

## REVIEW

# Vitamin D and type 2 diabetes: a systematic review

J Mitri<sup>1</sup>, MD Muraru<sup>2</sup> and AG Pittas<sup>1</sup>

<sup>1</sup>Division of Endocrinology, Diabetes and Metabolism, Tufts Medical Center, Boston, MA, USA and <sup>2</sup>Department of Internal Medicine, Carney Hospital, Dorchester, MA, USA

**Background/Objectives:** Vitamin D may modify the risk of type 2 diabetes mellitus. The aim of this review was to examine the association between vitamin D status and incident type 2 diabetes, and the effect of vitamin D supplementation on glycemic outcomes.

**Methods:** We performed a systematic review of English-language studies using MEDLINE through February 2011. Longitudinal cohort studies reporting associations between vitamin D status and incident type 2 diabetes, and randomized controlled trials (RCTs) of vitamin D supplementation, were included. Study characteristics and results were extracted, and study quality was assessed.

**Results:** A total of 8 observational cohort studies and 11 RCTs were included. In meta-analyses of observational studies, vitamin D intake >500 international units (IU)/day decreased the risk of type 2 diabetes by 13% compared with vitamin D intake <200 IU/day. Individuals with the highest vitamin D status (>25 ng/ml) had a 43% lower risk of developing type 2 diabetes (95% confidence interval 24, 57%) compared with those in the lowest group (<14 ng/ml). In *post hoc* analyses from eight trials among participants with normal glucose tolerance at baseline and in three small underpowered ( $n=32-62$ ) trials of patients with established type 2 diabetes, there was no effect of vitamin D supplementation on glycemic outcomes. In two trials among patients with baseline glucose intolerance, vitamin D supplementation improved insulin resistance.

**Conclusions:** Vitamin D may play a role in type 2 diabetes; however, to better define the role of vitamin D in the development and progression of type 2 diabetes, high-quality observational studies and RCTs that measure blood 25-hydroxyvitamin D concentration and clinically relevant glycemic outcomes are needed.

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## Introduction

Type 2 diabetes has become a significant global health care problem. In the United States alone, total prevalence is expected to more than double in the next few decades from 6% of the population in 2005 (16 million) to 12% in 2050 (48 million; Narayan *et al.*, 2006). From a worldwide perspective, the total number of people with diabetes is expected to rise from 171 million in 2000 to 366 million by 2030 (Wild *et al.*, 2004). Type 2 diabetes is associated with serious morbidity and increased mortality. Although therapies for type 2 diabetes and its complications have improved

over the last few decades, the increasing burden of type 2 diabetes highlights the need for innovative approaches for the prevention and management of the disease.

There is mounting evidence suggesting that vitamin D may influence several non-skeletal medical conditions, including cardiovascular disease, cancer, autoimmune disorders and type 2 diabetes. A potential role of vitamin D in type 2 diabetes is suggested by a reported seasonal variation in the control of glycemia in patients with type 2 diabetes, being worse in the winter when hypovitaminosis D is more prevalent (Campbell *et al.*, 1975). Additional evidence for a role of vitamin D in type 2 diabetes comes from a large number of cross-sectional studies, which have generally reported an inverse association between vitamin D status and prevalent hyperglycemia. Recently, longitudinal observational studies and intervention studies have also been published on the relationship between vitamin D and type 2 diabetes. We performed a systematic review

Correspondence: Dr AG Pittas, Division of Endocrinology, Diabetes and Metabolism, Tufts Medical Center, 800 Washington Street, #268, Boston, MA 02111, USA.

E-mail: apittas@tuftsmedicalcenter.org

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of longitudinal observational studies of vitamin D status and trials of vitamin D supplementation on glycemic outcomes.

## Materials and methods

### *Data sources and study selection*

We conducted a literature search for longitudinal observational studies of vitamin D status and development of type 2 diabetes, and randomized controlled trials (RCTs) evaluating the effect of vitamin D supplementation (cholecalciferol (D<sub>3</sub>) or ergocalciferol) with or without calcium supplementation on glycemic parameters.

Two authors (JM and MM) independently performed a search of MEDLINE and the Cochrane Database of Systematic Reviews through February 2011. Search terms were vitamin D and diabetes mellitus, and the search was limited to publications in English. The search included studies in which vitamin D status was assessed by either self-reported vitamin D intake, blood 25-hydroxyvitamin D (25(OH)D) concentration or 25(OH)D score predicted from self-reported data. Diabetes-related outcomes included incident type 2 diabetes and, in the context of RCTs only, change in glycemia (fasting plasma glucose, 2-h glucose level after an oral glucose tolerance test or hemoglobin A1c). Titles and abstracts of the resulting articles were examined, and full-text articles were retrieved after excluding non-eligible ones. Bibliographic references of recovered articles were examined to look for additional studies. We excluded animal studies, cross-sectional or retrospective case-control studies, and short-term (<1 month) randomized trials. Nested case-control studies in which data on vitamin D status was collected before outcome assessment were included. We excluded studies on type 1 diabetes because its pathophysiology is different from type 2 diabetes. We excluded studies in children, pregnant women and patients with conditions that affect vitamin D metabolism, such as chronic kidney disease stage 3 or higher or hyperparathyroidism, and trials that used a vitamin D preparation other than D<sub>3</sub>, ergocalciferol or non-oral routes of vitamin D administration.

### *Data extraction and quality assessment*

Data from each study were extracted by one of the reviewers and confirmed by the other. The extracted data included: study design; participant characteristics; cohort source; longest reported follow-up period; method of assessing vitamin D status or details of vitamin D supplementation; association between vitamin D (status or supplementation) and outcome; potential confounding variables adjusted for, with particular emphasis on age, race, weight and variables related to sun exposure (for example, season and location); method of ascertaining glycemia outcome, and statistical analysis.

Study quality was determined by the primary data extractor and confirmed by at least one other co-author. To inform the assessment of study quality, we considered factors in the Strengthening the Reporting of Observational Studies in Epidemiology statement for observational studies (von Elm *et al.*, 2007), nutrition-specific items from a critical appraisal of micronutrient systematic reviews (Lichtenstein *et al.*, 2008) and the Consolidated Standards of Reporting Trials statement for reporting clinical trials (Moher *et al.*, 2001). We used a three-category grading system for both observational studies and RCTs. Good quality studies adhere most closely to the commonly held concepts of high quality, including clear descriptions of the population and setting; unbiased assessments of vitamin D status and outcomes; appropriate statistical analysis including multivariate analysis adjusting for age, race, weight, and/or sun exposure and intention-to-treat analysis; no obvious reporting omissions or errors; and <20% dropouts. Fair quality studies have some deficiencies in the above criteria, but these are unlikely to result in major biases. Observational studies that measured vitamin D intake as the key predictor variable were rated fair. Poor quality studies have major deficiencies in design, analyses or reporting; hence, major bias could not be excluded.

### *Data synthesis and analysis*

Data were combined, whenever possible, for meta-analysis. The random effects model was used when at least three studies with a homogeneous predictor and outcome were available (DerSimonian and Laird, 1986). For observational studies, we synthesized relative risks, or hazard or odds ratios comparing the extreme categories of vitamin D status (highest versus lowest, as defined within each study), provided that the categories corresponded to similar levels of vitamin D intake or blood 25(OH)D concentration across studies. We tested between-study heterogeneity with the Q statistic (significant when  $P < 0.10$ ) and quantified its extent with  $I^2$  (0–100%), expressing the fraction of between-study variability attributable to heterogeneity rather than chance (>50% suggests high heterogeneity; Higgins *et al.*, 2003). RCTs were evaluated based on their characteristics, and meta-analyses were attempted whenever possible to pool the results. All calculations and graphs were obtained using Comprehensive Meta-Analysis version 2.2.050 (Biostat, Englewood, NJ, USA).

## Results

### *Longitudinal observational cohort studies*

Our search identified seven manuscripts that reported the association between vitamin D status and risk of developing type 2 diabetes using data from eight different cohort studies (Liu *et al.*, 2005, 2010; Pittas *et al.*, 2006, 2010; Knekt *et al.*, 2008; Kirii *et al.*, 2009; Anderson *et al.*, 2010; Table 1). The

**Table 1** Observational longitudinal cohort studies of vitamin D status (plasma or serum 25(OH)D concentration or self-reported vitamin D intake) and incident type 2 diabetes

Study, year (reference), cohort (country)	Male, %	Mean baseline age (range), years	White, %	n/N (incidence, %) <sup>a</sup>	Vitamin D measure; comparison <sup>b</sup>	Mean follow-up, years (start–end)	Results, adjusted RR, OR or HR (95% CI) P-value for trend	Outcome (ascertainment method)	Adjustments	Study Quality <sup>c</sup>
Liu et al., 2005 Women's Health Study (USA)	0	52 (45–75)	95	805/10 066 (8.0)	Vitamin D intake (total); ≥511 vs ≤159 IU/day	9 (ND)	0.73 (0.54, 0.99) P=0.02 <sup>d</sup>	Type 2 diabetes (validated self-report)	Age	Fair
Pittas et al., 2006 Nurses' Health Study (USA)	0	46 (30–55)	98	4843/83 779 (5.8)	Vitamin D intake (total); >800 vs ≤200 IU/day	20 (1980–2000)	0.87 (0.69, 1.09) P=0.67	Type 2 diabetes (validated self-report)	Age, BMI, exercise, residence, others <sup>e</sup>	Fair
Knekt et al., 2008 Finnish Mobile Clinic Health Examination Survey (Finland)	100	ND (40–74)	100	105/1628 (6.4); nested case-control study with 206 control participants	25(OH)D concentration; 30 vs 10 ng/ml (mean)	22 (1973–1994)	0.49 (0.15, 1.64) P=0.06	Type 2 diabetes (medication treated, registry based)	Age, BMI, exercise, season, others <sup>f</sup>	Good
Knekt et al., 2008 Mini-Finland Health Survey (Finland)	0	ND (40–74)	100	125/1699 (7.4); nested case-control study with 246 control participants	25(OH)D concentration; 25 vs 9 ng/ml (mean)		0.91 (0.37, 2.23) P=0.66		Age, BMI, exercise, season, others <sup>f</sup>	
Knekt et al., 2008 Mini-Finland Health Survey (Finland)	100	53 (40–69)	100	83/1948 (4.3); nested case-control study with 243 control participants	25(OH)D concentration; 31 vs 9 ng/ml (mean)	17 (1978–1994)	0.17 (0.05, 0.52) P<0.001	Type 2 diabetes (medication treated, registry based)	Age, BMI, exercise, season, others <sup>f</sup>	Good
Kirri et al., 2009 Japan Public Health Center-based Prospective Study (Japan)	0	ND (40–69)	100	99/2228 (4.4); nested case-control study with 289 control participants	25(OH)D concentration; 25 vs 8 ng/ml (mean)		1.45 (0.58, 3.62) P=0.83		Age, BMI, exercise, season, others <sup>f</sup>	
Kirri et al., 2009 Japan Public Health Center-based Prospective Study (Japan)	100	57 (40–69)	ND (~100% Japanese)	634/25 877 (2.4)	Vitamin D intake (total); 720 vs 188 IU/day (mean)	5 (1990–1998)	0.96 (0.74, 1.23) P=0.35	Type 2 diabetes (validated self-report)	Age, BMI, exercise, others <sup>g</sup>	Fair
Liu et al., 2010 Framingham Offspring Study (USA)	0	57 (40–69)	ND (~100% Japanese)	480/33 919 (1.4)	Vitamin D intake (total); 696 vs 192 IU/day (mean)	5 (1990–1998)	0.88 (0.67, 1.16) P=0.67	Type 2 diabetes (validated self-report)		
Pittas et al., 2010 Nurses' Health Study (USA)	54	60	~100	133/2956 (4.4)	Predicted 25(OH)D score; 22 vs 17 ng/ml (median)	7 (1991–2001)	0.60 (0.37, 0.97) P=0.03	Type 2 diabetes (medication treated, laboratory based)	Age, sex, waist circumference <sup>h</sup>	Fair
Pittas et al., 2010 Nurses' Health Study (USA)	0	46 (30–55)	98	608/32 826 (1.8); nested case-control study with 569 control participants	25(OH)D concentration; 33 vs 14 ng/ml (median)	14 (1990–2004)	0.52 (0.33, 0.83) P=0.008	Type 2 diabetes (validated self-report)	Age, BMI, exercise, season, race, others <sup>i</sup>	Good
Anderson et al., 2010 Intermountain Healthcare system (USA)	25	55	ND	NR/41 497 (NR)	25(OH)D concentration; ≤15 vs >30 ng/ml (median)	1.3 (2000–2009)	1.89 (1.54, 2.33) P<0.001	Diabetes (physician diagnosed based on International Classification of Disease, 9th edition code)	Age, gender, others <sup>j</sup>	Poor

Abbreviations: 25(OH)D, plasma or serum 25-hydroxyvitamin D; BMI, body mass index; HDL, high-density lipoprotein; HR, hazard ratio; IU, international unit; ND, no data; OR, odds ratio; RR, relative risk.

<sup>a</sup>Number of cases if nested case-control study.

<sup>b</sup>Highest/lowest-risk category versus reference category.

<sup>c</sup>Study quality is determined based on a three-category grading system, as described in the text.

<sup>d</sup>Estimated from reported data.

<sup>e</sup>Family history of diabetes, hypertension, calcium intake, smoking, alcohol, coffee and other diet.

<sup>f</sup>Smoking, education and medications.

<sup>g</sup>Family history of diabetes, smoking, diet (alcohol, coffee, magnesium and total energy) and hypertension.

<sup>h</sup>Family history of diabetes, hypertension, low HDL cholesterol, high triglycerides, impaired fasting glucose and diet.

<sup>i</sup>Fasting status, latitude, hypercholesterolemia, hypertension, family history of diabetes, smoking, physical activity, alcohol, multivitamin use and diet.

<sup>j</sup>Hypertension, hyperlipidemia, heart failure, infection, depression and renal failure.

To convert 25(OH)D concentration from ng/ml to nmol/l, multiply by 2.459.

studies included 238 423 participants, age range 30–75 years, the majority of whom were white (at least 80%) and who were followed for upward of 22 years for the development of incident type 2 diabetes. All studies assessed the exposure, vitamin D status, only once at baseline. Three studies did so by self-reported total vitamin D intake (Liu *et al.*, 2005; Pittas *et al.*, 2006; Kirii *et al.*, 2009); one study calculated a predicted 25(OH)D score (Liu *et al.*, 2010) and three studies (in four cohorts) measured blood 25(OH)D concentration (Knekt *et al.*, 2008; Anderson *et al.*, 2010; Pittas *et al.*, 2010). Ascertainment of the outcome, type 2 diabetes, was by validated self-report (Liu *et al.*, 2005; Pittas *et al.*, 2006, 2010; Kirii *et al.*, 2009), by a combination of self-report and laboratory measurement (Liu *et al.*, 2010) or by medical record data (Knekt *et al.*, 2008; Anderson *et al.*, 2010). Six studies reported multivariate adjusted results (Pittas *et al.*, 2006, 2010; Knekt *et al.*, 2008; Kirii *et al.*, 2009; Anderson *et al.*, 2010; Liu *et al.*, 2010); one study adjusted only for age (Liu *et al.*, 2005).

In the Women's Health Study, an intake of >511 international units (IU)/day of vitamin D was associated with a 27% lower risk of developing type 2 diabetes compared with an intake of <159 IU/day (Liu *et al.*, 2005). However, this analysis was limited because it did not adjust for any risk factors for type 2 diabetes other than age. In the Nurses' Health Study, after multivariate adjustment for age, body mass index (BMI) and non-dietary covariates, women who reported consumption of >800 IU/day of vitamin D had a 23% lower risk of developing incident type 2 diabetes, by validated self-report, compared with women who reported consumption of <200 IU/day (Pittas *et al.*, 2006). The association, however, was attenuated and became non-significant after adjusting for dietary factors (Table 1). The dietary variables responsible for attenuation of the results were magnesium and calcium, which share dietary sources with vitamin D. In the same study, women who reported the highest calcium (>1200 mg/day) and vitamin D (>800 IU/day) intakes (1.3% of the cohort) had a statistically significant 33% lower risk of type 2 diabetes compared with women with the lowest calcium (<600 mg/day) and vitamin D (<400 IU/day) intakes. In a Japanese cohort of men and women aged 40–70 years, over a 5-year follow-up period, there was no statistically significant association between higher (~700 IU/day) versus lower (~200 IU/day) self-reported intake of vitamin D intake, or higher (~600 to 800 mg/day) versus lower (~250 to 350 mg/day), calcium intake and incident type 2 diabetes (Kirii *et al.*, 2009). However, men and women who self-reported higher consumption of both vitamin D (>400 IU/day) and calcium (~600 to 800 mg/day) had an ~40% lower risk of type 2 diabetes. In the Framingham Offspring Study (men and women), investigators used a subsample of the cohort to develop a regression model to predict blood 25(OH)D concentrations from age, sex, BMI, month of blood sampling, total self-reported vitamin D intake, smoking status and total energy intake (Liu *et al.*, 2010). Using this model, a

predicted 25(OH)D score was calculated for each non-diabetic participant. The association between the predicted 25(OH)D score and incidence of type 2 diabetes, defined as the use of diabetes medication or laboratory values diagnostic for diabetes, was assessed during a mean average follow-up of 6 years. Compared with participants in the lowest tertile of the predicted 25(OH)D score, those in the highest tertile had a 40% lower risk of type 2 diabetes after multivariate adjustment.

There are three longitudinal observational studies that have reported the association between measured blood 25(OH)D concentration and incident type 2 diabetes (Knekt *et al.*, 2008; Anderson *et al.*, 2010; Pittas *et al.*, 2010); two were case-control studies nested within prospective cohorts (Knekt *et al.*, 2008; Pittas *et al.*, 2010) and one study used electronic medical records data captured during routine medical care (Anderson *et al.*, 2010). In the nested case-control studies, after a specified period of follow-up, blood samples from participants who developed type 2 diabetes and matched non-diabetic controls were retrieved from stored samples, and blood 25(OH)D was measured at a time when all participants were free from type 2 diabetes and blood concentrations of 25(OH)D concentration were compared between cases and controls. The study by Knekt *et al.* (2008), which pooled data from two cohorts in Finland (total of 7503 available participants) included 412 cases who developed type 2 diabetes during the follow-up period and 986 matched controls (partial results were published in an earlier manuscript by Mattila *et al.* (2007)). After multivariate adjustment including BMI, participants who were in the highest quartile of serum 25(OH)D levels at baseline (mean 25[OH]D 27.6 ng/ml), compared with those in the lowest quartile (mean 25[OH]D 8.9 ng/ml), had a 40% lower risk of developing incident type 2 diabetes. Men in the highest quartile (mean 25[OH]D 30 ng/ml) had a 72% lower risk of developing type 2 diabetes compared with men in the lowest quartile (mean 25[OH]D 10 ng/ml); there was no significant association among women. The second nested case-control study was conducted using data from 608 women with newly diagnosed type 2 diabetes and 559 controls who were enrolled in the Nurses' Health Study (Pittas *et al.*, 2010). After adjusting for matching variables and risk factors for diabetes including BMI, higher levels of plasma 25(OH)D were associated with a lower risk for type 2 diabetes. The odds ratio for incident type 2 diabetes in the top (median 25[OH]D 33.4 ng/ml) versus the bottom (median 25[OH]D 14.4 ng/ml) quartile was 0.52 (95% confidence interval (CI) 0.33–0.83). The association was consistent across subgroups of baseline BMI, age and calcium intake, although the association appeared to be stronger among overweight/obese versus normal weight women (odds ratio 0.46 versus 0.63, respectively). In this study, spline regression models showed no apparent threshold and no deviation from linearity for the relation between 25(OH)D and risk of incident type 2 diabetes, although the shape of the figure suggested a stronger decrease in risk within the higher range of plasma

25(OH)D concentrations above 30–35 ng/ml. The apparently inconsistent results among women in the Finnish and American cohorts may be explained by the higher baseline 25(OH)D levels in women in the Nurses' Health Study compared with the Finnish cohort (23 versus 15 ng/ml, respectively), which suggests that a potential threshold for 25(OH)D levels exists, above which the risk of type 2 diabetes declines. Anderson *et al.* (2010), using information from a large electronic database that contained 41 504 patient records with at least one measured 25(OH)D level, determined the relation between vitamin D levels and incident cardiometabolic diseases. After multivariate adjustment for various risk factors, compared with patients with 25(OH)D >30 ng/ml, those with 25(OH)D <15 ng/ml had an 89% increase in the risk of developing type 2 diabetes.

Another longitudinal observational study has also reported inverse associations between baseline 25(OH)D concentration and future glycemia and insulin resistance, but it did not report results on incident diabetes (Forouhi *et al.*, 2008).

After combining the data from three studies that assessed vitamin D status by vitamin D intake, there was a statistically significant association between vitamin D intake >500 IU/day with the development of newly diagnosed type 2 diabetes (relative risk 0.87, 95% CI, 0.76–0.99) versus vitamin D intake <200 IU/day (Figure 1). There was no heterogeneity among studies ( $Q=1.87$ ,  $P=0.6$ ,  $I^2=0\%$ ). After combining the data from four studies (five cohorts) that measured 25(OH)D as the predictor, participants with 25(OH)D >25 ng/ml had a 43% lower risk of developing type 2 diabetes (95% CI, 24%, 57%) when compared with individuals with 25(OH)D <14 ng/ml (Figure 2), with only small degree of heterogeneity ( $Q=9.7$ ,  $P=0.14$ ,  $I^2=38\%$ ).

#### Randomized trials of vitamin D and glycemic outcomes

The search identified 11 RCTs, which have reported the effects of vitamin D (ergocalciferol or D<sub>3</sub>) supplementation (with or without calcium) on measures of glycemia (Nilas and Christiansen, 1984; Hsia *et al.*, 2007; Pittas *et al.*, 2007a; Sugden *et al.*, 2008; de Boer *et al.*, 2008; Avenell *et al.*, 2009; Nagpal *et al.*, 2009; Zittermann *et al.*, 2009; Witham *et al.*, 2010; von Hurst *et al.*, 2010; Jorde *et al.*, 2010a) or incident diabetes by self-report (de Boer *et al.*, 2008; Avenell *et al.*, 2009; Table 2). Eight trials have included participants with normal glucose tolerance (Nilas and Christiansen, 1984; Hsia *et al.*, 2007; Pittas *et al.*, 2007a; de Boer *et al.*, 2008; Avenell *et al.*, 2009; Zittermann *et al.*, 2009; von Hurst *et al.*, 2010; Jorde *et al.*, 2010a), and three trials included participants with stable type 2 diabetes (Sugden *et al.*, 2008; Jorde and Figschau, 2009; Witham *et al.*, 2010). Study duration varied from 6 weeks to 9 years. Doses of vitamin D ranged from 400 to 8571 IU/day; however, several trials provided supplementation with large infrequent doses of vitamin D (Sugden *et al.*, 2008; Nagpal *et al.*, 2009; Witham *et al.*, 2010; Jorde *et al.*, 2010a,b). In three studies, vitamin D<sub>3</sub> was combined with calcium (Pittas *et al.*, 2007a; de Boer *et al.*,

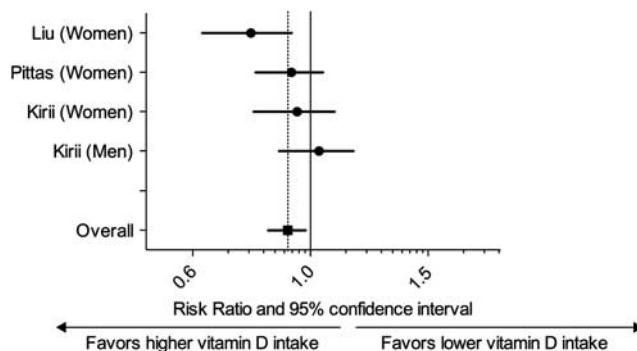


Figure 1 Meta-analysis of the association between self-reported vitamin D intake and incident type 2 diabetes.

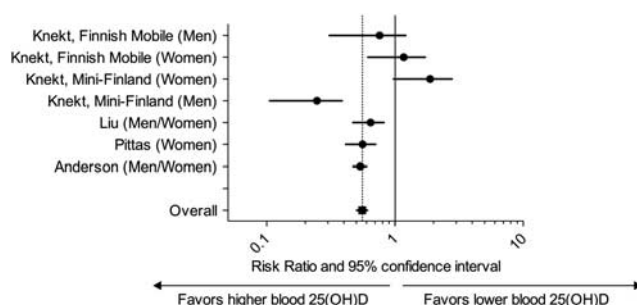


Figure 2 Meta-analysis of the association between baseline blood 25(OH)D concentration and incident type 2 diabetes.

2008; Jorde *et al.*, 2010a). Only the Women's Health Initiative and the Randomized Evaluation of Calcium and/OR vitamin D Trials were considered good quality studies (Hsia *et al.*, 2007; de Boer *et al.*, 2008; Avenell *et al.*, 2009). The trials were too heterogeneous to perform a meta-analysis.

#### Trials in participants with normal glucose tolerance

There was no effect of vitamin D supplementation on measures of glycemia including fasting plasma glucose or hemoglobin A1c and insulin resistance measured by homeostatic model assessment (HOMA) in participants with normal glucose tolerance at baseline in seven trials (Nilas and Christiansen, 1984; Hsia *et al.*, 2007; Pittas *et al.*, 2007a; de Boer *et al.*, 2008; Avenell *et al.*, 2009; Zittermann *et al.*, 2009; von Hurst *et al.*, 2010; Jorde *et al.*, 2010a). Similarly, vitamin D supplementation had no effect on incident type 2 diabetes in individuals with normal glucose tolerance (de Boer *et al.*, 2008; Avenell *et al.*, 2009). However, five of the studies were designed for non-glycemic outcomes, and the analyses on vitamin D and type 2 diabetes were *post hoc* (Nilas and Christiansen, 1984; Pittas *et al.*, 2007a; de Boer *et al.*, 2008; Avenell *et al.*, 2009; Jorde *et al.*, 2010a). Furthermore, all trials with the exception of the Women's Health Initiative Trial (de Boer *et al.*, 2008) and the Randomized Evaluation of Calcium and/OR vitamin D Trial

**Table 2** Randomized controlled trials of the effect of vitamin D (cholecalciferol or ergocalciferol) supplementation (with or without calcium) on glucose tolerance

Study, first author, year (country)	Men, %	Mean baseline age, years (range)	BMI, kg/m <sup>2</sup>	Participants	Mean baseline 25(OH)D concentration and calcium intake	Interventions (number of participants)	Study duration	Effect of vitamin D vs placebo (P-value)	Study quality (justification)
Nilas and Christiansen, 1984 (Denmark)	0	ND (45–54)	ND	Postmenopausal; healthy; n = 151	ND	D <sub>3</sub> 2000 IU/day (n = 25) vs 1(OH)D <sub>3</sub> 0.25 mcg/day (n = 23) vs placebo (n = 103). All received calcium, 500 mg/day	2 years	↔ FPG change, 2.16 vs -5.94 vs 2.34 mg/dl (P = 0.97)	Fair (post hoc analyses)
Pittas et al., 2007a (USA)	38	71 (≥65)	27	Normal fasting glucose; n = 222	30 ng/ml calcium intake, 750 mg/day	D <sub>3</sub> 700 IU/day plus calcium citrate 500 mg/day (n = 108) vs placebo (n = 114)	3 years	↔ FPG change, 2.70 vs 2.16 mg/dl (P = 0.55) ↔ IR <sub>HOMA</sub>	Fair (post hoc analysis)
de Boer et al., 2008 (USA)	52	71 (ND)	ND	Impaired fasting glucose; n = 92	30 ng/ml calcium intake, 680 mg/day	D <sub>3</sub> 700 IU/day plus calcium citrate 500 mg/day (n = 45) vs placebo (n = 47)	3 years	↓ FPG change, 0.36 vs 6.13 mg/dl (P = 0.042)	
	0	62 (50–79)	ND	Postmenopausal without diabetes	<32 ng/ml (for 89% of participants)	D <sub>3</sub> 400 IU/day plus calcium carbonate 1000 mg/day (n = 16 999) vs placebo (n = 16 952)	7 years	↔ IR <sub>HOMA</sub> ↔ Incidence of diabetes (self-reported); HR 1.01 (0.94–1.10; P = 0.95) ↔ Insulin secretion	Fair (post hoc analysis)
	0	ND (50–79)	ND	Normal fasting glucose; n = 1637		D <sub>3</sub> 400 IU/day plus calcium carbonate 1000 mg/day (n = 866) vs placebo (n = 771)	6 years	↔ IR <sub>HOMA</sub> ↔ FPG change, 3.80 vs 4.61 mg/dl (P = 0.32)	
	0	ND (50–79)	ND	Impaired fasting glucose; n = 1457		D <sub>3</sub> 400 IU/day plus calcium carbonate 1000 mg/day (n = 718) vs placebo (n = 739)	6 years	↔ FPG change, 3.93 vs 4.69 mg/dl (P = 0.79)	
Sugden et al., 2008 (UK)	53	64 (ND)	31	Stable type 2 diabetes; 25(OH)D <20 ng/ml; n = 34	15 ng/ml	D <sub>2</sub> 100 000 IU once (equivalent to 1785 IU/day; n = 17) vs placebo (n = 17)	8 weeks	↔ Hemoglobin A1c change, 0.01% vs -0.05% (P = 0.74) ↔ IR <sub>HOMA</sub> change, -39.7 vs -25.6 (P = 0.72) IR <sub>HOMA</sub> significantly improved if 25OHD rise > 5 ng/ml	Fair (completers only analysis; 20% dropout)
Avenell et al., 2009 (UK)	15	77 (≥70)	ND	History of fracture	ND	D <sub>3</sub> 800 IU/day (n = 2649) vs placebo (n = 2643; 2 × 2 factorial design with calcium carbonate 1000 mg/day)	2–5 years	↔ Incidence of diabetes (self-reported), intention-to-treat HR 1.11 (0.77–1.62; P = 0.57) ↔ Incidence of diabetes (self-reported), compliant HR (self-reported), 0.68 (0.40–1.16; P = 0.16) ↔ OGIS (change from baseline, ml/min*kg) 21.17 vs -8.89 (P = 0.055) ↔ IR <sub>HOMA</sub> change from baseline, 0.14 vs 0.16 (P = 0.95) ↔ QUICKI 0 vs 0 (P = 0.9)	Good (self-report; no data on baseline glucose control)
Nagpal et al., 2009 (India)	100	43 (>35)	26	Healthy; central obesity; n = 71	15 ng/ml	D <sub>3</sub> 120 000 IU three times (equivalent to 8571 IU/day; n = 35) vs placebo (n = 36)	6 weeks	↔ OGIS (change from baseline, ml/min*kg) 21.17 vs -8.89 (P = 0.055) ↔ IR <sub>HOMA</sub> change from baseline, 0.14 vs 0.16 (P = 0.95) ↔ QUICKI 0 vs 0 (P = 0.9)	Fair (25% dropout; no power; no primary outcome)
Zittermann et al., 2009 (Germany)	33	48 (18–70)	33	Healthy; BMI > 27 kg/m <sup>2</sup> ; n = 200	12 ng/ml	D <sub>3</sub> 3332 IU/day (n = 82) vs placebo (n = 83). All received weight reduction advice for 24 weeks	1 year	↔ Hemoglobin A1c change, -0.25% vs -0.25% (P = 0.96) ↔ FPG change, -3.8 vs -4.9 mg/dl (P = 0.39) ↔ Hemoglobin A1c change, 0.2% vs -0.2% (P = 0.90) ↔ FPG change, -3.6 vs 7.2 mg/dl (P = 0.43) ↔ IR <sub>HOMA</sub> 0.3 vs -0.2 (P = 0.58)	Fair (20% dropout)
Jorde and Figenschau, 2009 (Norway)	50	56 (21–75)	ND	Stable type 2 diabetes; n = 32	24 ng/ml	D <sub>3</sub> 40 000 IU/week (equivalent to 5714 IU/day; n = 16) vs placebo (n = 16)	26 weeks		Fair (insulin allowed)

**Table 2** Continued

Study, first author, year (country)	Men, %	Mean baseline age, years (range)	BMI, kg/m <sup>2</sup>	Participants	Mean baseline 25(OH)D concentration and calcium intake	Interventions (number of participants)	Study duration	Effect of vitamin D vs placebo (P-value)	Study quality (justification)
von Hurst et al., 2010 (New Zealand)	0	42 (23–68)	27.5	Insulin resistance (IR <sub>HOMA</sub> > 1.93 and TG/HDL ≥ 3); no diabetes; 25(OH)D < 20 ng/ml (50 nmol/l); n = 81	8 ng/ml	D <sub>3</sub> 4000 IU/day (n = 42) vs placebo (n = 39)	26 weeks	↔ FPG change, 1.8 vs 1.8 mg/dl (P = 0.82) ↓ IR <sub>HOMA</sub> change from baseline, -0.2 vs 0.2 (P = 0.02; highest effect seen when final 25OHD > 36 ng/ml) ↓ Insulin ↔ HOMA 2% B; C-peptide ↔ Hemoglobin A1c change, 0.09% vs 0.11% vs 0.09% (P = NS) ↔ FPG change, 0.02 vs 0.08 vs 0.08 mmol/l (P = NS) ↔ 2hPG change, 2.7 vs 6.5 vs -0.4 mg/day (P = NS) ↔ IR <sub>HOMA</sub> , 0.23 vs -0.05 vs 0.36 (P = NS) ↔ QUICKI ↔ Hemoglobin A1c change, 'no change' (data NR) ↔ FPG change, 'no change' (data NR) ↔ IR <sub>HOMA</sub> change, 'no change' (data NR)	Fair (23% dropout)
Jorde et al., 2010a (Norway)	36	38 (21–70)	35	Overweight/obese; no diabetes; n = 438	23 ng/ml	D <sub>3</sub> 40 000 IU/week (equivalent to 5714 IU/day; n = 150) vs D <sub>3</sub> 20 000 IU/week (equivalent to 2857 IU/day; n = 139) vs placebo (n = 149). All received calcium, 500 mg/day	1 year	Fair (post hoc analyses; 25% dropout; completes only analysis; no power calculations)	
Witham et al., 2010 (UK)	ND	65 (> 18)	31	Type 2 diabetes; 25(OH)D < 40 ng/ml (100 nmol/l); n = 61	18 ng/ml	D <sub>3</sub> 100 000 IU orally once (equivalent to 892 IU/day; n = 19) vs D <sub>3</sub> 200 000 IU orally once (equivalent to 1785 IU/day; n = 20) vs placebo (n = 22)	16 weeks	Fair (underpowered)	

Abbreviations: 2hPG, plasma glucose 2 h after 75 g glucose load; 25(OH)D, plasma or serum 25-hydroxyvitamin D; BMI, body mass index; D<sub>2</sub>, ergocalciferol; D<sub>3</sub>, cholecalciferol; FPG, fasting plasma glucose; HDL, high-density lipoprotein; HR, hazard ratio; IR<sub>HOMA</sub>, insulin resistance by homeostasis model assessment; IU, international unit; ND, no data; NS, not significant; OGIS, oral glucose insulin sensitivity; TG, triglyceride; QUICKI, quantitative insulin-sensitivity check index.

↓, decreased (statistically significant); ↑, increased (statistically significant); ↔, no difference (no statistical significance). To convert 25(OH)D concentration from ng/ml to nmol/l, multiply by 2.459 and to convert FPG from mg/dl to mmol/l, multiply by 0.0555

(Avenell *et al.*, 2009) were underpowered for glycemic outcomes. In several trials, including the two largest ones (de Boer *et al.*, 2008; Avenell *et al.*, 2009), adherence with supplementation was suboptimal, which may have limited drawing any conclusions. For example, in a *post hoc* analysis of the Randomized Evaluation of Calcium and/OR vitamin D Study, a community-based effectiveness trial designed for bone outcomes (Avenell *et al.*, 2009), supplementation with 800 IU/day of vitamin D<sub>3</sub> (given in a 2 × 2 factorial design with calcium carbonate) did not change the risk of self-reported type 2 diabetes; however, among study participants who were highly compliant with supplementation, there was a notable trend toward reduction in type 2 diabetes risk with vitamin D<sub>3</sub> (odds ratio 0.68; 95% CI 0.40–1.16).

#### *Trials in participants with type 2 diabetes*

There were three small underpowered RCTs in which participants with established type 2 diabetes were randomized to high infrequent doses of ergocalciferol (100 000 IU given once; *n* = 34; Sugden *et al.*, 2008) or vitamin D<sub>3</sub> (40 000 IU/week for 26 weeks; *n* = 36; Jorde and Figenschau, 2009 or 100 000 or 200 000 IU given once; *n* = 61; Witham *et al.*, 2010; Table 2). In these trials, there was no change in hemoglobin A1c; (Sugden *et al.*, 2008; Jorde and Figenschau, 2009; Witham *et al.*, 2010) fasting plasma glucose; (Jorde and Figenschau, 2009; Witham *et al.*, 2010) or insulin resistance (Jorde and Figenschau, 2009; Witham *et al.*, 2010) with vitamin D supplementation after a follow-up period of 8–26 weeks.

#### *Insulin resistance*

Among five trials in participants with normal glucose tolerance that reported insulin resistance as an outcome, four studies showed no effect of vitamin D supplementation (Pittas *et al.*, 2007a; de Boer *et al.*, 2008; Nagpal *et al.*, 2009; Jorde *et al.*, 2010a). In contrast, the study by Von Hurst *et al.* randomized non-diabetic insulin-resistant vitamin D-deficient (25(OH)D < 20 mg/dl) South Asian women, 23- to 68-years old, to 4000 IU/day of vitamin D<sub>3</sub> (*n* = 42) or placebo (*n* = 39) for 6 months. Significant improvement in insulin resistance, assessed by homeostasis model assessment (IR<sub>HOMA</sub>), was seen with vitamin D supplementation compared with placebo, which was more evident when the end point blood 25(OH)D concentration reached 32 mg/dl. Similarly, in a *post hoc* analysis of a trial designed to assess bone-related outcomes, the combined daily supplementation with 700 IU of vitamin D<sub>3</sub> and 500 mg of calcium as carbonate improved IR<sub>HOMA</sub>, only among those with glucose intolerance at baseline but had no effect among those with normal glucose tolerance (Pittas *et al.*, 2007a).

#### *Combined vitamin D and calcium*

Two trials have reported the effect of combined vitamin D<sub>3</sub> and calcium supplementation versus placebo on type 2

diabetes risk; both analyses were *post hoc*. In the Women's Health Initiative Trial, vitamin D<sub>3</sub> (400 IU/day) and calcium supplementation (1000 mg/day) failed to reduce the risk of developing self-reported type 2 diabetes over a 7-year period and there was also no significant effect of treatment on simple indices of insulin resistance (de Boer *et al.*, 2008). The Women's Health Initiative Trial used a low dose of vitamin D and allowed all participants to take vitamin D supplements on their own during the trial. Although the effect of supplementation on 25(OH)D concentration was not reported, based on dose and compliance, it has been estimated to be only 2 ng/ml (Lappe *et al.*, 2007), which is a very unlikely increment to be associated with any change in risk of cardiometabolic disease, based on data from observational studies. In the trial by Pittas *et al.* (2007a), combined supplementation with vitamin D<sub>3</sub> and calcium carbonate did not have an effect on fasting plasma glucose levels. However, there was an interaction between baseline glycemia and supplementation on changes in glycemia. In a subgroup analysis, among participants with impaired fasting glucose at baseline, combined vitamin D<sub>3</sub> and calcium carbonate supplementation attenuated the increase in fasting glycemia that occurs over time in this population, but it had no effect on glycemia among subjects with normal glucose tolerance at baseline (Pittas *et al.*, 2007a), suggesting that vitamin D may benefit only individuals at high risk for type 2 diabetes.

## Discussion

Overall, observational longitudinal studies have shown an inverse association between the vitamin D status (25(OH)D or self-reported vitamin D intake) and the development of type 2 diabetes. In RCTs, vitamin D supplementation did not show any beneficial effects on glycemic measures among persons with normal glucose tolerance but there were beneficial effects among patients with glucose intolerance or insulin resistance at baseline.

From a biological perspective, the presence of the vitamin D receptor in many cell types and organs, and the local production of 1, 25(OH)<sub>2</sub>D in several extrarenal organs, including β-pancreatic cells, supports potential broad-ranging effects of vitamin D outside of skeletal health, including type 2 diabetes. Vitamin D is thought to have both direct (by the activation of the vitamin D receptor) and indirect (by the regulation of calcium homeostasis) effects on various mechanisms related to the pathophysiology of type 2 diabetes, including impaired pancreatic-β cell function and insulin resistance (Pittas *et al.*, 2007b).

Several possible reasons may account for the attenuation of the association between vitamin D and type 2 diabetes seen in observational studies and published RCTs. The inverse association between vitamin D status and glycemic outcomes may be confounded by a variety of factors. Vitamin D status is an excellent marker of 'good' health, including positive associations with young age, normal body



weight and a healthy lifestyle (Prentice *et al.*, 2008). A lower vitamin D status may be a reflection of chronic non-specific illness; therefore, the inverse association seen in observational studies, especially cross-sectional studies, may be due to reverse causation. Moreover, additional components in foods rich in vitamin D may have direct effects on glycemic outcomes or, alternatively, foods rich in vitamin D may replace other foods that increase risk of type 2 diabetes. Observational studies have also used single measurement of blood 25(OH)D concentration to define vitamin D status, which may not reflect vitamin D status over long periods, as risk factors for vitamin D deficiency increase with time (for example, aging, declining physical activity, changes in dietary habits, change in body weight or appearance of comorbidities). Therefore, inaccurate assessment of the exposure, especially when vitamin D status is assessed by vitamin D intake (Holden and Lemar, 2008), and uncontrolled or residual confounding may explain the results of the observational studies. Finally, the ascertainment of the outcome variable in observational studies is often done based on self-report or existing medical records, which may introduce additional unintended bias. Analyses within longitudinal observational studies in which the exposure is quantified by repeated measurements of 25(OH)D over time to accurately estimate vitamin D status over long periods and the outcomes are objectively assessed by use of laboratory measures will improve the validity of observational studies.

RCTs are less likely to be biased and/or affected by confounding, and therefore are considered more definitive type of studies. In published trials, there does not appear to be an effect of vitamin D supplementation on glycemia among populations with normal glucose tolerance at baseline; however, firm conclusions cannot be drawn because most studies were either small or *post hoc* analyses of completed trials. For example, the Women's Health Initiative Trial, which is the largest trial on vitamin D and calcium supplementation to date, reported no statistically significant effect on type 2 diabetes outcome. Potential explanations for the null finding of this trial include the low dose of vitamin D, which is also suggested by the lack of effect of supplementation on fractures, difficulties with medications adherence as <60% of participants were compliant by the end of the trial and the fact that the participants in both groups were allowed to take supplements in addition to the study medication. The study by Pittas *et al.* (2007a) showed a beneficial effect of vitamin D and calcium supplementation on fasting blood glucose and insulin resistance only in the group that had impaired fasting glucose at baseline. In this study, the effect size of combined vitamin D and calcium supplementation on fasting glycemia in the high-risk subgroup was similar to the effect size seen in the Diabetes Prevention Program Trial with intensive lifestyle or metformin therapy (Knowler *et al.*, 2002). However, in a similar subgroup analysis in the Women's Health Initiative Trial and in a smaller 1-year trial with weekly high-dose vitamin D

supplementation, there was no benefit of supplementation with vitamin D<sub>3</sub> among those with glucose intolerance (de Boer *et al.*, 2008; Jorde *et al.*, 2010a). In the trial by Avenell *et al.* (2009), a community-based effectiveness trial designed for bone outcomes, supplementation with vitamin D did not change the risk of self-reported type 2 diabetes; however, among study participants who were highly compliant with supplementation, there was a notable trend toward reduction in type 2 diabetes risk with vitamin D, which highlights the importance of efficacy versus effectiveness in community-based trials. In efficacy trials, internal validity (for example, did participants follow the intervention? Is there any proof that they did so? Is outcome measured in an objective way?) is emphasized and these trials are better at evaluating causality. In effectiveness trials, external validity (for example, how does the intervention do in 'real-life' situations?) is emphasized and these studies are better at informing policy changes. Additionally, several trials provided supplementation using large infrequent doses of vitamin D (Sugden *et al.*, 2008; Nagpal *et al.*, 2009; Witham *et al.*, 2010; Jorde *et al.*, 2010a, b), a commonly used clinical approach, the benefit of which has been questioned lately in the setting of studies showing increased risk of adverse outcomes (Dawson-Hughes and Harris, 2010; Sanders *et al.*, 2010). Finally, any trials with vitamin D may be difficult to interpret because (1) ultraviolet radiation contributes to serum 25(OH)D levels, (2) the level of oral intake of vitamin D is poorly assessed and varies between participants and (3) many factors such as genetics, BMI and diet have a role in the response to vitamin D intake and (4) participants start with a wide range in vitamin D levels at baseline.

Similarly, no conclusions can be drawn from the three trials that have included patients with type 2 diabetes because of several limitations: (1) all studies were underpowered (only 16–20 participants per arm); (2) only one study (Jorde and Figenschau, 2009) was designed for glycemic outcomes; however, it recruited only about half of the planned cohort; (3) only one study (Sugden *et al.*, 2008) reported baseline use of diabetes medications; however, in that study metformin use rate was much higher in the vitamin D arm; (4) changes in diabetes medications during the study duration were not reported and were not taken into account in the analyses; and (5) all three trials used large infrequent doses of vitamin D.

In conclusion, there is a biological plausibility of an important role of vitamin D in type 2 diabetes, and lower vitamin D status and intake are associated with higher risk of incident type 2 diabetes in observational studies; however, the effect of vitamin D supplementation on glycemic outcomes was not evident in small underpowered trials or *post hoc* analyses of larger trials. Overall, the available data are currently insufficient to support the contention that type 2 diabetes can be improved by raising 25(OH)D concentration. Confirmation of a potential beneficial effect of vitamin D on type 2 diabetes is needed in large trials

conducted in well-defined populations (for example, pre-diabetes, early type 2 diabetes and whites versus non-whites) specifically designed to test the hypothesis that vitamin D status is a direct contributor to type 2 diabetes pathogenesis. Such an intervention, if proven effective, could have substantial public health implications.

## Conflict of interest

The authors declare no conflict of interest.

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