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ABSTRACT

Type 2 diabetes is a major public health problem, accounting for significant premature mortality and morbidity. The growth in prevalence of the condition appears to be closely linked with obesity. Over the last 5 years, a number of large observational studies have suggested an association between the onset of type 2 diabetes and Vitamin D deficiency. Vitamin D has important effects on insulin action, and may impact on a number of pathways which may be of importance in the development of type 2 diabetes. This article reviews the evidence linking Vitamin D deficiency in the pathogenesis of type 2 diabetes, and suggests areas for urgent further research to determine whether Vitamin D replacement has a role in the prevention of type 2 diabetes.

INTRODUCTION

Burgeoning levels of type 2 diabetes (T2D) pose a worldwide public health crisis, affecting developed and developing countries.[1] While changes in obesity levels, diet and physical activity on the background of genetic risk factors appear to be fuelling this epidemic, other environmental factors may be influential in the development of T2D.[2]

Interest in Vitamin D and T2D was stimulated by early animal studies identifying a Vitamin D receptor (VDR) in pancreatic tissue,[3] and data showing that Vitamin D deficiency affected insulin secretion.[4] A link between the development of type 1 diabetes and vitamin D deficiency has been well described, and a recent meta-analysis of five observational studies suggests that children supplemented with vitamin D have a reduced risk for the development of type 1 diabetes.[5] Furthermore, a link between vitamin D deficiency and cardiovascular disease, and some cancers have been described.[6 7]

A review of the literature from over a decade ago has suggested a link between T2D or metabolic syndrome and vitamin D deficiency,[8] but a more recent systematic review and meta-analysis has suggested the association in many observational studies appears to be consistent and strong.[9]

We present an overview of the evidence suggesting an association between vitamin D deficiency and T2D, potential pathogenic mechanisms linking the two, and suggest areas for further research.

EPIDEMIOLOGY OF VITAMIN D DEFICIENCY

Serum concentrations of 25-hydroxyvitamin D (25 (OH)D) <50 nmol/l are widely accepted as indicative of deficiency.[10] It is now increasingly recognised that concentrations <75 nmol/l are physiologically important, and probably indicate vitamin D insufficiency. Certain patient groups are at increased risk of developing deficiency or insufficiency of vitamin D, including infants, adolescents and lactating women, due to increased requirements during these stages of life.

25(OH)D is frequently lower in people living at higher latitude. In countries situated outside of the tropics, serum vitamin D values vary in a seasonal manner, with concentrations towards the end of the summer period significantly higher than those found during late winter.[11] At latitudes above 40° north or south, photoconversion of 7-dehydrocholesterol to previtamin D does not occur to any great extent in winter months, and as latitude rises above these levels, even summer synthesis may be blunted.[10] Areas that receive high levels of sunlight, however, can also have populations with high incidence of vitamin D deficiency. Some areas of the Middle East, for example, have a prevalence of vitamin D deficiency ranging from 50–97%.[6] This may be due to traditional clothing which tends to cover most of the body, leaving very little skin exposed to sunlight, and therefore reducing the amount of vitamin D that can be synthesised.[12] The wearing of traditional clothing in immigrant populations who have moved to temperate climates may exacerbate the lack of sunlight exposure, leading to even higher risk of vitamin D deficiency among these immigrant populations.[13]

Vitamin D deficiency tends to affect black and South Asian populations to a greater extent than Caucasian populations as high levels of skin pigmentation absorbs UV-B light, hence limiting vitamin D production. If this deficiency is not adequately compensated for in dietary intake of vitamin D, then a deficient state can ensue. Other lifestyle factors may also be associated with lower vitamin D concentrations, such as reduced physical activity, and increased body mass index (BMI) due to deposition of vitamin D in adipose tissue, where it becomes biologically inactive and thus renders the person vitamin D deficient.[14] More recently, chewing of betel nut, also known as paan, has been shown to increase the expression of 24-hydroxylase, leading to increased values of the inactive vitamin D metabolite, 24,25 (OH)2D.[15]

MECHANISMS LINKING T2D AND VITAMIN D DEFICIENCY

Aside from its calcitropic effects, vitamin D has many physiological roles. Brain, prostate, breast, colon, pancreatic tissue, and immune cells carry VDRs.[16–18] Vitamin D appears to be important in numerous endocrine, autocrine and paracrine functions, and is an important regulator of gene expression, cell proliferation and differentiation.[19 20] A role in innate immunity is postulated, and deficiency can lead to susceptibility to infectious

diseases, such as tuberculosis,[21] and autoimmune conditions, such as type 1 diabetes.[22]

Vitamin D and its metabolites appear to have important effects on insulin synthesis, secretion and action, as well as components of inflammation, and all of these may have an influence on the pathogenesis of T2D.

Pancreatic β cell function

Several studies have noted an association between vitamin D and the physiological function of the pancreatic β cell. β Cells possess VDRs, and 1α-hydroxylase is expressed in pancreatic tissue, coincident with the expression of insulin.[23] Insulin secretion is calcium dependent,[24] and it is reported that vitamin D deficiency impairs glucose mediated insulin release.[25] Vitamin D supplementation improves stimulated insulin release in response to an oral glucose load, accompanied by an increase in serum calcium and a reduction in free fatty acids.[26]

Insulin resistance

Vitamin D may have two effects on insulin sensitivity: its role in mediating calcium metabolism may be important in the action of insulin, and its role in regulation of insulin receptor gene expression may also modulate insulin resistance.

Calcium is important in mediating increased glucose transport activity induced by muscle contraction.[27] In Wistar rats, an increase in cytosolic calcium ion concentration in muscle tissue appears to be responsible for increased glucose transport activity. Depletion of calcium may therefore reduce calcium available to aid glucose transport, and hence lead to insulin resistance.[28]

Vitamin D may aid insulin action by the regulation of insulin receptor gene expression, and hence increase insulin sensitivity.[29] Exposure of U-937 human promonocytic cells to 1,25(OH)D leads to significantly increased expression of mRNA encoding for insulin receptors, resulting in a maximum glucose transport which is 1.3-fold higher than untreated cells.[30] Vitamin D3 also appears to regulate human peroxisome proliferator activated receptor δ, a receptor that may have an important role in insulin sensitivity.[31] Genetically obese mice treated with peroxisome proliferator activated receptor δ agonist are noted to have lower postprandial concentrations of plasma glucose and insulin as well as an improvement in glucose tolerance.[32]

Inflammation

One of the key current hypotheses regarding the pathogenesis of T2D is based on inflammatory factors contributing to either insulin resistance or β cell dysfunction.[33] Subclinical elevations of inflammatory mediators such as interleukin-6 (IL6), C reactive protein (CRP), orosomucoid and sialic acid are related to the development of diabetes in middle aged adults.[34] Prospective study of non-diabetic subjects shows that higher baseline concentrations of fibrinogen, CRP and plasminogen activator inhibitor-1 leads to greater risk of developing T2D.[35]

The link between obesity and diabetes may be mediated through adipocytokines, such as tumour necrosis factor α (TNFα), IL6 and adiponectin. Animal and human studies have demonstrated that adipocytokines are major regulators of insulin sensitivity, potentially linking insulin resistance and obesity.[36] TNFα appears to potentiate insulin resistance by causing inhibition of autophosphorylation of tyrosine residues of the insulin receptor and inducing serine phosphorylation of insulin receptor substrate-1, which in turn causes serine phosphorylation of the insulin receptor in adipocytes and inhibits tyrosine phosphorylation.[37] Current evidence suggests that insulin action is highly dependent on the activity of the tyrosine kinase portion of the insulin receptor and its interaction with the insulin receptor substrate-1, therefore any alteration in this mechanism may lead to changes in insulin action. IL6 has also been demonstrated to inhibit insulin signal transduction in hepatocytes via interactions with suppressors of cytokine signalling-3.[38] Vitamin D appears to have important effects on inflammatory cytokines, by interfering with vitamin D response elements in the promoter region of a number of cytokine genes or transcription factors involved in cytokine generation.[39] Vitamin D can also interfere with cytokine generation by upregulating calbindin—a binding protein that protects against cytokine induced apoptosis.[40]

Cross-sectional evaluation of inflammatory markers, including plasma matrix metallopeptidase-9, tissue inhibitor of metalloproteinases-1 and serum CRP values, in 171 South Asian subjects shows a clear inverse relation to vitamin D status.[41] Randomisation of these subjects to high or low dose vitamin D supplementation leads to a greater reduction in plasma concentrations of matrix metallopeptidase-9, tissue inhibitor of metalloproteinases-1 and CRP post-supplementation, although to a much greater degree in the higher dose group. This suggests that vitamin D supplementation may ameliorate chronic inflammation in insulin resistant subjects.

EPIDEMIOLOGICAL EVIDENCE FOR A ROLE OF VITAMIN D DEFICIENCY IN THE PATHOGENESIS OF T2D

While a causal link between vitamin D deficiency and T2D has yet to be fully established, there are a number of lines of evidence to strongly suggest a link between vitamin D deficiency and the pathogenesis of T2D. The measurement of exposure to vitamin D is, however, problematic in many epidemiological studies, as the assessment of dietary dairy intake only covers a part of the intake of vitamin D, and does not include vitamin D synthesis from sunlight. In addition, seasonal changes in serum concentrations of vitamin D pose a further confounding variable in assessing vitamin D status in a cross sectional population.

Seasonality of T2D risk

Seasonal variation in the diagnosis and control of T2D has been noted. Population based studies have shown increased diagnosis of T2D in the winter months, along with poorer glycaemic control among established people with T2D in the winter months.[42] It is suggested that variability in vitamin D status may contribute to this observation, although variability in eating habits and physical activity between summer and winter months may also explain some of this seasonal variation.

Meta-analysis

Pittas and colleagues[9] have undertaken a systematic review and meta-analysis of the role of vitamin D and calcium in T2D. Their conclusions were that a consistent association between low vitamin D status and prevalent T2D was seen, with an OR of 0.36 (95% confidence interval (CI) 0.16 to 0.80) for T2D and 0.71 (CI 0.57 to 0.89) for metabolic syndrome in the highest versus the lowest vitamin D or dairy intake groups. Incident T2D showed a similar pattern with an odds ratio (OR) of 0.82 (CI 0.72 to 0.93) for highest verses lowest dairy intake.Table 1 highlights some of the data from these studies, and includes some more recently reported studies that were not included in the Pittas meta-analysis.

Observational studies

Cross sectional studies

A number of cross sectional studies suggest a link between low vitamin D status and the occurrence of T2D. The

Table 1 Studies of vitamin D status and risk of type 2 diabetes

	Participants	Study design	Findings
Third NHANES[43]	6228, multiethnic, non-diabetic	Cross sectional	OR for diabetes among highest quartile of 25(OH)D versus lowest quartile was 0.25 (95% CI 0.11 to 0.60) for whites, and 0.17 (95% CI 0.08 to 0.37) for Mexican Americans
Scragg R *et al* (1995)[46]	New Zealand Polynesian and Caucasian workforce of 5677 staff aged 40–64 years	Cross sectional	Serum 25(OH)D was significantly lower in newly detected cases with diabetes and IGT (n=238) compared with matched controls
Need AG *et al* (2005)[47]	753 postmenopausal women aged 35–94 years	Cross sectional	Fasting glucose inversely related to 25 (OH)D ($p< 0.01$)
British Birth Cohort Study (2008)[44]	6810 British white subjects born in 1958, surveyed during 2002–2004 (age 45 years)	Cross sectional	Metabolic syndrome prevalence lowest for highest tertile of 25(OH)D (OR 0.26, 95% CI 0.17 to 0.40)
Baynes KCR *et al*[48]	142 elderly Dutchmen (aged 70–88 years)	Cross sectional	1 h glucose and area under the glucose curve during a 75 g OGTT and total insulin concentrations were inversely associated with the serum concentration of 25(OH)D ($p<0.05$)
Mini Finland Health Survey[49]	4097 men and women aged 40–69 years not known to have diabetes	Prospective observational. Measurement of 25(OH)D at baseline. Follow-up 5 years	Relative risk between highest and lowest quartiles of serum 25(OH)D and incidence of T2D was 0.60 (95% CI 0.36 to 0.98)
Nurses Health Study[50]	83 779 females aged 30–55 years in 1976 with no history of diabetes, coronary heart disease, stroke, or cancer	Prospective observational. Assessment of dietary intake of dairy products. Follow-up 20 years, with 4843 incident cases of T2D	Women with the highest calcium (>1200 mg/day) and vitamin D (>800 IU/day) intakes had the lowest risk of diabetes (RR 0.67, 95% CI 0.49 to 0.90), compared to women with lowest intake (<600 mg of calcium and <400 IU of vitamin D)
Women's Health Study[51]	37 183 women without a history of diabetes, cardiovascular disease, and/or cancer at baseline	Prospective observational. Assessment of dietary intake of dairy food. 1603 incident cases of T2D	Women with the highest quintile of dairy intake had the lower risk of diabetes (RR 0.79, 95% CI 0.67 to 0.94), compared to women with lowest intake
Health Professionals follow-up study[52]	41 254 male health care professionals aged 40–75 years of age in 1986	Prospective observational. Assessment of dietary intake of dairy food. Follow-up 12 years. 1243 incident cases of T2D	RR for men in the top quintile of total dairy intake was 0.77 (95% CI 0.62 to 0.95) compared with those in the lowest quintile
MRC Ely study[53]	524 non-diabetic men and women aged 40–69 years	Prospective observational	Baseline 25(OH)D was associated inversely with 10 year risk of hyperglycaemia and insulin resistance
Finnish Mobile Clinic[54]	Men and women aged 40–74 years and non-diabetic	Nested case control, followed up for 22 years. 412 incident cases of T2D	OR between highest and lowest quartiles for 25(OH)D was 0.28 (95% CI 0.10 to 0.81) in men and 1.14 (0.60 to 2.17) in women
Cigolini M *et al* (2006)[55]	459 consecutive type 2 diabetic outpatients and 459 non-diabetic controls	Case control	143 (31.1%) of 459 patients had a history of CVD. The prevalence of CVD was higher among those with lower 25(OH)D concentrations ($p<0.01$)

Continued

Table 1 Continued

	Participants	Study design	Findings
Targher G *et al* (2006)[56]	390 consecutive type 2 diabetic patients and 390 non-diabetic controls	Case control	Age and sex adjusted prevalence of hypovitaminosis D higher in diabetic patients. Patients with hypovitaminosis D had a greater carotid intimal medial thickness and prevalence of carotid atherosclerotic plaques (74.6% vs 38.9%, $p<0.001$)
Isaia G *et al* (2001)[75]	799 postmenopausal women, 66 of whom were identified as having T2D	Case control	25(OH)D concentrations significantly lower in diabetic versus non-diabetic ($p<0.008$), as well as prevalence of deficiency (39% vs 25%)
Zemel MB *et al* (2004)[64]	32 obese adults age 18–60 years	Randomised trial of standard calcium, high calcium or high dairy for 24 weeks	The high dairy group exhibited a significant improvement in glucose tolerance after 24 weeks on the diet, whereas the other two groups exhibited no change. 27% decrease in the area under the glucose curve for the high dairy group ($p<0.01$), whereas there was no significant change for the low or high calcium groups
Boucher BJ (1995)[45]	59 British Bangladeshis	Randomised trial of vitamin D in high and low risk patients	100000 IU vitamin D by intramuscular injection, led to rise in 25(OH)D concentrations, but no effect on HH glucose tolerance
Borissova AM (2003)[65]	10 females with T2D on oral hypoglycaemic agents, 17 age and BMI matched females with normal glucose tolerance	Randomised trial of cholecalciferol in T2D patients and normal controls	Cholecalciferol 1332 IU daily for 1 month. A significant correlation between the change in first phases of insulin secretion and the change in 25(OH)D concentration occurred after vitamin D3 supplementation ($p<0.018$). The results showed a non-significant decrease of 21.4% in insulin resistance after 1 month
Orwoll E *et al* (1994)[66]	20 diabetic subjects	Double blind, placebo controlled, crossover trials of 1,25-dihydroxyvitamin D treatment (1 μg/day for 4 days)	No effect on fasting or stimulated glucose, insulin, C-peptide, or glucagon concentrations
Pittas *et al* (2007)[67]	314 Caucasian adults aged 65 years or over without diabetes	Double blind randomised trial of 500 mg calcium citrate and 700 IU vitamin D3 or placebo daily for 3 years	Among participants with IFG at baseline, those on calcium–vitamin D supplements had a lower rise in FPG at 3 years compared with those on placebo (0.02 mmol/l (0.4 mg/dl) vs 0.34 mmol/l (6.1 mg/dl), respectively, $p=0.042$).

BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; FPG, fasting plasma glucose; IFG, impaired fasting glucose; NHANES, National Health and Nutrition Examination Survey; OGTT, oral glucose tolerance test; OR, odds ratio; RR, relative risk; T2D, type 2 diabetes; 25(OH)D, 25-hydroxyvitamin D.

Third National Health and Nutrition Examination Survey examined 25(OH)D serum values, serum insulin and glucose concentrations in 6228 participants all aged over 20, with white, black and Mexican ethnicities all being included.[43] Serum 25 (OH)D values varied from 8.7–243.6 nmol/l with the mean concentration being highest in the white population and lowest in the African American population. Lifestyle factors also appeared to affect the serum concentration; participants with higher levels of physical activity (vigorous activity >12 times in the past month) and lower BMIs (≤23 kg/m^2) were found to have higher concentrations. Analysis showed a strong inverse trend between the odds of developing T2D and serum 25(OH)D among white and Mexican Americans, after adjusting for age, sex, BMI, physical activity and season. This link was not observed among African Americans, suggesting that ethnic variation in risk of T2D and vitamin D deficiency may exist, possibly due to decreased sensitivity to vitamin D.

Examination of 6810 participants of the British Birth Cohort, born in 1958, showed that factors associated with metabolic; syndrome also tended to be associated with concentrations of 25(OH)D.[44] All components used to define metabolic syndrome, including glycated haemoglobin, were significantly associated with 25(OH)D. Overall, the study found a clear inverse relation between 25(OH)D concentration and metabolic syndrome, with a 74% risk reduction for T2D among those persons with 25(OH) D concentrations in the highest tertile, compared to the lowest.

Among East London Bangladeshi subjects, vitamin D status was significantly lower among those at risk of T2D compared to those at lower risk.[45] Other studies showing an inverse association between vitamin D status and T2D have been reported from New Zealand,[46] Australia[47] and Holland.[48]

Cohort studies

Several cohort studies have also noted an association between vitamin D depletion and T2D. The Mini-Finland Health Survey examined 4097 subjects and found a significant inverse association between serum 25(OH)D and risk of T2D.[49] Over 17 years of follow-up 187 participants commenced medication for the treatment of T2D, and the relative risk for the development of diabetes between the highest and the lowest quartile of serum 25(OH)D was 0.60 (95% CI 0.36 to 0.98). The Nurses Health Study followed 83 779 registered nurses in the USA using medical and lifestyle questionnaires.[50] Over 20 years follow-up, 4843 incident cases of T2D occurred. The study demonstrated that an average daily intake of 511 IU of vitamin D was associated with a lower incidence of T2D compared to an average daily intake of 159 IU (2.7% vs 5.6%). A similar result was found by the Women's Health Study, with the demonstration of an inverse association between dairy consumption, especially low fat dairy consumption, and incidence of T2D, independent of other factors related to T2D.[51] Results from the Health Professionals Follow-up Study of 41 254 male participants has also shown an inverse relation between dairy consumption and the incidence of T2D, after adjustment for other known risk factors.[52] In a recently reported prospective analysis of the MRC Ely study, an inverse relation between 25(OH)D and glycaemic status at 10 years was found.[53]

Pooled analysis of over 27 000 subjects who were part of the Finnish Mobile Clinic study followed up for over a decade showed a clear reduction in risk for the development of T2D in subjects with a higher serum vitamin D concentration at baseline.[54] While seasonal variation in serum vitamin D concentrations may have affected the strength of this association, the results remained highly statistically significant.

Case control studies

A link between complications of T2D and vitamin D deficiency has been suggested. An Italian study of 459 patients with T2D found an increased risk of cardiovascular disease among patients with low 25(OH)D concentrations compared to those who were vitamin D replete (OR 1.7, 95% CI 1.1 to 2.6).[55] Examination of the intima–media thickness (IMT) of patients with T2D also shows a strong inverse association between 25(OH)D concentration and IMT, and on multivariate analysis, low vitamin D status strongly predicted IMT in these patients.[56] Severity of retinopathy has been linked to lower vitamin D status in a Turkish population.[57]

EVIDENCE FROM GENETIC STUDIES

Vitamin D exerts its effects through the VDR, which is a nuclear receptor of the steroid receptor family. The *VDR* gene is located on chromosome 12q13.1 and comprises 14 exons and a large promoter region. As VDR and vitamin D binding proteins can be found in β cell pancreatic tissue, it is possible to hypothesise that the genetic profile of the *VDR* gene may contribute to the development of T2D. A large number of polymorphisms of the *VDR* gene have been identified, most of which have an unknown functional effect, with the most common being ApaI, BsmI, FokI and TaqI polymorphisms.[58 59] Certain polymorphisms occur at a higher rate in certain ethnic groups.

A number of studies have shown a link between the VDR polymorphisms and T2D in different ethnic groups. The Rancho Bernardo study used a cohort of 1545 Caucasian adults, with no previous diagnosis of diabetes.[60] Of the 1545 cohort, 242 subjects developed diabetes over 10 years, and newly diagnosed persons with diabetes had a higher prevalence of the VDR aa genotype compared to those without diabetes (27.4% vs 20.3%), along with a significantly higher prevalence of glucose intolerance in non-diabetic persons with aa genotype compared with those with Aa and AA genotypes. Levels of insulin resistance and secretion however, as assessed by Homeostatic Model Assessment (*HOMA),* did not differ between the three ApaI polymorphisms. Of those participants who expressed the BsmI VDR polymorph, those with the bb genotype showed more insulin resistance and this value was significantly higher compared to the HOMA-IR values achieved for the other allele combinations. A study of 1539 men from the German Federal Armed Forces compared fasting glucose values with low levels of physical activity and VDR BsmI polymorphism.[61] In the group who undertook <3 h a week of physical activity the gene carriers homozygous for the B allele had a significantly higher fasting glucose than those with the b allele. In the group with high physical activity this genetic effect was absent. Among Bangladeshis with ischaemic heart disease, diabetes or hypertension, there was an increased prevalence of the recessive homozygous TaqI and FokI VDR polymorphism compared to controls.[59]

Examination of the vitamin D binding protein (DBP) polymorphism among PIMA Indians, a population at high risk for the development of T2D, has found two missense polymorphisms in the *DBP* gene associated with significant differences in oral glucose tolerance.[62]

EVIDENCE FROM INTERVENTION STUDIES

Studies of diabetic animals have suggested an improvement in glycaemic status among diabetic rats treated with vitamin D. Supplementation of cholecalciferol (vitamin D3) to diabetic Wistar rats showed a significant reduction in plasma glucose concentration.[63]

Human studies have also been carried out to assess the effect of calcium and vitamin D on insulin activity and function. A randomised controlled trial assessing the effect of a low calorie diet high in dairy products on fat loss found that participants with the diet high in dairy products lost more body fat over a course of 24 weeks compared to those who diet was modified to increase the intake of calcium alone.[64] In addition, while glucose tolerance was similar in both groups at the beginning of the experiment, the high dairy group exhibited a significant improvement in glucose tolerance. This suggests that compounds found in dairy products are able to influence the concentrations of circulating insulin and decrease tolerance to glucose in obese patients.

There have been several other short term intervention studies using vitamin D replacement involving a small numbers of subjects. Among Bangladeshis in East London, short term vitamin D replacement led to increased insulin secretion, but has little impact on glycaemia.[45] Similar results have been noted in a Bulgarian study.[65] Four day supplementation with high dose vitamin D in a small number of patients showed improvement in insulin and C-peptide secretion in recently diagnosed patients with T2D, but no benefit in glucose homeostasis.[66] Post hoc analysis of a vitamin D supplementation trial for bone outcomes had no effect on glycaemia and insulin resistance in 221 patients, but patients with impaired fasting glucose at baseline had a significantly lower rise in fasting glucose at 3 years.[67]

While a number of studies support a link between vitamin D and T2D, there are some negative studies. In the Women's Health Initiative, a cohort of 33 951 postmenopausal women were randomised to receive calcium 1 g and vitamin D3 400 IU daily, or placebo.[68] Over a 7 year follow-up, supplementation did not appear to reduce the risk of developing T2D. This study, however, has significant limitations to provide definitive evidence of lack of effect of vitamin D, including too low a dose of vitamin D, poor concordance with therapy and possible significant calcium and vitamin D use in the control group.[69]

The question of whether D2 or D3 supplementation should be used has been raised by some. One study has found that vitamin D3 raises and maintains 25(OH)D concentrations to a substantially greater degree than does vitamin D2, with a differential potency of at least 3- to 10-fold.[70] It also found the concentration of serum 25(OH)D rapidly declined after 3 days in the vitamin D2 treated group, suggesting a substantially more rapid metabolism or clearance of the vitamin D2 metabolite. Conversely, a more recent study has shown that a 1000 IU dose of vitamin D2 daily was as effective as 1000 IU vitamin D3 in maintaining serum 25(OH)D3 values and did not negatively influence serum 25 (OH)D3 concentrations.[71]

CONCLUSIONS AND FURTHER RESEARCH

T2D is a common condition, which if inadequately controlled may give rise to many complications, leading to a high morbidity and mortality. Vitamin D deficiency is also encountered commonly, and there is considerable epidemiological evidence to suggest a role for vitamin D deficiency in the pathogenesis of T2D. Whether this link is causal, however, remains to be proved. A number of mechanisms linking vitamin D deficiency and T2D are postulated, and all are plausible. Small intervention studies show a beneficial effect in repletion of vitamin D on glucose tolerance and other indices of the metabolic syndrome.

There are several research questions, which still require definitive answers. Clearly it is important to know whether the vitamin D supplementation is effective in reducing risk for the development of T2D, as well as other metabolic indices. While a large, multicentre randomised controlled trial is needed to answer this question definitively, this is likely to be a costly and lengthy undertaking. Initially small, shorter, but adequately powered studies looking at end points such as CRP or endothelial function may be worthwhile undertaking, in order to see whether vitamin D supplementation has an important effect on these variables. The method, frequency and acceptability of the intervention will also need to be tested—for example, is intermittent oral supplementation adequate to increase vitamin D status in a sustained manner? Furthermore, whether vitamin D2 or D3 supplementation is more effective at raising and maintaining serum vitamin D status needs to be clarified. The safety of regular vitamin D supplementation should also be explored—particularly the avoidance of severe hypercalcaemia, despite its low risk. A further area for consideration would be the dose of vitamin D required to cause repletion of vitamin D status to sufficient concentrations. Studies demonstrating adequate concentrations for maintaining bone health have placed the optimum serum value between 50 and 80 nmol/l with, with some authorities suggesting that correct value to be around 70–80 nmol/l[10] As the amount of supplement needed to reach this concentration will differ significantly from subject to subject due to the amount of sunlight they are exposed to, either due to clothing or to foreign travel, a large dose may have to administered. Doses of 125 μg and 250 μg daily supplementation reached a plateau for serum 25 (OH)D at around 80 nmol/l over 4 months during the winter, indicating that doses of this magnitude may be required.

A randomised trial might best be conducted in people 'at risk' of T2D, in order to demonstrate a significant effect. Such people

Key learning points

- Vitamin D deficiency and insufficiency are extremely common.
- Animal and human studies suggest that vitamin D deficiency may contribute to β cell dysfunction, insulin resistance and inflammation that may result in T2D.
- A number of large observational studies suggest an association between low vitamin D status or low vitamin D intake and increased incidence of T2D.
- Genetic examination of VDR polymorphisms show an association with glucose intolerance.
- Small intervention studies show that vitamin D supplementation reduces systemic inflammation and improves glucose tolerance.

Current research questions

- Does vitamin D reduce metabolic abnormalities associated with the metabolic syndrome?
- Is Vitamins D2 or D3 supplementation most effective at raising serum concentrations of vitamin D?
- Which methods of supplementation are the most effective, safe and acceptable?
- Does vitamin D supplementation prevent the onset of diabetes in people at high risk, or in those with pre-diabetic conditions?
- Does vitamin D supplementation in people with T2D improve glycaemic control?
- Does vitamin D supplementation reduce the vascular complications of T2D.

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may have to be screened for metabolic syndrome, or perhaps a screening tool such as the recently developed QDSCORE may be useful to identify high risk patients.[72] Alternatively, treating patients with pre-diabetes (impaired fasting glucose or impaired glucose tolerance) may be useful to demonstrate effect.

While interventions to reduce obesity are known to have a major impact on diabetes risk,[73 74] they are costly and labour intensive. Vitamin D supplementation is a cheap, safe and simple intervention. If it can be demonstrated that vitamin D supplementation can reduce the risk of T2D, it may have significant implications for people at risk for development of this potentially devastating long term condition.

MULTIPLE CHOICE QUESTIONS; ANSWERS AFTER THE REFERENCES

1. In people with impaired glucose tolerance, lifestyle change can reduce the risk for development of type 2 diabetes by:

A. 58%
B. 32%
C. 75%
D. 14%

2. Vitamin D deficiency may be a factor in the development of:

A. Huntington's chorea
B. Type 1 diabetes
C. Thyrotoxicosis
D. Alopecia areata

3. Vitamin D insufficiency may contribute to the pathogenesis of type 2 diabetes by:

A. Increasing systemic inflammation
B. Increasing insulin resistance
C. Reducing insulin secretion
D. All of the above

4. The predominant source of vitamin D3 is:

A. Oily fish
B. The effect of sunlight on 7-dehydrocholesterol through the skin
C. Dairy products
D. Vitamin supplementation

5. 5—10 min of direct sunlight exposure to the arms and legs provides the following dose of vitamin D:

A. 3000 IU
B. 50 000 IU
C. 20 000 IU
D. 500 IU

Competing interests None.

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ANSWERS

1. A; 2. B; 3. D; 4. B; 5. A