Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study

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Summary

Background Dietary vitamin D supplementation is associated with reduced risk of type 1 diabetes in animals. Our aim was to ascertain whether or not vitamin D supplementation or deficiency in infancy could affect development of type 1 diabetes.

Methods A birth-cohort study was done, in which all pregnant women (n=12 055) in Oulu and Lapland, northern Finland, who were due to give birth in 1966 were enrolled. Data was collected in the first year of life about frequency and dose of vitamin D supplementation and presence of suspected rickets. Our primary outcome measure was diagnosis of type 1 diabetes by end of December, 1997.

Findings 12 058 of 12 231 represented live births, and 10 821 (91% of those alive) children were followed-up at age 1 year. Of the 10 366 children included in analyses, 81 were diagnosed with diabetes during the study. Vitamin D supplementation was associated with a decreased frequency of type 1 diabetes when adjusted for neonatal, anthropometric, and social characteristics (rate ratio [RR] for regular *vs* no supplementation 0·12, 95% CI 0·03–0·51, and irregular *vs* no supplementation 0·16, 0·04–0·74. Children who regularly took the recommended dose of vitamin D (2000 IU daily) had a RR of 0·22 (0·05–0·89) compared with those who regularly received less than the recommended amount. Children suspected of having rickets during the first year of life had a RR of 3·0 (1·0–9·0) compared with those without such a suspicion.

Interpretation Dietary vitamin D supplementation is associated with reduced risk of type 1 diabetes. Ensuring adequate vitamin D supplementation for infants could help to reverse the increasing trend in the incidence of type 1 diabetes.

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Introduction

Exactly what causes the destruction of insulin secreting β cells in the pancreas, and thus the development of type 1 diabetes, remains unknown, though cytokines, T cells, and macrophages have all been implicated.[1] In vitro, vitamin D acts as an immunosuppressive agent, reducing lymphocyte proliferation and cytokine production.[2] Furthermore, in animals, the administration of vitamin D ($1,25\ (OH)_2D_3$) seems to prevent development of type 1 diabetes.[3,4]

Factors in infancy can affect the risk of development of diabetes in later life. The results of a large case-control study suggest that vitamin D supplementation during early childhood can prevent type 1 diabetes.[5] Another study also found an inverse relation between maternal use of cod liver oil during pregnancy and the frequency of type 1 diabetes in their children.[6] Our aim was to ascertain whether or not dietary supplementation with vitamin D in infancy could reduce the risk of type 1 diabetes.

Methods

Participants

All women (n=12 055) living in Oulu and Lapland, northern Finland, whose pregnancy continued after the 24th week of gestation, and for whom the estimated date of delivery fell during 1966 were enrolled.[7] Between the 24th and 28th week of gestation, the women were asked to fill in a questionnaire to obtain background information. A questionnaire about the birth and the status of the neonate was filled in by the attending midwife.[7] 12 058 children were born alive out of 12 231 births. 10 821 (91% of those alive) children were followed up at age 1 year.[8] Data obtained during the children's visits to child welfare centres (on average 10 visits during the first year) was supplemented with information recorded at examinations done by public-health nurses and family doctors. Written consent from all children was asked for in connection with a follow-up survey done in 1997–98. Permission to collect outcome data using national registers was obtained form the ministry of social welfare and health. The ethics committee of the faculty of medicine, University of Oulu, approved the study.

Protocol

Frequency of vitamin D supplementation in the first year of life was recorded as regular, irregular, or none, on the basis of information provided by the mothers of the infants. Information on rickets, suspected by the health-care personnel, was obtained from the child's health records. The daily dose of vitamin D dependent on the product used was calculated, and we noted whether it was below (<2000 IU daily), within (2000 IU daily), or above (>2000 IU daily) the recommended dose. 84 children who were given cod liver oil were classified as having received the recommended dose. Information was available on whether a child had received an increased dose of vitamin D during the first year of life. However, data on serum concentrations of 25 $(OH)\ D_3$ were not available.

The main outcome measure of our study was a diagnosis of type 1 diabetes by end of December, 1997. We identified children who developed diabetes by matching their personal identification numbers with records held on the Central Drug Register of the Finnish Social Insurance Institution.[9] If individuals were diagnosed with diabetes at age 20 years or older, we checked hospital discharge registers, or medical files, or both to exclude type 2 diabetes. We followed up individuals until they were diagnosed with diabetes (n=81), emigrated (n=565), or died (n=215), or until the end of the study. We used the national cause of death register, maintained by Statistics Finland, to identify those who died.

Statistical analysis

We did analyses based on data amassed when children were aged 7–24 months (median 12).[10] For 96% of children, data were collected at age 11·5 months or later. 455 children were excluded from analysis, either because they declined to let us use their information (83), or due to lack of information about their use of vitamin D supplements (372). We calculated the incidence of type 1 diabetes dependent on vitamin D intake and occurrence of rickets, and stratified results according to background factors. We assessed the effect of exposures on the risk of type 1 diabetes with single and multiple term Cox-proportional hazards analyses. Infant age at the 1–year follow-up visit was included as a covariate in all models that contained growth rate in infancy. As a measure of birthweight standardised for gestational age, we used SD units (z scores), which give a sex–specific mean birthweight for the corresponding gestational week (based on last menstrual period). To avoid random variation in birthweight, caused by small numbers, we fitted a locally weighted scatterplot smoother to follow individual birthweights for gestational age assuming a normal distribution.[11] Growth rate (g per month) in infancy was standardised for age at time of 1-year follow up visit and determined for those children who had weight measured between 9 and 15 months of age. Standardised birthweight and growth were analysed by quartiles. Statistical analysis was done with STATA software (version 6).

Results

9124 (88·0%) children were given vitamin D supplements regularly, and 1210 (11·7%) irregularly. 32 (0·3%) infants were not given vitamin D. Of those who received vitamin D regularly, 8582 (94%) had the recommended daily amount, and 434 (5%) and 71 (1%) received more or less than the recommended amount, respectively. In the first year of life, 216 (2%) children who took vitamin D had suspected rickets (table 1). Of these, dietary supplementation was irregular in 56 (26%), and 132 (61%) had received an increased dose of the vitamin before age 1 year. Less educated mothers were more likely to irregularly supplement their children's diets with vitamin D than were well educated mothers (14% [928] *vs* 8% [263], p<0·001). Furthermore, the more children that a woman had, or the older she was, the more likely she seemed to be to irregularly supplement her child's diet (data not shown).

81 children were diagnosed with type 1 diabetes before 1998 (table 1). The median age at diagnosis was 14 years (range 1–31). Table 2 shows that children who took

	Total	No vitamin D supplementation	Low dose vitamin D*	High dose of vitamin D*	Suspected rickets	Diabetes
Total	10 366 (100%)	32 (0·3%)	71 (0·7%)	434 (4·8%)	216 (2·1%)	81 (0·8%)
Boys	5243 (51%)	15 (0·3%)	37 (0·8%)	219 (4·8%)	126 (2·4%)	45 (0·9%)
Girls	5123 (49%)	17 (0·3%)	34 (0·8%)	215 (4·7%)	90 (1·8%)	36 (0·7%)
Education of mother						
None/basic	6860 (66%)	24 (0·4%)	39 (0·7%)	295 (5·0%)	154 (2·2%)	62 (0·9%)
More than basic	3352 (33%)	7 (0·2%)	22 (0·7%)	136 (4·4%)	60 (1·8%)	18 (0·5%)
Unknown	154 (1%)	1 (0·7%)	10 (7·5%)	3 (2·2%)	2 (1·3%)	1 (0·7%)
Age (years) of mother						
<20	736 (7%)	1 (0·1%)	5 (0·7%)	28 (4·2%)	13 (1·8 %)	4 (0·5%)
20–30	5895 (57%)	15 (0·3%)	46 (0·9%)	251 (4·7%)	111 (1·9%)	48 (0·8%)
>30	3735 (36%)	16 (0·4%)	20 (0·6%)	155 (4·9%)	92 (2·5%)	29 (0·8%)
Parity†						
1	3281 (32%)	3 (0·1%)	21 (0·7%)	152 (4·9%)	56 (1·7%)	27 (0·8%)
2–3	4189 (40%)	10 (0·2%)	34 (0·9%)	164 (4·4%)	84 (2·0%)	26 (0·6%)
>3	2884 (28%)	19 (0·7%)	16 (0·7%)	118 (5·2%)	76 (2·6%)	28 (1·0%)
Unknown	12 (0·1%)	..	..	..	..	..
Gestational age (weeks)						
<38 (premature	841 (8%)	2 (0·2%)	10 (1·3%)	33 (4·3%)	20 (2·4%)	9 (1·1%)
38–41	7264 (70%)	24 (0·3%)	50 (0·8%)	320 (5·0%)	145 (2·0%)	58 (0·8%)
>41	1906 (18%)	6 (0·3%)	10 (0·6%)	61 (3·6%)	48 (2·5%)	12 (0·6%)
Unknown	355 (4%)	..	1 (0·3%)	20 (6·6%)	3 (9%)	2 (0·6%)
Standardised birthweight‡						
Lowest quartile	2503 (24%)	1 (0·04%)	15 (0·7%)	92 (4·1%)	60 (2·4%)	18 (0·7%)
Middle quartiles	5006 (48%)	22 (0·4%)	36 (0·8%)	207 (4·7%)	102 (2·0%)	42 (0·8%)
Highest quartile	2502 (24%)	9 (0·4%)	19 (0·9%)	115 (5·3%)	51 (2·0%)	19 (0·8%)
Unknown	355 (4%)	0	1 (0·3%)	20 (6·6%)	3 (9%)	2 (0·6%)
Standardised growth-rate in infancy‡						
Lowest quartile	2413 (23%)	13 (0·5%)	24 (1·1%)	95 (4·5%)	61 (2·5%)	14 (0·6%)
Middle quartiles	4823 (47%)	14 (0·3%)	23 (0·5%)	200 (4·7%)	94 (2·0%)	41 (0·8%)
Highest quartile	2403 (23%)	3 (0·1%)	18 (0·9%)	106 (5·0%)	45 (1·9%)	24 (1·0%)
Unknown	727 (7%)	2 (0·3%)	6 (1·0%)	33 (5·5%)	16 (2·2%)	2 (0·3%)

*In children who regularly took vitamin D; †At child's birth (includes stillbirths); ‡Birthweight standardised for gestational age, and growth rate (g/month) for age at measurement.

Table 1: **Characteristics of cohort**

	Type 1 diabetes	Time at risk (years)	Incidence per 100 000 years at risk	RR (95% CI)	Adjusted RR (95% CI)*
Use of vitamin D supplements					
None	2	981	204	1 (reference)	1 (reference)
Irregularly	12	36 143	33	0·16 (0·04–0·72)	0·16 (0·04–0·74)
Regularly	67	276 235	24	0·12 (0·03–0·47)	0·12 (0·03–0·51)
Dose of vitamin D†					
Low	2	2 093	96	1 (reference)	1 (reference)
Recommended	63	259 779	24	0·20 (0·05–0·84)	0·22 (0·05–0·89)
High	2	13 245	15	0·14 (0·02–0·97)	0·14 (0·02–1·01)
Suspected rickets‡					
No	77	306 945	25	1 (reference)	1 (reference)
Yes	4	6 414	62	2·6 (1·0–7·2)	3·0 (1·0–9·0)

*Adjusted for sex, neonatal (parity, gestational and maternal age), length of maternal education, social status, and standardised birth weight, and growth rate in infancy (suspected rickets adjusted in addition to the increased dose of vitamin D); †In children recieving vitamin D supplementation regularly.

Table 2: **Incidence rate and rate ratio (RR) of type 1 diabetes by the use of vitamin D supplements and suspected rickets in infancy**

vitamin D, irrespective of dose, had a lower rate of type 1 diabetes than those who did not. In children who received vitamin D supplementation regularly, the risk was reduced by about 80% if the child had received at least the recommended dose compared with those receiving less. Adjustment of results for social factors had only a negligible effect on observed effect estimates (data not shown). However, after adjustment for early growth and, in particular, for increased dose of vitamin D, the association between suspected rickets and type 1 diabetes was strengthened (table 2).

Discussion

Our results suggest that development of type 1 diabetes is associated with low intake of vitamin D and signs of rickets during the first year of life. In view of the fact that vitamin D acts as an immunosuppressive agent,[2,12] and that type 1 diabetes is believed to be an autoimmune disease,[1] these findings are not surprising. To be classified as an autoimmune disease, the progress of the disorder must be slowed down or prevented by immunosuppressive therapy.[13] We believe that vitamin D might somehow inhibit the autoimmune reaction targeted towards the β cells of the pancreas. Furthermore, impairment of immune system functioning by a suboptimum vitamin D status in infancy could have long-term effects on immune responses later in life. Our findings accord with those of two other studies.[5,6] Additionally, Baumgartl and colleagues[14] report that concentrations of 1,25 $(OH)_2D_3$ in the serum measured at matched time points throughout the year are lower in patients newly diagnosed with type 1 diabetes than in healthy controls.

The observed incidence rates in our cohort correspond well with those reported for the time period of the study.[15] Although among the most common chronic diseases in children, type 1 diabetes is relatively rare. Our study was done in Finland, which has the highest reported incidence of type 1 diabetes in the world,[16] and we enrolled a well-defined birth cohort comprising over 10 000 children. However, the number of incident cases, especially in the key exposure categories, was small. As a result, the effect estimates are imprecise. Although the consistency of our finding across all available indicators of vitamin D intake and status provides evidence of a true effect, the absolute magnitude of the effect needs to be further assessed.

Can our results be extrapolated to other populations? Supplementation of vitamin D is beneficial and safe only in people whose biological concentration of the vitamin is less than optimum. In northern Finland there are only 2 h of sun every day in December. Although there are 23 h of daylight every day in June, for most of the year exposure to daylight, and thus vitamin D production in the skin, is low by comparison with more southern areas. Vitamin D supplementation is, therefore, probably more important in this population than in others. However, supplementation with vitamin D is generally recommended for prevention of rickets in breast fed infants,[17] and in a case-control study done in seven European countries, the effect of vitamin D on the risk of type 1 diabetes did not differ between populations.[5] Slow changes in the genetic code cannot explain the steep increase seen in the frequency of type 1 diabetes.[16] However, an increase in the number of susceptibility genes for type 1 diabetes could help explain this trend, especially in northern areas, where immune responses might be impaired because of suboptimum vitamin D status.

Previous reports[5,6] lacked information on the dose of vitamin D in the supplements received by infants. In the Norwegian study,[6] children born to women who took cod liver oil during pregnancy had a reduced risk of type 1 diabetes. However, as mentioned by the researchers, their findings were inconclusive with respect to vitamin D supplementation in infancy. We recorded how regularly vitamin D supplements were taken, and the daily dose received. Furthermore, our information was taken from the childrens' health charts, which are a continuous prospective recording. For a few children, information was probably based on retrospective recall by the mother. However, we believe that the period of recall in these instances would have been short. Inaccuracies in classification on exposure in our study are unlikely to differ between individuals who developed type 1 diabetes and those who did not. Such non-differential misclassification is thus likely to lead to a dilution rather than exaggeration of the effect estimates.

In our study, there was a clear association between several indicators of social status and the practice of giving vitamin D supplements to the infant, which is in line with the healthier diet observed in children of families with higher socioeconomic status than in those with lower status.[18] Reported associations between parental social indicators and the risk of developing type 1 diabetes in children have been inconsistent.[19–21] In our study, a strong association of vitamin D supplementation with the incidence of type 1 diabetes remained even when adjusted for social factors, indicating that the observed finding cannot be accounted for by social confounding.

The recommended daily allowance of vitamin D in Finland for infants is about one tenth of what it was in the 1960s. In 1964 the recommended dose was reduced from 4000–5000 IU to 2000 IU per day,[22] and in 1975 it was further reduced to 1000 IU. In 1992 the dose was reduced again to 400 IU. However, during the 1980s, an increase

in the frequency of rickets occurred in Finland,[23] which cannot be explained by changes in the vitamin D recommendations. Decreased compliance with recommendations of vitamin D supplementation for infants might explain this situation.[23] Furthermore, the constant increase in the incidence of type 1 diabetes seen in Finland during the past decades[15] might be related to the combination of changes in compliance and dose recommendations of vitamin D supplementation for infants. The scientific basis for the current dose recommendation of vitamin D for infants was that it corresponded to the amount of vitamin D in a teaspoon of cod-liver oil, which had long been judged safe and effective in the prevention of rickets.[17,24] As has been suggested for adults,[24] discussions for increasing the current allowance of vitamin D for infants and children might be indicated. However, as vitamin D is potentially toxic, any changes in the recommendations, must be made with caution. We suggest that, before any changes are made, health workers ensure that all infants are receiving at least the amount of vitamin D indicated in the current recommendations.

Contributors

Elina Hyppönen drafted the paper and did statistical analyses. All the co-authors participated in study design, evaluation of results, and writing the manuscript.

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