Vitamin D in the prevention of type 1 diabetes: would increasing food fortification reduce the incidence?

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Abstract

This paper reviews data regarding the role of vitamin D in the genesis of type 1 diabetes (T1DM) and considers the hypothesis that vitamin D deficiency increases the incidence rate of T1DM. Vitamin D has actions on immune cells that would suppress autoimmunity with preservation of anti-infective actions. Geographical latitude and both season of diagnosis and of birth affect case numbers, most likely via the effect of UVB sunlight on vitamin D synthesis. Other factors, such as seasonal viral infections, may be important. Serum concentrations of 25(OH) vitamin D have mostly been found to be lower with diagnosis of T1DM.

Vitamin D deficiency is common, particularly in the UK. From data on vitamin D concentrations in non-diabetic controls in mostly southerly nations this review estimates the population mean serum 25(OH)D concentration associated with low T1DM incidence to be >80 nmol/l. Achieving this in Britain would require supplementing current intake with 1500-2000 IU vitamin D daily. Increased food fortification would be the most effective method. An estimate based on the limited data available suggests this might generate a 25-30% reduction in the incidence of T1DM.

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Introduction

The role of vitamin D in the pathogenesis of autoimmune disease and clinical type 1 diabetes mellitus (T1DM) remains controversial; and what should be done about it even more so. This review considers recent published data from various disciplines that impact on this issue.

The immunomodulatory effect of vitamin D

The histological hallmark of T1DM is inflammatory change in the pancreatic islets with invasion by macrophages, T helper (Th) cells (CD4+) and cytotoxic T cells (CD8+). Immune cells express the nuclear receptor for vitamin D and also the 1α hydroxylase enzyme for synthesis of 1,25 dihydroxyvitamin D (1,25$(OH)_2$D). Vitamin D alters macrophage development from M1 pro-inflammatory phenotype to M2 anti-inflammatory type.[1,2] It inhibits maturation of dendritic cells with reduced antigen presentation. Thus, dendritic cells have reduced capacity to prime CD4+ T cells which otherwise recruit cytotoxic CD8+ cells. The alterations to dendritic cell and macrophage maturation and cytokine production in turn cause a shift from Th1 to Th2 phenotype with less production of (Th1-derived) interferon gamma and interleukin 2 (IL2) which otherwise stimulate antigen-specific macrophages and cytotoxic T lymphocytes to attack the β-cell. Vitamin D also inhibits B cell maturation, memory B cell formation, differentiation into plasma cells and immunoglobulin synthesis including autoantibody generation.[1,2]

Thus, vitamin D down-regulates adaptive immunity. It has anti-inflammatory effects via several mechanisms and suppresses processes involved in autoimmunity. Vitamin D also has antimicrobial properties. Autoimmune disease may be triggered by certain infections and this would seem more likely with vitamin D deficiency.

The pathway of vitamin D action

The nuclear vitamin D receptor (VDR) is found in most cells, functioning as a transcription factor which binds to genomic vitamin D response elements. Four polymorphisms in the VDR gene--*Apa*I, *Bsm*I, *Taq*I and *Fok*I have been associated with risk of T1DM although findings are conflicting.[1-3] This may be due to small sample sizes with low power, differing populations studied, different racial groups and varying definitions of T1DM. *Bsm*I, *Apa*I and *Taq*I are in linkage disequilibrium with each other and with the polyA variable number tandem repeats (VNTR) in the 3'UTR of the VDR gene which contributes to expression. PolyA variants (short vs long regions) are associated with differences in VDR activity.[4] The Type 1 Diabetes Genetics Consortium did not find any association of VDR single length polymorphisms (SNPs) with T1DM.[5] Meta-analysis suggests that certain haplotypes contribute to disease susceptibility.[6] The TEDDY study found (following adjustment for HLA-DR-DQ and ancestry) a clear relationship between vitamin D concentration and seroconversion to islet antibody-positive status and that this relationship is modified by polymorphisms at the *Apa*I locus.[7]

Vitamin D binding protein (VDBP) is the main carrier of 1,25$(OH)_2$D in the circulation. Individuals with T1DM have lower circulating concentrations of VDBP; the significance is uncertain.[8]

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Polymorphisms in the VDBP gene alter binding of the vitamin and hence serum 25(OH)D concentrations. Some studies, but not all, show polymorphisms relating to T1DM.[3] Polymorphisms in the two main enzymes of vitamin D activation (25-hydroxylase and 1α-hydroxylase) have also been associated with T1DM.[9]

Thus, there is evidence that alterations in vitamin D activity due to genetic variation influence risk of T1DM. This supports the notion that vitamin D influences the development of T1DM in man.

Season, latitude and T1DM

Most circulating vitamin D (80-90%) is synthesised in the skin from 7-dehydrocholesterol under the influence of ultraviolet (UVB) sunlight. There is a minor contribution from diet: fatty fish (herrings, mackerel, salmon) are the best sources. With limited sunlight exposure vitamin D deficiency is common. Many centres have reported more cases of T1DM diagnosed in winter and fewer in summer, consistent with lower serum vitamin D concentrations in winter due to less sun exposure.[10,11] We and others have found a relationship between season of birth and risk of future T1DM, suggesting an effect during gestation.[10] Data from 51 regions of the world show that populations with low ultraviolet irradiation have a higher incidence of T1DM, strengthening the case that this effect is mediated by vitamin D.[12] In Denmark, increased hours of sun exposure during the mother's pregnancy predicted lower subsequent incidence of childhood T1DM.[13]

International comparisons show a clear relationship between latitude and incidence rate of T1DM. Increased rates of T1DM are observed as distance from the equator increases, most likely due to less sun exposure and lower vitamin D concentrations. There are a few notable exceptions such as Saudi Arabia and Kuwait but in the Middle East lower vitamin D levels have been demonstrated, implying that people restrict their sun exposure.[14,15] Other factors have been proposed to explain this variation in incidence, including seasonal viral infections, enterovirus infection and altered gut microbiota, but none seem as consistently different by season and latitude as sun exposure.

Vitamin D concentrations and T1DM

Circulating vitamin D concentrations in those with T1DM have been compared with those in healthy controls. In newly diagnosed T1DM in Sweden,[16] Italy,[17,18] Australia[19] and India[20] serum 25(OH)D concentrations were lower compared to controls. In American adults, preclinical 25(OH)D concentrations were lower in those who subsequently developed diabetes.[21,22] In those with established diabetes in Kuwait and Qatar T1DM patients had more vitamin D deficiency.[15,23] However, in Finland, Estonia and the US (the DAISY study) vitamin D concentrations did not predict islet antibody positivity or T1DM;[24-26] the same picture was seen in Florida, a "solar rich environment".[27]

The TEDDY study is a large, multinational, observational study of children selected as high risk for T1DM based on their HLA genotype or first-degree relatives with T1DM. The analysis of plasma 25(OH)D and risk of islet autoimmunity included 8,676 children and was controlled for genetic variation (HLA-DR-DQ and ancestry). In that analysis, vitamin D sufficiency (serum ≥50 v <50nmol/l) either in childhood or early infancy (before the age of four months) reduced risk of future islet antibody seropositivity (which strongly predicts T1DM), with odds ratios of 0.68 and 0.59, respectively.[7]

The notion that diabetes might cause low vitamin D levels (reverse causation), perhaps due to pre-diagnosis malaise resulting in less sun exposure, is not supported by longitudinal data from the TEDDY study. These showed consistently low vitamin D levels in those who later became islet antibody positive.[7] Thus, the majority of studies do show that lower serum vitamin D concentrations are associated with development of islet autoimmunity or T1DM.

Prevalence of vitamin D deficiency and relationship to intake in the UK, US and Scandinavia

Information on vitamin D intake and serum 25(OH)D concentrations in the UK is available from the National Diet and Nutrition Survey (NDNS), with the most recent published data collected between 2008 and 2012.[28] Despite fish having the highest vitamin D content, meat and meat products made the greatest contribution to vitamin D intake at all ages except in children below the age of three years where milk/milk products were the major source.

The UK daily intake of vitamin D was 300-400 IU (7·5-10ug)/day in those under the age of 18 months who were not breast fed (infant formula milk is vitamin D fortified) but under 130 IU/day in those who were breast fed. For children up to 18 years of age intake was <110 IU/day. Adults managed 150IU/day, with the elderly (>65 years) achieving intakes >200 IU/day due to more supplement use. Reference Nutrient Intake (which is 2SD above the estimated average requirement such that 97.5% of the population receive sufficient) has been set at 340 IU/day for infants 0-6 months of age, 280 IU for those aged 7 months to 3 years and 400 IU for people over the age of 65 years by the Committee on Medical Aspects of Food Policy, Department of Health, 1991.[28] Intake clearly falls short of this so since 2016 a 10ug (400 IU)/day supplement has been recommended for children below the age of 5 years (other than those given infant formula milk) and for all adults between October and March.[28]

Of the intakes assessed in the NDNS, 6% of those aged 5-11 months had serum 25(OH)D concentrations <25nmol/l (all of them breast feeding) and 2% had levels this low at 12-18 months. At age 4-18 years the mean serum 25(OH)D was 52.3 and 48 nmol/l in boys and girls, respectively. But 12.3% of boys and 15·6% of girls had 25(OH)D <25nmol/l. Higher proportions of individuals with circulating 25(OH)D concentrations <25nmol/l were seen in adults and the elderly.

In the US, data from NHANES 1988-2010 show mean serum 25(OH)D concentrations to be >60nmol/l, with a 5-6nmol/l increase from 2007 to 2010. Overall, 14-18% had serum 25(OH)D <40nmol/l, with substantial racial variation.[29] Some milk products in the US and Canada are fortified at 1ug (40 U) vitamin D per 100ml. Fulgoni estimated median vitamin D intake from all sources at 6ug (240U)/day.[30]

In Sweden a serum 25(OH)D concentration of 50nmol/l is recommended. In children aged 1-18 years from 1982-2013 some 34% were below this level, with 3% <25nmol/l.[31] The national average dietary requirement is 7.5ug (300 IU)/day. In 2014 only

16% of children aged 10-12 years achieved this.[32] There was some fortification of food in Sweden, some mandatory, some voluntary. Mandatory fortification of fluid milk products was substantially extended from autumn 2016.

Thus, vitamin D deficiency is common, particularly at northern latitudes. This is not only due to insufficient sun exposure. Oral intake (diet plus any supplements taken) is often below recommended levels.

The effect of dietary supplementation in early life

There are no prospective randomised controlled trials (RCTs) of the effect of vitamin D on T1DM incidence but retrospective cohort comparisons have been made. In northern Finland, taking 2000 IU of vitamin D daily in the first year of life reduced the risk of T1DM by the age of 21 years, with a relative risk (RR) of 0.12.[33] In a EURODIAB multicentre analysis involving seven nations oral vitamin D supplementation given in early childhood reduced the risk of T1DM before the age of 15 years by one third.[34]

In Norway, Stene and colleagues found that taking cod liver oil (CLO) during the first year of life reduced the incidence of T1DM (OR 0·74) but vitamin D supplements did not. Maternal use of CLO or vitamins during pregnancy was not beneficial.[35] In a previous smaller study the same group found that CLO during pregnancy did reduce the risk of T1DM before the age of 15 years (OR 0·30).[36] CLO is a significant source of vitamin D (10ug/5ml) and the long chain n3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Mothers' use of multivitamin supplements (5ug vitamin D per tablet) during pregnancy did not influence the future incidence of T1DM in their offspring. The authors suggest that reporting of multivitamin intake was less reliable. Also, CLO is likely to provide more vitamin D. Others found that maternal intake of vitamin D reduced diabetes-associated autoantibodies in the child at 1 year and 4 years.[37,38] EPA and DHA had no effect. However, a study from Finland did not show this association with autoantibodies or overt T1DM in the children.[39] Measurement of serum 25(OH)D concentrations showed that low levels in late pregnancy increase the risk of future childhood T1DM.[40]

Overall, enough positive studies make it difficult to dismiss a link between vitamin D in early life and subsequent childhood T1DM. These results are consistent with the finding that season of birth, by affecting gestational vitamin D levels, is also influential.[10] However, breast feeding protects against future T1DM[41] even though breast fed infants have lower vitamin D levels than those on infant formula milk (which is supplemented with vitamin D).[28] This discrepancy is not explained. It may relate to other factors associated with breast feeding which protect against T1DM.

For many years vitamin D has been added to some fat spreads (7.5 ug/100g), breakfast cereals (4.2 ug/100g) and infant formula milk in the UK.[28] Since the prevalence of vitamin D deficiency remains so high this measure is clearly insufficient to influence the incidence of T1DM. Mandatory food fortification was introduced in Finland in 2002/3, with vitamin D added to fat spreads (10ug/100g), fluid milk products and cereal-based drinks (0.5ug/100g).Serum vitamin D concentrations in children in Finland increased from 69.3$\pm$1.0 nmol/l in 1998-2002 to 84.9$\pm$1.3 nmol/l in 2003-2006 following food fortification and this was associated with a plateau in the T1DM incidence rate.[42] In 2010 the amount to be added was doubled. In adults >30 years of age who took fortified milk products but no additional supplements the mean increase (from 2011 to 2000) in serum 25(OH)D was 20nmol/l. In all, 91% of these individuals reached serum 25(OH)D concentration >50nmol/l (mean 65.2 nmol/l). Serum 25(OH)D concentrations improved most in subjects with low baseline vitamin D deficiency (<30nmol/l) and least in those who were already vitamin replete (>50nmol/l).[43]

Thus, further food fortification with vitamin D is practical and effective in raising D levels.

Recent changes in the incidence rate of T1DM

Incidence rates of T1DM are changing: some high-incidence countries, including Ireland, Sweden and Norway, report a slowing.[44-46] Rates in the US (for those aged 0-19 years) increased 1.8% annually from 2002 to 2012, up to 21.7 per 10^5 person-years in 2011-12,[47] but by 2021 were estimated at only 22.2 per 105 person-years.[48] Finland reported a reduction in the incidence rate from 57.9 in 2003-2006 to 52.2 cases per 10^5 person-years in 2015-18.[49] In Wales, modelling indicates the incidence rate has peaked and now shows a modest decline.[10] The change occurred earlier in the youngest-onset patients, in the same way that the youngest patients previously seemed to lead the rise in rates.

Vitamin D data offer two potential explanations for changing rates, related to the two sources of vitamin D. Since most vitamin D comes from sunlight exposure, climate change may have a role. Data from the Meteorological Office show more hours of sunlight in Wales progressively since 1980.[10] While this represents an increase of only two hours per week, the duration of sun exposure required to increase vitamin D level is only minutes.[50,51] The mean daily temperature has also increased, encouraging more time outdoors.

Increased intake of vitamin D through food fortification in Finland has been followed by reduced rates of T1DM.[42] In the US, increasing supplement use has been associated with higher serum vitamin D concentrations since 2007[29] and now with a slower rise in incidence, as described above. In Britain GPs have increasingly recognised the high prevalence of deficiency. Prescriptions of vitamin D have risen from 2 to 27 million over the past 18 years.[52] However, intake in the UK, even with supplements as recommended since 2016 (see above), will remain modest.[28] The Endocrine Society Practice Guidelines (USA) recommend 400-1000 IU/day up to age 18 and 1500-2000 IU/day for adults, including pregnant and lactating women.[53] Central European and Polish recommendations are similar but advise 2000 IU/day in adults and during pregnancy and breast feeding.[54,55]

What plasma level of vitamin D might optimally suppress islet autoimmunity and what dietary intake is required to achieve this?

Circulating 25(OH)D concentrations in control groups who did not develop T1DM in Sweden,[16] Italy,[17,18] Australia,[19] India[20] and the

US[21,22] had a weighted mean 25(OH)D concentration of 83.7 nmol/l. Similar levels for prevention have been suggested elsewhere.[16,53] However, the UK SACN has selected 25 nmol/l as the target plasma 25(OH)D concentration for bone health.[28] The recommended level is 40-50 nmol/l in the US and Canada (Institute of Medicine), Europe (European Food Safety Authority), Germany, Austria & Switzerland (DACH) and Nordic European countries (NORDEN).[56] It seems likely that the levels of vitamin D required for bone health are lower than those which suppress autoimmunity.

Comparing measured serum vitamin D levels in Britain with those seen in non-diabetic controls from lower latitudes, in the UK we need to increase our population vitamin D levels from a median of 45-50 to >80 nmol/l. Studies of dietary supplementation indicate that 100 IU of vitamin D supplement increases serum vitamin D concentration by 1.7-2.5 nmol/l. Thus, to achieve levels of >80nmol/l, 1500-2000 units of vitamin D per day above current intake are needed. Such estimates are of necessity rather broad brush owing to limited knowledge of the distribution of vitamin D levels in the population, individual differences in sunlight exposure, varying absorption and efficacy from different foods and different baseline vitamin concentrations; also because of variation in types and quantity of food consumed between individuals and different age groups.

The recently published VITAL RCT randomised males >50 years and females >55 years of age to vitamin D 2000 IU/day or placebo, with incidence of any autoimmune disease as an endpoint.[57] Autoimmune disease was reduced (HR 0.78) by vitamin D over the course of 5.3 years. The VITAL study found consistent effects across all autoimmune diseases, and that effects increased over time.

The only reliably documented adverse effect of vitamin D is hypercalcaemia. Case reports of vitamin D toxicity are associated with serum 25(OH)D concentrations >300 nmol/l and more usually 600-1000 nmol/l.[28] The US Academy of Sciences Institute of Medicine reports that supplementation up to 10,000IU of vitamin D per day is safe and tolerable in adults.[58]

What reduction in the incidence rate of T1DM might be achievable?

Based on our seasonal data, if we saw summertime case numbers of T1DM all year round this would give a 10% reduction in annual incidence rate.[10] Further, we can look at the vitamin D levels in patients from nations closer to the equator where incidence rates are lower. 25(OH)D levels of 74.1 in Italy,[18] 91.4 in Australia[19] and 72.5 and 97.0 nmol/l in the US[21,22] are associated with incidence rates of 19.7,[59] 25.0[60] and 21.7[47] cases per 10^5 person-years, respectively. If serum 25(OH)D concentrations in Wales were increased to these levels we might expect to achieve similar incidence rates: this would represent a reduction from the current 30 (per 10^5 person-years aged under 15 years) in Wales by 25-30%. Alternatively, analysis of serum 25(OH)D concentrations in the TEDDY study indicated that a 5 nmol/l increase in serum 25(OH)D would reduce the risk of seroconversion to islet antibody positive with odds ratio 0.93 (all subjects, irrespective of vitamin D sufficiency).[7] Thus, an increase in 25(OH)D levels of 30 nmol/l might be expected to reduce the rate from 30 to 19.4 new cases per 10^5 person-years. There is considerable uncertainty attached to such estimates.

Key messages

- Data from multiple disciplines suggest that vitamin D suppresses autoimmunity
- Plasma 25(OH) vitamin D concentrations are low in the UK
- Food fortification with vitamin D offers a safe and effective means of raising intake and is the method most likely to achieve a broad population increase in plasma levels
- From published data one can estimate this could result in a 25-30% reduction in the incidence of T1DM

Conclusions

This review suggests that a substantially higher vitamin D intake is needed in Britain to reduce rates of T1DM and perhaps other autoimmune conditions. A similar policy is being implemented in Finland, where a reduction in incidence of T1DM has now been reported. A prospective RCT to prove the link to T1DM has been widely recommended but has not been achieved and may be impossible owing to the relatively low incidence rate of T1DM in the general population. However, the VITAL study (above) provides RCT support for the hypothesis.

Evidence continues to accumulate that increasing vitamin D intake would reduce the incidence of T1DM and other autoimmune diseases. Vitamin D deficiency is common, particularly at northern latitudes. The current rather modest degree of food supplementation and supplement recommendations in the UK address bone health but not autoimmune disease. Food fortification with higher doses of vitamin D would seem to be the best way forward. The recently demonstrated reduction in T1DM incidence in Finland suggests that this approach works. Food fortification should aim to achieve an additional daily intake of 1500-2000 IU in order to obtain median population serum 25(OH)D concentrations >80 nmol/l. Owing to the many variables involved such estimates are of necessity crude but I estimate that a reduction in the incidence of T1DM of 25-30% might be expected. Such calculations are based on limited evidence. Monitoring with case registries will remain important. Increased vitamin D intake may also reduce the incidence of other autoimmune disorders.[2,57]

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