on pancreatic insulin secretion and glucose tolerance has been confirmed both in rodents^{55–57} and humans⁵⁸.

If vitamin D is critical to the maintenance of normal pancreatic β -cell function, and specifically to insulin secretion, it is possible that therapeutic intervention with vitamin D might thwart the development of insulin resistance or T2D in some patients. In pre-diabetic, insulin resistant individuals, some studies suggest that vitamin D supplementation does improve insulin sensitivity: In a study of 81 South Asian women in New Zealand with hypovitaminosis D ($< 50 \text{ nmol/L}$) and insulin resistance ($\text{HOMA-IR} = 1.93$), randomized, placebo-controlled (42:39) intervention with placebo or 4000 IU/day for 6 months, resulted in significant improvements in insulin sensitivity, but no change in C-peptide, a measure of insulin secretion.⁵⁹ However, as reported in a meta-analysis conducted by Pittas, *et al* reviewing English-language studies published prior to 2009 (from MEDLINE and the Cochrane Central Register of Controlled Trials), in 5 randomized adult trials examining participants with normal baseline glucose tolerance, vitamin D supplementation (duration range 0.5–7 years) had no significant effect on fasting plasma glucose or incidence of diabetes⁶⁰. Similarly, results of the RECORD study⁶¹, a placebo-controlled trial providing 800 IU vitamin D₃ and 1000 mg calcium daily to 5292 participants ages ≥ 70 years, failed to demonstrate any protective effect against the development of self-reported T2D over the 24–62 month follow-up period.

Moreover, several studies suggest that in patients with *established* T2D, treatment with cholecalciferol does not acutely improve glycemic control, insulin secretion or insulin sensitivity.⁶⁰ For example, a placebo-controlled trial in twenty-eight Asian Indian patients with moderately controlled T2D demonstrated that 300,000 IU of intramuscular D₃

produced no change over a 4-week period in fructosamine, fasting plasma glucose or homeostasis model assessment of insulin resistance, despite a significant increase in 25OHD levels in the treated group⁶². Similarly, in a Chinese study of 109 patients (>50 years of age) with T2D, 2000 IU D3 per day given for 3 months to those with vitamin D levels <50 nmol (36% of subjects) did not impact gluco-metabolic control during the treatment interval.⁶³ Given that dietary vitamin D intake accounts for <10% of vitamin D supply, however, results of these intervention studies are probably not surprising.

The effects of vitamin D treatment on β -cell function have also been investigated in T1D, though predominantly as an immunomodulating agent, to potentially interrupt the autoimmune-mediated destruction of β -cells⁵⁴. However, in subjects with recent onset T1D, supplementation with calcitriol [1,25(OH)₂D; 0.25 μ g/day] for 9⁶⁴ or 24⁶⁵ months was not effective in improving pancreatic β -cell function, as assessed by C-peptide measurement, or in lessening insulin requirements in these individuals. Moreover, vitamin D deficiency at diagnosis was not associated with lower C-peptide levels at 24 months.⁶⁵

Diabetes-specific mechanisms contributing to vitamin D deficiency

Genetic variation in the vitamin D axis in diabetes

The vitamin D receptor (VDR) gene had been investigated as a candidate gene impacting T1D susceptibility, as well as susceptibility to T1D complications^{66–67}. However, published reports have been inconsistent, possibly due to differences in the ethnicity of studied populations, or to differences in ultraviolet radiation exposure in different regions.⁶⁸ Data suggests that VDR genomic binding positions are overrepresented near genes associated with T1D risk⁶⁹. Additionally, the prevalence of certain VDR gene polymorphisms has been associated with T1D susceptibility in populations from Uruguay (FokI)⁷⁰, South Croatia (Tru9I)⁷¹, Japan (BsmI)⁷², Crete (FokI, BsmI, ApaI and TaqI)⁷³, Germany⁷⁴ and Southern India Asians (BsmI).⁷⁵ Other evidence does not appear to support a role for vitamin D receptor gene variations in either the development of diabetes or the incidence of diabetic osteopathy. The Type 1 Diabetes Genetics Consortium genotyped 38 single nucleotide polymorphisms (SNPs) of the VDR gene in over 1600 T1D nuclear families, and found no association of VDR SNPs with T1D⁷⁶. Similarly, a study of 207 T1D patients and 249 controls from Portugal found no association between VDR gene polymorphisms and T1D susceptibility⁷⁷. While a study of 233 T1D patients and 191 healthy controls from North India analyzing four VDR SNPs (FokI, BsmI, ApaI, TaqI) identified an interaction between VDR and the HLA-DRB1 0301 allele, they attributed this to the presence of vitamin D response elements (VDRE) in the promotor region of the HLA-DRB1 0301 allele.⁷⁸

Genetic variants of the 1 α -hydroxylase gene (CYP27b1) may also affect susceptibility to T1D.⁷⁹ Similarly, genetic association of some other vitamin D metabolism genes [GC (vitamin D transport), DHCR7 (cholesterol synthesis), CYP2R1 and CYP24A1 (vitamin D hydroxylation)] has recently been associated with genetic risk for T1D in the British population.²¹

With respect to skeletal complications, in a study of 90 Turkish patients with T1D, an analysis of VDR gene polymorphisms (BsmI, ApaI, TaqI, FokI, Cdx-2 binding site) revealed no difference in markers of bone turnover among different VDR genotypes, and no correlation of genotype with DEXA measurements in these patients.⁸⁰ Similarly, in a study of German patients with T1D, VDR genotypes were not associated with differences in bone turnover markers between diabetics and non-diabetics⁷⁴.

A few studies suggest that polymorphisms in the VDR gene are also associated with the prevalence of T2D in specific populations^{81–83}. Many other studies, however, have not

confirmed an association of VDR gene polymorphisms with T2D susceptibility^{84–87} or with T2D vascular complications⁸⁸, though an association of VDR SNPs with components of the metabolic syndrome phenotype^{86, 89–91} or with insulin secretion^{83, 89} have been reported. The association of VDR gene polymorphisms on bone mineral density in patients with T2D remains unclear⁹².

Vitamin D and albuminuria

Data from >15,000 adult participants in the Third National Health and Nutrition Examination Survey (NHANES III) demonstrated, by cross-sectional analysis, an association between hypovitaminosis D and increased urinary albumin excretion rate (UAER); specifically, a step-wise increase in the prevalence of albuminuria was seen with decreasing quartiles of vitamin D concentration.⁹³ Similarly, data from NHANES 2001–2006, examining 1216 adults specifically with diabetes again identified an association between vitamin D deficiency and/or insufficiency and diabetic albuminuria.⁹⁴ In contrast, a longitudinal observational study of 289 adults with T2D in Denmark did *not* find an association between vitamin D levels and UAER. Moreover, they state that “severe vitamin D deficiency at baseline did not predict progression to micro- or macroalbuminuria” when subjects were followed for a median of 15 years.⁹⁵

Exaggerated urinary loss of vitamin D binding protein (DBP) in T1D, particularly in persons with albuminuria, might contribute mechanistically to vitamin D deficiency in this disease. Ordinarily, the DBP + 25OHD complex within the glomerular filtrate is endocytosed in the renal proximal tubule. Once within the epithelial cell, 25OHD is released, hydroxylated by 1 α -hydroxylase to 1,25(OH)₂D, and the active hormone is then returned to the circulation.¹⁴ In our own study of 115 subjects with type 1 diabetes compared with 55 age-matched healthy control subjects, we found a significant increase in the urinary excretion of DBP in subjects with T1D compared with controls.²⁰ Moreover, urine DBP concentrations correlated with UAER and vitamin D deficiency or insufficiency was more prevalent in diabetic subjects with albuminuria, coincident with the increase in urine DBP excretion.²⁰ Using a proteomics approach, we also compared the urine proteome from 12 healthy non-diabetic individuals, 12 subjects with T1D yet normal urinary albumin excretion rates and 12 subjects with T1D and microalbuminuria.⁹⁶ The urine abundance of megalin and cubilin, multiligand receptors expressed in kidney proximal tubule cells and involved with the re-uptake of the DBP + 25OHD complex (Figure 1B), was significantly increased in albuminuric T1D subjects, compared to both non-albuminuric groups, suggesting aberrant shedding of these re-uptake receptors.

Observations in rodent models have extended these mechanistic insights. Several studies have shown that in rodent models of STZ-induced diabetes, circulating concentrations of 1,25(OH)₂D are typically decreased.^{97–98} Increased clearance of 1,25(OH)₂D has been postulated as a mechanism by which this may occur. Specifically, following a 12-day infusion of 1,25(OH)₂D, STZ-induced diabetic rats showed a greater than 50% increase in the metabolic clearance rate of 1,25(OH)₂D⁹⁹; moreover, these diabetic animals had lower serum DBP levels. And in keeping with our observations in the human urine proteome⁹⁶, recent studies from our laboratory have shown that in the diabetic DBA/2J nephropathy-prone mouse, with increasing duration of diabetes and worsening nephropathy and albuminuria, urine excretion of megalin, DBP and 25OHD increases progressively over time.¹⁰⁰ In the Zucker rat, a model of T2D, serum concentrations of 25OHD and 1,25(OH)₂D are also reduced, while urinary 25OHD, 1,25(OH)₂D and DBP excretion are increased compared to lean controls.¹⁰¹ Thus, exaggerated renal losses of vitamin D metabolites and the carrier protein, DBP, provide a possible mechanistic explanation in animal models of T1D and T2D by which vitamin D clearance is amplified in diabetes. We can speculate that a similar mechanism may be operative in humans.

Data from clinical investigations – a role for vitamin D in diabetic osteopathy

While numerous studies have examined the prevalence of hypovitaminosis D in various diabetes populations, clinical data examining a direct role for vitamin D in either the pathogenesis or in the treatment of diabetic osteopathy are scarce. Over 25 years ago, an analysis of 14 patients with T1D and 168 patients with T2D identified decreased bone mass in ~43% of T1D and ~38% of T2D subjects, but reported that 25OHD levels in both T1D and T2D subjects were similar to those of controls.^{102–103} Similarly, a study of 45 Caucasian patients with T1D (age 7–18 years), reported no difference in circulating 25OHD levels between non-osteopenic diabetic patients and osteopenic diabetics (cortical thickness > 2SD below the mean normal value).⁶ However, differences in therapeutic options and objectives utilized at the time would likely have resulted in less stringent glucometabolic control in these patients and might not reflect current standards of care. In 1998, a study of premenopausal British women with T1D (n=31), T2D (n=21) or non-diabetic controls (n=20) demonstrated that femoral neck BMD and 25OHD levels were significantly lower in subjects with T1D and serum 25OHD levels negatively correlated with serum collagen type 1 C-terminal propeptide ($r = -0.56$, $p < 0.001$). Similar findings were not observed in the T2D subjects, however.¹⁰⁴ More recently, we have analyzed serum concentrations of 25OHD, undercarboxylated osteocalcin (UC-OC) and GLA-carboxylated osteocalcin (GLA-OC) in 115 subjects with type 1 diabetes (T1D), ages 14–40 years, compared with 55 age-matched control subjects. Circulating concentrations of 25OHD were lower in subjects with T1D¹⁰⁵. Also, in the T1D subgroup, GLA-OC concentrations correlated with 25OHD ($p = 0.009$), perhaps inferring a positive effect of 25OHD on bone quality in diabetes¹⁰⁵.

Data from animal modeling – a role for vitamin D in diabetic osteopathy

The efficacy of vitamin D treatment on diabetic osteoporosis has been examined only minimally in animal models. In the *db/db* mouse model of T2D, administration of low-dose 1 α -hydroxyvitamin D3 (0.1 μ g/kg) for 5 days each week for 4 weeks prevented reductions in femoral BMD observed in untreated diabetic mice. This low dose of 1 α -hydroxyvitamin D3 did not alter weight, food intake, water consumption, PTH or calcium concentrations, suggesting a primary, not secondary, affect on bone.¹⁰⁶ In the STZ-induced rat model of T1D, femoral BMD is decreased, yet treatment with 1 α -hydroxyvitamin D3, again at a low dose of 0.1 μ g/kg/day, improved significantly the low BMD observed in the diabetic rat.¹⁰⁷ Together these studies suggest a positive role of a vitamin D analog in treating diabetic osteoporosis in rodent models of T1D and T2D; however, additional studies have not been performed to confirm these findings in other models of diabetic osteoporosis, and, to our knowledge, no animal studies have examined the affect of vitamin D to prevent fracture or improve bone strength of the diabetic skeleton.

Summary

The direct role of vitamin D in the metabolic homeostasis of diabetic bone remains a much understudied association. Human and animal models of diabetes suggest that diabetes is commonly associated with vitamin D insufficiency. Furthermore, enhanced renal losses of vitamin D-DBP complexes may compound vitamin D deficiency in diabetes. However, future studies are clearly needed to determine whether vitamin D status can be directly related to or is predictive of measures of bone quality (not just BMD) and the risk to fracture in those with diabetes. Furthermore, clinical trials with vitamin D supplementation will ultimately provide a definitive answer as to the role that vitamin D status may or may not play in the prevention or reversal of diabetic osteopathy in humans. Available data to date

would suggest that the greatest impact of vitamin D intervention might be seen in individuals with T1D or in diabetes (T1D or T2D) with albuminuria.

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Figure 1.

Comparing the normal (A) and the diabetic (B) condition, a hypothetical mechanism for vitamin D insufficiency in diabetes is diagrammed. Specifically, in the non-diabetic, non-albuminuric individual (A), the circulating 25OHD + DBP complex is filtered across the renal glomerulus, transported to the proximal tubule (PT), where it binds to megalin or cubilin receptors, two multiligand receptors involved with the re-uptake of filtered albumin and megalin/cubilin ligands including DBP. Once endocytosed by the PT epithelial cell, 25OHD is released and hydroxylated by 1α -hydroxylated to $1,25(\text{OH})_2\text{D}$. Minimal excretion of DBP or vitamin D metabolites is anticipated. However, in diabetes (B), exaggerated renal loss of DBP and vitamin D metabolites might occur, perhaps as a consequence of albuminuria alone, or due to aberrant shedding or abnormal functioning of the megalin or cubilin reuptake receptors.