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Vitamin D supplementation and diabetes-related autoimmunity in the ABIS study

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Abstract: Supplementation with vitamin D during infancy, as well as intake of vitamin D during pregnancy, has been associated with decreased risk of type 1 diabetes or diabetes-related autoantibodies in children. The primary aim of this report was to investigate whether vitamin D supplementation during infancy is associated with diabetes-related autoimmunity at 1 and 2.5 yr in the children. Second, we examined whether consumption of vitamin-D-containing supplements during pregnancy is related to risk of autoimmunity in the offspring. Screening questionnaires were completed for 16 070 infants after delivery, including a food-frequency questionnaire regarding the mother's use of dietary supplements during pregnancy. Parents of 11 081 and 8805 infants completed a follow-up questionnaire regarding the use of vitamin supplementation at 1 and 2.5 yr, respectively. Autoantibodies against glutamic acid decarboxylase and islet antigen-2 (IA-2) were analyzed in whole blood from 8694 children at 1 yr and 7766 children at 2.5 yr. Supplementation with AD-drops was not associated with autoantibodies at 1 or 2.5 yr. Use of vitamin-D-containing supplements during pregnancy was associated with reduced diabetes-related autoimmunity at 1 yr (adjusted odds ratio: 0.707, confidence interval: 0.520–0.962, p = 0.028) but not at 2.5 yr. In conclusion, no association was found between an intermediate dose of vitamin D supplementation during infancy and development of diabetes-related autoantibodies at 1 and 2.5 yr. Use of vitamin-D-containing supplements during pregnancy was associated with reduced development of glutamic acid decarboxylase autoantibodies or IA-2A in the offspring at 1 yr, but not at 2.5 yr.

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Supplementation with vitamin D in infancy has been associated with decreased risk of type 1 diabetes in two studies (1, 2). This finding was not supported by a Norwegian study, although supplementation with cod-liver oil (rich in vitamin D) did have a protective effect against development of type 1 diabetes (3). The protective effect observed by Hypponen et al. (2) was seen at a high dose (50 μg/d), while a relatively low dose was studied by Stene and Joner (3). In Sweden, parents are recommended to give their child AD-drops containing 10 μg of vitamin D per day during the first 5 yr of life. It is not known whether this intermediate dose during infancy protects against diabetes-related autoimmunity in children.

Use of cod-liver oil during pregnancy has also been associated with reduced risk of type 1 diabetes in the offspring (4), although this could not be confirmed in the final analysis (3). Maternal intake of vitamin D from food during pregnancy has been associated with reduced risk of islet autoimmunity in children, while vitamin D intake from multivitamin supplements did not associate with appearance of autoantibodies in the offspring (5).

A possible protective effect of vitamin D on risk for developing type 1 diabetes is supported in animal studies (6, 7). Vitamin D acting as an immunosuppressive agent is one suggested mechanism (2).

The ABIS (All Babies in Southeast Sweden) study is a large, prospective, population-based cohort study of children born during 1997–1999. The primary aim of this report is to investigate whether vitamin D supplementation during infancy is associated with diabetes-related autoimmunity at 1 and 2.5 yr in the children.

Second, we examine whether consumption of vitamin-D-containing supplements during pregnancy is related to risk of autoimmunity in the offspring.

Research design and methods

Out of 21 700 invited infants, screening questionnaires were completed for 16 070 infants after delivery. This questionnaire gave information about the newborn infant, family history for disease, and also included a food-frequency questionnaire regarding the mother's dietary intake as well as use of dietary supplements during pregnancy. Parents of 11 081 infants completed a follow-up questionnaire at 1 yr regarding the use of vitamin supplementation, as well as a frequency questionnaire about the infants' dietary intakes during the first year. At 2.5 yr, 8805 parents completed a follow-up questionnaire. Among the group of 11 081 children, there is a slight underrepresentation of younger parents, low education level in the mother, parents of foreign origin, and smoking during pregnancy compared with the 16 070 children participating at birth. This is also the case for the group of 8805 children participating at 2.5 yr. However, family history for type 1 diabetes did not differ between participants and dropouts at baseline, 1 and 2.5 yr.

In the screening questionnaire, the mother answered the following question: 'Did you use any vitamin or mineral supplementation during pregnancy?' (Predefined answers: Yes/No/Do not know) 'If so, what kind did you use?' (Open answer). The vitamin D content of the different brands of vitamin and mineral supplements was later checked upon. The mothers who used vitamin supplements containing $\geq$5 μg of vitamin D were in the analysis compared with those who did not take any supplements.

At the 1 and 2.5 yr follow-up, the following question was asked: 'Did your child receive supplementation with AD-drops?' (Predefined answers: Yes/No/Do not know). AD-drops are a vitamin solution containing 68 μg of cholecalciferol per milliliter.

Autoantibodies against glutamic acid decarboxylase and islet antigen-2 (IA-2) were analyzed in whole blood from 8694 children at 1 yr and 7766 children at 2.5 yr by using an immunoprecipitation method (8). Levels of glutamic acid decarboxylase antibodies (GADAs) or IA-2A above the 95th percentile for healthy children were considered positive. Diabetes-related autoimmunity was defined as being positive for one of the two autoantibodies, or both. At 1 yr, four of the children had developed diabetes. At 2.5 yr, 22 children (0.3%) had developed diabetes.

Statistics

The χ^2-test, *t*-test, and Mann–Whitney *U*-test were used to compare groups. Odds ratios with 95% confidence intervals were estimated using logistic regression. Possible confounders (familial type 1 diabetes, maternal education, maternal age, delivery mode, weight increase from birth, breast-feeding duration, introduction of cow's-milk protein, fish intake) were adjusted for in the analysis.

SPSS for Windows (version 11.5.1, 2002, Chicago, IL, USA) was used for all statistical analysis.

Ethics

This study was part of the ABIS study, which has been approved by the Research Ethics Committees of the Faculty of Health Sciences, Linköping University, and the Medical Faculty of Lund University. Mothers gave their consent after careful written and oral information and information via videotape was provided.

Results

Ninety-nine percent of the infants had been given AD-drops during the first year and 87.8% at the 2.5-yr follow-up. Nonsupplementation at 2.5 yr was significantly associated with shorter breast-feeding duration but not with socioeconomic factors such as the parents' education, marital status, age, or ethnic background.

At 1 yr, 5.0% were positive for GADA and 4.7% for IA-2A, while 8.9% were positive for GADA and/or IA-2A. At 2.5 yr, 4.6% were positive for GADA and 4.6% for IA-2A, while 8.7% were positive for GADA and/or IA-2A.

Supplementation with AD-drops during the first year was not associated with autoantibodies at 1 yr (Table 1). Supplementation with AD-drops until 2.5 yr of age was not associated with autoantibodies at 2.5 yr (Table 1). The results did not differ in children who were delivered in spring/summer vs. those born in autumn/winter.

Fifty-six percent (56.1%) of the mothers reported use of vitamin or mineral supplementation during pregnancy. Twenty-seven percent (27.2%) took vitamin-D-containing multivitamin supplements. Those who used vitamin-D-containing supplements were of a higher age (30 vs. 29 yr, $p < 0.001$), a higher proportion had >12 yr of education (48 vs. 31%, $p < 0.001$), and a higher proportion had a frequent intake of fish (one or two times per week or more) during pregnancy (35 vs. 28%, $p < 0.001$). They also had a longer breast-feeding duration ($p < 0.001$) and introduced cow's milk later ($p < 0.001$) compared with those who did not take any supplements. Use of vitamin-D-containing supplements during pregnancy was associated with reduced diabetes-related autoimmunity at 1 yr but not at 2.5 yr (Table 1).

Table 1. Association between vitamin D supplementation during infancy, and use of vitamin-D-containing supplements during pregnancy and diabetes-related autoantibodies at the age of 1 and 2.5 yr, respectively

	OR (CI)	Adjusted OR (CI)
Diabetes-related autoantibodies at 1 yr		
Supplementation with AD-drops during the first year	0.864 (0.374–1.996)	0.519 (0.125–2.160)
Use of vitamin-D-containing supplements during pregnancy	0.726 (0.562–0.939) p = 0.015	0.708 (0.520–0.964) p = 0.028
Diabetes-related autoantibodies at 2.5 yr		
Supplementation with AD-drops until 2.5 yr	0.981 (0.749–1.286)	0.939 (0.660–1.334)
Use of vitamin-D-containing supplements during pregnancy	1.102 (0.859–1.414)	1.251 (0.906–1.729)

CI, confidence interval; OR, odds ratio.

Discussion

In Sweden, vitamin D supplementation is normally given in the form of synthetic AD-drops, and the recommended dose is 10 μg of cholecalciferol. Compliance with supplementation with AD-drops in Sweden is high compared with other European countries (9, 10).

In the study by Hypponen et al., children who received the recommended dose of 50 μg/d had a reduced risk of type 1 diabetes compared with those who received less than the recommended dose (2). This dose is five times the recommended level of intake in Sweden (11). In Norway, the recommended intake of cod-liver oil is 5 mL/d (10 μg vitamin D), which showed protective effects in one study (3). It has, however, been speculated if the bioavailability of vitamin D from cod-liver oil could be increased compared with that from other supplements, or that the protective effects are caused by other substances such as long-chain n-3 or n-6 fatty acids (3, 4).

It should be recognized that we had a low power to detect an association between use of AD-drops at 1 yr and diabetes-related autoantibodies since as many as 99% reported use of this supplement. We cannot, therefore, rule out that such an association exists.

Only one study has previously shown an association between intake of vitamin D during pregnancy and autoantibodies in the offspring (5). In our study, none of the mothers used supplements containing vitamin D only and we cannot, therefore, say if the protective effect observed is related to vitamin D *per se* or if it is related to the combination of vitamin D and other vitamins, although other vitamins or minerals without vitamin D did not show this effect. It is also difficult to explain why we observe a protective effect at 1 yr but not at 2.5 yr.

In conclusion, no association was found between an intermediate dose of vitamin D supplementation during infancy and development of diabetes-related autoantibodies at 1 and 2.5 yr. Use of vitamin-D-containing supplements during pregnancy was associated with reduced development of GADA or IA-2A in the offspring at 1 yr, but not at 2.5 yr.

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References

1. The Eurodiab Substudy 2 Study Group. Vitamin D supplement in early childhood and risk for type I (insulin-dependent) diabetes mellitus. Diabetologia 1999: 42: 51–54.
2. Hypponen E, Laara E, Reunanen A, Jarvelin MR, Virtanen SM. Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. Lancet 2001: 358: 1500–1503.
3. Stene LC, Joner G. Use of cod liver oil during the first year of life is associated with lower risk of childhood-onset type 1 diabetes: a large, population-based, case-control study. Am J Clin Nutr 2003: 78: 1128–1134.
4. Stene LC, Ulriksen J, Magnus P, Joner G. Use of cod liver oil during pregnancy associated with lower risk of type I diabetes in the offspring. Diabetologia 2000: 43: 1093–1098.
5. Fronczak CM, Baron AE, Chase HP et al. In utero dietary exposures and risk of islet autoimmunity in children. Diabetes Care 2003: 26: 3237–3242.
6. Mathieu C, Waer M, Laureys J, Rutgeerts O, Bouillon R. Prevention of autoimmune diabetes in NOD mice by 1, 25 dihydroxyvitamin D3. Diabetologia 1994: 37: 552–558.
7. Giulietti A, Gysemans C, Stoffels K et al. Vitamin D deficiency in early life accelerates type 1 diabetes in non-obese diabetic mice. Diabetologia 2004: 47: 451–462.
8. Knip M, Kukko M, Kulmala P et al. Humoral beta-cell autoimmunity in relation to HLA-defined disease susceptibility in preclinical and clinical type 1 diabetes. Am J Med Genet 2002: 115: 48–54.

9. Lande B, Andersen LF, Baerug A et al. Infant feeding practices and associated factors in the first six months of life: the Norwegian infant nutrition survey. Acta Paediatr 2003: 92: 152–161.
10. Freeman V, van't Hof M, Haschke F. Patterns of milk and food intake in infants from birth to age 36 months: the Euro-growth study. J Pediatr Gastroenterol Nutr 2000: 31 (Suppl. 1): S76–S85.
11. Axelsson I, Gebre-medhin M, Hernell O, Jakobsson I, Michaelsen KF, Samuelson G. [The AD-drops can be replaced by D-drops]. Lakartidningen 1999: 96: 2200–2204.