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RESEARCH ARTICLE

The use of dietary supplements, and the association between supplemental vitamin D and glycaemic control in adult individuals with type 1 diabetes

Aila J. Ahola[1,2,3] | **Valma Harjutsalo**[1,2,3,4] | **Per-Henrik Groop**[1,2,3,5] | **on behalf of the FinnDiane Study Group**

[1]Folkhälsan Institute of Genetics, Folkhälsan Research Center, Helsinki, Finland

[2]Department of Nephrology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

[3]Research Program for Clinical and Molecular Metabolism, Faculty of Medicine, University of Helsinki, Helsinki, Finland

[4]National Institute for Health and Welfare, Helsinki, Finland

[5]Department of Diabetes, Central Clinical School, Monash University, Melbourne, Victoria, Australia

Correspondence
Per-Henrik Groop, Folkhälsan Research Center, University of Helsinki, Biomedicum Helsinki C318b, PO Box 63, FI-00014, Helsinki, Finland.
Email: per-henrik.groop@helsinki.fi

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Abstract

Aims: To assess the dietary supplement use in adult individuals with type 1 diabetes, and to study the association between vitamin D supplementation and glycaemic control in an observational cross-sectional study.

Methods: The study subjects were participants of the Finnish Diabetic Nephropathy Study. Data were included from all individuals with type 1 diabetes with estimated glomerular filtration rate ≥60 mL/min/1.73 m^2, who had completed a diet questionnaire. In the questionnaire, the participants reported dietary supplement use for the past 30 days. A thorough investigation with an assessment of the blood panel was conducted at the study visit.

Results: Data were available from 1181 individuals (43% men, mean ± SD age 45 ± 13 years). Altogether 62% of the sample reported supplement use; 56% reported some vitamin or mineral and 27% reported non-vitamin and non-mineral supplement use. Supplement use was more frequent among women and those supplementing had better overall health. In the study sample, of the vitamins and minerals, vitamin D (45%) and magnesium (31%), respectively, were the most frequently reported. In the multivariable models, vitamin D supplementation was associated with better glycaemic control. Starting from a daily dose of ≥30 μg, there was evidence of improving glycaemic control with higher doses of supplemental vitamin D (e.g., for 30 μg: B [Wald Confidence Internal], *p*-value, −2.76 [−5.03 to −0.49], 0.017).

Conclusions: Supplement use was frequent in this sample of adult individuals with type 1 diabetes. Due to potential drug–supplement interactions, the attending physicians should be aware of their patients' supplement use. The causality between vitamin D supplementation and glycaemic control should be assessed in a randomized controlled trial.

KEYWORDS
dietary supplements, glycaemic control, type 1 diabetes, vitamin D

1 | INTRODUCTION

No specific recommendations exist for the use of dietary supplements in the management of diabetes. Instead, a diet that conforms to the dietary guidelines is considered to cover the nutrient needs, with some exceptions related to vitamin D, rendering it unnecessary to use dietary supplements.[1] Despite this, dietary supplement use is common. In the National Health and Nutrition Examination Survey (NHANES), 52% of the general population and 58% of those with diabetes reported the use of some dietary supplements.[2,3] Moreover, in a recent report on Danish individuals with either type 1 or type 2 diabetes, as many as 99% of the respondents reported the use of supplements.[4]

Supplement use is a rather unexplored area in individuals with type 1 diabetes. However, in one study, the rate of non-vitamin and non-mineral (NVNM) supplement use was almost two times more common in individuals with type 2 diabetes as compared to those with type 1 diabetes.[5] Importantly, dietary supplement use in type 1 diabetes may be of concern due to potential side effects and drug–supplement interactions. Clinicians should, therefore, be aware of potential supplement use when treating individuals with type 1 diabetes.

Of the dietary supplements, the use of vitamin D is among the ones most frequently reported.[3] Beyond its well-known role in bone health, vitamin D is also acknowledged for its extra-skeletal effects. Of relevance to individuals with diabetes, lower serum 25-hydroxyvitamin D concentrations have, in some studies, been associated with insulin resistance,[6] severity of diabetic ketoacidosis,[7] higher insulin requirements,[7,8] and worse glycaemic control.[7] While some vitamin D intervention studies have shown reductions in fasting blood glucose and HbA_{1c} concentrations, glycaemic variability, insulin need and frequency of hypoglycaemia,[9,10] a number of studies have reported no improvements in glycaemic control,[11–16] insulin sensitivity,[14] insulin requirement,[15] or β-cell function.[15,17] Moreover, in one study, the reduction in HbA_{1c} was only reported in those with worse glycaemic control at baseline,[18] and in another study such improvements were only observed in individuals with type 2 diabetes, and not in those with type 1 diabetes.[19]

The aim of this study was two-fold. First, we assessed the frequency of supplement use in a large sample of adult individuals with type 1 diabetes. Second, we investigated the association between vitamin D supplement use and HbA_{1c}. Based on the available literature in other populations, we hypothesised that supplement use is frequent in this sample and that vitamin D supplementation is associated with better glycaemic control.

What's new?

- Dietary supplement use is an unexplored area in type 1 diabetes and no specific recommendations exist for the use of supplements for individuals with diabetes.
- Supplement use was frequent in this large sample of well-defined individuals with type 1 diabetes and was associated with better overall health. In particular vitamin D supplementation beyond a daily dose of ≥30 μg was associated with improved glycaemic control.
- Due to potential drug–supplement interactions, physicians should be aware of their patients' supplement use.

2 | METHODS

The study sample comprised of participants in the Finnish Diabetic Nephropathy (FinnDiane) Study. Launched in 1997, the FinnDiane Study aims at identifying risk factors for diabetes complications in type 1 diabetes. The nutrition sub-study was introduced to the FinnDiane Study protocol in 2007. With ongoing recruitment and prospective study visits the dietary assessment, for individual participants, took place either at baseline or at any of the follow-up visits. Of the individuals taking part in the FinnDiane study visits between August 2007 and September 2020 ($n = 2285$), we excluded those, who had not completed a diet questionnaire ($n = 809$), did not have type 1 diabetes ($n = 7$), or had an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 or missing eGFR value ($n = 288$) (Flow chart, Figure S1), from these cross-sectional analyses. Type 1 diabetes was defined as diabetes onset before the age of 40 years and permanent insulin treatment initiated within a year from the diagnosis. The Ethics Committee of Helsinki and Uusimaa Hospital District approved the study protocol (reference number 491/E5/06). The study was carried out in accordance with the Declaration of Helsinki and its later amendments. Written informed consent was obtained from all individuals prior to study participation.

The procedures taking place at the FinnDiane Study visits have been previously explained in detail.[20] Briefly, participants' height and body weight were measured for the calculation of body mass index (BMI). Following a minimum of 10-min rest, seated blood pressure was measured twice. The mean of the two measurements was calculated. Serum lipids, lipoproteins and creatinine concentrations were centrally determined, while glycated haemoglobin (HbA_{1c}) was measured locally using a standardized assay. The equation by Levey et al.[21] was used to calculate eGFR. Current smoking was self-reported on a questionnaire. Smoking was defined as smoking at least one cigarette per day for at least 1 year. The self-reported daily insulin dose was adjusted for measured body weight. Based on the dates, the visits were divided into four seasons: winter (December–February), spring (March–May), summer (June–August) and fall (September–November).

The methods to collect data on dietary intake in the FinnDiane Study have previously been published.[20] In short, the study participants completed a self-administered structured diet questionnaire where, amongst other information, the types and doses of dietary supplements used in the prior 30 days were reported. From these reports, we identified all participants using any dietary supplements, vitamin, or mineral supplements (vitamin A, thiamine, riboflavin, niacin, vitamin B6, vitamin B12, folate, vitamin C, vitamin D, vitamin E, magnesium, zinc, selenium, iodine, calcium, iron and copper) or NVNM supplements (coenzyme Q_{10}, various herbal remedies, plant extracts, homeopathic products and supplemental plant and fish oils). In addition to retrieving data on supplement use, we also used the diet questionnaire data to calculate a diet score, as previously explained.[22] Briefly, we compared the questionnaire entries with the national dietary recommendations[1] and estimated the degree to which the participants adhered to these recommendations. Such recommendations were found for fish, fresh vegetables, cooked vegetables, fruits and berries, soft drinks, sweet pastries, candy, low-fat liquid milk products, vegetable-based spreads, vegetable-oil-based cooking fats and salt. For each of these 11 items, those more closely adherent scored 2 points, while those with the lowest levels of adherence scored 0 points. The total score ranging between 0 and 22 was calculated with higher scores suggesting a closer adherence to the overall recommendations. Upon returning the diet questionnaire, participants completed two 3-day food records with a 2- to 3-month interval. The days were allocated and consisted of two consecutive weekdays and 1 week-end day. Aivo Diet software (version 2.0.2.3, AIVO, Turku, Finland), based on the Finnish National Food Composition Database, was used to calculate mean daily energy, vitamin and mineral intakes. In the analyses with the food record data, all participants with plausible energy intake (5.0–14.6 MJ) were included. Finally, we calculated the percentage of individuals meeting the dietary recommendations in those reporting (dietary intake plus supplement intake) and not reporting (dietary intake) the use of a given vitamin or mineral supplement.[1]

Participant characteristics are presented as frequencies for categorical variables and medians (interquartile ranges) for continuous variables with non-normal distribution. Between-group comparisons, in these respective variables, were done with the Chi-squared test and Mann–Whitney U-test. General linear regression analysis was applied to study the association between vitamin D supplement use and glycaemic control. We selected variables with known association with HbA_{1c} in the multivariable model. In addition, the four-level variable reflecting seasonality was included as seasonality is associated with vitamin D supplementation. Finally, supplemental vitamin B12 was included as, of the non-vitamin D-supplements, it was observed to associate with HbA_{1c}. The models were, thus, adjusted for sex, age, BMI, insulin dose, current smoking status, season, diet score and supplemental vitamin B12. All analyses were conducted with IBM SPSS Statistics for Windows, Version 25.0 (IBM). A two-tailed p-value <0.05 was chosen to designate statistical significance.

3 | RESULTS

Data were available from 1181 individuals (43% men, mean ± standard deviation age 45 ± 13 years). Altogether, 38% of the sample reported no supplement use, while 27% and 56% self-reportedly used some NVNM and vitamin or mineral supplement use, respectively (Table 1). Compared to individuals not reporting any supplement use, those reporting (62% of the sample) were more frequently women, were less frequently current smokers, had lower BMI, insulin dose, blood pressure and HbA_{1c} and triglyceride concentration, but higher HDL-cholesterol concentration. Supplement use was also associated with closer adherence to the dietary recommendations.

3.1 | The use of NVNM supplements

Fish oil supplements formed the largest group of NVNM supplements (in 22% of the total sample) (Table 2). The use of the other NVNM supplements, beyond that of fish oil, was infrequent. Altogether, 2.5% supplemented with proteins, peptides, or amino acids, 2.4% with herbal preparations, 1.8% with plant oils, 1.3% with ubiquinone, 0.9% with conjugated linoleic acid, 0.5% with homeopathic preparations and 1.9% with other supplements.

3.2 | The use of vitamin and mineral supplements

Of the vitamins, vitamin D was most frequently supplemented with 45% of the sample reporting its use, followed by supplemented vitamin B6 (31%), vitamin B12 (31%),

TABLE 1 Participant characteristics of 1181 adult individuals with type 1 diabetes divided by the self-reported supplement use.

	Supplement use						
	No	Yes		NVNM		Vitamins or minerals	
	n = 449 (38%)	*n* = 732 (62%)	*p*[a]	*n* = 314 (27%)	*p*[a]	*n* = 655 (56%)	*p*[a]
Men, *n* (%)	250 (56)	261 (36)	<0.001	115 (37)	<0.001	226 (35)	<0.001
Current smoker, *n* (%)	68 (16)	67 (9.4)	0.002	282 (8.1)	0.002	59 (9.3)	0.001
Age, years	45 (35–57)	43 (35–54)	0.204	46 (37–56)	0.741	43 (35–53)	0.116
Diabetes duration, years	26 (18–40)	28 (19–39)	0.832	31 (20–40)	0.145	27 (19–38)	0.949
BMI, kg/m^2	25.8 (23.8–28.4)	25.2 (23.0–28.2)	0.034	25.0 (23.1–27.9)	0.034	25.2 (23.0–28.2)	0.028
eGFR, mL/min/1.73 m^2	103 (89–114)	103 (89–113)	0.827	100 (88–110)	0.136	103 (90–113)	0.975
Insulin dose, IU/kg	0.62 (0.49–0.80)	0.55 (0.43–0.71)	<0.001	0.54 (0.41–0.71)	<0.001	0.55 (0.43–0.70)	<0.001
SBP, mmHg	139 (126–151)	133 (123–144)	<0.001	133 (124–146)	0.001	132 (122–143)	<0.001
SBP (no AHT med.), mmHg	132 (122–143)	128 (119–139)	0.016	130 (120–142)	0.199	128 (119–138)	0.008
SBP (with AHT med.), mmHg	146 (135–160)	138 (128–150)	<0.001	140 (130–152)	0.008	137 (127–148)	<0.001
DBP, mmHg	78 (71–85)	76 (70–83)	0.001	77 (70–82)	0.005	76 (70–83)	<0.001
DBP (no AHT med.), mmHg	79 (72–84)	77 (70–83)	0.027	76 (70–83)	0.026	76 (70–83)	0.012
DBP (with AHT med.), mmHg	78 (71–87)	76 (69–82)	0.004	77 (70–81)	0.080	75 (69–81)	0.001
HbA_{1c}, mmol/mol	64 (57–74)	63 (55–70)	0.009	62 (54–70)	0.003	63 (54–70)	0.004
HbA_{1c}, %	8.0 (7.4–8.9)	7.9 (7.2–8.6)	0.009	7.8 (7.1–8.6)	0.003	7.9 (7.1–8.6)	0.004
Cholesterol, mmol/L	4.5 (4.0–5.1)	4.6 (4.1–5.2)	0.133	4.6 (4.1–5.3)	0.049	4.6 (4.1–5.2)	0.105
Cholesterol (no LL med.), mmol/L	4.6 (4.1–5.2)	4.7 (4.2–5.3)	0.123	4.8 (4.3–5.4)	0.036	4.8 (4.2–5.4)	0.071
Cholesterol (with LL med.), mmol/L	4.3 (3.8–4.9)	4.3 (3.8–4.9)	0.965	4.3 (3.7–5.0)	0.856	4.3 (3.8–4.9)	0.797
HDL-cholesterol, mmol/L	1.5 (1.3–1.9)	1.6 (1.4–1.9)	0.001	1.7 (1.4–2.0)	<0.001	1.6 (1.4–2.0)	<0.001
HDL-cholesterol (no LL med.), mmol/L	1.5 (1.3–1.9)	1.6 (1.4–1.9)	0.030	1.7 (1.4–2.0)	<0.001	1.6 (1.4–1.9)	0.020
HDL-cholesterol (with LL med.), mmol/L	1.5 (1.2–1.8)	1.6 (1.3–2.0)	0.005	1.7 (1.4–1.9)	0.014	1.6 (1–4 – 2.0)	0.005
Triglycerides, mmol/L	1.0 (0.8–1.3)	0.9 (0.7–1.3)	<0.001	0.9 (0.7–1.2)	<0.001	0.9 (0.7–1.3)	0.001
Triglycerides (no LL med.), mmol/L	0.9 (0.7–1.2)	0.9 (0.7–1.2)	0.090	0.8 (0.7–1.1)	0.009	0.9 (0.7–1.2)	0.143
Triglycerides (with LL med.), mmol/L	1.1 (0.9–1.5)	1.0 (0.8–1.3)	0.001	0.9 (0.8–1.2)	0.003	1.0 (0.8–1.3)	0.002
Diet score	11 (8–13)	11 (9–14)	0.024	12 (9–14)	0.001	11 (9–14)	0.056

Note: Data are presented as frequencies for categorical variables and medians (interquartile ranges) for continuous variables with skewed distribution. For these respective variables, each group with reported supplement use was compared against those with no reported supplement use using Chi-squared test and Mann–Whitney U-test.

Abbreviations: AHT med., antihypertensive medication; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LL med, lipid-lowering medication; NVNM, non-vitamin and non-mineral; SBP, systolic blood pressure.

[a]Compared to those with no reported supplement use (*n* = 449).

vitamin C (31%), thiamine (29%), riboflavin (28%), folate (28%), niacin (28%), vitamin E (21%) and vitamin A (14%) (Table 3). Of the minerals, magnesium was the most frequently supplemented (31%), followed by zinc (25%), selenium (19%), iodine (17%), calcium (16%), iron (9.7%) and copper (8.6%). Individuals who reported supplementing with thiamine and zinc also reported diets with lower thiamine and zinc densities compared with those with no reports of the use of these supplements. The use of a given vitamin or mineral supplement significantly increased the frequency of meeting the dietary recommendations for that nutrient compared to those with no supplement use.

TABLE 2 The types and frequencies of non-vitamin and non-mineral (NVNM) supplements reported.

	n (%) of those reporting NVNM supplement use, *n* = 314	*n* (%) of the total sample, *n* = 1181
Fish oil supplements	264 (84)	264 (22)
Proteins/peptides/amino acids	30 (9.6)	30 (2.5)
Herbal preparations	28 (8.9)	28 (2.4)
Plant oils	21 (6.7)	21 (1.8)
Ubiquinone	15 (4.8)	15 (1.3)
Conjugated linoleic acid	11 (3.5)	11 (0.9)
Homeopathic preparations	6 (1.9)	6 (0.5)
Other	22 (7.0)	22 (1.9)

3.3 | Vitamin D supplement use and glycaemic control

Compared to individuals not reporting, those reporting the use of vitamin D supplements had a lower median HbA_{1c} (63 [54–70] vs. 64 [57–73] mmol/mol, $p = 0.003$). The curve exhibiting the association between vitamin D supplement use and HbA_{1c} is shown in Supplementary Figure S2. In the adjusted model, supplemental vitamin D remained associated with lower HbA_{1c} (B, −1.91 [95% Wald Confidence Interval, −3.47 to −0.35], $p = 0.016$). We additionally compared the HbA_{1c} of individuals with different amounts of supplemented vitamin D. In these multivariable analyses, individuals with vitamin D supplement use of <20 and ≥20 μg had comparable glycaemic control (Table 4). However, comparing individuals with supplemental vitamin D use of <30 and ≥30 μg, <40 and ≥40 μg, <50 and ≥50 μg, <60 and ≥60 μg and <70 and ≥70 μg showed that in all comparisons the individuals with higher intakes had better glycaemic control.

4 | DISCUSSION

In the current study, 62% of adult individuals with type 1 diabetes reported using some dietary supplements during the past 30 days. In all, 56% of the sample self-reportedly used some vitamins or minerals and approximately one-fourth reported the use of NVNM supplements. While the supplement use in individuals with type 1 diabetes has not previously been investigated in detail, the current observations are comparable with those done in a few mixed samples of individuals with type 1 and type 2 diabetes. In one such sample from Austria, one-third of the respondents reported the current use of some complementary or alternative medicine, with vitamins and minerals, herbal medicine and cinnamon being those most frequently reported.[23] In another sample of individuals with diabetes, 55% of the respondents reported the use of some form of vitamin, mineral or NVNM supplement.[5] In that study, the rate of NVNM supplement use was almost two times higher in individuals with type 2 diabetes, compared to those with type 1 diabetes. Among the individuals with diabetes taking part in the NHANES, 58% of the sample reported some supplement use.[3] By far the highest frequency of supplement use, 99% of the sample, was reported in a Danish sample of individuals with diabetes.[4] The reasons for the high frequency of supplement use were not evident. Importantly, details on the sampling procedure would have been valuable for estimating the representativeness of the sample. In the same paper, however, the authors compared their observations with those done in the Danish general population. There, the reported rate of supplement use, 64%, was closer to that also observed in the current study. Of note, the observed frequency of vitamin D supplement use (45%), in the current study, was comparable to that seen in the Finnish general population (33% in 25–65-year-old men, 53% in 25–44-year-old women and 57% in 45–64-year-old women).[24]

Use of any dietary supplements, in the current study, was more frequent in women and was associated with better overall health. The more frequent supplement use in women has also been reported in several earlier studies.[2,3,23] The better health in those reporting supplement use could be related to the healthy user bias, meaning that individuals who, in general, take better care of themselves also tend to use dietary supplements. Indeed, also in previous studies dietary supplement use has been associated with higher health awareness and interest in self-care,[23] and the intention to eat healthy.[25] Based on the diet score, in the current study, there was some indication of healthier dietary habits in those reporting supplement use. However, calculated from the diet records, no major differences were observed in the nutrient densities of those supplementing and not supplementing with a given nutrient. Instead, for thiamine and zinc, the dietary nutrient densities were in fact somewhat higher in those not reporting the respective supplement use. The use of a given vitamin or mineral supplement was associated with a higher frequency of meeting the respective dietary recommendations. However, the current study does not answer the questions of whether dietary supplement use was, in all cases, essential for the health; whether the supplement use, in some cases, resulted in overdosing; or whether a more prudent dietary intake would have been sufficient for meeting the recommendations.

Due to the recent interest in the extra-skeletal effects of vitamin D, we also investigated the association between

TABLE 3 Frequencies of vitamin and mineral supplement use, median intakes from supplements, dietary intake of vitamins and minerals in those reporting and not reporting supplement use and frequencies of meeting the dietary recommendations for individual vitamins and minerals in those reporting and not reporting supplement use.

	Total sample ($n = 1181$)		Dietary intake by MJ ($n = 914$)					Meeting dietary recommendation		
	Supplement users		Reporting supplement use		Not reporting supplement use			Reporting supplement use[a]	Not reporting supplement use	
	n (%)	Intake from supplements	*n* (%)	Intake from diet	*n* (%)	Intake from diet	p[b]	*n* (%)	*n* (%)	p[b]
Vitamins										
Vitamin D (μg)	536 (45)	20 (10–30)	443 (48)	0.95 (0.66–1.33)	471 (52)	1.00 (0.67–1.35)	0.471	426/443 (96)	142/471 (30)	<0.001
Vitamin B6 (mg)	371 (31)	2.2 (1.4–10.0)	304 (33)	0.24 (0.21–0.28)	610 (67)	0.24 (0.21–0.28)	0.408	304/304 (100)	537/610 (88)	<0.001
Vitamin B12 (μg)	364 (31)	3.0 (2.5–10.0)	297 (32)	0.33 (0.22–0.47)	617 (68)	0.33 (0.22–0.46)	0.430	294/297 (99)	413/617 (67)	<0.001
Vitamin C (mg)	363 (31)	80 (75–500)	302 (33)	14.9 (10.1–21.0)	612 (67)	15.3 (10.6–21.7)	0.478	298/302 (99)	481/612 (79)	<0.001
Thiamine (mg)	346 (29)	1.4 (1.1–14.6)	283 (31)	0.17 (0.15–0.20)	631 (69)	0.18 (0.16–0.21)	0.005	282/283 (99)	493/631 (78)	<0.001
Riboflavin (mg)	334 (28)	1.6 (1.4–10.0)	274 (30)	0.23 (0.20–0.28)	640 (70)	0.24 (0.21–0.27)	0.452	273/274 (99)	566/640 (89)	<0.001
Folate (μg)	334 (28)	300 (200–400)	275 (30)	35.6 (29.3–43.2)	639 (70)	35.6 (29.9–41.7)	0.845	269/275 (98)	236/639 (37)	<0.001
Niacin (NE)	331 (28)	16 (15–31)	272 (30)	2.12 (1.57–2.69)	642 (70)	1.98 (1.55–2.61)	0.119	267/272 (98)	342/642 (53)	<0.001
Vitamin E (α-TE)	252 (21)	10 (10–12)	205 (22)	1.33 (1.15–1.59)	709 (78)	1.31 (1.11–1.53)	0.136	205/205 (100)	484/709 (68)	<0.001
Vitamin A (RE)	166 (14)	400 (300–400)	139 (15)	93 (76–128)	775 (85)	93 (72–127)	0.604	131/139 (94)	374/775 (48)	<0.001
Minerals										
Magnesium (mg)	365 (31)	125 (100–350)	304 (33)	47 (40–54)	610 (67)	48 (42–54)	0.155	297/304 (98)	494/610 (81)	<0.001
Zinc (mg)	300 (25)	10 (10–15)	245 (27)	1.49 (1.35–1.67)	669 (73)	1.54 (1.38–1.72)	0.029	245/245 (100)	636/669 (95)	<0.001
Selenium (μg)	218 (19)	50 (50–55)	181 (20)	8.1 (7.1–9.7)	733 (80)	8.4 (7.4–9.8)	0.147	180/181 (99)	578/733 (79)	<0.001
Iodine (μg)	206 (17)	150 (100–150)	171 (19)	26 (22–31)	743 (81)	26 (23–31)	0.418	170/171 (99)	640/743 (86)	<0.001
Calcium (mg)	194 (16)	500 (120–500)	161 (18)	129 (112–157)	753 (82)	135 (108–163)	0.522	152/161 (94)	593/753 (79)	<0.001
Iron (mg)	114 (9.7)	10 (10–20)	92 (10)	1.56 (1.36–1.82)	822 (90)	1.59 (1.38–1.81)	0.663	90/92 (98)	483/822 (59)	<0.001
Copper (mg)	101 (8.6)	1.0 (0.7–1.0)	84 (9)	0.18 (0.15–0.21)	830 (91)	0.18 (0.15–0.20)	0.861	84/84 (100)	774/830 (93)	0.007

Note: Intakes are reported as median (interquartile range), and between-group comparisons were done with the Mann–Whitney U-test. Categorical variables are presented as *n* (%), and between-group comparisons were done using the Chi-squared test.

[a]Taking into account both dietary intake and supplement use.

[b]Comparing those reporting and not reporting supplement use.

TABLE 4 Association between the reported dose of vitamin D supplement use and HbA_{1c}.

Dose of vitamin D supplement (μg)	*n*[a]	HbA_{1c} (mmol/mol, [%]) if supplementing the amount shown in the first column	HbA_{1c} (mmol/mol, [%]) if supplementing less than shown in the first column or not supplementing at all	Adjusted difference (calculated for mmol/mol values)	*p*
≥20	293	64 (63–66), [8.1 (7.9–8.2)]	65 (64–66), [8.1 (8.0–8.2)]	−0.80 (−2.57 to 0.97)	0.374
≥30	150	62 (60–65), [7.8 (7.6–8.1)]	65 (64–66), [8.1 (8.0–8.2)]	−2.52 (−4.81 to −0.23)	0.031
≥40	113	62 (59–64), [7.8 (7.5–8.0)]	65 (64–66), [8.1 (8.0–8.2)]	−3.00 (−5.61 to −0.40)	0.024
≥50	99	61 (58–64), [7.7 (7.5–8.0)]	65 (64–66), [8.1 (8.0–8.2)]	−3.96 (−6.73 to −1.18)	0.005
≥60	45	60 (56–64), [7.6 (7.3–8.0)]	65 (64–66), [8.1 (8.0–8.2)]	−4.95 (−9.04 to −0.86)	0.018
≥70	36	59 (54–63), [7.5 (7.1–7.9)]	65 (64–66), [8.1 (8.0–8.2)]	−6.05 (−10.71 to −1.39)	0.011

Note: HbA_{1c} concentrations are shown as the mean (95% Wald Confidence Interval). General linear regression. Models are adjusted for sex, age, BMI, insulin dose, current smoking status, season, diet score and dose of supplemental vitamin B12.

[a]The number of individuals with supplemental vitamin D dose at the shown level.

its supplemental use and glycaemic control. In these analyses, we observed that those reporting supplemental vitamin D use had lower HbA_{1c} concentrations compared to those not supplementing. While the unadjusted difference in HbA_{1c} between those reporting and not reporting vitamin D supplementation is unlikely clinically significant, the adjusted models investigating the role of increasing dosage, further strengthened the results. Importantly, these analyses were adjusted for several potential confounders, including age, sex, BMI, season and a number of self-management variables, suggesting that there was an independent association between vitamin D supplementation and glycaemia that would extend beyond the healthy lifestyle. These results were further strengthened when we observed evidence suggesting increasing benefits associated with higher vitamin D doses. Indeed, no difference in glycaemic control was evident when we used a cut-off value of 20 μg. However, beyond this, that is in the comparisons between those supplementing with ≥30 and <30 μg, ≥40 and <40 μg, ≥50 and <50 μg, ≥60 and <60 μg and ≥70 and <70 μg, the glycaemic control was in all cases better in those with higher dosing. Furthermore, with increasing vitamin D dose, also the B-value was observed to decrease which could be suggestive of a dose–response.

The previous reports on vitamin D and glycaemia in type 1 diabetes are mixed. While low serum 25-hydroxyvitamin D concentrations have been associated with insulin resistance and higher insulin requirements, also observations of no association have been reported.[6–8,15,26] In one study, individuals with severe vitamin D deficiency had higher HbA_{1c} concentrations compared to the other participants,[7] but no association between serum 25-hydroxyvitamin D and HbA_{1c} was reported in another.[27] Perchard et al. observed a negative correlation between serum 25-hydroxyvitamin D concentration and HbA_{1c} at baseline, but reported no improvement in glycaemic control following a single large dose of cholecalciferol.[11] A small sample size and inclusion of children with short diabetes duration, with potential residual insulin secretion, may have confounded the observations. In another study, a six-month vitamin D intervention significantly increased the C-peptide levels of children in the active intervention arm but resulted in no improvement in glycaemic control.[12] Furthermore, a number of studies have shown improved glycaemic control following a vitamin D intervention.[9,10,28,29] However, with a missing control group, it cannot be excluded that the improvement was caused by a more meticulous self-care associated with the participation in the study. Finally, in one study, a clinically significant decrease in HbA_{1c} was observed in individuals with type 2 diabetes receiving vitamin D supplementation for the management of vitamin D deficiency.[19] However, no such improvement was observed in those with type 1 diabetes.

A few mechanisms could explain the association between vitamin D and glycaemia. First, low serum vitamin D concentration results in elevated parathyroid hormone (PTH) levels which, in turn, is associated with impaired glucose tolerance and decreased insulin sensitivity.[30] Vitamin D may also impact insulin sensitivity via its role in immunomodulation.[31] Finally, serum vitamin D stimulates the expression of insulin receptors and thus could improve the cellular intake of glucose.[32]

For assessing the frequency of supplement use, the current cross-sectional study design was well-suited. Instead, in the analyses with the associations between supplement use and glycaemic control, causality may not be assumed in this observational study with secondary data analysis. While our observations are hypothesis-generating, given the continuing improvement in glycaemic control with increasing vitamin D dosing, the study results need to be interpreted with caution. Another important limitation, of this study, is the use of a self-report method for collecting data on supplement use. Unlike for medication, however, no registers are available for supplement purchases. Both under-reporting, in those either forgetting or failing to report supplement use and over-reporting, if supplement use was perceived socially desirable, may have taken place. Whether misreporting is related to glycaemic control is not known. An additional limitation, related to this study, is that we did not measure the serum vitamin D concentrations. Data on the vitamin D status may have provided additional information that was not otherwise available. Data on socio-economic status were not available for the current analyses. This could have potentially influenced the results as dietary supplements, including those of vitamin D, are not reimbursable by the national health care system. Finally, due to measurement errors and large variability in daily food intake, the food record method for collecting data on dietary vitamin and mineral intake may be limited.

The major strengths of this study are the large sample size and a well-defined study sample. Some selection bias may, however, be expected as those with greater interest in their health more readily take part in health-related studies. The likely consequence of this is the dilution of the current observations. Finally, due to the low number, we excluded individuals with eGFR $<60\,mL/min/1.73\,m^2$ from the current analyses. With advancing kidney failure, changes in both HbA_{1c} and supplement use may be expected. Therefore, separate analyses may be warranted. Due to the exclusion of individuals with evidence of kidney impairment, the current observations may only be generalizable to other individuals with type 1 diabetes with preserved kidney function.

In conclusion, the use of dietary supplements was common in this large sample of adult individuals with type 1 diabetes. Due to potential side effects and drug-supplement interactions, the high frequency of supplement use may have clinical relevance. The use of supplements was more common in women and was associated with better overall health. Of the vitamins and minerals, vitamin D and magnesium, respectively, were most frequently reported. Supplementation with vitamin D was associated with better glycaemic control even after adjustments for several important confounders. The results were suggestive of a dose–response with higher vitamin D doses being associated with lower HbA_{1c}. The causality between vitamin D dosing and improved glycaemic control should be assessed in a randomized controlled trial.

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CONFLICT OF INTEREST STATEMENT

Professor Per-Henrik Groop has received investigator-initiated grants from Eli Lilly and Roche, is an advisory board member for AbbVie, Astellas, Astra Zeneca, Bayer, Boehringer-Ingelheim, Eli Lilly, Janssen, Medscape, MSD, Mundipharma, Novartis, Novo Nordisk and Sanofi. He has received lecture honoraria from Astellas, Astra Zeneca, Bayer, Boehringer-Ingelheim, Eli Lilly, Elo Water, Genzyme, Medscape, MSD, Mundipharma, Novartis, Novo Nordisk, PeerVoice, Sanofi and Sciarc. All the other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

According to the General Data Protection Regulation of the European Union (679/2016), the principles of data protection should apply to any information concerning an identified or identifiable natural person and personal data which have undergone pseudonymisation, which could be attributed to a natural person by the use of additional information should be considered to be information on an identifiable natural person. Thus, according to the GDPR, all pseudonymized data are considered personal data and cannot be published openly.

ORCID

Aila J. Ahola https://orcid.org/0000-0001-5200-4597

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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