Vitamin D supplementation in early childhood and risk of type 1 diabetes: a systematic review and meta-analysis

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CRD summary
This review assessed the possible relationship between vitamin D supplementation in early childhood and reduction of the risk of developing type 1 diabetes. It found evidence, from observational studies, that supplementation may be protective. The authors highlighted the weaknesses in the included studies and their cautious conclusion, that more robust studies are needed to confirm their findings, was appropriate.

Authors' objectives
To explore the possible relationship between vitamin D supplementation in early childhood and reduction in the risk of developing type 1 diabetes.

Searching
MEDLINE, EMBASE, CINAHL and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to June 2007, without language restrictions; search terms were reported. Bibliographies of all retrieved articles were screened for additional studies.

Study selection
Randomised controlled trials and observational studies that assessed the potential association between vitamin D supplementation in early childhood and risk of type 1 diabetes were eligible for inclusion. Cod liver oil was classified as vitamin D supplementation. Observational studies were included if they: compared risk of type 1 diabetes in people who were supplemented with vitamin D versus risk in those who were not supplemented; controlled for potential confounders by participant matching, or used risk adjustment in the analysis; provided sufficient data to calculate relative risks (RRs) or odds ratios (ORs) with 95% confidence intervals (CIs).

All included studies were conducted in Europe (where reported); one study included data from seven countries. All but one of the included studies were case-control studies. Case selection was from national childhood diabetes registers and control selection was from a mixture of clinical settings, population registers and schools. Exposure data were collected by questionnaire or interview. No details were provided for the remaining, cohort study. Confounders considered varied across the studies and included: age; sex; breastfeeding and weaning variables; maternal age; maternal education, maternal use of vitamin D supplements in pregnancy; smoking during pregnancy; drugs taken during pregnancy; type of delivery; low birth weight; study centre; number of siblings; family history of type 1 diabetes; neonatal and most common childhood diseases; history of surgical operations; and severe infections. Most studies included cases up to 15 years of age; one study used a higher cut-off of 30 years.

Studies were independently assessed for inclusion by two reviewers and disagreements were resolved by consensus.

Assessment of study quality
Two reviewers independently assessed the methodological quality of included studies using the Critical Appraisal Skills Programme (PHRU, Oxford, UK) tool for case-control studies. Studies were assigned an overall rating of A (low risk of bias), B (moderate risk of bias), or C (high risk of bias) using criteria published in version 4 of the Cochrane reviewers’ handbook.

Data extraction
Data were extracted to calculate odds ratios for case-control studies and relative risks for the cohort study, with 95% confidence intervals, for the effect of vitamin D supplementation in infancy on development of type I diabetes. Authors were contacted for missing or unclear data.

Two reviewers independently extracted data using a predefined form.
Methods of synthesis
A pooled odds ratio, with 95% confidence intervals, was calculated using the Mantel-Haenszel fixed-effect method. Between study heterogeneity was assessed using the Cochran Q test and by visual inspection of the forest plot.

Results of the review
Five studies, four case-control and one cohort, were included in the review; the total number of participants was unclear. The four case-control studies included a total of 1,528 cases and 5,156 controls. All of the case-control studies were retrospective and open to recall bias. All but one of the case-control studies used “healthy children” as controls and did not confirm diabetes status. None of the studies used an objective method to determine vitamin D status or attempted to quantify the total amount of vitamin D intake from the diet or exposure to the sun. None of the studies included ethnic background as a potential confounder. All included studies were graded B.

Three case control studies, providing ten data sets (n=6455, 1429 cases and 5026 controls), were included in the meta-analysis. The risk of developing type 1 diabetes was significantly reduced in participants who were supplemented with vitamin D (pooled OR 0.71, 95% CI 0.60 to 0.84); there was no evidence of statistically significant heterogeneity. Results were similar for the single cohort study, where the rate risk for regular versus no vitamin D supplementation was 0.12 (95% CI 0.03 to 0.51) and 0.16 (95% CI 0.04 to 0.74) for irregular versus no vitamin D supplementation.

Two studies considered the effect of vitamin D dose and found some evidence of decreasing risk of type 1 diabetes with increasing vitamin D frequency or use of recommended dose. One study considered duration of vitamin D supplementation and found no difference between supplementation for less than or more than one year. One study assessed the timing of vitamin D supplementation and found lower risk in those supplemented between seven and 12 months of age than in those supplemented between zero and six months of age.

Authors’ conclusions
There was evidence from observational studies that vitamin D supplementation in infancy might be protective against the development of type 1 diabetes, but more robust studies are needed to confirm this conclusion.

CRD commentary
The review addressed a clearly stated research question and defined appropriate inclusion criteria. A number of sources were searched for relevant studies and no language restrictions were applied. Robust methods were reported to minimise error and bias in the review process.

Although some details of the included case-control studies were reported and the confounding factors considered by each study were listed, the methods used to adjust for/assess the impact of confounding factors were not reported; variation of confounding factors considered, between studies, and omission of some potentially relevant factors were highlighted by the authors. Only limited details of the single cohort study were reported.

The meta-analysis used was broadly appropriate and the authors’ conclusion was suitably cautious, given the weaknesses of the included studies.

Implications of the review for practice and research
Practice: The authors did not make any recommendations for practice.

Research: The authors stated that adequately powered, randomised controlled trials, with long periods of follow-up, would be required to establish causality between vitamin D status and type 1 diabetes, and to determine the best formulation, dose, duration and period of supplementation with vitamin D.

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