Vitamin D Status and Glucose Homeostasis in the 1958 British Birth Cohort

The role of obesity

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OBJECTIVE — Obesity is a well-known risk factor for vitamin D deficiency. We evaluated the interrelationship between vitamin D status, body size, and glucose homeostasis, measured by HbA_{1c} (A1C).

RESEARCH DESIGN AND METHODS — Data are from the survey of the 45-year-old 1958 British birth cohort (2002–2004). Information on A1C, 25-hydroxyvitamin D [25(OH)D; an indicator of vitamin D status], and BMI was collected from 7,198 Caucasian subjects.

RESULTS — 25(OH)D was <75 nmol/l in 80% of the obese subjects (BMI ≥30 kg/m^2) versus 68% of the other subjects ($P < 0.0001$). Serum 25(OH)D decreased and A1C increased by increasing BMI ($P < 0.0001$ for both comparisons). There was a nonlinear association between 25(OH)D and A1C: a steep linear decrease in A1C by 25(OH)D until 65 nmol/l and only smaller decreases with further increases. There was evidence for effect modification by BMI in the association between 25(OH)D and A1C ($P < 0.0001$), and differences appeared stronger for participants with higher compared with lower BMIs. After adjustment for sex, season, geographical location, physical activity, and social class, percent change in A1C by 10-nmol/l increase in 25(OH)D was −0.21 (95% CI −0.31 to −0.11) for BMI <25 kg/m^2, −0.25 (−0.37 to −0.13) for BMI 25–29.9 kg/m^2, −0.65 (−0.95 to −0.34) for BMI 30–34.9 kg/m^2, and −1.37 (−2.09 to −0.64) for BMI ≥35 kg/m^2.

CONCLUSIONS — Body size was a strong determinant for 25(OH)D, with concentrations being suboptimal in most obese participants. Randomized controlled trials [using dosages sufficient to improve 25(OH)D also for the obese] are required to determine whether clinically relevant improvements in glucose metabolism can be obtained by vitamin D supplementation.

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Obesity is an established risk factor for vitamin D deficiency (1–3). Total body fat is inversely associated with serum 25-hydroxyvitamin D [25(OH)D; a measure of vitamin D status], and higher storage in adipose tissue is a plausible explanation for increased rates of deficiency in obese individuals (4). Obesity is the most important known determinant of type 2 diabetes and related disturbances in glucose metabolism. Vitamin D deficiency is also suspected to be a risk factor for type 2 diabetes (5), although it has been argued that the influence of vitamin D is weak and that obesity may modify the association between 25(OH)D and insulin sensitivity (6). Observational studies suggest that the association between 25(OH)D and impairments in glucose metabolism is independent of body size (5,7,8). However, body size has been accounted for only by adjustment for BMI, and more detailed investigation of the role of obesity has not been undertaken, possibly due to lack of power in previous studies. We investigated the interrelationship between 25(OH)D and obesity in relation to glucose metabolism (measured by HbA_{1c} [A1C]) in the 1958 British birth cohort aged 45 years.

RESEARCH DESIGN AND METHODS

— Participants in the cohort were all born in England, Scotland, or Wales during 1 week in March 1958 (n = 16,751). A detailed description of the study is provided elsewhere (9). At age 45 years, a target population (12,069 individuals currently living in Britain) was invited to participate in a biomedical assessment: of these, 78% (n = 9,349) participated in a questionnaire survey and 81% (n = 7,591) also provided blood samples from which 25(OH)D was measured. A total of 154 non-Caucasian subjects and 61 participants who had type 1 diabetes (self-reported at 42 years of age) or who used insulin (45 years of age) were excluded. Among the remainder, 88 participants had type 2 diabetes, of whom 73 used one or more types of oral medication (42 sulfonylureas, 55 biguanides, and 10 other). The main analyses were conducted on 7,189 participants, with full information on A1C, 25(OH)D, and BMI. Written consent for the use of information in medical studies was obtained from cohort members. The 45-year survey was approved by the South-East Multi-Centre Research Ethics Committee.

A1C was measured in a nonfasted venous blood sample, using liquid chromatography, and the results were standardized to the Diabetes Control and Complications Trial (10,11). 25(OH)D was measured using automated application of the IDS OCTEIA enzyme immunoassay on the Dade-Behring BEP2000 analyzer [sensitivity 5.0 nmol/l; linearity up to at least 155 nmol/l; and imprecision 7.2, 5.5, and 6.9% at 25(OH)D concentration levels of 16.1, 72.5, and 94.8 nmol/l, respectively] (12). 25(OH)D was standardized according to the mean of the vitamin D External Quality Assurance Survey (13,14).

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Abbreviations: 25(OH)D, 25-hydroxyvitamin D.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.
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Table 1—*Interrelation between 25(OH)D, BMI, and A1C in the 1958 British birth cohort (aged 45 years)*

		25(OH)D (nmol/l)				
	Geometric mean	<25	25–49.9	50–74.9	≥75	*P*
All		7.8 (561)	33.4 (2,424)	34.2 (2,459)	24.2 (1,745)	
BMI*						
Normal	54.6†	7.8 (196)	29.3 (738)	34.0 (857)	29.0 (731)	
Overweight	53.9	6.1 (181)	32.6 (968)	36.1 (1,072)	25.3 (753)	
Obese	47.8	9.3 (112)	40.9 (497)	32.1 (390)	17.7 (215)	
Severely obese	42.6	15.0 (72)	46.1 (221)	29.2 (140)	9.6 (46)	
	$P < 0.0001$					
			A1C			
All		5.37	5.26	5.16	5.12	<0.0001
BMI*						
Normal	5.12‡	5.15	5.17	5.11	5.09	<0.0001
Overweight	5.15	5.30	5.18	5.15	5.12	<0.0001
Obese	5.30	5.55	5.31	5.21	5.20	<0.0001
Severely obese	5.63	5.68	5.75	5.47	5.44	0.0001
	$P < 0.0001$					

Data are (%) *n* or geometric mean. All means are standardized by sex and season. *P* values test for trend in linear regression is adjusted for sex and season. *Normal: BMI <25 kg/m^2, $n = 2,522$; overweight, BMI 25–29.9 kg/m^2, $n = 2,974$; obese: BMI 30–34.9 kg/m^2, $n = 1,214$; and severely obese: BMI >35 kg/m^2, $n = 479$. †Geometric mean of 25(OH)D. ‡Geometric mean of A1C.

Statistical analysis

Natural log transformation was used to reduce skewness in the distribution for A1C, 25(OH)D, and BMI. Log-transformed values were used in calculating means (i.e., geometric means) and for the outcome in linear regression analyses. Main analyses were repeated by restricting data to participants without disturbances in glucose metabolism ($n = 7,064$); individuals with type 2 diabetes and/or A1C >7% were excluded ($n = 125$). Broken-stick regression was used to determine break point for the change in slope in the association between 25(OH)D and A1C (15). Multiple imputation (10 cycles) was used for missing information on waist circumference or physical activity ($n = 238$) (16). All analyses were carried out using STATA version 9.

RESULTS — Serum 25(OH)D level decreased and A1C increased with increasing BMI (Table 1, *column 1*). 25(OH)D was <75 nmol/l in 80% of the obese subjects versus 68% of the nonobese subjects ($P < 0.0001$). There was an inverse but nonlinear association between 25(OH)D and A1C (curvature, $P < 0.0001$). Graphical examination and break-point analysis showed that the trend of decreasing A1C by increasing 25(OH)D was the steepest for concentrations ≤65 nmol/l, with a weaker association at higher concentrations.

Participants with disturbed glucose metabolism, as indicated by type 2 diabetes or A1C >7%, had higher BMIs than others (geometric mean standardized by season and sex: 33.3 vs. 26.8 kg/m^2, $P < 0.0001$) and lower 25(OH)D concentrations (36.9 vs. 52.7 nmol/l, $P < 0.0001$). When subjects with disturbed glucose metabolism were excluded, the association between 25(OH)D and A1C weakened: the percentage change in A1C per 10-unit increase was −0.27 (95% CI −0.33 to −0.20) compared with −0.49 (−0.58 to −0.40) in the full sample, after adjustment for sex, season, physical activity, geographical location, and social class. Further adjustment for BMI and waist circumference attenuated the association between 25(OH)D and A1C (−0.16 [−0.22 to −0.10] and −0.27 [−0.36 to −0.18], for the restricted and full samples, respectively). The association between A1C and 25(OH)D was weaker for normal-weight individuals than for obese individuals (Table 1): tests for interaction were significant in the restricted ($P = 0.03$) and full ($P < 0.0001$) sample. In the full sample, the adjusted percentage change in A1C per 10-nmol/l increase in 25(OH)D was −0.21 (−0.31 to −0.11) for BMI <25 kg/m^2, −0.25 (−0.37 to −0.13) for BMI 25–29.9 kg/m^2, −0.65 (−0.95 to −0.34) for BMI 30–34.9 kg/m^2, and −1.37 (−2.09 to −0.64) for BMI ≥35 kg/m^2.

CONCLUSIONS — The main strength of our study lies in the large sample of participants with information on 25(OH)D, BMI, and glucose metabolism, with sufficient power for detailed investigation of these interrelated biomarkers. An additional strength is the availability of relevant confounding factors. Because of practical limitations, fasting samples or glucose tolerance tests are not available, which is the main limitation of the study; we cannot discount underlying measurement error in A1C diluting observed associations.

Together with previous findings (5,7,8), our results suggest that current vitamin D status may influence glucose metabolism. Also, our study suggests that the reported association between vitamin D and glucose metabolism (5,7,8) may depend on body size. Interestingly, these data suggested that the decrease in A1C with increasing 25(OH)D was the steepest in levels <65 nmol/l, with some small decreases with further increases. This fits in well with current estimates for optimal status for bone health (75 nmol/l) (13). In this population, >80% of obese participants had 25(OH)D <75 nmol/l. These findings are potentially important for public health, if improvement in vitamin D status in obese individuals reduces the otherwise inevitable adverse effects of excess weight for glucose metabolism. However, our findings need to be confirmed in further studies before the implications for public health can be established. Randomized controlled trials [using dosages sufficient to improve 25(OH)D levels for

the obese] are required to determine whether clinically relevant improvements in glucose metabolism can be obtained by vitamin D supplementation.

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