

Vitamin D Status in Relation to Glucose Metabolism and Type 2 Diabetes in Septuagenarians

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OBJECTIVE—Vitamin D deficiency is thought to be a risk factor for development of type 2 diabetes, and elderly subjects at northern latitudes may therefore be at particular risk.

RESEARCH DESIGN AND METHODS—Vitamin D status was assessed from serum concentrations of 25-hydroxyvitamin D₃ [25(OH)D₃] in 668 Faroese residents aged 70–74 years (64% of eligible population). We determined type 2 diabetes prevalence from past medical histories, fasting plasma concentrations of glucose, and/or glycosylated hemoglobin (HbA_{1c}).

RESULTS—We observed 70 (11%) new type 2 diabetic subjects, whereas 88 (13%) were previously diagnosed. Having vitamin D status <50 nmol/L doubled the risk of newly diagnosed type 2 diabetes after adjustment for BMI, sex, exposure to polychlorinated biphenyls, serum triacylglyceride concentration, serum HDL concentration, smoking status, and month of blood sampling. Furthermore, the HbA_{1c} concentration decreased at higher serum 25(OH)D₃ concentrations independent of covariates.

CONCLUSIONS—In elderly subjects, vitamin D sufficiency may provide protection against type 2 diabetes. Because the study is cross-sectional, intervention studies are needed to elucidate whether vitamin D could be used to prevent development of type 2 diabetes.

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Vitamin D plays a pivotal role in calcium metabolism, and vitamin D deficiency may be associated with a range of serious diseases, including cancer, cardiovascular disease, and type 2 diabetes (1). Although the underlying biological mechanisms are poorly understood, the association of low serum 25-hydroxyvitamin D₃ [25(OH)D₃] concentrations with type 2 diabetes may be mediated through effects on glucose homeostasis and, in particular, a direct effect of vitamin D on the β -cell function, and thus insulin secretion (2). Several studies have suggested that low vitamin D status also contributes to insulin resistance (3). Low vitamin D status is associated with markers of impaired glucose metabolism, such as glycosylated hemoglobin (HbA_{1c})

(4,5). However, most of these studies focused on heterogeneous groups of middle-aged subjects.

The main dietary source of vitamin D is fatty ocean fish and other marine foods, and therefore, inadequate intake of seafood can result in low 25(OH)D₃ concentrations in serum. In addition, vitamin D is formed in humans by subcutaneous photosynthesis from its precursor, 7-dehydrocholesterol (1). Consequently, in countries at high latitude, such as the Nordic countries, very little pre-vitamin D is formed during the winter months (from October through March). In addition, older age is associated with a decrease in 7-dehydrocholesterol concentration in the human skin (6). Paired with possible reductions in sunlight exposure (7),

gastrointestinal absorption of vitamin D may decrease (8), thereby leaving the elderly at increased risk of vitamin D deficiency at an age where type 2 diabetes is particularly common.

Given the limited available data on the relationship of vitamin D insufficiency with glucose homeostasis among subjects older than 70 years, we examined serum 25(OH)D₃ concentrations and various markers of insulin resistance and glucose metabolism in a population-based sample of elderly residents from the Faroe Islands, a North Atlantic fishing community located at a latitude of 62°N between Norway and Iceland.

RESEARCH DESIGN AND METHODS

This study is part of a larger project examining the possible health effects of lifetime exposure to marine food and pollutants. The Faroe Islands constitute a unique setting at northern latitude in which the residents have an increased exposure to methylmercury and persistent organic pollutants, including polychlorinated biphenyls (PCB), because of their intake of traditional marine food, including pilot whale meat and blubber. To examine subjects aged 70–74 years, a cohort of Faroese men and women born in the mid-1930s was established.

All 1,131 Faroese citizens born between 2 January 1934 and 31 August 1937 received a letter of invitation, 713 of whom gave consent and were examined, corresponding to a participation rate of 64%, taking into account 14 deceased subjects. There were no differences in regard to sex or age between participants and nonparticipants. One subject was excluded because of the presence of alcoholic pancreatitis. Furthermore, sufficient serum for determination of vitamin D status was not available from 44 subjects; thus, 668 subjects are included in the current study.

The participants were asked to fast and arrive before breakfast to undergo blood sampling and a thorough clinical examination. BMI was calculated as weight in kilograms divided by square of

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height in meters. All participants traveled to the same examination location and were examined by the same research nurses and a single physician. The participants completed current health, past medical history, and lifestyle questionnaires, including summary information on the frequency of fish dinners during the last year. The type of fish was not specified, and neither was the portion size.

Assessment of type 2 diabetes and markers of glucose metabolism

A fasting capillary blood sample was used to determine blood glucose concentration using a direct-reading glucose biosensor (Precision Xceed and Abbott Precision Xtra Plus strips; Abbott Diabetes Care, Copenhagen, Denmark). Because plasma has higher water content than whole blood, the blood values were transformed to plasma glucose concentration by multiplying by 1.12 as recommended by the manufacturer. Fasting venous blood samples were collected by phlebotomy to perform HbA_{1c} analyses by high-pressure liquid chromatography. All HbA_{1c} values were given as relative concentration, % (Diabetes Control and Complications Trial, DCCT, aligned results). HbA_{1c} % values were converted to International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) units (millimoles per moles) by the following equation: HbA_{1c} (DCCT) % = 0.0915 × HbA_{1c} (IFCC) mmol/mol + 2.15, provided by the laboratory. EDTA-plasma was used for determination of fasting plasma insulin concentration by time-resolved fluoroimmunoassay (AutoDelfia; PerkinElmer Life and Analytical Sciences, Walla Oy, Turku, Finland). The analytical imprecision of these assays was <5%. Serum HDL and triacylglycerides were measured by an enzymatic colorimetric reaction, using a Modular P analyzer (Roche Diagnostics, Indianapolis, IN).

Diabetic subjects were identified from self-reported doctor's diagnosis and the reported use of hypoglycemic medication; subjects were also classified as diabetic if they reported use of diabetes medication without reporting a diagnosis of diabetes. In participants not previously diagnosed, type 2 diabetes was considered to be present if the fasting plasma glucose was ≥ 7.0 mmol/L and/or if the HbA_{1c} was $\geq 6.5\%$ (9). Insulin resistance was estimated by the homeostasis model assessment (HOMA-IR) and calculated as $FPI \times FPG / 22.5$ (10),

where FPI is fasting plasma insulin and FPG is fasting plasma glucose. β -Cell dysfunction was determined by calculating the HOMA β -index of $(20 \times FPI)/(FPG \times 3.5)$ (10).

Vitamin D status

After storage at -80°C , serum 25(OH)D₃ concentrations were assessed using liquid chromatography-tandem mass spectrometry (LC-MS/MS) as described previously (11). The lower detection limit was 10 nmol/L, and the coefficient of variation was 9.6% at 20 nmol/L and 6.7% at 60 nmol/L.

Statistical analysis

Means (SD) were calculated for variables showing normal distribution and median and 25–75th percentiles (interquartile range [IQR]) for those deviating from it. When transformations were insufficient to obtain normal distribution, we applied nonparametric Spearman's correlation coefficient. When appropriate, multiple regression analysis was carried out. Covariate adjustment included BMI, sex, smoking status, and serum triacylglyceride concentration.

A logistic regression model was used to assess the association between serum 25(OH)D₃ concentration and the risk of having type 2 diabetes. Control subjects were nondiabetic subjects, i.e., subjects with fasting blood glucose ≤ 6 mmol/L. Vitamin D status was used as a binary exposure variable, i.e., dichotomized at above (sufficient) or below 50 nmol/L (deficient), and in the simple model, sex was used as an obligate covariate. In the adjusted model, additional covariates were included, i.e., BMI, serum triacylglycerides, serum HDL, PCB exposure (sum of major PCB congeners CB-138, CB-153, and CB-180 multiplied by 2 [12]), smoking, and month of blood sampling. In addition, we examined the association between vitamin D status and risk of having 1) newly diagnosed type 2 diabetes or 2) a known diagnosis of type 2 diabetes using the same models separately. Finally, the same approach was used to estimate the influence of fish intake on risk of having type 2 diabetes using subjects reporting fish intake less than or equal to two times per week as a reference group. In the models, we further tested whether there was evidence of an interaction effect between vitamin D status and sex and vitamin D status and obesity. A value of $P < 0.05$ (two-tailed)

was taken to indicate statistical significance. Stata version 11.0 (Stata Corporation, College Station, TX) was used for statistical analyses. The study was approved by the Faroese Ethical Review Committee and the U.S. institutional review board. All participants provided written informed consent.

RESULTS—In the current study, the cohort consisted of 327 women and 341 men with a mean age of 72.5 years. A total of 158 septuagenarians (24%) had type 2 diabetes, of whom 88 (13%) had been previously diagnosed with the disease and 70 new subjects (11%) were identified in the current study. More than half of the subjects had vitamin D deficiency, as suggested by a serum 25(OH)D₃ concentration below 50 nmol/L (median, 47.6 nmol/L; IQR, 29.8–64.8 nmol/L). The main characteristics of the current study population are shown in Table 1.

Vitamin D deficiency, i.e., 25(OH)D₃ < 50 nmol/L, was associated with an 80% increase in the sex-adjusted odds of having diabetes (newly diagnosed and previously diagnosed subjects) compared with sufficient vitamin D status (odds ratio [OR] 1.80 [95% CI 1.23–2.64]; $P = 0.002$). After further adjustment for BMI, serum triacylglycerides, serum HDL, PCB exposure, smoking, and month of blood sampling, the association between vitamin D deficiency and type 2 diabetes remained, and the OR was only marginally affected (OR 1.67 [1.11–2.50]; $P = 0.013$).

In the separate analyses of previously undiagnosed and diagnosed subjects, we found that the sex-adjusted OR for having newly diagnosed type 2 diabetes in the presence of vitamin D deficiency had more than doubled (OR 2.25 [95% CI 1.31–3.85]; $P = 0.003$). After further adjustment for BMI, serum triacylglycerides, serum HDL, PCB exposure, smoking, and month of blood sampling, the association between vitamin D deficiency and newly diagnosed type 2 diabetes remained unchanged (OR 1.99 [1.14–3.48]; $P = 0.022$), whereas the adjusted OR for pre-existing diabetes in vitamin D deficiency was reduced considerably by similar adjustment (OR 1.48; $P = 0.132$) (Table 2).

We performed logistic regression analysis on the impact of fish dinner frequencies on the risk of type 2 diabetes. Frequent fish intake (more than twice a week) did not appear to alter the odds of having type 2 diabetes (OR 1.09 [95% CI 0.64–1.86]; $P = 0.744$).

Table 1—Baseline clinical and biochemical characteristics of 668 Faroese septuagenarians by vitamin D status

Variable	25(OH)D <50 nmol/L	25(OH) ≥50 nmol/L	P value
Women, n (%)	157 (43.9)	170 (54.8)	0.005
Age (years)	72.5 (1.17)	72.4 (1.07)	0.533
Systolic blood pressure (mmHg)	151 (21.5)	148 (21.3)	0.125
Waist (cm)	103.1 (40.31)	97.2 (15.25)	0.021
Weight (kg)	83.4 (14.98)	78.1 (14.71)	<0.001
BMI (kg/m ²)	29.5 (4.75)	28.2 (4.44)	<0.001
Plasma glucose (mmol/L)	5.6 (4.8–6.1)	5.4 (4.9–6.1)	0.671
HbA _{1c} (mmol/mol)*	42.1 (38.80–46.45)	41.0 (38.80–44.26)	0.007
Plasma insulin (pmol/L)	40 (27–61)	38 (26–53)	0.034
HOMA-IR†	9.8 (6.1–15.8)	9.0 (6.1–13.4)	0.035
HOMA-B‡	40.7 (27.2–58.3)	39.8 (26.3–54.1)	0.042
Triacylglyceride (mmol/L)	1.5 (0.70)	1.5 (0.77)	0.657
HDL-cholesterol (mmol/L)	1.5 (0.35)	1.6 (0.37)	0.003
Total PCB‡ (μg/g lipid)	8.9 (4.8–14.7)	8.0 (4.7–13.4)	0.195

Data are means (SD) or median (25–75th percentile). *HbA_{1c} (IFCC) mmol/mol can be converted to HbA_{1c} (DCCT) % by the following equation: HbA_{1c} (DCCT) % = 0.0915 × HbA_{1c} (IFCC) mmol/mol + 2.15; †HOMA-IR = (fasting plasma insulin × fasting plasma glucose)/22.5; ‡HOMA-B = (20 × fasting plasma insulin)/(fasting plasma glucose × 3.5); ‡sum of major PCB congeners CB-138, CB-153, and CB-180 multiplied by 2 (12).

Obesity is a risk factor for vitamin D deficiency, and obese subjects had a lower serum 25(OH)D₃ concentration than nonobese subjects (11). Furthermore, we have previously demonstrated in this cohort (11) that women have higher serum 25(OH)D₃ concentration and tend to have lower BMI. However, we did not find any interaction between vitamin D status and sex ($P = 0.19$) or vitamin D status and obesity ($P = 0.84$) on risk of diabetes.

Statistically significant bivariate correlations were observed between serum 25(OH)D₃ concentration and several indicators of glucose metabolism, including

HbA_{1c} ($r_s = -0.10$; $P = 0.01$), fasting plasma insulin ($r_s = -0.10$; $P = 0.01$), HOMA-IR ($r_s = -0.10$; $P = 0.01$), and HOMA-B ($r_s = -0.10$; $P = 0.01$), whereas the plasma glucose concentration ($r_s = -0.01$; $P = 0.78$) was not correlated with 25(OH)D₃ concentration. However, because BMI was strongly associated with vitamin D status ($r_s = -0.17$; $P < 0.0001$), the observed associations of 25(OH)D₃ with fasting plasma insulin and the HOMA indexes were substantially reduced after adjustment for BMI, sex, smoking status, and serum triacylglyceride concentration, where none of them

were statistically significant (Table 3). However, HbA_{1c} decreased at higher serum 25(OH)D₃ concentrations after adjustment ($\beta = -0.026$, $P = 0.026$). Excluding subjects with physician-diagnosed type 2 diabetes resulted in a smaller effect that was no longer significant, probably because of reduced variation in HbA_{1c} concentration and fewer observations ($\beta = -0.012$, $P = 0.112$) (Table 2). Finally, multiple regression analysis did not reveal any association between frequency of fish dinners and the HbA_{1c} concentration (results not shown).

CONCLUSIONS—In this cross-sectional analysis of a population-based sample of septuagenarians, we found that the 25(OH)D₃ concentration was inversely associated with the risk of newly diagnosed type 2 diabetes after adjustment for BMI and other established risk factors for type 2 diabetes. Subjects with 25(OH)D₃ concentration below 50 nmol/L had the doubled risk of newly diagnosed diabetes compared with those having higher serum concentrations. Therefore, our data suggest an inverse association between the serum concentration of 25(OH)D₃ and the odds of newly diagnosed type 2 diabetes, thereby suggesting a protective role of vitamin D against the development of the disease, as suggested previously (13). In further support of this association, we observed an increasing concentration of HbA_{1c} with decreasing 25(OH)D₃ concentration, and this association was independent of BMI, serum triacylglycerides, smoking status, and sex. Vitamin D deficiency showed a much weaker OR for type 2 diabetes previously diagnosed, as could perhaps have been anticipated, given the vigorous clinical management of the disease and the longer time interval between disease development and the assessment of vitamin D status. The confidence interval for the OR for the two groups of type 2 diabetes continues to overlap considerably, and therefore, the slight difference should not be overinterpreted (Table 2).

HbA_{1c} is considered an indicator of average blood glucose concentrations during the preceding 2 to 3 months and, thus, a long-term marker of glucose homeostasis (14). Abnormalities may be a result of changes in insulin secretion and insulin-stimulated uptake of glucose in muscle and fat tissue. In vitro studies and laboratory animal studies suggest possible mechanisms for the effects of the active form of vitamin D, i.e., 1,25(OH)₂D,

Table 2—Unadjusted and adjusted OR for type 2 diabetes in elderly Faroese aged 70–74 years

25(OH)D ₃	Nondiabetic*	No. subjects	Crude OR† (95% CI)	P value	Adjusted OR‡ (95% CI)	P value
All type 2 diabetic subjects						
≥50 nmol/L	218	55	1.00		1.00	
<50 nmol/L	217	103	1.80 (1.23–2.64)	0.002	1.67 (1.11–2.50)	0.013
New subjects (b)						
≥50 nmol/L	218	22	1.00		1.00	
<50 nmol/L	217	48	2.24 (1.31–3.86)	0.003	1.99 (1.14–3.48)	0.016
Previously known subjects (c)						
≥50 nmol/L	218	33	1.00		1.00	
<50 nmol/L	217	55	1.57 (0.97–2.52)	0.064	1.47 (0.89–2.49)	0.132

Data are OR (95% CI) expressed for binary traits. *Nondiabetic subjects have fasting blood glucose ≤6 mmol/L; †the crude model is adjusted for sex and compares the odds of either overall type 2 diabetes (all type 2 diabetic subjects), newly diagnosed type 2 diabetes (new subjects), or known type 2 diabetes in subjects (previously known subjects) with 25(OH)D <50 nmol/L with the odds in subjects with 25(OH)D ≥50 nmol/L (reference group); ‡the adjusted model includes sex, BMI, total PCB, month of blood sampling, serum triacylglyceride concentration, serum HDL concentration, and smoking status.

Table 3—Linear regression coefficients for the association between 25(OH)D₃ and markers of glucose metabolism in elderly Faroese including or excluding subjects with known diabetes

	n*	β-Estimate† (95% CI)	P value
All subjects			
Insulin	659	−0.015 (−0.109 to 0.079)	0.755
Glucose	648	−0.002 (−0.007 to 0.003)	0.459
HbA _{1c}	659	−0.026 (−0.049 to −0.003)	0.026
HOMA-IR	646	−0.016 (0.043–0.011)	0.249
HOMA-B	646	−0.021 (−0.123 to 0.082)	0.691
Subjects without known diabetes			
Insulin	573	0.010 (−0.075 to 0.095)	0.824
Glucose	563	0.00008 (−0.004 to 0.004)	0.967
HbA _{1c}	573	−0.011 (−0.027 to 0.005)	0.192
HOMA-IR	561	−0.002 (−0.025 to 0.021)	0.869
HOMA-B	561	0.012 (−0.091 to −0.117)	0.806

*Numbers vary because of varying missing sample material for each biochemical analysis. †Adjustment included BMI, sex, smoking status, and serum triacylglyceride concentration.

on both insulin secretion and insulin sensitivity as reviewed by Pittas and Dawson-Hughes (15). For instance, in mice expressing a functionally inactive mutant vitamin D receptor, blood glucose concentrations were increased and serum insulin was reduced, as was insulin mRNA. Pancreatic β-cells express the vitamin D receptor and the enzyme 1-α-hydroxylase, thus suggesting that the active form of vitamin D has a functional role in these cells. Even though the current study cannot elucidate the likely mechanisms involved, our results appear highly plausible given the findings in experimental studies.

In this Faroese population of septuagenarians, 37% are obese (11). Increased fat mass adversely influences glucose metabolism, in part by increasing insulin resistance, and is also linked with lower 25(OH)D concentrations in serum (16–18). Therefore, we adjusted our data for BMI. The results suggest that the negative impact of vitamin D deficiency on HbA_{1c} and newly diagnosed type 2 diabetes risk is independent of increased fat mass. However, because BMI does not distinguish visceral from subcutaneous fat, some misclassification of adiposity may have occurred, thereby possibly causing some uncertainty in regard to the relative influence of serum 25(OH)D₃ and adiposity in diabetes development.

Our study results are comparable with studies on vitamin D status and type 2 diabetes in younger populations (4,16,19,20), and the current study extends this association to 70 years of age and older. Vitamin D status is known to

be lower in the elderly compared with the young as the subcutaneous synthesis of vitamin D decreases with increasing age, due to a reduced concentration of 7-dehydrocholesterol in the skin (1) and reduced absorption of oral vitamin D (8). Hence, if the relationship between vitamin D status and glucose homeostasis is causal, the age-related decline in circulating concentration of 25(OH)D may augment the increase in risk of type 2 diabetes with age. In addition, our results suggest that this relationship is not the result of increased fish intake, in agreement with the existing, somewhat equivocal evidence in regard to this effect (21,22). These differences may be a result of variations in fish intake to inherent differences in the populations examined and the study designs.

Among the strengths of our study, we examined a general population sample with a high prevalence of both vitamin D deficiency (11) and type 2 diabetes. However, the current study is limited by its cross-sectional design and its single measurement of vitamin D status. Nonetheless, a recent study demonstrated excellent tracking and that the correlation of serum 25(OH)D₃ concentrations sampled 14 years apart was similar to that seen for other cardiovascular risk factors and that most subjects with vitamin D deficiency were still deficient 14 years later (23).

Patients with type 2 diabetes and elevated HbA_{1c} concentrations are at increased risk of cardiovascular disease and total mortality compared with patients with lower HbA_{1c} levels (24). Thus, clinical management focuses on glycemic

control, including treatment of other modifiable cardiovascular risk factors to reduce the macro- as well as microvascular complications. The inverse association between serum 25(OH)D₃ and HbA_{1c} suggests that vitamin D supplementation could be considered a possible means for supporting glycemic control of type 2 diabetes. However, some intervention studies have shown inconclusive results on the effect of vitamin D on HbA_{1c} and type 2 diabetes (15). For example, the Women Health's Initiative demonstrated that daily supplementation with 10 μg of vitamin D₃ for a median follow-up time of 7 years did not reduce the risk of type 2 diabetes in postmenopausal women (25). However, the doses used were probably too low to bring about the necessary concentrations of circulating 25(OH)D₃. Therefore, further randomized clinical intervention studies are needed to elucidate the impact of vitamin D on the risk of type 2 diabetes.

In summary, our study extends previous findings that a high vitamin D status protects against type 2 diabetes in younger subjects to subjects older than 70 years. Likewise, our findings suggest an inverse association between HbA_{1c} and 25(OH)D₃ also in the elderly. Because our study has a cross-sectional design, formal confirmation requires intervention studies with appropriate doses to elucidate whether vitamin D supplementation could be used to counter the worldwide epidemic of type 2 diabetes. In this regard, the need to identify the necessary daily intake of vitamin D should include the possible effect on reducing the risk of type 2 diabetes, with special emphasis on the dietary needs of the elderly.

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C.D. designed the current study within the cohort study established by P.W. and P.G. and researched data, performed statistical analyses, and drafted the manuscript. M.S.P. and P.W. carried out the clinical examinations and established the clinical database. P.G. designed the current study within the cohort study established by P.W. and P.G. C.D., P.G., and P.W. have the primary responsibility for the final content. All authors contributed to

critical comments to the manuscript and approved the final version.

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