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Type I Diabetes in Children and Vitamin D

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Abbreviations

T1DM – Type 1 Diabetes Mellitus

T2DM – Type 2 Diabetes Mellitus

AAP – American Academy of Pediatrics

HgbA1C – Hemoglobin A1C

What's Known on This Subject:

Type 1 diabetes is increasing in children both nationally and in West Virginia. Vitamin D supplementation early in life has been shown to be protective against the development of type 1 diabetes.

What This Study Adds:

Our systematic literature review gathers an overwhelming amount of evidence regarding the relationship of Type 1 diabetes and vitamin D supplementation. By doing so we are able to encourage further study to clarify the effective dosage of supplementation and to emphasize the potential benefits of providing currently recommended supplementation.

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Abstract

Vitamin D deficiency is associated with multiple childhood diseases including type 1 diabetes mellitus (T1DM). T1DM in children is becoming more prevalent, with a 23% increase nationally from 2001 to 2009. Similarly, West Virginia has had an 8.1% increase in children with type 1 Diabetes from 2008/2009 to 2010/2011. This article highlights the association between vitamin D and type 1 diabetes and discusses vitamin D's potential role in the reduction and management of T1DM in children.

Introduction

The incidence of type 1 diabetes mellitus (T1DM) in children rose 23% nationally between 2001 and 2009.[1] More recently, West Virginia's T1DM in children dramatically rose 8.1% from 2008/2009 to 2010/2011.[2] T1DM is an autoimmune disease that results in the destruction of pancreatic beta cells, resulting in insulin dependence. Multiple genes and environmental factors have been implicated in triggering the onset of T1DM.[3]

A large case control study by the EURODIAB group suggests that regular vitamin D supplementation in childhood can help prevent the development of T1DM characterized by a progressive autoimmune destruction of pancreatic beta cells.[4] Exact mechanisms that confer this protection are not defined but studies suggest that the biologically active form of vitamin D – 1, 25 hydroxyvitamin D3 – is an immunomodulator.[5,6] Vitamin D supplementation reduces lymphocyte proliferation and promotes a shift of type 1 T helper to type 2 T helper cell immune response.[5,6] Therefore, a deficiency of vitamin D may predispose the beta cells to autoimmune destruction.[7-9]

Vitamin D deficiency is common among chronic and newly diagnosed type 1 diabetics.[10] Since vitamin D levels are affected by sun exposure, the fact that multiple studies showed that T1DM is more commonly diagnosed in winter would support an association.[10,11] Studies have also shown a positive correlation between latitude and T1DM diagnosis.[11,12] For West Virginia, our location increases our risk of vitamin D deficiency because little if any cutaneous production of vitamin D occurs from mid-October to mid-March.[12,13] It is worth noting that living in a temperate climate does not automatically confer potential protection against T1DM because sufficient vitamin D levels are needed for protective benefits.[14,15] To account for these geographic differences, multiple groups have recommended vitamin D supplementation. The American Academy of Pediatrics (AAP) in 2008 increased their recommendation for vitamin D supplementation to 400 IU per day for all children beginning in infancy.[16] Compliance with these recommendations is concerning with less than half of infants and children receiving this amount of vitamin D.[17]

This article further explores the literature as it pertains to three aspects of vitamin D and type 1 diabetes. First it considers the finding of vitamin D deficiency at the time of diagnosis of type 1 diabetes. Second, potential effects of vitamin D in the prevention of type 1 diabetes are considered. Finally, the possible importance of vitamin D supplementation in already diagnosed individuals with T1DM is examined.

Methods

The National Library of Medicine Medline database was systematically searched through May 31, 2013 for vitamin D and type 1 diabetes

in children. Search terms included "type 1 diabetes", "vitamin D deficiency", and "childhood vitamin D supplementation." This search resulted in 71 articles which were then screened by all four authors in order to eliminate those dealing with animal studies, adults, type 2 diabetes, genomic analysis and other diseases such as asthma and atopic dermatitis. This resulted in a total of 17 articles remaining that were specific to vitamin D and type 1 diabetes in children (ages 0-20). All 17 of these articles are listed in Table 1 and include meta-analyses, other systematic literature reviews, birth cohort studies, case control studies, randomized control studies and observational studies. Table 1 details each article in regard to the author, year, design, and findings.

Results

An association between vitamin D deficiency and the diagnosis of T1DM was apparent in multiple studies. A German study of 49 newly diagnosed type 1 diabetics within 48 hours of initial hospitalization showed that there was a significant decrease of 1,25 hydroxyvitamin D3 or 1,25(OH)2D3 in the subjects compared to controls without disease (39±2 vs. 55±4 pg/ml).[18] A study of 170 young Qatari children and 170 case controls demonstrated an association between lower levels of Vitamin D and T1DM. There was a significant difference found in the mean level of vitamin D (p= 0.0009).[15] A Swedish study investigated 459 young adults with newly diagnosed T1DM at the time of diagnosis, as well as 138 of those subjects 8 years later. The levels of plasma 25-hydroxyvitamin D was significantly lower in type 1 diabetics than in controls at diagnosis (82.5 vs. 96.7 nmol/l; p<0.0001) and eight years later plasma levels had continued to decrease in children with T1DM.[19] Interestingly, there was no relationship between the documented vitamin D levels and HgA1C suggesting that vitamin D has no influence on blood glucose control. On a similar note, another study aimed to assess whether the degree of diabetic control has an association with Vitamin D. Patients with established T1DM were categorized as either controlled or poorly controlled diabetics and the level of Vitamin D was not found to be significantly different. [20] A study in Italy revealed lower levels of both 1,25 – (OH)2D3 and 25-(OH) D3 in 88 newly diagnosed type 1 diabetics compared to controls living in the same geographical areas.[6] Similarly a Northern Indian study evaluated the Vitamin D levels of 50 recently diagnosed children.[14] The mean levels of vitamin D were significantly lower in these cases (20.02±10.63 ng/ml, 50.05±26.57 mmol/l) compared with the 50 control children. Of these children with significantly low Vitamin D levels, 33 (66%) had presented in significant ketoacidosis. Contrary to the multiple studies showing an inverse association between

Table 1.

REFERENCE	AUTHOR	YEAR	DESIGN	FINDINGS
4	EURODIAB Study Group	1999	Case control study	• 7 centers in Europe studied 820 T1DM patients aged birth to 14 and 2335 controls • Found Vitamin D supplementation in infancy was associated with a decreased risk of developing T1DM. Combined odds ratio of children was 0.67
6	Pozzilli, P. et al.	2005	Surveillance study	• 88 consecutive newly diagnosed T1DM and in 57 healthy age and sex matched subjects • Mean levels of both 25OHD3 and 1,25OH2D3 were significantly lower in patients compared to controls ($p<0.01$ and $p<0.03$, respectively)
10	Janner, M. et al.	2010	Prospective cross sectional study	• 129 diabetic youth • The vitamin D levels of diabetics showed marked seasonal fluctuations, but no relationship to diabetic control.
11	Alemzadeh, R. et al.	2008	Retrospective Case-cohort	• 127 children and adolescents (ages 6.0-17.9 years) who met the criteria for obesity (BMI >95th percentile) • Although mean serum glucose levels and HbA1c were similar among groups, serum insulin levels were slightly highers in the *hypovitaminosis D* group than in the vitamin D-sufficient group, but did not reach statisitical significance
14	Borkar, V.V. et al.	2010	Cross sectional case control study	• 50 children aged 6-12 years within one week of diagnosis of T1DM and in 50 healthy children • Mean levels of Vitamin D were significantly lower in patients compared to their controls [20.02 ± 10.63 ng/ml vs. 26.16 ± 12.28 ng/ml, $p = 0.009$]
15	Bener, A. et al.	2009	Matched case-control study	• Studied 170 diabetics and 170 controls of male and female Qatari children (less than 16 years old) • Vitamin D deficiency was considerably higher in T1DM children (90.6%) compared to controls (85.3%) • There was a significant difference found in the mean value of Vitamin D between T1DM and non-diabetic children ($p=0.009$). • Vitamin D supplementation with breast milk was very poor in diabetic children (47.7%). • Family history of Vit. D deficiency was higher in diabetics compared to non-diabetics ($p<0.012$).
18	Baumgartl, H.J. et al.	1991		• 49 recently diagnosed diabetics were compared with 42 healthy controls • A marked decrease of 1,25OH2D3 was found at the onset of diagnosis compared to normal controls ($p <0.01$). • Grouping of patients according to season demonstrated that the decrease of 1,25OH2D3 was present primarily during the summer months and likely due to a loss of seasonal rhythm of this hormone observed in healthy controls ($p<0.001$)
19	Littorin, B. et al.	2006	Cross sectional study	• Plasma 25OHD3 levels were measured in 459 patients at the time of diagnosis and in 138 of those patients 8 years later • At diagnosis, plasma 25OHD3 were signficantly lower in patients with T1DM than in controls ($p<0.0001$). • 8 years later, plasma 25OHD3 had decreased in patients ($p=0.04$). • Plasma levels of 25OHD3 were significantly lower in diabetic males than females at diagnosis and followup ($p<0.0001$ and $p=0.048$, respectively)

REFERENCE	AUTHOR	YEAR	DESIGN	FINDINGS
20	Simmons, J. et al.	2011	Cross sectional study	• 57 adolescents with T1DM who had HbA1c > 9% (unfavorable control) and <9% (favorable control). • Study revealed no difference between HbA1c groups in Vitamin D status. • The prevalence of vitamin D deficiency was similar to that of the general population.
21	Mutlu, A. et al.	2011	Cross sectional study	• Evaluated 120 children and adolescents (aged 3-20) levels of 25OHD, Parathyroid hormone, and Alkaline phosphatase, as well as A1c and daily insulin requirements. • Controls were more likely to be Vitamin D deficient, compared to only 21.7% T1DM patients. • There were no correlations between insulin requirements and 25OHD level.
22	Zipitis, C.S. and A.K. Akobeng	2008	Meta-analysis	• Total number of participants was 1429 cases and 5026 controls Data from the case control studies showed risk of T1DM was significantly reduced in infants who were supplemented with Vitamin D compared to those who were not (pooled odds ratio 0.71, 95% CI 0.60 to 0.84)
23	Hypponen, E. et al.	2001	Birth cohort study	• 10,821 children were included in the analysis and followed up at one year Vitamin D supplementation was associated with a decreased frequency of T1DM. • Regular vs no supplementation 0.12 (95% CI 0.03-0.51) and irregular vs no supplementation 0.16 (95% CI 0.04-0.74) • Children who regularly took the supplementation had a RR of 0.22 (0.05-0.89) compared to those that received less than the recommended amount.
24	Brekke, H.K. and J. Ludvigsson	2007	Birth cohort study	• 16,070 infants were included at birth, and 11,081 and 8805 at 1 and 2.5 years, respectively • Use of vitamin D associated supplements during pregnancy was associated with a reduced diabetes related autoimmunity at 1 yr (adjusted odds ratio 0.707, p=0.028), but not at 2.5 years
25	Greer, R.M. et al.	2007	Retrospective	• Children and adolescents with diabetes were more than 3x as likely to have vitamin D deficiency as those in the control group
26	Svoren, B.M. et al.	2009	Cross sectional study	• 25OHD3 was measured in 128 youth with T1DM • The majority of youth with T1DM had inadequate levels: insufficiency (61%) or deficiency (15%), with only 24% being sufficient. • Participants with Vitamin D deficiency were significantly older (p<0.001) and had a longer diabetes disease duration (p<0.01) and had lower HbA1c (p=0.05)
27	Frazer, T.E. et al.	1981		• 45 white insulin dependent age 7-18yr diabetics • Circulating 24,25OH2D3 was significantly elevated and 1,25OH2D3 was significantly decreased. • The increase in 24,25OH2D3 was seen in diabetics with the most severe bone loss and maximally increased during the first 5 years of disease
28	Kaur, H. et al.	2011	Cross sectional study	• Vitamin D levels were measured in 517 patients age 8-20 • Retinopathy was more prevalent in patients with vitamin D deficiency (18 vs. 9%, p=0.02). • In logistic regression, retinopathy was associated with vitamin D deficiency (odds ratio 2.12 CI 1.03-4.33), diabetes duration (1.13, 1.05-1.23), and HbA1c (1.24, 1.02-1.50).

vitamin D levels and T1DM, one study showed that vitamin D deficiency was higher in healthy controls as compared to diabetics.[21]

The preponderance of evidence demonstrates that vitamin D deficiency is apparent at the time of diagnosis of T1DM, as well as throughout the course of the disease. This has led to additional studies attempting to determine whether supplementation could potentially prevent TIDM. A systematic review and meta-analysis sought to determine whether or not the development of T1DM was associated with a lack of vitamin D supplementation.[22] This analysis showed that the risk of T1DM was significantly reduced in infants supplemented with vitamin D compared to infants who were not (pooled odds ratio 0.71, 95% CI 0.60 to 0.84). The study also showed some evidence of a dose response, but further research is needed to confirm this finding. A birth cohort study in Finland was done to determine whether dietary vitamin D supplementation was associated with a reduced risk of T1DM.[23] Serum levels were analyzed at birth and again at one year in 10,821 children. Supplementation was associated with a significantly decreased occurrence of T1DM. Children who took any supplementation, regardless of dose, had a lower rate of development of T1DM than children who receive no supplementation. Regular supplementation (400IU) was associated with an 80% reduction of the risk for development of T1DM.[17] The EURODIAB case control study compared 800 T1DM children to 2000 healthy controls and also found that supplementation of vitamin D in infancy decreased the risk of T1DM.[4] The effect was most obvious in patients with a later onset of disease. Notably those who received supplementation for one year or less showed a similar reduction in risk as compared to those with supplementation for a year or longer. Lastly, a study of vitamin D supplementation during infancy with follow up at 1 and 2.5 years was performed to determine the effects of supplementation on development of T1DM. This study also looked at whether consumption of vitamin D during pregnancy had an effect on development of disease in the child.[23] The use of a vitamin D containing supplement during pregnancy was associated with a reduction of diabetes related autoimmunity at 1 year of age, but no difference at 2.5 years of age.

Vitamin D deficiency remains present throughout the course of the disease and in some cases will actually worsen as the duration of illness lengthens. This leads one to consider whether vitamin D supplementation is important in the management of those already diagnosed. A matched case control study evaluated the extent of vitamin D deficiency in populations of children already diagnosed with T1DM.[15] This study showed that vitamin D deficiency was considerably higher in T1DM children (90.6%) compared to non-diabetic children (85.6%). A similar Australian study demonstrated that children and adolescents with T1DM were three times more likely to have a deficiency of vitamin D as compared to the control group.[25] A cross sectional study of adolescents with T1DM determined that participants with a longer duration since diagnosis had more severe vitamin D deficiency.[26] In patients with a preexisting diagnosis of T1DM, circulating levels of inactive 24, 25-(OH) 2D concentrations were significantly elevated; whereas active 1, 25-(OH) 2D3 was significantly decreased. The increase in levels of 24, 25-(OH) 2D was more severe in diabetics with significant bone loss. It was also maximally increased during the first 5 years of clinical disease.[27] Since vitamin D may confer protection through anti-inflammatory effects, retinopathy is a possible complication in diabetics, especially with insufficient vitamin D levels.[28] In a cross sectional study of 157 adolescents aged 8-20 attending diabetes complications assessment services, retinopathy was more common in young adults with T1DM than controls. These results were independent of duration of illness or hemoglobin AIC (HgbA1C).

Discussion

Although there is no vitamin D level that has been established as either protective or predictive for the development of T1DM, multiple studies have demonstrated the importance of vitamin D supplementation early in infancy and childhood and its preventative effects on autoimmune disease. Nearly all of the studies in this review mention that vitamin D acts through immunomodulation and can be preventative in the development of Type 1 diabetes. Some studies have indicated a possible dose dependent response when supplemented in infancy with a greater effect of supplementation from 7-12 months of age versus birth to 6 months.[22]

Another direction of research focuses on whether some individuals are genetically predisposed to a vitamin D deficiency, therefore at greater risk of T1DM. Vitamin D gene receptor polymorphisms have been linked to T1DM that may interfere with absorption of Vitamin D in the gut.[6] Normally, vitamin D leads to a reduction of lymphocyte proliferation and cytokine production in the gut mucosa. Early in infancy, vitamin D helps in the development and maturation of the gut mucosa and limits the exposure to large molecular weight proteins with potentially antigenic properties, such as cow's milk. Thus susceptible individuals may not be able to adequately absorb vitamin D in their diets due to the genetic predisposition leading to T1DM. However, further research is needed to determine the impact of this possible genetic link.

Conclusion

In conclusion, an overwhelming amount of evidence has shown that vitamin D deficiency may be implicated in the development of T1DM in the pediatric population. Furthermore, vitamin D supplementation early in life has shown to be protective against the development of the disease. However, further research is needed to determine the significance of vitamin D levels and supplementation on development and course of T1DM. Evidence of effective dosage of supplementation as well as duration is needed to develop a standard of care for the prevention of this disease. Although the research is inconclusive, it is clear that vitamin D supplementation is recommended and even a modest dose may be beneficial. In light of the fact that Type 1 diabetes is increasing in our pediatric population in West Virginia, it seems we should at least ensure that we are giving the dosage of vitamin D currently recommended by the AAP.

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