# Effects of Vitamin D Supplementation on Insulin Sensitivity and Insulin Secretion in Subjects With Type 2 Diabetes and Vitamin D Deficiency: A Randomized Controlled Trial

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*Diabetes Care 2017;40:872–878 | https://doi.org/10.2337/dc16-2302*


## OBJECTIVE

**In observational studies, low vitamin D levels are associated with type 2 diabetes (T2D), impaired glucose metabolism, insulin sensitivity, and insulin secretion. We evaluated the efficacy of vitamin D supplementation on insulin sensitivity and insulin secretion in subjects with T2D and low vitamin D (25-hydroxyvitamin D [25(OH)D] <50 nmol/L).**

## RESEARCH DESIGN AND METHODS

**Sixty-two men and women with T2D and vitamin D deficiency participated in a 6-month randomized, double-blind, placebo-controlled trial. Participants received a single dose of 400,000 IU oral vitamin $D_3$ or placebo, and the vitamin D group received an additional 200,000 IU $D_3$ if serum 25(OH)D was <100 nmol/L after 4 weeks. Primary end points were total $R_d$ by euglycemic clamp with assessment of endogenous glucose production and first-phase insulin secretion by intravenous glucose tolerance test.**

## RESULTS

**In the vitamin D group, the mean ± SD baseline serum 25(OH)D of 38.0 ± 12.6 nmol/L increased to 96.9 ± 18.3 nmol/L after 4 weeks, 73.2 ± 13.7 nmol/L after 3 months, and 53.7 ± 9.2 nmol/L after 6 months. The total exposure to 25(OH)D during 6 months (area under the curve) was 1,870 ± 192 and 1,090 ± 377 nmol/L per week in the vitamin D and placebo groups, respectively ($P < 0.001$). Insulin sensitivity, endogenous glucose production, and glycemic control did not differ between or within groups after treatment ($P = 0.52$). First-phase insulin secretion did not change significantly after treatment ($P = 0.10$).**

## CONCLUSIONS

**Replenishment with a large dose of vitamin $D_3$ to patients with T2D and vitamin D deficiency did not change insulin sensitivity or insulin secretion. These findings do not support such use of therapeutic vitamin $D_3$ supplementation to improve glucose homeostasis in patients with T2D.**


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*Received 27 October 2016 and accepted 11 April 2017.*

*Clinical trial reg. no. NCT00992797, clinicaltrials.gov.*

*This article is featured in a podcast available at http://www.diabetesjournals.org/content/diabetes-core-update-podcasts.*

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The role of vitamin D in noncommunicable chronic diseases and the potential impact of vitamin D supplementation as a preventive and therapeutic measure are unclear and debated (1,2). In cross-sectional epidemiological studies, insufficient vitamin D status is associated with the development of obesity, the metabolic syndrome, and type 2 diabetes (T2D) in many but not all reports (3–5). The main pathophysiological features of T2D are impaired insulin sensitivity and insulin secretion, and in observational studies, vitamin D deficiency has been linked to both insulin resistance and decreased β-cell function. Evidence from randomized controlled trials of vitamin D supplementation on glucose metabolism is conflicting (4,6–8), and studies in established T2D usually have been limited by sample size, short duration, use of low supplemental doses of vitamin D, and use of surrogate measures of insulin sensitivity and insulin secretion (9–13). The objective of this randomized controlled trial, therefore, was to investigate the efficacy of high-bolus–dose vitamin D supplementation on insulin sensitivity and insulin secretion in subjects with T2D and vitamin D deficiency.

## RESEARCH DESIGN AND METHODS

We performed a single-center, parallel-group, double-blind, randomized, placebo-controlled trial in 62 men and women with T2D and vitamin D deficiency, testing the efficacy of high-dose vitamin $D_3$ (cholecalciferol) supplementation on insulin sensitivity and insulin secretion after 6 months of follow-up as measured by euglycemic-hyperinsulinemic clamp and intravenous glucose tolerance test (IVGTT). Primary outcome assessments were done after 6 months, and safety outcomes were recorded at 4 weeks and 3 months after randomization. The study was performed at the diabetes research laboratory of Oslo University Hospital and was approved by the South-Eastern Norway Regional Committee for Medical and Health Research Ethics (Oslo, Norway). All subjects provided written informed consent before participation in the trial.

We recruited patients from our department of endocrinology outpatient clinic, from general practices, through posters in the hospital lobby and in pharmacies, and from advertisements in local newspapers. A screening visit was performed to check eligibility. Eligible individuals were men and women >18 years of age with T2D, regardless of type of antidiabetic treatment; of Nordic or South Asian ethnicity; and with vitamin D deficiency defined as serum 25-hydroxyvitamin D [25(OH)D] ≤50 nmol/L. Exclusion criteria were 25(OH)D >50 nmol/L, serum level of free calcium >1.35 mmol/L, $HbA_{1c}$ >11% (97 mmol/mol), autoimmune diabetes (elevated anti-GAD or anti-IA2 autoantibodies), and BMI >45 kg/$m^2$. Subjects with malignancy, history of kidney stones, cardiovascular events in the past 6 months, glomerular filtration rate <30 mL/min/1.73 $m^2$, blood pressure >160/100 mmHg, or chronic inflammatory disease in the active phase and pregnant or lactating women were not allowed to participate. South Asian ethnicity was defined as being an immigrant from Bangladesh, Pakistan, India, or Sri Lanka or being born to parents from these countries. Subjects were not allowed to use high-dose vitamin D supplements during the trial and were requested to not change their dietary habits or their use of multivitamins.

After enrollment in the study, subjects were randomly assigned to treatment with vitamin $D_3$ or placebo in a 1:1 allocation ratio. Randomization was done with MINIM (Minimization Program for Allocating Patients to Clinical Trials, Department of Clinical Epidemiology, The Royal London Hospital Medical College, London, U.K.) (14). The minimization algorithm ensured a balanced allocation of subjects across the intervention groups for the following important prognostic factors: screening 25(OH)D concentration, screening $HbA_{1c}$, BMI, and Nordic or South Asian ethnicity. Subject randomization and safety monitoring as well as study drug labeling and dispensing were done by staff not involved in the clinical trial or recruitment. All subjects, clinical investigators, and outcome assessors were blind to treatment allocation.

Oral liquid vitamin $D_3$ 200,000 IU/ampoule was purchased from Novartis Santé Familiale S.A.S. Subjects randomized to vitamin D supplementation were given a single dose of 400,000 IU vitamin $D_3$ dissolved in 0.5 dL orange juice with added lemon essences to mask the smell and taste of the liquid vitamin $D_3$, whereas placebo was given as only orange juice with added lemon essences. At week 4, 25(OH)D concentrations in serum were measured, and if <100 nmol/L, subjects allocated to the vitamin D group were given an additional 200,000 IU vitamin $D_3$. All others were given placebo orange juice. All investigational medication was taken under supervision to ensure 100% compliance, and all subjects in both groups were given calcium supplementation of 250 mg b.i.d. during a run-in period of 4 weeks before randomization and throughout the 26-week study period to optimize calcium intake.

The coprimary study outcomes were insulin sensitivity and insulin secretion. Insulin secretion was estimated by IVGTT, and insulin sensitivity by euglycemic-hyperinsulinemic clamp, with indirect calorimetry and estimation of endogenous glucose production (EGP) as previously described (15). Briefly, a primed, continuous infusion of [6,6-2H2]-glucose (Cambridge Isotope Laboratories, Andover, MA) was maintained throughout the experiment. After a 2-h tracer equilibration period, the IVGTT was performed; 50% glucose 0.3 g/kg was injected intravenously and blood drawn for glucose, insulin, and C-peptide measurements at 0, 2, 4, 6, 8, 10, 15, 20, and 30 min. Insulin secretion was calculated as the incremental area under the curve (AUC) for insulin time 0–8 min (incremental $insulin_{AUC\ 0–8\ min}$) and as increase in C-peptide from 0 to 30 min. Insulin secretion adjusted for insulin sensitivity (the disposition index) was calculated as the product of incremental $insulin_{AUC\ 0–8\ min}$ and total $R_d$. After the IVGTT, a euglycemic clamp was started with an insulin infusion rate of 80 mU/$m^2$/min by using human insulin (Actrapid; Novo Nordisk, Bagsværd, Denmark). A variable infusion of glucose 200 mg/mL enriched with 8 mg [6,6-2H2]glucose/g glucose was continually adjusted to maintain euglycemia. The clamp was maintained for a minimum of 150 min until at least 30 min of stable euglycemia was obtained. Insulin sensitivity was calculated as total $R_d$, including both the exogenous glucose infusion rate and the EGP estimated by the stable isotope dilution method (15). Oxidative and nonoxidative glucose metabolism was assessed with indirect calorimetry by using a Jaeger Oxycon Pro (Viasys Healthcare, Höchberg, Germany) computerized flow-through canopy gas analyzer system. On the basis of $VO_2$

and $VCO_2$ measurements, carbohydrate and lipid oxidation rates were calculated by using modified Frayn equations.

Whole-blood glucose was measured by the glucose oxidase method (YSI 2300; Yellow Springs Instruments, Yellow Springs, OH), and plasma glucose was calculated (whole-blood glucose × 1.119). $HbA_{1c}$ was measured by high-performance liquid chromatography on a Tosoh G7 Analyzer (Tosoh Bioscience, Tokyo, Japan), serum insulin and C-peptide by using DELFIA immunofluorometric assays (PerkinElmer Life Sciences [formerly Wallac Oy], Turku, Finland), and 25(OH)D with a radioimmunoassay kit (DiaSorin, Stillwater, MN). [6,6-2H2]Glucose was measured by liquid chromatography tandem mass spectrometry through turbulent flow chromatography (RXT1; Cohesive Technologies, Franklin, MA) combined with tandem mass spectrometry (Sciex API 3000; Applied Biosystems, Foster City, CA) at the Clinical Metabolomics Core Facility (Rigshospitalet, Copenhagen, Denmark). Free calcium was measured on a Rapidlab 348 pH/blood gas analyzer (Bayer Diagnostics, Reading, U.K.) and creatinine by enzymatic method on a Modular P chemistry analyzer (Roche, Mannheim, Germany).

Oversight was provided by a safety committee. Before the week 4 titration and after 3 and 6 months, free calcium and kidney function were measured, and the laboratory values were monitored by independent safety personnel. Any safety measurements outside the normal range were repeated and appropriate actions taken. Subjects with hypercalcemia (free calcium ≥1.36 nmol/L) were not given an additional dose of vitamin D. Safety outcomes were hypercalcemia, kidney function, and reported adverse events.

Study power was calculated with SPSS SamplePower 2.0 software (IBM Corporation, Chicago, IL). A sample size of 30 subjects in each of the two treatment groups provided 80% power to detect a 1.0 mg/kg/min difference in mean change from baseline in insulin sensitivity as measured by $R_d$. An SD of 1.3 mg/kg/min was used in the calculation, which was derived from our previous studies in patients with T2D. In addition, the sample size provided a 10% allowance for drop-outs.

Data are presented as mean ± SD or median (interquartile range) unless otherwise specified. We analyzed nonnormally distributed data log-transformed or by using nonparametric methods as appropriate. Student *t* tests or Mann-Whitney *U* tests were used for comparison of continuous variables between groups, and paired-sample *t* tests were used for within-group analyses of change. For comparison of categorical data between patient groups, the $\chi^2$ test for independence was used. One-way between-group ANCOVA was performed, with preliminary checks to ensure no violation of the assumptions of normality, linearity, homogeneity of variances, and homogeneity of regression slopes. Data were analyzed as intention to treat with the last observation carried forward. Total exposure to vitamin D during the study period was calculated as the individual areas under the serum concentration curves derived from the measurements at baseline and after 4, 13, and 26 weeks and by using the trapezoidal rule. A two-sided $P < 0.05$ was deemed significant and not adjusted for multiple testing. Statistical analyses were performed with SPSS version 19.0 software.

## RESULTS

### Study Recruitment and Follow-up

We screened 191 patients with T2D to randomly allocate 62 subjects to treatment with vitamin D ($n = 33$) and placebo ($n = 29$) (Fig. 1). The main exclusion criteria were 25(OH)D concentrations >50 nmol/L or previous kidney stone disease. Three subjects withdrew consent during the study.

### Baseline Characteristics

Twenty-five (40.3%) subjects were women, 43 were of Nordic ethnicity, and 19 were of South Asian ethnicity. Subject were (mean ± SD) 55.7 ± 9.5 years old, their BMI was 31.9 ± 4.9 kg/m$^2$ and $HbA_{1c}$ 7.8 ± 1.4% (62 mmol/mol), and their diabetes duration was 10.0 ± 6.4 years. Only 10 subjects did not use glucose-lowering medication, and 27 were treated with insulin. Subject characteristics showed a fairly typical population of patients with T2D, 8% and 16%, respectively, reported macro- or microvascular complications, 63% used statins, 61% used blood pressure–lowering drugs, and 32% used aspirin. Further baseline subject characteristics are presented in Table 1.

### Serum Levels of 25(OH)D

The mean serum 25(OH)D concentrations increased from 38.0 ± 12.6 nmol/L at baseline in the vitamin D group to 96.9 ± 18.3 and 73.2 ± 13.7 nmol/L after 4 weeks and 3 months, respectively. In the placebo group, the mean 25(OH)D concentration was 36.8 ± 12.6 nmol/L at baseline and did not change significantly throughout the study. After 6 months, the mean 25(OH)D concentration was 53.7 ± 9.2 nmol/L in the vitamin D group and 38.2 ± 12.9 nmol/L in the placebo group ($P < 0.001$), thus maintaining a difference of >15 nmol/L over the 6-month period. The total exposure to 25(OH)D during 6 months ($AUC_{0–26\ weeks}$) was 1,870 ± 192 nmol/L per week in the vitamin D group and 1,090 ± 377 nmol/L per week in the placebo group ($P < 0.001$). In the vitamin D group, 16 (48.5%) subjects reached the target serum 25(OH)D of ≥100 nmol/L after 4 weeks, and the remaining 17 (51.5%) subjects were given a second dose of 200,000 IU vitamin $D_3$ according to protocol.

### Outcomes

No significant differences were found between the vitamin D and placebo groups in the primary end points. The change in insulin sensitivity measured as the total $R_d$ between baseline and 6-month follow-up showed no significant difference between the vitamin D and placebo groups ($P = 0.52$) and no significant changes in insulin sensitivity within either group (Table 2). The change in first-phase insulin secretion measured as the incremental $insulin_{AUC\ 0–8\ min}$ did not differ between groups ($P = 0.10$), and no within-group changes during treatment were found. The increase in C-peptide after IVGTT, measured as ΔC-peptide 0–30 min, was significantly lower in the vitamin D group postintervention ($P = 0.017$). Insulin secretion adjusted for insulin sensitivity (the disposition index) did not change during the study period ($P = 0.67$). Glycemic control, measured as fasting plasma glucose and $HbA_{1c}$, did not change during the study and did not differ between groups; fasting levels of insulin and C-peptide also did not change (Table 2). HOMA indexes did not change and were not different within or between groups (data not shown). No significant interaction existed between the vitamin D level at baseline and the changes in

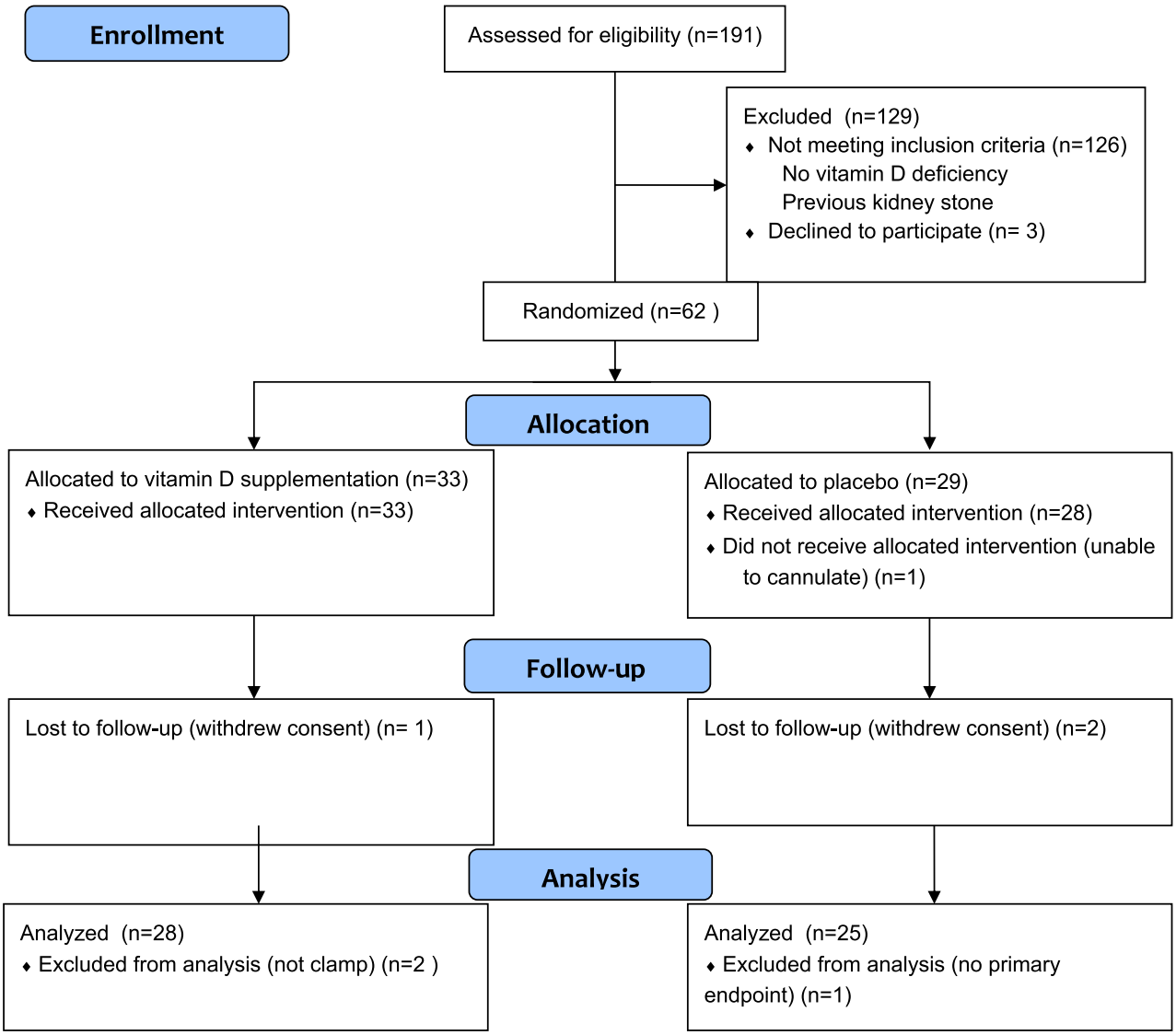


**Figure 1**—Flow diagram.

insulin secretion or action after administration of vitamin D.

Glucose-lowering medication was minimally changed during the trial; however, small adjustments in insulin doses were allowed, and no differences were observed between the two groups. In the subset of patients that did not change glucose-lowering medication during the study, the results remained the same.

Resting energy expenditure decreased significantly within the vitamin D group (−69 ± 133 kcal/day; $P = 0.03$), but neither energy expenditure nor substrate utilization differed significantly between the vitamin D and placebo groups after treatment. There was a tendency for a reduction in fat oxidation both in fasting state and during the euglycemic clamp after the vitamin D intervention; however, the difference in change between groups was not significant (Table 2).

### Safety

Overall, no important safety issues arose during administration of vitamin D. A transient rise in serum creatinine levels 4 weeks after randomization was seen in five subjects in the vitamin D group and four in the placebo group. The serum level of free calcium increased to levels slightly above the laboratory's upper normal reference limit in three patients in the placebo group but none in the vitamin D group. All values returned to baseline within 6 months and did not have clinical implications. Four adverse events qualified as serious adverse events, and all occurred in the placebo group. These serious adverse events included noncardiac chest pain before randomization, one myocardial infarction, one severe infection of the hand as a result of a *Mycobacterium marinum* infection, and one traumatic jaw fracture.

## CONCLUSIONS

In this randomized controlled trial of vitamin D versus placebo in subjects with T2D and low levels of vitamin D, a high single dose of 400,000 IU vitamin $D_3$ supplemented with a second dose after 4 weeks if serum levels of 25(OH)D were <100 nmol/L did not improve insulin sensitivity or insulin secretion. The results are in line with a small study from Denmark that used high doses of vitamin D (16) and

**Table 1—Subject characteristics at baseline**

| Characteristic | Vitamin D ($n$ = 33) | Placebo ($n$ = 29) |
|---|---|---|
| Age (years) | 55.5 ± 9.2 | 55.9 ± 9.2 |
| Women | 15 (45.4) | 10 (34.5) |
| Ethnicity[a] | | |
| Nordic white | 23 (69.7) | 20 (69.0) |
| South Asian | 10 (30.3) | 9 (31.0) |
| Weight (kg) | 92.8 ± 16.6 | 92.8 ± 18.5 |
| BMI (kg/m$^2$) | 32.5 ± 5.1 | 31.1 ± 4.7 |
| Serum 25(OH)D (nmol/L) | 38.0 ± 11.9 | 36.8 ± 12.6 |
| Diabetes duration (years) | 11.9 ± 6.6 | 7.9 ± 5.7 |
| $HbA_{1c}$ (% [mmol/mol]) | 7.9 ± 1.4 [62] | 7.6 ± 1.3 [60] |
| Diabetes treatment | | |
| Diet | 2 (6.1) | 8 (27.5) |
| OAH[b] | 13 (39.4) | 12 (41.4) |
| Insulin ± OAH | 18 (54.5) | 9 (31.0) |

Data are mean ± SD or $n$ (%). OAH, oral antihyperglycemic agent. [a]Ethnic groups are those identified by subjects themselves. [b]Includes metformin, sulfonylureas, pioglitazone, exenatide, and dipeptidyl peptidase 4 inhibitors.

several other studies that investigated the effect of vitamin D supplementation on glucose metabolism in various patient populations. Grimnes et al. (6) found no effect of 20,000 IU/week vitamin D supplementation on insulin sensitivity or insulin secretion in subjects with normal glucose tolerance, and similarly, Wagner et al. (8) found no effects of 30,000 IU/week in subjects with prediabetes or nonpharmacologically treated T2D. Jorde et al. (17) recently reported no effect of vitamin D supplementation for 5 years in preventing the development of T2D in subjects with prediabetes. In contrast, vitamin D supplementation was reported to improve insulin secretion in the Calcium and Vitamin D for Diabetes Mellitus study in patients with prediabetes and normal vitamin D levels (7), and a recent review reported beneficial effects of vitamin D supplementation in poorly controlled diabetes (13).

Strengths of this study include the randomized, double-blind design; the directly observed drug consumption; and the use of a gold standard methodology for assessing the end points. This method enabled us to measure fasting EGP and insulin sensitivity as well as carbohydrate and fat metabolism in both the basal and the hyperinsulinemic state. Many previous studies on vitamin D and insulin sensitivity have used surrogate markers, such as the HOMA indexes or the less-reproducible oral glucose tolerance test.

The main advantage of giving the vitamin D supplementation as one or two high doses only was to secure 100% compliance with the medication, as all interventional medication was taken under supervision. Moreover, all subjects got a rapid and significant increase in 25(OH)D

**Table 2—Effects of vitamin D supplementation on insulin sensitivity, insulin secretion, and glucose metabolism**

| | Vitamin D | | | Placebo | | | |
|---|---|---|---|---|---|---|---|
| | Baseline | Δ Study end | Within-group $P$ value | Baseline | Δ Study end | Within-group $P$ value | Between-group $P$ value |
| Fasting plasma glucose (mmol/L) | 11.3 ± 3.5 | 0.6 ± 2.6 | 0.32 | 10.0 ± 3.1 | 0.6 ± 2.8 | 0.26 | |
| $HbA_{1c}$ (%) | 7.9 ± 1.4 | −0.3 ± 0.9 | 0.11 | 7.5 ± 1.3 | −0.2 ± 0.5 | 0.052 | 0.98 |
| Fasting insulin (mmol/L) | 105 ± 143 | 1 ± 8 | 0.91 | 123 ± 99 | 21 ± 90 | 0.25 | 0.38 |
| Fasting C-peptide (pmol/L) | 1,026 ± 430 | 8 ± 264 | 0.87 | 1,162 ± 373 | 44 ± 242 | 0.37 | 0.73 |
| $AIR_g$ 0–8 | 161 ± 226 | 11 ± 28 | 0.70 | 294 ± 282 | −37 ± 276 | 0.51 | 0.10 |
| ΔC-peptide max | 484 ± 433 | −91 ± 378 | 0.20 | 592 ± 351 | 2 ± 215 | 0.97 | 0.04 |
| Glucose infusion rate (μmol/kg FFM/min) | 30.1 ± 17.0 | −0.6 ± 14.3 | 0.83 | 25.0 ± 14.4 | −0.5 ± 10.3 | 0.83 | 0.68 |
| Total $R_d$ (μmol/kg FFM/min) | 43.8 ± 20.3 | 1.9 ± 25.0 | 0.69 | 33.9 ± 15.4 | 2.3 ± 15.2 | 0.47 | 0.52 |
| Basal EGP (μmol/kg FFM/min) | 18.3 ± 6.6 | 1.6 ± 10.3 | 0.42 | 15.9 ± 6.2 | 1.7 ± 5.5 | 0.17 | 0.37 |
| Clamp EGP (μmol/kg FFM/min) | 12.9 ± 9.5 | 4.4 ± 17.4 | 0.19 | 9.5 ± 5.6 | 3.8 ± 6.8 | 0.012 | 0.17 |
| Basal glucose oxidation (μmol/kg FFM/min) | 7.1 ± 4.7 | 0.6 ± 4.6 | 0.50 | 7.1 ± 4.2 | 0.3 ± 7.1 | 0.84 | 0.88 |
| Basal nonoxidative glucose consumption (μmol/kg FFM/min) | 9.7 ± 8.0 | 1.9 ± 7.6 | 0.24 | 9.1 ± 6.9 | 1.8 ± 7.7 | 0.31 | 0.66 |
| Basal fat oxidation (mg/kg FFM/min) | 1.25 ± 0.39 | −0.09 ± 0.40 | 0.27 | 1.19 ± 0.35 | 0.01 ± 0.64 | 0.94 | 0.61 |
| Clamp glucose oxidation (μmol/kg FFM/min) | 13.0 ± 5.7 | 0.6 ± 6.5 | 0.63 | 11.8 ± 6.1 | −0.3 ± 7.5 | 0.85 | 0.47 |
| Clamp nonoxidative glucose consumption (μmol/kg FFM/min) | 29.3 ± 21.8 | 3.2 ± 25.1 | 0.52 | 22.8 ± 16.4 | 5.3 ± 15.1 | 0.15 | 0.87 |
| Clamp fat oxidation (mg/kg FFM/min) | 0.92 ± 0.42 | −0.15 ± 0.39 | 0.08 | 0.74 ± 0.46 | 0.11 ± 0.56 | 0.41 | 0.20 |
| Resting energy expenditure (kcal/day) | 1,677 ± 319 | −60 ± 133 | 0.034 | 1,720 ± 325 | −17 ± 246 | 0.75 | 0.31 |
| Clamp energy expenditure (kcal/day) | 1,759 ± 351 | −59 ± 182 | 0.12 | 1,756 ± 333 | −100 ± 232 | 0.07 | 0.82 |

Data are mean ± SD. $AIR_g$, acute insulin response to glucose; FFM, free fat mass.

concentrations, which may be important to obtain the possible beneficial effects of 25(OH)D in nonskeletal tissue because local 1α-hydroxylation is suggested to demand a concentration of at least 75 nmol/L. To our knowledge, this study is the first to assess the effect of vitamin D on substrate utilization in subjects with dysglycemia or T2D. No significant between-group effects on energy metabolism after vitamin D supplementation were observed, which is in line with an indirect calorimetry study in patients with stage 3–4 chronic kidney failure (18).

A limitation of the current study may be that sufficiently high serum levels of vitamin D were not maintained throughout the study, and we observed a significant reduction in mean 25(OH)D from 4 weeks to 6 months in the intervention group that may have influenced the findings. However, total 25(OH)D $AUC_{0–26\ weeks}$, as a measure of vitamin D exposure, was >70% increased in the vitamin D group, and the mean 25(OH)D level was still significantly higher in the intervention group than in the control group at study end. Still, we cannot exclude that vitamin 25(OH)D may have acute, nongenomic effects on pancreatic β-cell function or insulin sensitivity that might have vanished and, therefore, was not detected by our study design. Another possible limitation is the broad inclusion criteria. The inclusion of patients with different ethnic backgrounds, on a variety of glucose-lowering medications, and with differences in diabetes duration may have caused heterogeneity in the study sample that might have masked a positive effect in subgroups. However, sensitivity analyses in subgroups of subjects with T2D duration of <2 years and in those with preserved first-phase insulin secretion did not change the results. The broad inclusion criteria increase the generalizability of the findings, and we consider the trial population fairly representative of the T2D population. We included subjects of both Nordic and South Asian ethnicity because people of South Asian origin living in Norway and many other western countries have a higher prevalence of T2D and vitamin D deficiency, and some data have pointed to a different response to vitamin D supplementation across ethnic groups (19). However, again, our subanalyses showed no trends toward a difference in effects between the two ethnic groups. Only six subjects in the intervention group had severe vitamin D deficiency (defined as a baseline level ≤25 nmol/L), and the study had low power to detect a potential effect in such subjects alone. However, no effect of vitamin D supplementation on insulin sensitivity or insulin secretion was observed in this subgroup as was no significant interaction between the degree of vitamin D deficiency and the changes in insulin secretion or action. Although serum levels of vitamin D undergo seasonal variations in Norway, study subjects were evenly recruited throughout the year, and the results were unaffected by adjustments for seasonal time of inclusion. Furthermore, the mean level of 25(OH)D in the control group did not change.

The findings complement and support those of other randomized trials that reported no significant effect of vitamin D supplementation on important glucose regulatory mechanisms like insulin secretion and insulin action in subjects with only moderate or no vitamin D deficiency. At present, we suggest that a high bolus dose of vitamin D supplementation is not recommended for this purpose.

**Acknowledgments.** The authors thank research nurses Åse Halsne and Gøril Vinje at Oslo University Hospital for invaluable work in the study.

**Funding.** This study was supported by grants from the Norwegian Extra Foundation, the South-Eastern Norway Regional Health Authority, and the Norwegian Diabetes Association. The authors thank the Simon Fougner Hartmann Foundation for providing financial support for the YSI glucose analyzer.

**Duality of Interest.** No conflicts of interest relevant to this article were reported.

**Author Contributions.** H.L.G. researched data, performed clinical assessments, and wrote the manuscript. C.W. researched data, performed clinical assessments, and contributed to manuscript writing, review, editing, and discussion. K.A. researched data and reviewed and edited the manuscript. E.F.E. and K.I.B. researched data, reviewed and edited the manuscript, and contributed to the discussion. K.I.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Prior Presentation.** Parts of this study were presented in poster form at the European Association for the Study of Diabetes 49th Annual Meeting, Barcelona, Spain, 23–27 September 2013.

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