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LETTER

The role of vitamin D in the aetiology of type 1 diabetes. Reply to Korsgren O [letter]

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Abbreviations
25OHD 25-Hydroxyvitamin D
HBD2 Human β-defensin-2

To the Editor: We would like to thank Dr Olle Korsgren for his interest in our work and for the valuable comments on our paper [1]. We highly appreciate the interesting arguments by Dr Korsgren describing the potential mechanisms explaining the slightly lower 25-hydroxyvitamin D (25OHD) concentrations in children who later develop islet autoimmunity or type 1 diabetes [2].

We agree with Dr Korsgren that various adverse changes in the immune system are likely to occur very early in the disease process in children who will eventually go on to develop islet autoimmunity or type 1 diabetes. These include, for example, changes in the composition of the gut microbiome [3] and changes in the gastrointestinal tract leading to slight malabsorption, as interestingly pointed out by Dr Korsgren [2].

To understand better the role of vitamin D in these early signs of an ongoing disease process, we recently analysed the association between serum 25OHD concentration and intestinal inflammatory markers (human β-defensin-2 [HBD2] and calprotectin) analysed from stool samples in the DIABIMMUNE study [4]. The DIABIMMUNE study includes children with HLA-conferred susceptibility to type 1 diabetes, followed from birth to 3 years of age in Finland, Estonia and Russia. In this study, the 25OHD concentrations were available from the Finnish and Estonian children only and therefore the analyses were performed using data of these two countries.

HBD2 is an antimicrobial peptide involved in the intestinal host defence that has been associated, for example, with inflammatory bowel disease in children [5]. Faecal calprotectin is a sensitive inflammation marker of the gastrointestinal tract that has been shown to correlate, for example, with endoscopic severity of paediatric Crohn's disease [6, 7]. The precise role of these intestinal inflammatory markers during the early development of the infant immune system has not been evaluated thoroughly.

We measured infant 25OHD, HBD2 and calprotectin concentrations at 3 and 6 months of age. We found that at 6 months of age, calprotectin concentrations were higher in children that had serum 25OHD concentration <75 nmol/l compared with ≥75 nmol/l ($p = 0.009$) (Table 1).

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Table 1 HBD2 and calprotectin concentrations in relation to 25OHD concentration at 3 and 6 months of age

Age	25OHD (nmol/l) (number of children)	HBD2 (ng/ml)	Calprotectin (mg/kg)
3 months	<75 (39)	330	207
	≥75 (19)	331	148
p value		0.99	0.22
6 months	<75 (47)	185	111
	≥75 (26)	154	43
p value		0.41	0.009

The direct association between intestinal inflammatory markers and islet autoimmunity or type 1 diabetes could not be analysed in the DIABIMMUNE study, since in the relatively small cohort there are only a few children that have developed islet autoimmunity or type 1 diabetes.

As suggested by Dr Korsgren, a lower serum concentration of 25OHD might be a consequence of ongoing inflammation, possibly in the gastrointestinal tract, and thus be a marker of adverse processes in the immune system. However, how early gastrointestinal inflammation might cause vitamin D malabsorption or reduced 25OHD levels is currently unknown. Altogether, vitamin D may be an important player, keeping up adequate immunological defences and affecting autoimmunity in the gastrointestinal tract [8, 9] and elsewhere. Therefore, its role in type 1 diabetes development needs to be studied further.

Data availability The authors confirm that, for approved reasons, some access restrictions apply to the data underlying the findings. Researchers interested in using the data are required to follow the terms of a number of clauses designed to ensure the protection of privacy and compliance with relevant Finnish laws. Data are available upon request due to ethical restrictions, pending approval from the Coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa.

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