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ARTICLE

Lower levels of plasma 25-hydroxyvitamin D among young adults at diagnosis of autoimmune type 1 diabetes compared with control subjects: results from the nationwide Diabetes Incidence Study in Sweden (DISS)

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Abstract
Aims/hypothesis Low plasma vitamin D concentrations may promote the development of type 1 diabetes. To test this hypothesis, we measured plasma 25-hydroxyvitamin D (25OHD) in young adults with type 1 diabetes.
Methods The nationwide Diabetes Incidence Study in Sweden (DISS) covers 15- to 34-year-old people with newly diagnosed diabetes. Blood samples at diagnosis were collected during the 2-year period 1987/1988. Patients with islet antibodies (islet cell antibodies, GAD antibodies or tyrosine phosphatase-like protein antibodies) were defined as having autoimmune type 1 diabetes. Plasma 25OHD was measured in samples taken from 459 patients at the time of diagnosis, and in 138 of these subjects 8 years later. The results were compared with age- and sex-matched control subjects (n=208).
Results At diagnosis, plasma 25OHD levels were significantly lower in patients with type 1 diabetes than in control subjects (82.5±1.3 vs 96.7±2.0 nmol/l; p<0.0001). Eight years later, plasma 25OHD had decreased in patients

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(81.5±2.6 nmol/l; p=0.04). Plasma 25OHD levels were significantly lower in diabetic men than in diabetic women at diagnosis (77.9±1.4 vs 90.1±2.4 nmol/l; p<0.0001) and at follow-up (77.1±2.8 nmol/l vs 87.2±4.5 nmol/l; p=0.048).
Conclusions/interpretation The plasma 25OHD level was lower at diagnosis of autoimmune type 1 diabetes than in control subjects, and may have a role in the development of type 1 diabetes. Plasma 25OHD levels were lower in men than in women with type 1 diabetes. This difference may be relevant to the high incidence of type 1 diabetes among young adult men.

Keywords 25-Hydroxyvitamin D · 25OHD · Autoimmunity · GADA · IA-2A · ICA · Islet antibodies · Type 1 diabetes · Vitamin D

Abbreviations

25OHD	25-hydroxyvitamin D
DISS	Diabetes Incidence Study in Sweden
GADA	GAD antibodies
IA-2	tyrosine phosphatase-like protein
IA-2A	tyrosine phosphatase-like protein antibodies
ICA	islet cell antibodies

Introduction

Type 1 diabetes is an autoimmune disease and environmental factors contribute to its development [1]. Vitamin D has been associated with type 1 diabetes [2]. Several studies suggest that vitamin D supplementation in early childhood decreases the risk of developing type 1 diabetes [3–5]. Moreover, there is an inverse correlation between vitamin D intake during pregnancy and the presence of islet antibodies in the offspring [6]. This observation suggests an immunological mechanism behind the association between vitamin D and type 1 diabetes. The immunological concept has support from the finding of 1,25-hydroxyvitamin D_3 receptors on monocytes and activated T cells [7]. Also, polymorphism in the vitamin D receptor gene has been shown to be associated with susceptibility to type 1 diabetes [8]. The biologically active form of vitamin D may be a modulator of the immune system [9]. Chemokines produced by beta cells recruit pathogenic [10] and regulatory T cells [11]. A vitamin D analogue has been shown to downregulate the production of proinflammatory chemokines, thereby inhibiting T cell recruitment and the development of type 1 diabetes in NOD mice [12]. Vitamin D deficiency may promote beta cell destruction in humans. Nutritional status with respect to vitamin D is best represented by the circulating concentration of plasma 25-hydroxyvitamin D (25OHD) [13].

There is a high incidence of type 1 diabetes, with a clear male preponderance, among young adults in Sweden [14]. Associations between mean temperature and latitude versus the incidence of type 1 diabetes [15] favour a correlation between sunlight and type 1 diabetes. Latitude can dramatically affect the production of vitamin D_3 in the skin. This implies an association between sunshine and type 1 diabetes, and vitamin D may be the connection. The higher incidence of type 1 diabetes among men as compared with women in Sweden may be related to differences in vitamin D metabolism or sensitivity between sexes.

To assess whether there is an association between vitamin D and autoimmune type 1 diabetes in young adults, we measured plasma 25OHD at the time of diagnosis of autoimmune type 1 diabetes and at follow-up 8 years later. The aim was to test the hypothesis that low plasma vitamin D concentrations are associated with the development of type 1 diabetes in young adults, particularly males.

Subjects and methods

Since 1983, all newly diagnosed 15- to 34-year-old patients with diabetes mellitus in Sweden have been registered prospectively in the nationwide population-based Diabetes Incidence Study in Sweden (DISS) [16]. During a 2-year period (1987/1988), at the time of DISS registration, soon after diagnosis, patients were asked to donate a blood sample for measurement of islet antibodies [17]. Control subjects matched with the probands for age (born on the same day), sex and residence (living in the same county) were also asked to donate blood samples. Samples were taken at random (in terms of time of day) and plasma was collected in EDTA and sent unfrozen by surface mail to a central laboratory. Plasma was frozen at −20°C and stored until analysis. During the 2-year period, plasma samples at the time of diagnosis were obtained from 636 (76%) of 839 registered patients (Fig. 1) and islet antibodies were found in 82% (521 of 636). Among patients with islet antibodies, plasma for determination of 25OHD was available from 88% (459 of 521). Eight years later, all patients were invited to a follow-up study and 312 with islet antibodies at diagnosis accepted [18]. Out of these, a follow-up sample was available in 138 patients (44%) for 25OHD assessment. Plasma samples at follow-up were taken at a median of 8.6 years (range 3.1) after diagnosis. Of the 1,678 control subjects recruited for the study, 280 (17%) donated plasma samples and 208 were available for 25OHD measurement. Participation rates of patients and control subjects are given in Table 1. Assessment of 25OHD was conducted 16–17 years after the diagnosis of diabetes, 7–8 years after

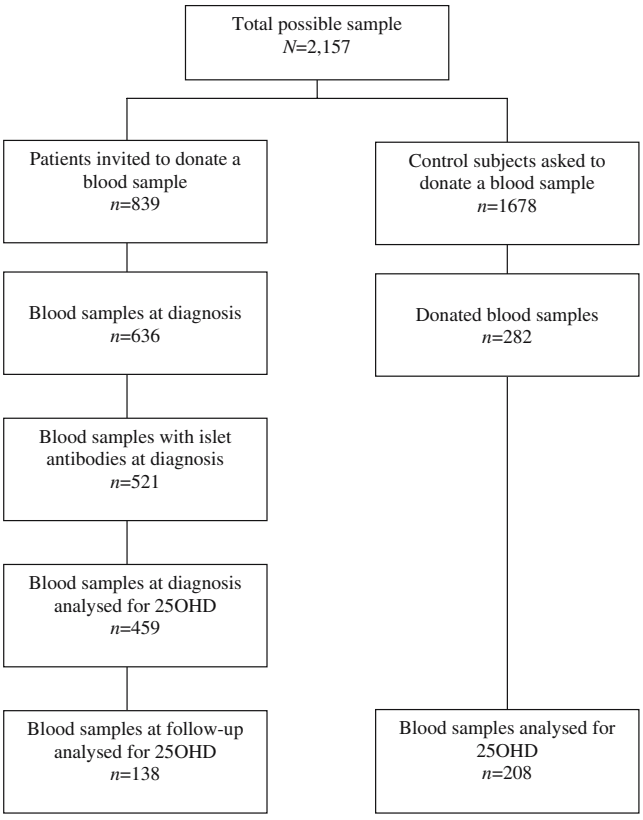

Fig. 1 Flowchart of blood samples in the DISS 87/88 cohort at diagnosis and follow-up

follow-up in patients and 16–17 years after sampling in control subjects.

Laboratory assays

Islet cell antibodies (ICA) were determined by a prolonged immunofluorescence assay [19]. GAD antibodies (GADA) [20] and tyrosine phosphatase-like protein antibodies (IA–2A) [21] were determined by radioligand binding assay based on ^{35}S-methionine labelled human recombinant in vitro transcribed-translated GAD65 and IA-2, respectively. For the patients from whom a blood sample was taken at follow-up, HbA_{1c} was measured by an HPLC method [22]. The normal reference interval was 4.0–5.2%. Different 25OHD assays yield markedly different results [23]. In this study, all analyses were done in the same assay. The plasma concentration of 25OHD was measured by the Nichols Advantage 25OHD assay [24]. This assay is based on chemiluminescence detection and vitamin D binding protein for competitive displacement. The reference range was 25–170 nmol/l and the detection limit 10 nmol/l (4 ng/ml). Reproducibility from four different pools with ranges of 27.5–145 nmol/l yielded a within-run CV of 4.5–3.6%; the total CV was 7.8%. On repeated thawing there was a slight but insignificant increase in the concentration of 25OHD with increasing numbers of thawings, as also shown by others [25].

Statistical analysis

The paired *t* test was used to test for differences between the baseline and follow-up samples, and Student's *t* test (for normally distributed data) or the Mann–Whitney *U* test (for non-normally distributed data) were used for comparisons between patients with diabetes and control subjects. As the plasma 25OHD level covaries with BMI, correction was made by univariate analysis of variance. Differences in frequencies were evaluated with the χ^2 test. Associations between variables were estimated by calculating Pearson's correlation coefficients or Spearman's ρ. Significance was accepted for p values <0.05. Data were analysed using SPSS (Chicago, IL, USA). Results are reported as means±SEM.

Results

At time of diagnosis

Patients were slightly younger than control subjects (p=0.027) and, as expected, there was a male predominance among the patients (Table 2). Close to the time of diagnosis

Table 1 Participation rate and plasma 25OHD at diagnosis in young adults with autoimmune type 1 diabetes and control subjects in public health regions 1–6 in Sweden (region 1 is the southernmost and region 6 the northernmost)

	Public health region						Total
	1	2	3	4	5	6	
Participation rate (%)							
Patients	95	90	94	91	81	83	88
Control subjects	21	20	29	12	18	29	22
25OHD (nmol/l) (mean±SEM)							
Patients	80.4±3.5[a]	83.6±3.5[a]	82.7±3.7[b]	78.1±2.4[c]	85.6±3.1[b]	87.8±5.1[d]	82.5±1.3[c]
Control subjects	96.7±5.5	97.5±4.9	96.6±3.9	99.1±4.5	99.2±4.8	89.7±5.3	96.7±2.0

Test of difference between patients and control subjects: [a] p<0.05; [b] p<0.01; [c] p<0.001; [d] p=0.48

Table 2 Clinical characteristics and plasma 25OHD at diagnosis in young adults with type 1 diabetes vs control subjects (mean±SEM)

Characteristic	Patients (n=459)	Control subjects (n=208)	Test of difference between patients and controls (p value)
Males/females	1.6	1.1	0.016
Age (years)	24.4±0.3	25.6±0.5	0.027
25OHD (nmol/l)			
All	82.5±1.3	96.7±2.0	<0.0001
Males	77.9±1.4[a]	93.9±2.7[b]	<0.0001
Females	90.1±2.4	99.7±2.9	0.014

Test of difference by sex: [a] p<0.0001; [b] p=0.15

of diabetes, plasma 25OHD levels were significantly lower in patients than in control subjects (82.5±1.3 vs 96.7±2.0 nmol/l; p<0.0001; Fig. 2). Amongst patients, the mean concentration of 25OHD was significantly lower in men than in women (77.9±1.4 vs 90.1±2.4 nmol/l; p<0.0001). Furthermore, the mean concentration of 25OHD was significantly (p<0.0001) lower in diabetic men compared with control men, as well as in diabetic women compared with control women (p=0.014). Amongst control subjects, there was no significant difference in plasma 25OHD levels between the sexes.

Figure 3 shows that there was a seasonal fluctuation in plasma 25OHD level, with significantly higher values from June to December compared with January to May, in both patients (p=0.0001) and control subjects (p=0.03). The concentration of 25OHD was significantly (p<0.05) lower in patients compared with control subjects in March, April, May, August, September, October and December. As the seasonal variation of plasma 25OHD was similar in patients and control subjects, this could not explain differences in levels between patients and control subjects. The concentration of 25OHD was not affected by location of residence (Table 1). Besides the northernmost region (87.8±5.1 vs 89.7±5.3 nmol/l; p=0.48), all across Sweden plasma 25OHD levels were significantly lower in patients than in control subjects. The month of blood sampling did not differ between patients and control subjects (p=0.16).

At follow-up 8 years after diagnosis

Among patients with blood samples both at diagnosis and at follow-up, the concentration of 25OHD was lower at follow-up (86.3±2.6 vs 81.5±2.6 nmol; p=0.04). There was a positive correlation between the concentrations of 25OHD at diagnosis and at follow-up (r=0.57; p<0.0001). There was no correlation between the concentration of 25OHD and HbA_{1c} (r=0.042; p=0.62). At follow-up, the concentration of 25OHD was significantly lower in men than in women (77.1±2.8 vs 87.2±4.5 nmol/l; p=0.048).

Discussion

Our study showed that the mean 25OHD level at the time of diagnosis was lower among young adults at the time of diagnosis of type 1 diabetes than among control subjects. The levels in the patients were also lower at follow-up

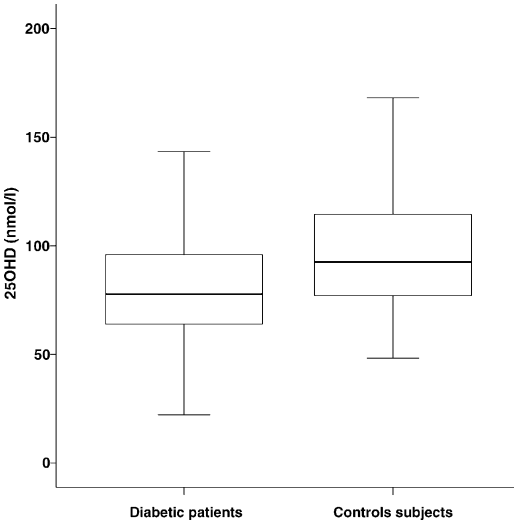

Fig. 2 Box plot of plasma 25OHD levels close to the time of diagnosis in 459 patients with autoimmune type 1 diabetes and 208 control subjects. Data are presented as box-and-whisker plots showing the 10th, 25th, 50th (median), 75th and 90th percentiles

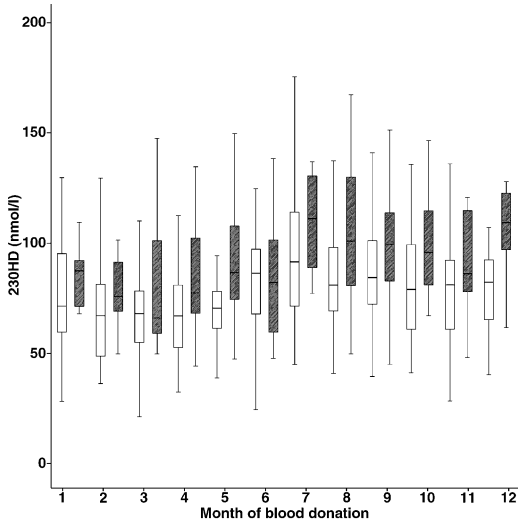

Fig. 3 Box plot of plasma 25OHD levels close to the time of diagnosis in 459 patients with autoimmune type 1 diabetes (*white boxes*) and 208 control subjects (*hatched boxes*) with regard to month of blood donation. Data are presented as box-and-whisker plots showing the 10th, 25th, 50th (median), 75th and 90th percentiles

8 years after diagnosis than at the time of diagnosis. Hence, lower concentrations of 25OHD were consistent in patients with type 1 diabetes. The clearly lower levels of plasma 25OHD in men than in women with type 1 diabetes was another pertinent finding. The discrepancy in 25OHD levels between patients with type 1 diabetes and control subjects was not due to differences in seasonal fluctuations of 25OHD levels between patients and control subjects, neither did the date for blood sampling deviate between patients and control subjects. Hence, we have no reason to believe that factors related to time of the year or geographical variation explain why our patients with type 1 diabetes had low plasma 25OHD levels.

To avoid misclassification, we employed islet antibodies as objective criteria of type 1 diabetes [26–28]. To our knowledge, this is the first study reporting low plasma 25OHD levels in young adult patients with objective type 1 diabetes. Indeed, 54% of patients at diagnosis demonstrated levels of 25OHD below 80 nmol/l, levels regarded as belonging to the interval where vitamin D deficiency should be considered [29]. The lower levels found at diagnosis compared with control subjects support the idea that vitamin D deficiency may be an important factor behind the development of type 1 diabetes, perhaps with an immunological background [6–11].

The lower mean levels of 25OHD in diabetic men compared with diabetic women at diagnosis fits with the concept that vitamin D deficiency might be the reason behind the markedly higher incidence of type 1 diabetes among postpubertal men compared with postpubertal women noted in Sweden [14] and in other populations [30, 31]. The difference in incidence between sexes is not obviously related to HLA [32]. Our study infers that vitamin D is of interest in this context. There was no significant sex difference regarding plasma 25OHD levels in our 208 control subjects. In a large reference group of more than 6,000 individuals, slightly but significantly higher serum 25OHD values were found in men [33], whereas the opposite was observed in our patients with type 1 diabetes. Further studies are clearly warranted to clarify the role of low vitamin D concentrations as a risk factor for the development of type 1 diabetes among young adults, particularly men. It is of special importance to evaluate serum or plasma samples from prediabetic individuals before and after the development of islet antibodies or type 1 diabetes, as in the Diabetes Trial-type 1 [34] or ENDIT [35]. We lack samples collected before the diagnosis of diabetes in our patients. According to the cross-sectional nature of our study, no information was available on plasma 25OHD levels before diagnosis. Our finding of low plasma 25OHD levels soon after the diagnosis of type 1 diabetes underlines vitamin D deficiency as a factor to consider in the pathogenesis of type 1 diabetes. However, we also noted lower plasma 25OHD levels 8 years after diagnosis compared with levels at diagnosis, and there was no correlation between the concentrations of 25OHD and HbA_{1c}. This indicates that the diabetic state per se is a reason for low 25OHD levels and is not secondary to any hyperglycaemic or insulin-resistant state.

In keeping with this, type 2 diabetes has been linked to vitamin D hypovitaminosis [36]. Vitamin D hypovitaminosis seems to inhibit insulin release [37] and increase insulin resistance [33, 38]. Indeed, in a pilot study, vitamin D_3 treatment improved insulin secretion and insulin resistance in patients with type 2 diabetes [39]. Further studies, however, are apparently needed to establish the role of vitamin D in type 2 diabetes. It could be that the initiation of type 1 diabetes is related to low vitamin D concentrations whilst the lowering of 25OHD levels during the years after diagnosis is a consequence of disturbed metabolism due to diabetes. Indeed, this may explain why bone density is lower in type 1 than in type 2 diabetes [40].

In conclusion, young adult patients with type 1 diabetes showed lower 25OHD levels soon after their diagnosis compared with control subjects. In addition, 25OHD levels were clearly lower in men than in women with type 1 diabetes. Lower vitamin D concentrations may contribute to the development of type 1 diabetes, especially in young adult men, who have a particularly high incidence of type 1 diabetes.

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Duality of interest statement P. Blom is an employee of Electra-Box Diagnostica, Tyresö, Sweden. This company sponsored the assay reagents. There was no duality of interest for any of the other authors.

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