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Review Article

A Review On the link between Vitamin D and Diabetes Mellitus

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ABSTRACT

Serum vitamin D levels of 50 - 125 nmol/L are considered sufficient, 30 - 49 nmol/L as insufficient and below 30 nmol/L as overtly deficient. Large demographics of the general population are affected, the majority being at below optimal blood levels for a variety of reasons. A study published in the Archives of Internal Medicine has estimated Vitamin D deficiency levels in approximately 85% in the general population. The role of vitamin D in diabetes (autoimmune type 1, type 2 diabetes mellitus) is considerable. Deficiency or insufficiency of vitamin D is linked to autoimmune dysfunction potentially playing a significant part in development of type 1 autoimmune diabetes in both children and adults. There is also an observable relationship between vitamin D deficiency and glucose intolerance, insulin resistance and insulin secretion. There is an association between increased development of diabetic neuropathy in vitamin D deficient diabetics. Vitamin D deficiency is an independent risk factor for neuropathy after adjusting for demographic factors, BMI, comorbidity, use of medications for neuropathy and diabetes duration.

Introduction

Prevalence of Vitamin D deficiency

Vitamin D has seen a resurgence of interest and study for human health in the last decade. Though ongoing studies continue to refine our definitions of normal blood level measurements and recommended dietary allowances, a deceptively high composition of all age groups in the American population are routinely found deficient both clinically and subclinically of this fat soluble vitamin. A study published in the Archives of Internal Medicine has estimated Vitamin D deficiency levels in approximately 85% in the general population (1). The Institute of Medicine in 2001 – 2006 reported two-thirds of their study population to have sufficient vitamin D (25-hydroxyvitamin D (25(OH) D) value of 50–125 nmol/L), one-quarter to be at risk of vitamin D inadequacy (serum 25 (OH) D 30–49 nmol/L), and the remainder of 8% to be at risk of vitamin D deficiency (serum 25 (OH) D less than 30 nmol/L). The risk of vitamin D deficiency varies across age, sex, racial and ethnic distributions. Lower prevalence rates were observed in younger population cohorts, particular males and non-Hispanic Whites. Pregnant or lactating women were also seen to have higher levels of Vitamin D (2). The risk of vitamin D deficiency increased between 1988 – 1994 and 2001 – 2002 in both sexes but did not change between 2001 – 2002 and 2005 – 2006 (3).

Vitamin D and its effects:

Fat-soluble Vitamin D undergoes biological enzymatic alteration and activation into a hormone form physiologically (4). The active form of vitamin D, calcitriol (1, 25-(OH) 2 D3), mechanistically resembles a hormone by structurally altering vitamin D receptors (VDRs) <steroid receptor type> on the cell membrane as well as in the nucleus. Said structural alteration incites specific genetic expression (5). There is rapidly growing awareness about the importance of the "sunshine vitamin" - vitamin D for health. Vitamin D deficiency is postulated to coadjute pathogenically in developmental risk of cancers of the colon, breast and prostate, hypertension and cardiovascular disease, osteoarthritis, and immune dysfunction permitting infections and autoimmune disorders, namely multiple sclerosis, Type I and Type II diabetes and rheumatoid arthritis (4). Solar ultraviolet-B rays absorbed dermatologically are a critical source of this nutrient. Modern lifestyle practices discourage natural acquisition of levels historically present to facilitate evolution, and thus the existing systemic dependence on levels now rarely naturally occurring. It is theorized that early Hominidae evolved

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near the equatorial belt where exposure to sunlight was intense year round, and primitive Homo Sapiens had routine intense solar UVB exposure, now not observed in modern humans. The Institute of Medicine and the Endocrine Society have revised vitamin D levels such that less than 20ng per mL (50 nmol /L) to be interpreted as deficient. Levels in excess of 30 ng /mL are considered as sufficient (6).

Vitamin D and Type I diabetes:

Central to autoimmune type 1 diabetes is immune mediated destruction of pancreatic islet beta cells. According to the American Diabetes Association, about 5% of diabetics in the United States are afflicted with type 1 diabetes, of which 60% of the cases onset after twenty years of age (8). Studies have found associations between low levels of vitamin D and potential increase in risk of type 1 diabetes. However, many of the early studies only indirectly observed the link through studies designed to correlate vitamin D levels in pregnancy/childhood to the risk of developing type 1 diabetes in children. Other research conducted among adults found an association between high vitamin D levels and a decreased risk of multiple sclerosis, an autoimmune disease genetically and epidemiologically related to type 1 diabetes suggesting that vitamin D deficiency may be a risk factor for autoimmune pathologies (9). Numerous retrospective and observational studies have demonstrated a high prevalence of 25(OH) D deficiency in patients with type 1 diabetes therefore suggesting a contributory role in the pathogenesis of type 1 diabetes. A cross-sectional study from Switzerland reported 60 to 84% of type 1 diabetics to be 25-OH D deficient (10). Similarly, a case control study in Qatar found 90.6% of type 1 diabetic children versus 85.3% of non-diabetic children to have low vitamin D levels (11). In a North Indian case control study, 58% of type 1 diabetics had 25(OH) D deficiency (12). In the Northeastern USA, 15% of type 1 diabetics have overt 25(OH) D deficiency and 61% are vitamin D insufficient (13). Further, the Diabetes Incidence Study in Sweden (DISS), reported 25(OH) D level to be lower in diabetics not only at the onset of diabetes but also during the 8-year follow up period (14). Despite these observations, a study in Florida (a state famous for its tropical sun and warm temperature) found no difference in 25-OH D levels in diabetics compared to the controls (15).Having adequate levels of vitamin D during young adulthood may reduce the risk of adult-onset type 1 diabetes by as much as 50%, according to researchers at Harvard School of Public Health (HSPH). Findings such as these have tremendous public health implications, and if confirmed in future studies, could introduce a role for vitamin D supplementation for prevention of autoimmune diseases in children and adults alike. Kassandra L. Munger, et al. address that the possibility of preventing disease with supplementary vitamin D1,000-4,000 IU/day (a dose generally considered safe) may in fact exist (16).

Vitamin D and Type II Diabetes

Central to type 2 diabetes mellitus are decreased secretion of insulin, and insulin resistance. Both of these processes are linked to vitamin D deficiency (17). Type 2 diabetes is growing at the rate of about one million newly diagnosed cases per year in the USA alone (18). Various cross-sectional studies have shown an association between low vitamin D levels and key pathogenic mechanisms in type 2 diabetes like insulin resistance, and impaired glucose tolerance. Yet unclear however is the relative risk of type 2 diabetes when associated with vitamin D deficiency (19). In a recent 5 year follow-up study, out of 1080 participants, 10.5% had a serum 25(OH)D deficiency (<10 ng/mL), 51.6% had an insufficiency (10.0–19.9 ng/mL), and 38.0% had acceptable levels (≥20 ng/mL). Having adjusted the variables for age, sex, blood pressure, lifestyle habits, significant family history, seasonal changes, parathyroid hormone secretion, and also high-sensitivity C-reactive protein, participants with 25(OH) D deficiency had an increased risk of type 2 diabetes independently of their body mass index, HOMA2-IR, and IGI. It is highly suggestive that vitamin D metabolism may play a role in type 2 diabetes pathogenesis independently of other known risk factors (20). The Australian Diabetes, Obesity, and Lifestyle study also showed that vitamin D deficiency was associated with an increased risk of developing diabetes and metabolic syndrome at 5-year follow-up (21). Similarly, Pittas et al, also found vitamin D deficiency to be a predisposing factor for diabetes risk in white women though the results could not be directly extrapolated to men or nonwhite women (22). The role of vitamin D in glucose derangements was also suggested by evidence provided by Needet et al, who found an association between serum 25(OH) D and fasting glucose levels in postmenopausal white women, and found a dramatic deterioration in blood glucose in the presence of 25(OH) D levels below 40 nmol/l (23). On the contrary, other studies have shown no significant association between 25(OH) D levels and incidence of diabetes (24-33). Zipitis and Akobeng in their recent meta-analysis concluded that vitamin D supplementation may offer some protection against the development of type 1 diabetes during infancy (34). In adult patients with recent-onset of type 1 diabetes, a randomized controlled trial found benefit in supplementation with 1, 25 (OH) D which temporarily reduced insulin requirements (35). The apparent reduction of type 1 diabetes may be due to the immunomodulatory effects of vitamin D, protecting from or arresting the immune process responsible for autoimmune destruction of pancreatic insulin secreting cells (36). Further studies are warranted particularly in subjects with high risk of developing diabetes. Based on the hypothesized mechanism of action of vitamin D, these subjects may benefit from regular, structured regimens of vitamin D supplementation.

Vitamin D and Diabetic Neuropathy

Diabetic neuropathy etiopathogenesis is understood to be related to chronically elevated blood sugar levels resulting in changes to nerve tissue vasculature resulting in detrimental metabolic changes permanently affecting nerve function. A recent study published in the Archives of Internal Medicine reported that vitamin D deficiency was more prevalent in diabetics and could be associated with diabetic peripheral neuropathy (37). An association between diabetic neuropathy and Type 2 diabetes has been described in the National Health and Nutrition Examination

Survey (NHANES) from the USA and a study from Kuwait by Shehab et al. In both studied populations, prevalence of vitamin D deficiency was high. In the NHANES study, vitamin D levels < 75 nmol / l (30 ng / ml) were present in 92% Hispanic and 98% non-Hispanic black people when compared with 76% in non-Hispanic white people. In both the NHANES and Kuwaiti studies, the risk for developing peripheral neuropathy was 25-35%. While both studies had a relatively small sample size, the trend is clearly observable (38). Vitamin D plays an important role in preventing nerve damage and maintaining healthy pain receptors and in nerve repair and growth. Vitamin D insufficiency is associated with peripheral neuropathy symptoms even after adjusting for demographic factors, BMI, comorbidity, use of medications for neuropathy and diabetes duration. However, Vitamin D deficiency is an independent risk factor for peripheral neuropathy and therefore further studies are required to obtain therapeutic guidelines for prevention and therapy.

Conclusion:

Based on the review of the studies described above, vitamin D deficiency has a direct link to the development of type I diabetes and also plays a major role in worsening insulin resistance and secretion, augmenting the risk of developing type 2 diabetes along with diabetic neuropathy. Recent compelling evidence suggests conflicting and inconclusive results due to the different populations studied, chemical formulations of vitamin D, doses, and time frame of supplementation. Long term prospective supplementation studies are warranted in this area of because of potential therapeutic and preventative possibilities in type I and type II diabetes, along with diabetic neuropathy associated with vitamin D deficiency.

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