0021-972X/07/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 92(6):2017–2029

doi: 10.1210/jc.2007-0298

REVIEW: The Role of Vitamin D and Calcium in Type 2 Diabetes. A Systematic Review and Meta-Analysis

Anastassios G. Pittas, Joseph Lau, Frank B. Hu, and Bess Dawson-Hughes

Divisions of Endocrinology, Diabetes and Metabolism (A.G.P., B.D.-H.), and Clinical Research (J.L.), Tufts-New England Medical Center, Boston, Massachusetts 02111; Harvard School of Public Health and Channing Laboratory (F.B.H.), Boston, Massachusetts 02115; and Bone Metabolism Laboratory (B.D.-H.), Jean Mayer U.S. Department of Agriculture Human Nutrition Research Center on Aging, Tufts University, Boston, Massachusetts 02111

Context: Altered vitamin D and calcium homeostasis may play a role in the development of type 2 diabetes mellitus (type 2 DM).

Evidence Acquisition and Analyses: MEDLINE review was conducted through January 2007 for observational studies and clinical trials in adults with outcomes related to glucose homeostasis. When data were available to combine, meta-analyses were performed, and summary odds ratios (OR) are presented.

Evidence Synthesis: Observational studies show a relatively consistent association between low vitamin D status, calcium or dairy intake, and prevalent type 2 DM or metabolic syndrome [OR (95% confidence interval): type 2 DM prevalence, 0.36 (0.16–0.80) among nonblacks for highest *vs*. lowest 25-hydroxyvitamin D; metabolic syndrome prevalence, 0.71 (0.57–0.89) for highest *vs*. lowest dairy intake]. There are also inverse associations with incident type 2 DM or metabolic syndrome [OR (95% confidence interval): type 2 DM incidence, 0.82 (0.72–0.93) for highest *vs*. lowest combined vitamin D and calcium intake; 0.86 (0.79–0.93) for highest *vs*. lowest dairy intake]. Evidence from trials with vitamin D and/or calcium supplementation suggests that combined vitamin D and calcium supplementation may have a role in the prevention of type 2 DM only in populations at high risk (*i.e*. glucose intolerance). The available evidence is limited because most observational studies are cross-sectional and did not adjust for important confounders, whereas intervention studies were short in duration, included few subjects, used a variety of formulations of vitamin D and calcium, or did *post hoc* analyses.

Conclusions: Vitamin D and calcium insufficiency may negatively influence glycemia, whereas combined supplementation with both nutrients may be beneficial in optimizing glucose metabolism. **(*J Clin Endocrinol Metab* 92: 2017–2029, 2007)**

THE INCIDENCE OF type 2 diabetes mellitus (type 2 DM) is increasing at an alarming rate both nationally and worldwide, with more than 1 million new cases per year diagnosed in the United States alone (1). Diabetes is the fifth leading cause of death in the United States, and it is also a major cause of significant morbidity. Although our current methods of treating type 2 DM and its complications have improved, prevention of the disease is preferable. Indeed, epidemiological data suggest that nine of 10 cases of type 2 DM could be attributed to habits and forms of modifiable behavior (2). Potentially modifiable environmental risk factors for type 2 DM have been identified, the major one being obesity. Although weight loss (achieved by any means) has been shown to be successful in delaying type 2 DM, it is difficult to achieve and maintain long term. Therefore, identification of environmental and easily modified risk factors is urgently needed to prevent development of type 2 DM in the 41 million Americans who are at risk of the disease (3).

The major and most well-known function of vitamin D is to maintain calcium and phosphorus homeostasis and promote bone mineralization. However, recent evidence suggests that vitamin D and calcium homeostasis may also be important for a variety of nonskeletal outcomes including neuromuscular function and falls, psoriasis, multiple sclerosis, and colorectal and prostate cancer (4, 5). Based on basic and animal studies, vitamin D and calcium have also been suspected as modifiers of diabetes risk. Vitamin D insufficiency has long been suspected as a risk factor for type 1 diabetes based on animal and human observational studies (6). More recently, there is accumulating evidence to suggest that altered vitamin D and calcium homeostasis may also play a role in the development of type 2 DM. The purpose of our systematic review was to examine: 1) the association between vitamin D and calcium status and risk of type 2 DM; and 2) the effect of vitamin D and/or calcium supplementation on glucose metabolism.

Materials and Methods

We searched MEDLINE for English-language literature through January 2007 for observational studies on the association between vitamin D/calcium status (defined by serum 25-hydroxyvitamin D (25-OHD) concentration, and vitamin D, calcium, or dairy intake) and type 2 DM (prevalence or incidence) and for randomized controlled trials of the effect of vitamin D and/or calcium supplementation in nonpregnant adults on outcomes related to glucose homeostasis. We also examined metabolic syndrome (prevalence or incidence) as an outcome of interest, given that insulin resistance, a feature of type 2 DM, is considered to be a central mechanism underlying the metabolic syndrome. Search terms included *diabetes*, *hyperglycemia*, *glucose*, *glycohemoglobin*, *metabolic syn-*

First Published Online March 27, 2007

Abbreviations: $[Ca^{2+}]_i$, Intracellular cytosolic calcium; CI, confidence interval; HOMA, homeostatic model assessment; OHD, hydroxyvitamin D; OR, odds ratio(s); type 2 DM, type 2 diabetes mellitus.

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.

drome, *insulin resistance*, *homa*, *homeostasis model assessment*, *β-cell function*, *insulin secretion*, *vitamin D*, *calcium*, *dairy*, *milk* and related terms. Additional publications were identified from citations from the recovered articles, review articles, and personal reference lists. We excluded letters, abstracts, and conference proceedings that were not published in full in peer-reviewed journals (7). We excluded studies in children because insulin dynamics are evolving during childhood, especially during puberty (8, 9). We excluded studies of type 1 diabetes (or insulin-requiring diabetes of unclear type), hemodialysis, hyperparathyroidism, and other conditions or medications that affect vitamin D metabolism (*e.g.* epilepsy). Qualitative synthesis of available data were performed due to the large heterogeneity in the methods for assessing outcomes among the studies. However, when data were available to combine, meta-analyses using a random-effects model (10) were performed, and summary odds ratios (OR) are presented. For certain studies that reported a confidence interval (CI) that was asymmetric around the mean, we used a conservative approach and included in the meta-analysis the widest CI reported.

Potential Mechanisms for the Effects of Vitamin D and Calcium on Type 2 DM

For glucose intolerance and type 2 DM to develop, defects in pancreatic β-cell function, insulin sensitivity, and systemic inflammation are often present (11, 12). There is evidence that vitamin D and calcium influence these mechanisms, as summarized next and in Table 1.

Pancreatic β-cell function

There are several lines of evidence supporting a role for vitamin D in pancreatic β-cell function, as shown in Table 1. Vitamin D appears to affect exclusively the insulin response to glucose stimulation, whereas it does not appear to influence basal insulinemia (13, 14). The direct effect of vitamin D may be mediated by binding of its circulating active from, 1,25-OHD, to the β-cell vitamin D receptor. Alternatively, activation of vitamin D may occur within the β-cell by the 1-α-hydroxylase enzyme, which was recently shown to be expressed in β-cells (15). The indirect effects of vitamin D may be mediated via its important and well-recognized role in regulating extracellular calcium and calcium flux through the β-cell (Table 1). Insulin secretion is a calcium-dependent process (16); therefore, alterations in calcium flux can have adverse effects on β-cell secretory function. We speculate that inadequate calcium intake or vitamin D insufficiency may alter the balance between the extracellular and intracellular β-cell calcium pools, which may interfere with normal insulin release, especially in response to a glucose load. Some (17–21), but not all (22, 23), studies in several cohorts with varied baseline vitamin D status have reported an association between vitamin D deficiency and impaired glucose-mediated insulin release. Vitamin D supplementation improved insulin release in some (17, 21, 23, 24), but not all (21, 23, 25), small-scale short-term randomized trials.

Insulin resistance

Vitamin D may have a beneficial effect on insulin action either directly, by stimulating the expression of insulin receptor and thereby enhancing insulin responsiveness for glucose transport (26), or indirectly via its role in regulating extracellular calcium and ensuring normal calcium influx through cell membranes and adequate intracellular cytosolic calcium $[Ca^{2+}]_i$ pool (Table 1). Calcium is essential for insulin-mediated intracellular processes in insulin-responsive tissues such as skeletal muscle and adipose tissue (27–29), with a very narrow range of $[Ca^{2+}]_i$ needed for optimal insulin-mediated functions (30). Changes in $[Ca^{2+}]_i$ in primary insulin target tissues may contribute to peripheral insulin resistance (30–37) via impaired insulin signal transduction (29, 34), leading to decreased glucose transporter-4 activity (34, 38). Associations between low vitamin D level and decreased insulin sensitivity have been reported in cross-sectional studies (18–23, 39, 40). Some (19, 40), but not all (23), observational studies have shown an inverse association between vitamin D or calcium status and insulin resistance. Results from randomized trials on the effect of vitamin D and/or calcium supplementation on insulin resistance show either no effect (23, 41–45) or improvement (46–48) of insulin action with supplementation.

Inflammation

It is currently recognized that type 2 DM is associated with systemic inflammation (12, 49, 50). Systemic inflammation has been linked primarily to insulin resistance, but elevated cytokines may also play a role in β-cell dysfunction by triggering β-cell apoptosis. Vitamin D may improve insulin sensitivity and promote β-cell survival by directly modulating the generation and effects of cytokines (Table 1). There are very limited and conflicting data from human studies that have directly examined the relationship between vitamin D or calcium status and systemic inflammation in relation to type 2 DM (48, 51–53).

Evidence from Observational Human Studies

What is the association between vitamin D status and prevalent type 2 DM or metabolic syndrome?

The role of vitamin D in type 2 DM is suggested by a seasonal variation in glycemic control reported in patients with type 2 DM being worse in the winter (54–56), which may, at least in part, be due to prevalent hypovitaminosis D in the winter. In cross-sectional studies (Table 2), inverse associations between serum 25-OHD and measurements of glycemia or presence of type 2 DM have been reported in a variety of cohorts (18, 19, 40, 57–59), but the relationship is not consistent (18, 19, 23, 40, 60, 61). In the largest cross-sectional study to date from National Health and Nutrition Examination Survey (NHANES) data, serum 25-OHD concentration (after multivariate adjustment) was inversely associated with diabetes prevalence in a dose-dependent pattern in non-Hispanic whites and Mexican-Americans (40, 57). In the same study, 25-OHD concentration also correlated with measures of insulin resistance [estimated by homeostatic model assessment (HOMA-R) based on fasting glucose

TABLE 1. Potential mechanisms and evidence to support a benefit for vitamin D and calcium in type 2 DM

Mechanisms	Evidence
Improvement in pancreatic β-cell function	
Direct effect of vitamin D on insulin secretion	Presence of specific vitamin D receptors in pancreatic β-cells (94)
	Expression of 1-α-hydroxylase enzyme in pancreatic β-cells (15)
	Impaired insulin secretory response in mice lacking functional vitamin D receptors (14)
	Presence of the vitamin D response element in the human insulin gene promoter (95)
	Transcriptional activation of the human insulin gene by 1,25-OHD (96)
	Vitamin D deficiency impairs glucose-mediated insulin secretion from rat pancreatic β-cells *in vitro* (13, 97–99) and *in vivo* (100, 101)
	Supplementation with vitamin D restores insulin secretion in animals (13, 97, 99, 100, 102)
Indirect effect of vitamin D on insulin secretion	Vitamin D contributes to normalization of extracellular calcium, ensuring normal calcium flux through cell membranes and adequate $[Ca^{2+}]_i$ pool
	Regulation of calcium flux and $[Ca^{2+}]_i$ in the pancreatic β-cell via regulation of calbindin, a cytosolic calcium-binding protein (103)
Calcium effect on insulin secretion	Alterations in calcium flux can have adverse effects on insulin secretion, a calcium-dependent process (16)
	Calcium repletion alone normalized glucose tolerance and insulin secretion in vitamin D-depleted rats (104)
	In people without diabetes, hypocalcemia is associated with impairment of insulin release (105, 106)
	In diabetes patients, an oral calcium load augments glucose-induced insulin secretion (107)
	Patients with resistance to 1,25-OHD were found to have abnormal insulin secretion only if they were hypocalcemic (108)
Improvement in insulin action	
Direct effect of vitamin D on insulin action	Inverse association between 25-OHD levels and sarcopenia (109)
	Presence of vitamin D receptor in skeletal muscle (110)
	Vitamin D stimulates the expression of insulin receptor and enhances insulin responsiveness for glucose transport *in vitro* (26)
	Vitamin D directly activates peroxisome proliferator activator receptor-δ (111), a transcription factor implicated in the regulation of fatty acid metabolism in skeletal muscle and adipose tissue (112)
Indirect effect of vitamin D on insulin action	Vitamin D contributes to normalization of extracellular calcium, ensuring normal calcium influx through cell membranes and adequate $[Ca^{2+}]_i$ pool
Calcium effect on insulin action	Calcium is essential for insulin-mediated intracellular processes in insulin-responsive tissues such as skeletal muscle and adipose tissue (27–29) with a very narrow range of $[Ca^{2+}]_i$ needed for optimal insulin-mediated functions (30)
	Changes in $[Ca^{2+}]_i$ in primary insulin target tissues contributes to alterations in insulin action (30–37)
	Impairment of insulin receptor phosphorylation, a calcium-dependent process (113) leading to impaired insulin signal transduction (29, 34) and decreased glucose transporter-4 activity (34, 38)
	Changes in $[Ca^{2+}]_i$ modulate adipocyte metabolism, which may promote triglyceride accumulation via increased *de novo* lipogenesis and inability to suppress insulin-mediated lipolysis leading to fat accumulation (114, 115)
	Patients with type 2 DM exhibit impaired cellular calcium homeostasis including defects in skeletal muscle, adipocytes, and liver (116)
Improvement in systemic inflammation	
Effects of vitamin D on cytokines	Vitamin D interacts with vitamin D response elements in the promoter region of cytokine genes to interfere with nuclear transcription factors implicated in cytokine generation and action (117–119)
	Vitamin D can down-regulate activation of nuclear factor-κB (117, 119, 120), which is an important regulator of genes encoding proinflammatory cytokines implicated in insulin resistance (121)
	Vitamin D interferes with cytokine generation by up-regulating expression of calbindin (94, 122, 123), a cytosolic calcium-binding protein found in many tissues including pancreatic β-cells (94, 123). Calbindin has been shown to protect against cytokine-induced apoptosis that may occur after a rise in cytosolic free calcium $[Ca^{2+}]_I$ (124).
Effects of calcium on cytokines	Changes in $[Ca^{2+}]_i$ may lead to cytokine-induced apoptosis (85)

and insulin levels] but did not correlate with β-cell function (estimated by HOMA-β). No correlation between 25-OHD and diabetes prevalence or measures of insulin resistance or β-cell function was seen in non-Hispanic blacks. This lack of association may be explained by the observation that non-whites exhibit a different vitamin D, calcium, and PTH homeostasis compared with whites (62).

Combining data from all studies that reported on the association between 25-OHD level and prevalent type 2 DM (40, 60, 61, 63), the summary OR was 0.54 (95% CI, 0.23–1.27)

TABLE 2. Cross-sectional studies reporting an association between vitamin D status, calcium intake, dairy intake, and prevalence of type 2 DM/metabolic syndrome in nonpregnant adults

First author, year (Ref.)	Sex	Age, mean or range (yr)	Cohort	Outcome (assessment)	Predictor, range, or category	Main study results	Adjustments	Comments and other outcomes
Vitamin D status (25-OHD concentration or vitamin D intake)								
Orwoll, 1994 (23)	M/F	40–70	Non-insulin-treated type 2 DM (n = 20)	FPG	25-OHD, NR	25-OHD not associated with FPG		25-OHD not associated with IR (fasting insulin)
Baynes, 1997 (18)	M	76	Nondiabetics (n = 142)	FPG, 2hPG	25-OHD, 1–75 ng/ml	25-OHD not associated with FPG or 2hPG	BMI, skinfold, exercise, smoking, alcohol	25-OHD inversely associated with 1hPG (r = −0.2), GLU_{AUC} (r = −0.3)
Wareham, 1997 (60)	M/F	40–65	Nondiabetics (n = 1,057)	IGT (2hPG)	25-OHD, <23 to >25 ng/ml	OR 1.00, 1.03 (1.01–1.05)		
Chiu, 2004 (19)	M/F	26	Nondiabetics (n = 126)	FPG, 2hPG	25-OHD, 5–75 ng/ml	25-OHD inversely associated with 1hPG, 2hPG; 25-OHD not associated with FPG	Age, sex, race, BMI, WHR, blood pressure	25-OHD inversely associated with 1hPG, IR (clamp). 25-OHD not associated with insulin release
Scragg, 2004 (40)	M/F	>20	NHANES (n = 2,766 non-Hispanic whites)	Type 2 DM (FPG)	25-OHD, <18 to >32 ng/ml	OR 1.00, 0.25 (0.11–0.60)	Age, sex, race, BMI, exercise, season	25-OHD inversely associated with IR (HOMA)
	M/F	>20	NHANES (n = 1,726 Mexican-Americans)	Type 2 DM (FPG)	25-OHD, <18 to >32 ng/ml	OR 1.00, 0.17 (0.08–0.37)	Age, sex, race, BMI, exercise, season	25-OHD inversely associated with IR (HOMA)
	M/F	>20	NHANES (n = 1,726 non-Hispanic blacks)	Type 2 DM (FPG)	25-OHD, <18 to >32 ng/ml	OR 1.00, 3.40 (1.07–10.86)	Age, sex, race, BMI, exercise, season	
Ford, 2005 (57)	M/F	>20	NHANES (n = 8,241)	Type 2 DM (FPG)	25-OHD, <19 to >38 ng/ml	OR 1.00, 0.17 (0.08–0.37)	Age, sex, race, exercise, smoking, alcohol, diet, vitamin use, cholesterol, CRP, education, season	
Need, 2005 (58)	F	63	Nondiabetics, (n = 753)	FPG	25-OHD, NR	25-OHD (>16 ng/ml) inversely associated with FPG	Age, BMI	
Snijder, 2006 (61)	M/F	75	(n = 1,235)	Type 2 DM (self-report)	25-OHD, <10 to ≥30 ng/ml	OR 1.0, 1.23 (0.50–3.02)	Age, sex, WHR, exercise, smoking, alcohol, region, season	
Hypponen and Power, 2006 (59)	M/F	45	Caucasians (n = 7,198)	Hemoglobin A1c (%)	25-OHD, <10 to ≥30 ng/ml	Hemoglobin A1c concentration 5.4%, 5.1%	Sex, season	Association pronounced among obese
Chiu, 2004 (19)	M/F	26	Nondiabetics (n = 126)	Metabolic syndrome	25-OHD, 5–75 ng/ml	25-OHD inversely associated with metabolic syndrome	Age, sex, race, BMI, WHR, blood pressure	
Ford, 2005 (57)	M/F	>20	NHANES (n = 8,241)	Metabolic syndrome	25-OHD, <19 to >38 ng/ml	OR 1.00, 0.46 (0.32–0.67)	Age, sex, race, exercise, smoking, alcohol, diet, vitamin use, cholesterol, CRP, education, season	
Liu, 2005 (66)	F	>45	Women's Health Study (n = 10,066)	Metabolic syndrome	Vitamin D intake, ≤159 to ≥511 IU/d	OR 1.00, 1.05 (0.84–1.32)	Age, exercise, smoking, alcohol, vitamin use, history of myocardial infarction, calcium intake	
Calcium intake								
Liu, 2005 (66)	F	>45	Women's Health Study (n = 10,066)	Metabolic syndrome	Calcium intake, ≤ 610 to ≥1,284 mg/d	OR 1.00, 0.68 (0.55–0.83)	Age, exercise, smoking, alcohol, vitamin use, history of myocardial infarction, vitamin D intake	
Dairy intake								
Mennen, 2000 (78)	M	30–64	n = 2,439	FPG	≤1 to >4 servings/d	Dairy intake inversely associated with FPG	Age, WHR, energy intake	
Azadbakht, 2005 (79)	M/F	18–74	Tehranian adults (n = 827)	IGT (FPG>110 mg/dl)	<1.7 to ≥3.1 servings/d	OR 1.00, 0.88 (0.73–1.09)	Age, sex, BMI, WHR, exercise, smoking, energy intake, calcium intake	

TABLE 2. *Continued*

First author, year (Ref.)	Sex	Age, mean or range (yr)	Cohort	Outcome (assessment)	Predictor, range, or category	Main study results	Adjustments	Comments and other outcomes
Mennen, 2000 (78)	F	30–64	n = 2,537	Metabolic syndrome	≤1 to >4 servings/d	OR 1.00, 0.76 (0.47–2.66)	Age, WHR, energy intake	
Mennen, 2000 (78)	M	30–64	n = 2,439	Metabolic syndrome	≤1 to > 4 servings/d	OR 1.00, 0.63 (0.40–0.99)	Age, WHR, energy intake	Dairy intake inversely associated with FPG (OR not provided)
Azadbakht, 2005 (79)	M/F	18–74	Tehranian adults (n = 827)	Metabolic syndrome	<1.7 to ≥3.1 servings/d	OR 1.00, 0.82 (0.64–0.98)	Age, sex, BMI, WHR, exercise, smoking, energy intake, calcium intake	
Liu, 2005 (66)	F	>45	Women's Health Study (n = 10,066)	Metabolic syndrome	<0.9 to >3 servings/d	OR 1.00, 0.66 (0.55–0.80)	Age, exercise, smoking, alcohol, vitamin use, history of myocardial infarction	

BMI, Body mass index; M, male; F, female; FPG, fasting plasma glucose; NR, not reported; NGT, normal glucose tolerance (based on FPG or 2hPG); IGT, impaired glucose tolerance (based on FPG or 2hPG); type 2 DM, type 2 diabetes mellitus (based on FPG, 2hPG, or self-report); 1hPG, plasma glucose 1 h after 75-g glucose load; 2hPG, plasma glucose 2 h after 75-g glucose load; GLU_{AUC}, glucose area-under-the-curve after 75-g glucose load; IR, insulin resistance; CRP, C-reactive protein; WHR, waist-hip-ratio; ↓, decreased (statistically significant), ↑, increased (statistically significant), ↔, no difference (no statistical significance); NHANES, National Health and Nutrition Examination Survey; BWHS, Black Women's Health Study; CARDIA, Coronary Artery Risk Development in Young Adults study; HPFS, Health Professionals Follow-up Study. To convert 25-OHD concentration to SI units, multiply by 2.459.

for the highest *vs.* the lowest 25-OHD concentration (25–38 *vs.* 10–23 ng/ml, respectively), but with significant heterogeneity among studies. When we excluded the data on non-Hispanic blacks, there was a statistically significant inverse association between 25-OHD concentration and prevalent type 2 DM [OR 0.36 (95% CI, 0.16–0.80)].

Vitamin D intake and 25-OHD concentration have also been inversely associated with prevalence of metabolic syndrome (19, 57). In the largest study using NHANES data, serum 25-OHD concentration (after multivariate adjustment, but not including calcium intake) was inversely associated with having the metabolic syndrome (57) among both sexes and all three major racial or ethnic groups (57). The components of the metabolic syndrome that were independently associated with low 25-OHD were abdominal obesity and hyperglycemia; therefore, the results of this study may simply reflect the inverse association between serum 25-OHD and body weight or fatness (40, 64, 65). In a recent cross-sectional analysis of the Women's Health Study, a large randomized trial designed to evaluate the effects of low-dose aspirin and vitamin E in cardiovascular disease, the inverse association between vitamin D intake and prevalence of metabolic syndrome was dissipated after adjustment for calcium intake (66).

In most (17, 51, 59, 63, 67–72), but not all (69, 73, 74), case-control studies, patients with type 2 DM or glucose intolerance are found to have lower serum 25-OHD concentration compared with controls without diabetes (Table 3).

What is the association between vitamin D status and incident type 2 DM or metabolic syndrome?

Two prospective studies have examined the association of vitamin D intake with incident type 2 DM (Table 4). In the Women's Health Study, an intake of 511 IU/d of vitamin D or more was associated with lower risk of incident type 2 DM compared with an intake of 159 IU/d or less (2.7 *vs.* 5.6% of the cohort developed type 2 DM, respectively) (66). However, this analysis did not adjust for other risk factors of type 2 DM or calcium intake. Recently, our group examined the association between vitamin D and calcium intakes and incident type 2 DM among 83,806 women in the Nurses Health Study, a large prospective observational cohort (52). After adjusting for age, BMI, and nondietary covariates, we observed a significant inverse association between total (food + supplements) vitamin D intake and risk of type 2 DM. The association was attenuated after adjusting for dietary factors, in particular, magnesium and calcium.

What is the association between calcium intake and prevalent type 2 DM or metabolic syndrome?

A potentially important role for calcium status in the development of type 2 DM is suggested by case control studies in which calcium intake was found to be lower in patients with diabetes compared with controls (72). In the analysis from the Women's Health Study, calcium intake (after adjustment for vitamin D intake) was inversely associated with prevalence of metabolic syndrome (66).

TABLE 3. Case-control studies reporting an association between vitamin D status, calcium intake, and type 2 DM or metabolic syndrome in nonpregnant adults

First author, year (Ref.)	Sex	Age, mean or range (yr)	Cases/outcome measure	Control group	Predictor	Main study results	Adjustments	Comments and other outcomes
Vitamin D status (25-OHD concentration or vitamin D intake)								
Heath, 1979 (74)	M/F	18–75	Type 2 DM, n = 82	n = 40	25-OHD	↔ 25-OHD in type 2 DM *vs.* controls (35 *vs.* 38–44 ng/ml)		
Christiansen, 1982 (67)	M	36	Insulin-treated type 2 DM, n = 26	Age-, sex- matched, n = 14	25-OHD	↓ 25-OHD in type 2 DM *vs.* controls (17 *vs.* 22 ng/ml)		25-OHD not associated with C-peptide level
Stepan, 1982 (68)	M/F	40–70	Sulfonylurea-treated type 2 DM, n = 22	Blood donors, n = 30	25-OHD	↓ 25-OHD in type 2 DM *vs.* controls (9 *vs.* 14 ng/ml)		
Ishida, 1985 (73)	M/F	19–80	Type 2 DM, n = 168	n = 78	25-OHD	↔ 25-OHD in type 2 DM *vs.* controls (30 *vs.* 28 ng/ml)		
Nyomba, 1986 (69)	M/F	34–60	Bantu insulin-treated type 2 DM, n = 20	Bantu, n = 36	25-OHD	↓ 25-OHD in type 2 DM *vs.* controls (26 *vs.* 35 ng/ml)		
	M/F	14–63	Caucasian diet- and insulin-treated type 2 DM, n = 44	Caucasian, n = 26	25-OHD	↔ 25-OHD in type 2 DM *vs.* controls (34 *vs.* 33 ng/ml)		
Pietschamann, 1988 (70)	M/F	62	Type 2 DM, n = 38	Age-, sex-matched, n = 17	25-OHD	↓ 25-OHD in type 2 DM *vs.* controls (8 *vs.* 15 ng/ml)		
Boucher, 1995 (17)	M/F	40–57	IGT/type 2 DM, n = 44	Age-, sex-matched, n = 15	25-OHD	↓ 25-OHD in IGT/type 2 DM *vs.* controls (28 *vs.* 30 ng/ml)		
Scragg, 1995 (63)	M/F	40–64	IGT/newly diagnosed type 2 DM, n = 238	Age-, sex-, ethnicity-, date-matched, n = 238	25-OHD	OR 1.00, 0.36 (0.19–0.71) (>33 *vs.* ≤24 ng/ml)	BMI, exercise, cholesterol, hypertension	Nested case-control study
Aksoy, 2000 (71)	M/F	57	Type 2 DM with retinopathy, n = 66	Season-matched, n = 20	25-OHD	↓ 25-OHD in type 2 DM *vs.* controls (12 *vs.* 24 ng/ml)		
Isaia, 2001 (72)	F	NR	Type 2 DM, n = 66	n = 66	25-OHD	↓ 25-OHD in type 2 DM *vs.* controls (9 *vs.* 11 ng/ml)	Age, time since menopause	
Cigolini, 2006 (51)	M/F	61	Type 2 DM, n = 459	Age-, sex-matched, n = 459	25-OHD	↓ 25-OHD in type 2 DM *vs.* controls (20 *vs.* 24 ng/ml)		
Hypponen and Power, 2006 (59)	M/F	45	Type 2 DM, n = 125	Sex-, season- matched, n = 7,073	25-OHD	↓ 25-OHD in type 2 DM *vs.* controls (15 *vs.* 21 ng/ml)		
Calcium intake								
Isaia, 2001 (72)	F	NR	Type 2 DM, n = 66	n = 66	Calcium intake	↓ Calcium intake in type 2 DM *vs.* controls (679 *vs.* 792 mg/d)	Age, time since menopause	

See Table 2 legend for abbreviations. To convert 25-OHD concentration to SI units, multiply by 2.459.

TABLE 4. Prospective studies reporting an association between vitamin D status, calcium intake, dairy intake, and incidence of type 2 DM/metabolic syndrome in nonpregnant adults

First author, year (Ref.)	Sex	Age at baseline, mean or range (yr)	Cohort, total no./no. of cases	Outcome (assessment)	Predictor, lowest and highest category	Main study results	Adjustments	Comments
Vitamin D status (25-OHD concentration or vitamin D intake)								
Liu, 2005 (66)	F	>45	Women's Health Study, 10,066/NR	Type 2 DM (validated self-report)	Vitamin D intake, ≤159 IU/d and ≥511 IU/d	% of cohort with type 2 DM, 5.6 and 2.7	Age	
Pittas, 2006 (52)	F	46	Nurses Health Study, 83,779/4,843	Type 2 DM (validated self-report)	Vitamin D intake ≤200 IU/d and >800 IU/d	Relative risk, 1.00, 0.87 (0.69–1.09)	Age, BMI, exercise, diabetes family history, smoking, alcohol, coffee, diet, hypertension, calcium intake	
Calcium intake								
Liu, 2005 (66)	F	>45	Women's Health Study, 10,066/NR	Type 2 DM (validated self-report)	Calcium intake ≤610 mg/d and ≥1,284 mg/d	% of cohort with type 2 DM, 5.6 and 2.7	Age	
Pittas, 2006 (52)	F	46	Nurses Health Study, 83,779/4,843	Type 2 DM (validated self-report)	Calcium intake ≤600 mg/d and >1,200 mg/d	Relative risk, 1.00, 0.79 (0.70–0.90)	Age, BMI, exercise, diabetes family history, smoking, alcohol, coffee diet, hypertension, calcium intake	
van Dam, 2006 (76)	F	39	BWHS, 41,186/1,964	Type 2 DM (validated self-report)	Calcium intake, 219 mg/d and 661 mg/d	Relative risk, 1.00, 0.86 (0.74–1.00)	Age, BMI, exercise, diabetes family history, smoking, alcohol, coffee, diet, education	Association dissipated after adjustment for magnesium intake
Pereira, 2002 (77)	M/F	18–30	CARDIA, 3,157	Metabolic syndrome (ATP-3 criteria)	Calcium intake, <600 mg/d and >1200 mg/d	Relative risk, 1.00, 0.79 (0.61–1.03), among overweight (BMI >25) only	Age, sex, BMI, exercise, smoking, diet, vitamin use, energy intake	Association dissipated after adjusting for dairy intake
Combined vitamin D and calcium intake								
Pittas, 2006 (52)	F	46	Nurses Health Study, 83,779/4,843	Type 2 DM (validated self-report)	Vitamin D and calcium, ≤400 IU/d and ≤600 mg/d, >800 IU/d and >1200 mg/d	Relative risk, 1.00, 0.67 (0.49–0.90)	Age, BMI, exercise, diabetes family history, smoking, alcohol, coffee, diet, hypertension	
Dairy intake								
Choi, 2005 (80)	M	53	HPFS 41,254/1,243	Type 2 DM (validated self-report)	0.5 servings/d and 4.1 servings/d	Relative risk, 1.00, 0.82 (0.67–0.1.00)	Age, BMI, exercise, diabetes family history, smoking, diet, cholesterol, hypertension	Adjustment for calcium intake reduced statistical significance of dairy intake
Liu, 2006 (81)	W	55	Women's Health Study 37,183/1,603	Type 2 DM (validated self-report)	Low-fat, <0.9 servings/d and ≥ 3 servings/d	Relative risk, 1.00, 0.80 (0.67–0.95)	Age, BMI, exercise, diabetes family history, smoking, diet, hormone use, cholesterol, hypertension	Inverse association persisted after adjusting for calcium, vitamin D intake
Pittas, 2006 (52)	F	46	Nurses Health Study, 83,779/4,843	Type 2 DM (validated self-report)	<1 servings/d and ≥3 servings/d	Relative risk, 1.00, 0.89 (0.81–0.99)	Age, BMI, exercise, diabetes family history, smoking, alcohol, coffee, diet, hypertension	
van Dam, 2006 (76)	F	39	Nondiabetics (black) 41,186/1,964	Type 2 DM (validated self-report)	Low-fat, 0 servings/d and >1 serving/d	Relative risk, 1.00, 0.87 (0.76–1.00)	Age, BMI, exercise, diabetes family history, smoking, alcohol, coffee, diet, education	
Pereira, 2002 (77)	M/F	18–30	CARDIA, 3,157/909	Metabolic syndrome (ATP-3 criteria)	<1.5 servings/d and ≥5 servings/d	Relative risk, 1.00, 0.31 (0.14–0.70) among overweight (BMI >25) only	Age, sex, BMI, exercise, smoking, diet, energy intake, vitamin use, calcium and vitamin D intake	

See Table 2 legend for abbreviations. To convert 25-OHD concentration to SI units, multiply by 2.459.

What is the association between calcium intake and incident type 2 DM or metabolic syndrome?

In prospective studies, low calcium intake is consistently found to be inversely associated with incident type 2 DM (52, 66, 75, 76) or the metabolic syndrome (77). In the Nurses Health Study, total (food + supplements) calcium intake was inversely associated with incident type 2 DM after complete multivariate adjustment, including vitamin D intake (52). A similar inverse association was seen in the Black Women's Health Study, a prospective cohort of approximately 59,000 women aged 21–69 yr at baseline (76). In the latter study, there was no adjustment for vitamin D status, but the association was attenuated after adjustment for magnesium intake. After combining data from the latter two studies, the summary OR (95% CI) for incident type 2 DM was 0.82 (0.72–0.93) for the highest *vs.* the lowest calcium intake (661–1200 *vs.* 219–600 mg/d, respectively). The results of these studies highlight an important role for calcium intake.

What is the association between dairy intake and type 2 DM or metabolic syndrome?

The association between calcium and vitamin D status and type 2 DM can also be assessed from studies that report the effects of intake of dairy products on measurements of glycemia and metabolic syndrome. After combining data from cross-sectional studies, the summary OR for prevalence of metabolic syndrome was 0.71 (95% CI, 0.57–0.89) for the highest dairy intake (3–4 servings per day) *vs.* lowest (0.9–1.7 servings per day) (66, 78, 79), with no apparent heterogeneity among studies. In prospective studies, a moderate inverse association of dairy intake with incident type 2 DM (52, 76, 80, 81) or metabolic syndrome (77) is consistently reported. The summary OR for incident type 2 DM was 0.86 (95% CI, 0.79–0.93) for the highest *vs.* lowest dairy intake (3–5 *vs.* <1.5 servings per day, respectively) (52, 76, 80, 81) with no apparent heterogeneity among studies. It is important to note that although calcium and vitamin D are important components of dairy products, their contribution to the measured outcomes cannot be separated from other components in dairy products.

Summary of evidence from human observational studies and future directions

The evidence from observational studies suggests an association between low vitamin D status and calcium intake (including low dairy intake) and risk of type 2 DM or metabolic syndrome. However, definite conclusions from these studies are limited for a variety of reasons. 1) In cross-sectional or case-control studies, vitamin D or calcium status was measured in patients with glucose intolerance or established diabetes; therefore, these measures may not reflect vitamin D or calcium status before diagnosis and, as a result, the causative nature of the observed associations cannot be established. 2) There is considerable variability in studied cohorts [normal glucose tolerance *vs.* diabetes (newly diagnosed *vs.* established), ethnicity, latitude *etc.*]. 3) In most studies, there is a lack of adjustment for important confounders, such as adiposity, physical activity, and importantly, vitamin D or calcium status (for calcium or vitamin D studies, respectively). To clarify the individual contribution of each nutrient to future type 2 DM risk, in the Nurses Health Study, our group examined the combined effects of total (food + supplements) vitamin D and calcium intake on risk of incident type 2 DM (Fig. 1). We observed that, after multivariate adjustment, women with the highest calcium (>1200 mg/d) and vitamin D (>800 IU/d) intake (1.3% of the cohort) had a 33% lower risk of type 2 DM compared with women with the lowest calcium (<600 mg/d) and vitamin D (<400 IU/d) intakes. The lower risk seen with the combined intake was more than that seen with the highest intake of each nutrient separately, which highlights the importance of both nutrients as potential type 2 DM risk modifiers and the need to take into consideration both nutrients in observational studies.

Evidence from Intervention Human Studies

What is the effect of vitamin D supplementation on type 2 DM?

There are four small-scale short-term and two long-term controlled trials that have examined the effect of supplementation with a variety of formulations of vitamin D on type 2 DM parameters. Among 18 young healthy men, supplementation with 1,25-$(OH)_2D_3$ for 7 d did not change fasting glycemia or insulin sensitivity (42). In another small study (n = 14) in patients with type 2 DM, 2 μg/d IU of 1-OHD_3 administration daily for 3 wk enhanced insulin secretion but had no effect on post-load glucose tolerance (24). Ljunghall *et al.* (41) randomized 65 middle-aged men with impaired glucose tolerance or mild diabetes and sufficient vitamin D levels at baseline to 0.75 μg/d of 1-OHD_3 or placebo for 3 months and found no effect in fasting or stimulated glucose tolerance. In that trial, participants had sufficient vitamin D levels at baseline (mean 25-OHD, 38 ng/ml). In a crossover trial, 20 patients with type 2 DM and vitamin D deficiency were treated for 4 d with 1 μg/d of 1,25-OHD, and no change was seen in fasting or stimulated glucose, insulin, or C-peptide concentrations, but an improvement in insulin and C-peptide secretion was seen in

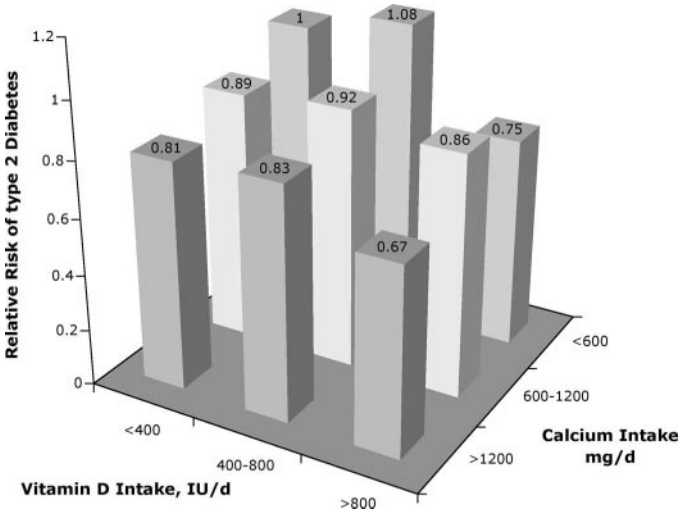

FIG. 1. Adjusted relative risk of incident type 2 DM in the Nurses Health Study by calcium and vitamin D intake (52).

patients with diabetes of short duration (23). The intervention period in this trial was too short to draw definitive conclusions, but it does suggest that vitamin D supplementation at an early stage in the development of diabetes (*i.e.* glucose intolerance) may be of benefit in delaying progression to clinical type 2 DM, which is supported by more recent data described below (48). Lastly, in a *post hoc* analyses of a 2-yr trial designed for bone-related outcomes, supplementation with vitamin D_3 or 1-OHD_3 had no effect on fasting glycemia in postmenopausal nondiabetic women (82).

What is the effect of calcium or dairy supplementation on type 2 DM?

There is limited evidence of an effect of calcium supplementation on diabetes-related parameters from trials that have examined the effects of calcium either alone or as a component of dairy products (Table 5). In 20 nondiabetic patients with essential hypertension, supplementation with 1,500 mg/d of calcium *vs.* placebo for 8 wk did not influence fasting glycemia but improved insulin sensitivity, as measured by euglycemic hyperinsulinemic clamp (46). Trials with small numbers of nondiabetic participants that have examined the effects of calcium supplementation as a component of dairy products in relation to glycemia or insulin resistance have shown conflicting results, but most studies show a neutral effect (43–45, 47, 83).

What is the effect of combined vitamin D and calcium supplementation on type 2 DM?

In a recent report from our group, *post hoc* analyses of a trial designed for bone-related outcomes showed that combined supplementation with 700 IU of vitamin D_3 and 500 mg of calcium as calcium citrate malate had no effect on glycemia or insulin resistance in 221 adults over age 65 with normal glucose tolerance at baseline (48). However, among participants with impaired fasting glucose at baseline, those who took combined vitamin D_3 and calcium supplements had a significantly lower rise in fasting glycemia and insulin resistance at 3 yr compared with those on placebo (0.4 *vs.* 6.1 mg/dl, respectively) (48). The effect size with combined vitamin D and calcium supplementation seen in this high-risk group was similar in magnitude to the progression of fasting glycemia seen in the Diabetes Prevention Program with intensive lifestyle or metformin (0.2 mg/dl in the lifestyle and 0.2 mg/dl in the metformin arm *vs.* 5.5 mg/dl in placebo) (84).

Summary of evidence from human intervention studies and future directions

It is difficult to draw definitive conclusions from the available intervention studies with vitamin D and/or calcium supplementation because most studies were short in duration, included few subjects, used a variety of formulations and combinations of vitamin D and calcium among various cohorts, or used *post hoc* analyses. Furthermore, the contribution of vitamin D and/or calcium in studies with dairy are difficult to interpret because dairy may have additional components affecting glucose metabolism. However, the overall evidence suggests that vitamin D alone probably has no effect in healthy individuals, but combined vitamin D and calcium supplementation may have a role in the prevention of type 2 DM, especially in populations at risk for type 2 DM such as those with glucose intolerance.

Optimal Intake of Vitamin D and Calcium in Relation to Type 2 DM

Currently recommended intake for calcium is 1200 mg/d for adults older than 50 yr, and for vitamin D, 400 IU/d for those aged 51–70 yr and 600 IU/d for those older than 70 yr (85). However, there is growing consensus that vitamin D intakes above the current recommendations may be associated with better health outcomes. Optimal levels of 25-OHD have not been defined, but for a variety of skeletal and nonskeletal outcomes, the most advantageous serum concentration of 25-OHD appears to be 30–40 ng/ml (4). In relation to type 2 DM, it is difficult to draw a definitive conclusion about an optimal level because available studies were done in a variety of cohorts with a large range of 25-OHD levels (Table 2). However, the data suggest that serum 25-OHD concentrations above 20 ng/ml are desirable, but those above 40 ng/ml may be better. To achieve such a 25-OHD concentration, an intake of approximately 1000 IU/d of vitamin D is needed (4, 86). In relation to calcium intake for type 2 DM, the evidence suggests that intakes above 600 mg/d are desirable, but intakes above 1200 mg may be optimal (Tables 2–5 and Fig. 1).

Data from NHANES III show that vitamin D insufficiency (25-OHD $<$ 25 ng/ml) may affect up to half of the noninstitutionalized adolescent and adult population in the United States, even in the southern latitudes during the winter (87). Additional studies have shown a prevalence of vitamin D insufficiency ranging from 36–100% in a variety of populations including healthy young adults to hospitalized elderly individuals (52, 88–90). Insufficiency of calcium status is difficult to document biochemically, but there is concern that Americans are not meeting the recommended intake for calcium (91, 92). Adjusted for day-to-day variation, the median reported intake of calcium in the U.S. population declines with age (ages 51–70 yr, 708 mg/d for men and 571 mg/d for women; older than 70 yr, 702 mg/d for men and 517 mg/d for women) (85, 93). Combined insufficiency in vitamin D and calcium intake may be even more prevalent. In the Nurses Health Study, the group of female nurses with the highest intake of calcium ($>$1200 mg/d) and vitamin D ($>$800 IU/d) that was associated with the lowest risk of incidence type 2 DM was only 1.3% of the cohort (52).

Therefore, given the potential link between vitamin D, calcium, and diabetes described above, it is plausible that the rising incidence of type 2 DM may, at least in part, be due to suboptimal vitamin D and calcium status of the U.S. adult population. Furthermore, certain determinants of adequate vitamin D and calcium status (aging, physical inactivity, dark skin, and obesity) are also strong risk factors for type 2 DM. Although this may simply reflect confounding, the link between these risk factors and type 2 DM may, at least partially, be mediated by vitamin D and calcium insufficiency.

TABLE 5. Randomized controlled trials of the effect of vitamin D and/or calcium supplementation on glucose tolerance

First author, year (Ref.)	Sex	Age, mean or range (yr)	Study participants	25-OHD concentration and calcium intake at baseline	Intervention		Main outcome (glycemia)	Comment and other outcomes
					Type and dose	Duration		
Vitamin D alone								
Nilas, 1984 (82)	F	45–54	Nondiabetic, n = 151	NR	Vitamin D_3 2,000 IU/d (n = 25) *vs.* $1OHD_3$ 0.25 μ g/d (n = 23) *vs.* placebo (n = 103); all received 500 mg/d calcium	104 wk	↔FPG (change from baseline, [mg/dl]: +2.2 *vs.* −0.33 *vs.* +0.1269)	
Inomata, 1986 (24)	M/F	36–80	Type 2 DM; n = 14	NR	$1OHD_3$ 2 μ g/d (n = 7) *vs.* placebo (n = 7)	3 wk	↔GLU_{AUC} (change from baseline [mg/2 h/dl]: −21.2 *vs.* −2.3)	↑, INS_{AUC}
Ljunghall, 1987 (41)	M	61–65	IGT/mild type 2 DM, n = 65	25-OHD 38 ng/ml	$1OHD_3$ 0.75 μ g/d (n = 33) *vs.* placebo (n = 32)	12 wk	↔FPG (baseline to end-of-study [mg/dl]: 117 to 117 *vs.* 115 to 117); ↔A1c (baseline to end [%]: 6.46 to 5.90 *vs.* 6.28 to 5.70)	↔ IR_{IVGTT}
Orwoll, 1994 (23)	M/F	40–70	Non-insulin-treated type 2 DM, n = 20	25-OHD 14 ng/ml	1,25-OHD 1 μ g/d *vs.* placebo (crossover trial, n = 20)	4 d	↔FPG (baseline to end-of-study [mg/dl]: 214 to 209 *vs.* 214 to 198); ↔ meal-stimulated PG (data NR)	↔ IR_{FI}, ↔ INS_{AUC} ↑ INS_{AUC} if diabetes of short duration
Fliser, 1997 (42)	M	26	Healthy, nondiabetic, n = 18	NR	$1,25(OH)_2D_3$ 1.5 μ g/d (n = 9) *vs.* placebo (n = 9)	1 wk	↔ FPG (baseline to end-of-study [mg/dl]: 84 to 86 *vs.* 86 to 88)	↔ IR_M
Calcium alone or dairy supplementation								
Sanchez, 1997 (46)	M/F	25–56	Nondiabetic with essential hypertension, n = 20	NR	Calcium 1500 mg/d (n = 10) *vs.* placebo (n = 10)	8 wk	↔ FPG (baseline to end-of-study [mg/dl]: 99 to 102 *vs.* 96 to 93)	↓ IR_M
Barr, 2000 (43)	M/F	55–85	Nondiabetic, n = 204	Calcium intake, 649–801 mg/d	Skim/low-fat milk (3 servings/d) (n = 101) *vs.* usual diet (n = 100)	12 wk	↑ FPG (baseline to end-of-study, [mg/dl] 94 to 94 *vs.* 95 to 95); ↔A1c (data NR)	↔IR_{FI}
Zemel, 2004 (47)	M/F	18–60	Nondiabetic, obese, n = 32	NR	High dairy (calcium 1300 mg/d) [n = 11] *vs.* high calcium (calcium 1300 mg/d) [n = 11] or low calcium (500 mg/d) [n = 10]; all received energy restriction (−500 kcal/d)	24 wk	↔ FPG (data NR); ↓ GLU_{AUC} (change from baseline, [%] −27 *vs.* NR *vs.* NR)	↔INS_{AUC}, ↓ IR_{FI}, not adjusted for weight loss
Bowen, 2005 (44)	M/F	25–64	Nondiabetic, overweight, n = 50	Calcium intake, 787–899 mg/d	High dairy protein (calcium 2400 mg/d) [n = 25] *vs.* high mixed protein (calcium 500 mg/d) [n = 25]; all received energy restriction	16 wk	↔ FPG (data NR); ↔ GLU_{AUC} (data given)	↔ IR_{FI}, INS_{AUC}, protein source was altered
Thompson, 2005 (45)	M/F	25–70	Nondiabetic obese, n = 90	NR	Dairy, 2 servings/d [n = 29] *vs.* dairy, 4 servings/d [n = 30]; all received energy restriction (−500 kcal/d)	48 wk	↔FPG (change from baseline [mg/dl]: −1.4 *vs.* −4.0); ↔ 2hPG (change from baseline [mg/dl]: 1.6 *vs.* −5.4)	↔ INS_{120}, IR_{FI}
Combined vitamin D plus calcium supplementation								
Pittas, 2006 (48)	M/F	71	Normal fasting glucose, n = 222	25-OHD, 30 ng/ml; calcium intake, 750 mg/d	D_3 700 IU/d + calcium citrate 500 mg/d (n = 108) *vs.* placebo (n = 114)	3 yr	↔ FPG (change from baseline [mg/dl]: 2.7 *vs.* 2.2)	↔ IR_{HOMA}
	M/F		Impaired fasting glucose, n = 92	25-OHD, 30 ng/ml; calcium intake, 680 mg/d	D_3 700 IU/d + calcium citrate 500 mg/d (n = 45) *vs.* placebo (n = 47)	3 yr	↓ FPG (change from baseline [mg/dl]: 0.4 *vs.* 6.1)	↓ IR_{HOMA}

NR, Not reported; IGT, impaired glucose tolerance (based on FPG or 2hPG); Type 2 DM, type 2 diabetes mellitus (based on FPG, 2hPG or self-report); FPG, fasting plasma glucose; 2hPG, plasma glucose 2 h after 75-g glucose load; GLU_{AUC}, glucose area-under-the-curve after 75-g glucose load; INS_{AUC}, insulin area-under-the-curve after 75-g glucose load; INS_{120}, insulin value at 120 min after glucose load is given; IR, insulin resistance; 25-OHD: 25-hydroxyvitamin D; IR_{FI}, insulin resistance by fasting insulin; IR_{HOMA}, insulin resistance by homeostasis model assessment; IR_M, insulin resistance after euglycemic hyperinsulinemic clamp; IR_{IVGTT}, insulin resistance after iv glucose tolerance test; ↓, decreased (statistically significant); ↑, increased (statistically significant); ↔, no difference (no statistical significance). To convert 25-OHD concentration to SI units, multiply by 2.459; to convert FPG to SI units, multiply by 0.0555.

Conclusion and Future Directions

There appears to be a relationship between insufficient vitamin D and calcium status and type 2 DM. However, the available human data are limited because most observational studies are cross-sectional, whereas prospective studies have not measured 25-OHD concentration, and there is a paucity of randomized controlled trials with vitamin D and/or calcium supplementation specifically designed for outcomes related to type 2 DM. Although the evidence to date suggests that vitamin D and calcium deficiency influences postprandial glycemia and insulin response while supplementation may be beneficial in optimizing these processes, our understanding of the exact mechanisms by which vitamin D and calcium may promote β-cell function or ameliorate insulin resistance and systemic inflammation is incomplete. It is also not clear whether the effects are additive or synergistic.

Future research should focus on studies within prospective observational cohorts to clarify and quantify the association between calcium intake and 25-OHD concentration, rather than self-reported intake of vitamin D, and incident type 2 DM and should define the individual contributions of each nutrient on type 2 DM risk. Additionally, there is a need for randomized trials to examine the effects of vitamin D and/or calcium supplementation with intermediary endpoints (glucose tolerance, insulin secretion, insulin sensitivity) and ultimately with incident type 2 DM. The results of future studies will define the clinical role of vitamin D and calcium as potential interventions for prevention and management of type 2 DM, which will have significant public health implications because vitamin D and calcium insufficiency is common in U.S. adults, and both interventions can be implemented easily and inexpensively in clinical practice.

Acknowledgments

Received February 8, 2007. Accepted March 19, 2007.

Address all correspondence and requests for reprints to: Anastassios G. Pittas, M.D., M.Sc., Division of Endocrinology, Diabetes and Metabolism, Tufts-New England Medical Center, 750 Washington Street, #268, Boston, Massachusetts 02111. E-mail: apittas@tufts-nemc.org.

This work was supported by National Institutes of Health research grants K23 DK61506 and R01 DK76092 (to A.G.P.), U01 AG010353 (to B.D.-H.) and U.S. Department of Agriculture Grant 59-1950-9001 (to B.D.-H.).

The authors have no conflict of interest to disclose.

References

1. **Mokdad AH, Ford ES, Bowman BA, Dietz WH, Vinicor F, Bales VS, Marks JS** 2003 Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. JAMA 289:76–79
2. **Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, Willett WC** 2001 Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. N Engl J Med 345:790–797
3. **Benjamin SM, Valdez R, Geiss LS, Rolka DB, Narayan KM** 2003 Estimated number of adults with prediabetes in the US in 2000: opportunities for prevention. Diabetes Care 26:645–649
4. **Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B** 2006 Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. Am J Clin Nutr 84:18–28
5. **Holick MF** 2006 High prevalence of vitamin D inadequacy and implications for health. Mayo Clin Proc 81:353–373
6. **Mathieu C, Badenhoop K** 2005 Vitamin D and type 1 diabetes mellitus: state of the art. Trends Endocrinol Metab 16:261–266
7. **Toma M, McAlister FA, Bialy L, Adams D, Vandermeer B, Armstrong PW** 2006 Transition from meeting abstract to full-length journal article for randomized controlled trials. JAMA 295:1281–1287
8. **Bloch CA, Clemons P, Sperling MA** 1987 Puberty decreases insulin sensitivity. J Pediatr 110:481–487
9. **Polonsky KS, Given BD, Hirsch L, Shapiro ET, Tillil H, Beebe C, Galloway JA, Frank BH, Karrison T, Van Cauter E** 1988 Quantitative study of insulin secretion and clearance in normal and obese subjects. J Clin Invest 81:435–441
10. **DerSimonian R, Laird N** 1986 Meta-analysis in clinical trials. Control Clin Trials 7:177–188
11. **Weyer C, Bogardus C, Mott DM, Pratley RE** 1999 The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. J Clin Invest 104:787–794
12. **Hu FB, Meigs JB, Li TY, Rifai N, Manson JE** 2004 Inflammatory markers and risk of developing type 2 diabetes in women. Diabetes 53:693–700
13. **Bourlon PM, Billaudel B, Faure-Dussert A** 1999 Influence of vitamin D3 deficiency and 1,25 dihydroxyvitamin D3 on de novo insulin biosynthesis in the islets of the rat endocrine pancreas. J Endocrinol 160:87–95
14. **Zeitz U, Weber K, Soegiarto DW, Wolf E, Balling R, Erben RG** 2003 Impaired insulin secretory capacity in mice lacking a functional vitamin D receptor. FASEB J 17:509–511
15. **Bland R, Markovic D, Hills CE, Hughes SV, Chan SL, Squires PE, Hewison M** 2004 Expression of 25-hydroxyvitamin D3–1α-hydroxylase in pancreatic islets. J Steroid Biochem Mol Biol 89–90:121–125
16. **Milner RD, Hales CN** 1967 The role of calcium and magnesium in insulin secretion from rabbit pancreas studied in vitro. Diabetologia 3:47–49
17. **Boucher BJ, Mannan N, Noonan K, Hales CN, Evans SJ** 1995 Glucose intolerance and impairment of insulin secretion in relation to vitamin D deficiency in east London Asians. Diabetologia 38:1239–1245
18. **Baynes KC, Boucher BJ, Feskens EJ, Kromhout D** 1997 Vitamin D, glucose tolerance and insulinaemia in elderly men. Diabetologia 40:344–347
19. **Chiu KC, Chu A, Go VL, Saad MF** 2004 Hypovitaminosis D is associated with insulin resistance and β-cell dysfunction. Am J Clin Nutr 79:820–825
20. **Gedik O, Akalin S** 1986 Effects of vitamin D deficiency and repletion on insulin and glucagon secretion in man. Diabetologia 29:142–145
21. **Borissova AM, Tankova T, Kirilov G, Dakovska L, Kovacheva R** 2003 The effect of vitamin D3 on insulin secretion and peripheral insulin sensitivity in type 2 diabetic patients. Int J Clin Pract 57:258–261
22. **Lind L, Pollare T, Hvarfner A, Lithell H, Sorensen OH, Ljunghall S** 1989 Long-term treatment with active vitamin D (α-calcidol) in middle-aged men with impaired glucose tolerance. Effects on insulin secretion and sensitivity, glucose tolerance and blood pressure. Diabetes Res 11:141–147
23. **Orwoll E, Riddle M, Prince M** 1994 Effects of vitamin D on insulin and glucagon secretion in non-insulin-dependent diabetes mellitus. Am J Clin Nutr 59:1083–1087
24. **Inomata S, Kadowaki S, Yamatani T, Fukase M, Fujita T** 1986 Effect of 1 α (OH)-vitamin D3 on insulin secretion in diabetes mellitus. Bone Miner 1:187–192
25. **Nyomba BL, Auwerx J, Bormans V, Peeters TL, Pelemans W, Reynaert J, Bouillon R, Vantrappen G, De Moor P** 1986 Pancreatic secretion in man with subclinical vitamin D deficiency. Diabetologia 29:34–38
26. **Maestro B, Campion J, Davila N, Calle C** 2000 Stimulation by 1,25-dihydroxyvitamin D3 of insulin receptor expression and insulin responsiveness for glucose transport in U-937 human promonocytic cells. Endocr J 47:383–391
27. **Ojuka EO** 2004 Role of calcium and AMP kinase in the regulation of mitochondrial biogenesis and GLUT4 levels in muscle. Proc Nutr Soc 63:275–278
28. **Wright DC, Hucker KA, Holloszy JO, Han DH** 2004 Ca2+ and AMPK both mediate stimulation of glucose transport by muscle contractions. Diabetes 53:330–335
29. **Williams PF, Caterson ID, Cooney GJ, Zilkens RR, Turtle JR** 1990 High affinity insulin binding and insulin receptor-effector coupling: modulation by Ca2+. Cell Calcium 11:547–556
30. **Draznin B, Sussman K, Kao M, Lewis D, Sherman N** 1987 The existence of an optimal range of cytosolic free calcium for insulin-stimulated glucose transport in rat adipocytes. J Biol Chem 262:14385–14388
31. **Segal S, Lloyd S, Sherman N, Sussman K, Draznin B** 1990 Postprandial changes in cytosolic free calcium and glucose uptake in adipocytes in obesity and non-insulin-dependent diabetes mellitus. Horm Res 34:39–44
32. **Byyny RL, LoVerde M, Lloyd S, Mitchell W, Draznin B** 1992 Cytosolic calcium and insulin resistance in elderly patients with essential hypertension. Am J Hypertens 5:459–464
33. **Ohno Y, Suzuki H, Yamakawa H, Nakamura M, Otsuka K, Saruta T** 1993 Impaired insulin sensitivity in young, lean normotensive offspring of essential hypertensives: possible role of disturbed calcium metabolism. J Hypertens 11:421–426
34. **Zemel MB** 1998 Nutritional and endocrine modulation of intracellular calcium: implications in obesity, insulin resistance and hypertension. Mol Cell Biochem 188:129–136
35. **Draznin B, Sussman KE, Eckel RH, Kao M, Yost T, Sherman NA** 1988 Possible role of cytosolic free calcium concentrations in mediating insulin resistance of obesity and hyperinsulinemia. J Clin Invest 82:1848–1852
36. **Draznin B, Sussman KE, Kao M, Sherman N** 1988 Relationship between cytosolic free calcium concentration and 2-deoxyglucose uptake in adipocytes isolated from 2- and 12-month-old rats. Endocrinology 122:2578–2583
37. **Draznin B, Lewis D, Houlder N, Sherman N, Adamo M, Garvey WT,**

LeRoith D, Sussman K 1989 Mechanism of insulin resistance induced by sustained levels of cytosolic free calcium in rat adipocytes. Endocrinology 125:2341–2349
38. **Reusch JE, Begum N, Sussman KE, Draznin B** 1991 Regulation of GLUT-4 phosphorylation by intracellular calcium in adipocytes. Endocrinology 129: 3269–3273
39. **Lind L, Hanni A, Lithell H, Hvarfner A, Sorensen OH, Ljunghall S** 1995 Vitamin D is related to blood pressure and other cardiovascular risk factors in middle-aged men. Am J Hypertens 8:894–901
40. **Scragg R, Sowers M, Bell C** 2004 Serum 25-hydroxyvitamin D, diabetes, and ethnicity in the Third National Health and Nutrition Examination Survey. Diabetes Care 27:2813–2818
41. **Ljunghall S, Lind L, Lithell H, Skarfors E, Selinus I, Sorensen OH, Wide L** 1987 Treatment with one-α-hydroxycholecalciferol in middle-aged men with impaired glucose tolerance–a prospective randomized double-blind study. Acta Med Scand 222:361–367
42. **Fliser D, Stefanski A, Franek E, Fode P, Gudarzi A, Ritz E** 1997 No effect of calcitriol on insulin-mediated glucose uptake in healthy subjects. Eur J Clin Invest 27:629–633
43. **Barr SI, McCarron DA, Heaney RP, Dawson-Hughes B, Berga SL, Stern JS, Oparil S** 2000 Effects of increased consumption of fluid milk on energy and nutrient intake, body weight, and cardiovascular risk factors in healthy older adults. J Am Diet Assoc 100:810–817
44. **Bowen J, Noakes M, Clifton PM** 2005 Effect of calcium and dairy foods in high protein, energy-restricted diets on weight loss and metabolic parameters in overweight adults. Int J Obes (Lond) 29:957–965
45. **Thompson WG, Rostad Holdman N, Janzow DJ, Slezak JM, Morris KL, Zemel MB** 2005 Effect of energy-reduced diets high in dairy products and fiber on weight loss in obese adults. Obes Res 13:1344–1353
46. **Sanchez M, de la Sierra A, Coca A, Poch E, Giner V, Urbano-Marquez A** 1997 Oral calcium supplementation reduces intraplatelet free calcium concentration and insulin resistance in essential hypertensive patients. Hypertension 29:531–536
47. **Zemel MB, Thompson W, Milstead A, Morris K, Campbell P** 2004 Calcium and dairy acceleration of weight and fat loss during energy restriction in obese adults. Obes Res 12:582–590
48. **Pittas AG, Harris SS, Stark PC, Dawson-Hughes B** 2007 The effects of calcium and vitamin D supplementation on blood glucose and markers of inflammation in non-diabetic adults. Diabetes Care 30:980–986
49. **Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM** 2001 C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA 286:327–334
50. **Duncan BB, Schmidt MI, Pankow JS, Ballantyne CM, Couper D, Vigo A, Hoogeveen R, Folsom AR, Heiss G** 2003 Low-grade systemic inflammation and the development of type 2 diabetes: the atherosclerosis risk in communities study. Diabetes 52:1799–1805
51. **Cigolini M, Iagulli MP, Miconi V, Galiotto M, Lombardi S, Targher G** 2006 Serum 25-hydroxyvitamin D3 concentrations and prevalence of cardiovascular disease among type 2 diabetic patients. Diabetes Care 29:722–724
52. **Pittas AG, Dawson-Hughes B, Li T, Van Dam RM, Willett WC, Manson JE, Hu FB** 2006 Vitamin D and calcium intake in relation to type 2 diabetes in women. Diabetes Care 29:650–656
53. **Timms PM, Mannan N, Hitman GA, Noonan K, Mills PG, Syndercombe-Court D, Aganna E, Price CP, Boucher BJ** 2002 Circulating MMP9, vitamin D and variation in the TIMP-1 response with VDR genotype: mechanisms for inflammatory damage in chronic disorders? QJM 95:787–796
54. **Campbell IT, Jarrett RJ, Keen H** 1975 Diurnal and seasonal variation in oral glucose tolerance: studies in the Antarctic. Diabetologia 11:139–145
55. **Behall KM, Scholfield DJ, Hallfrisch JG, Kelsay JL, Reiser S** 1984 Seasonal variation in plasma glucose and hormone levels in adult men and women. Am J Clin Nutr 40:1352–1356
56. **Ishii H, Suzuki H, Baba T, Nakamura K, Watanabe T** 2001 Seasonal variation of glycemic control in type 2 diabetic patients (letter). Diabetes Care 24:1503
57. **Ford ES, Ajani UA, McGuire LC, Liu S** 2005 Concentrations of serum vitamin D and the metabolic syndrome among U.S. adults. Diabetes Care 28:1228–1230
58. **Need AG, O'Loughlin PD, Horowitz M, Nordin BE** 2005 Relationship between fasting serum glucose, age, body mass index and serum 25 hydroxyvitamin D in postmenopausal women. Clin Endocrinol (Oxf) 62:738–741
59. **Hypponen E, Power C** 2006 Vitamin D status and glucose homeostasis in the 1958 British birth cohort: the role of obesity. Diabetes Care 29:2244–2246
60. **Wareham NJ, Byrne CD, Carr C, Day NE, Boucher BJ, Hales CN** 1997 Glucose intolerance is associated with altered calcium homeostasis: a possible link between increased serum calcium concentration and cardiovascular disease mortality. Metabolism 46:1171–1177
61. **Snijder M, van Dam R, Visser M, Deeg D, Seidell J, Lips P** 2006 To: Mathieu C, Gysemans C, Giulietti A, Bouillon R. [Comment on: Vitamin D and diabetes; 48:1247–1257 (2005)] Diabetologia 49:217–218
62. **Bell NH, Greene A, Epstein S, Oexmann MJ, Shaw S, Shary J** 1985 Evidence for alteration of the vitamin D-endocrine system in blacks. J Clin Invest 76:470–473
63. **Scragg R, Holdaway I, Singh V, Metcalf P, Baker J, Dryson E** 1995 Serum 25-hydroxyvitamin D3 levels decreased in impaired glucose tolerance and diabetes mellitus. Diabetes Res Clin Pract 27:181–188
64. **Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF** 2000 Decreased bioavailability of vitamin D in obesity. Am J Clin Nutr 72:690–693
65. **Parikh SJ, Edelman M, Uwaifo GI, Freedman RJ, Semega-Janneh M, Reynolds J, Yanovski JA** 2004 The relationship between obesity and serum 1,25-dihydroxy vitamin D concentrations in healthy adults. J Clin Endocrinol Metab 89:1196–1199
66. **Liu S, Song Y, Ford ES, Manson JE, Buring JE, Ridker PM** 2005 Dietary calcium, vitamin D, and the prevalence of metabolic syndrome in middle-aged and older U.S. women. Diabetes Care 28:2926–2932
67. **Christiansen C, Christensen MS, McNair P, Nielsen B, Madsbad S** 1982 Vitamin D metabolites in diabetic patients: decreased serum concentration of 24,25-dihydroxyvitamin D. Scand J Clin Lab Invest 42:487–491
68. **Stepan J, Wilczek H, Justova V, Havranek T, Skrha F, Wildtova Z, Formankova J, Pacovsky V** 1982 Plasma 25-hydroxycholecalciferol in oral sulfonylurea treated diabetes mellitus. Horm Metab Res 14:98–100
69. **Nyomba BL, Bouillon R, Bidingija M, Kandjingu K, De Moor P** 1986 Vitamin D metabolites and their binding protein in adult diabetic patients. Diabetes 35:911–915
70. **Pietschmann P, Schernthaner G, Woloszczuk W** 1988 Serum osteocalcin levels in diabetes mellitus: analysis of the type of diabetes and microvascular complications. Diabetologia 31:892–895
71. **Aksoy H, Akcay F, Kurtul N, Baykal O, Avci B** 2000 Serum 1,25 dihydroxy vitamin D (1,25(OH)2D3), 25 hydroxy vitamin D (25(OH)D) and parathormone levels in diabetic retinopathy. Clin Biochem 33:47–51
72. **Isaia G, Giorgino R, Adami S** 2001 High prevalence of hypovitaminosis D in female type 2 diabetic population. Diabetes Care 24:1496
73. **Ishida H, Seino Y, Matsukura S, Ikeda M, Yawata M, Yamashita G, Ishizuka S, Imura H** 1985 Diabetic osteopenia and circulating levels of vitamin D metabolites in type 2 (noninsulin-dependent) diabetes. Metabolism 34:797–801
74. **Heath 3rd H, Lambert PW, Service FJ, Arnaud SB** 1979 Calcium homeostasis in diabetes mellitus. J Clin Endocrinol Metab 49:462–466
75. **Colditz GA, Manson JE, Stampfer MJ, Rosner B, Willett WC, Speizer FE** 1992 Diet and risk of clinical diabetes in women. Am J Clin Nutr 55:1018–1023
76. **van Dam RM, Hu FB, Rosenberg L, Krishnan S, Palmer JR** 2006 Dietary calcium and magnesium, major food sources, and risk of type 2 diabetes in U.S. black women. Diabetes Care 29:2238–2243
77. **Pereira MA, Jacobs Jr DR, Van Horn L, Slattery ML, Kartashov AI, Ludwig DS** 2002 Dairy consumption, obesity, and the insulin resistance syndrome in young adults: the CARDIA Study. JAMA 287:2081–2089
78. **Mennen LI, Lafay L, Feskens EJM, Novak M, Lepinay P, Balkau B** 2000 Possible protective effect of bread and dairy products on the risk of the metabolic syndrome. Nutr Res 20:335–347
79. **Azadbakht L, Mirmiran P, Esmaillzadeh A, Azizi F** 2005 Dairy consumption is inversely associated with the prevalence of the metabolic syndrome in Tehranian adults. Am J Clin Nutr 82:523–530
80. **Choi HK, Willett WC, Stampfer MJ, Rimm E, Hu FB** 2005 Dairy consumption and risk of type 2 diabetes mellitus in men: a prospective study. Arch Intern Med 165:997–1003
81. **Liu S, Choi HK, Ford E, Song Y, Klevak A, Buring JE, Manson JE** 2006 A prospective study of dairy intake and the risk of type 2 diabetes in women. Diabetes Care 29:1579–1584
82. **Nilas L, Christiansen C** 1984 Treatment with vitamin D or its analogues does not change body weight or blood glucose level in postmenopausal women. Int J Obes 8:407–411
83. **Zemel MB, Richards J, Milstead A, Campbell P** 2005 Effects of calcium and dairy on body composition and weight loss in African-American adults. Obes Res 13:1218–1225
84. **Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM** 2002 Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 346:393–403
85. **Food and Nutrient Board, Institute of Medicine** 2003 Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D and fluoride. Washington, DC: National Academy Press
86. **Hollis BW** 2005 Circulating 25-hydroxyvitamin D levels indicative of vitamin D sufficiency: implications for establishing a new effective dietary intake recommendation for vitamin D. J Nutr 135:317–322
87. **Looker AC, Dawson-Hughes B, Calvo MS, Gunter EW, Sahyoun NR** 2002 Serum 25-hydroxyvitamin D status of adolescents and adults in two seasonal subpopulations from NHANES III. Bone 30:771–777
88. **McKenna MJ** 1992 Differences in vitamin D status between countries in young adults and the elderly. Am J Med 93:69–77
89. **Gloth 3rd FM, Gundberg CM, Hollis BW, Haddad Jr JG, Tobin JD** 1995 Vitamin D deficiency in homebound elderly persons. JAMA 274:1683–1686
90. **Thomas MK, Lloyd-Jones DM, Thadhani RI, Shaw AC, Deraska DJ, Kitch BT, Vamvakas EC, Dick IM, Prince RL, Finkelstein JS** 1998 Hypovitaminosis D in medical inpatients. N Engl J Med 338:777–783
91. **Fleming KH, Heimbach JT** 1994 Consumption of calcium in the U.S.: food sources and intake levels. J Nutr 124:1426S–1430S

92. **Subar AF, Krebs-Smith SM, Cook A, Kahle LL** 1998 Dietary sources of nutrients among US adults, 1989 to 1991. J Am Diet Assoc 98:537–547
93. **Nusser SM, Carriquiry AL, Dodd KW, Fuller WA** 1996 A semiparametric transformation approach to estimating usual daily intake distributions. J Am Stat Assoc 91:1440–1449
94. **Johnson JA, Grande JP, Roche PC, Kumar R** 1994 Immunohistochemical localization of the 1,25(OH)2D3 receptor and calbindin D28k in human and rat pancreas. Am J Physiol 267:E356–E360
95. **Maestro B, Davila N, Carranza MC, Calle C** 2003 Identification of a vitamin D response element in the human insulin receptor gene promoter. J Steroid Biochem Mol Biol 84:223–230
96. **Maestro B, Molero S, Bajo S, Davila N, Calle C** 2002 Transcriptional activation of the human insulin receptor gene by 1,25-dihydroxyvitamin D(3). Cell Biochem Funct 20:227–232
97. **Norman AW, Frankel JB, Heldt AM, Grodsky GM** 1980 Vitamin D deficiency inhibits pancreatic secretion of insulin. Science 209:823–825
98. **Kadowaki S, Norman AW** 1984 Dietary vitamin D is essential for normal insulin secretion from the perfused rat pancreas. J Clin Invest 73:759–766
99. **Tanaka Y, Seino Y, Ishida M, Yamaoka K, Yabuuchi H, Ishida H, Seino S, Seino Y, Imura H** 1984 Effect of vitamin D3 on the pancreatic secretion of insulin and somatostatin. Acta Endocrinol (Copenh) 105:528–533
100. **Cade C, Norman AW** 1986 Vitamin D3 improves impaired glucose tolerance and insulin secretion in the vitamin D-deficient rat *in vivo*. Endocrinology 119:84–90
101. **Chertow BS, Sivitz WI, Baranetsky NG, Clark SA, Waite A, Deluca HF** 1983 Cellular mechanisms of insulin release: the effects of vitamin D deficiency and repletion on rat insulin secretion. Endocrinology 113:1511–1518
102. **Clark SA, Stumpf WE, Sar M** 1981 Effect of 1,25 dihydroxyvitamin D3 on insulin secretion. Diabetes 30:382–386
103. **Sooy K, Schermerhorn T, Noda M, Surana M, Rhoten WB, Meyer M, Fleischer N, Sharp GW, Christakos S.** 1999 Calbindin-D(28k) controls [Ca(2+)] (i) and insulin release. Evidence obtained from calbindin-d(28k) knockout mice and β-cell lines. J Biol Chem 274:34343–34349
104. **Beaulieu C, Kestekian R, Havrankova J, Gascon-Barre M** 1993 Calcium is essential in normalizing intolerance to glucose that accompanies vitamin D depletion in vivo. Diabetes 42:35–43
105. **Yasuda K, Hurukawa Y, Okuyama M, Kikuchi M, Yoshinaga K** 1975 Glucose tolerance and insulin secretion in patients with parathyroid disorders. Effect of serum calcium on insulin release. N Engl J Med 292:501–504
106. **Gedik O, Zileli MS** 1977 Effects of hypocalcemia and theophylline on glucose tolerance and insulin release in human beings. Diabetes 26:813–819
107. **Fujita T, Sakagami Y, Tomita T, Okamoto Y, Oku H** 1978 Insulin secretion after oral calcium load. Endocrinol Jpn 25:645–648
108. **Hochberg Z, Borochowitz Z, Benderli A, Vardi P, Oren S, Spirer Z, Heyman I, Weisman Y** 1985 Does 1,25-dihydroxyvitamin D participate in the regulation of hormone release from endocrine glands? J Clin Endocrinol Metab 60:57–61
109. **Visser M, Deeg DJ, Lips P** 2003 Low vitamin D and high parathyroid hormone levels as determinants of loss of muscle strength and muscle mass (sarcopenia): the Longitudinal Aging Study Amsterdam. J Clin Endocrinol Metab 88:5766–5772
110. **Simpson RU, Thomas GA, Arnold AJ** 1985 Identification of 1,25-dihydroxyvitamin D3 receptors and activities in muscle. J Biol Chem 260:8882–8891
111. **Dunlop TW, Vaisanen S, Frank C, Molnar F, Sinkkonen L, Carlberg C** 2005 The human peroxisome proliferator-activated receptor δ gene is a primary target of 1α,25-dihydroxyvitamin D3 and its nuclear receptor. J Mol Biol 349:248–260
112. **Luquet S, Gaudel C, Holst D, Lopez-Soriano J, Jehl-Pietri C, Fredenrich A, Grimaldi PA** 2005 Roles of PPAR δ in lipid absorption and metabolism: a new target for the treatment of type 2 diabetes. Biochim Biophys Acta 1740:313–317
113. **Plehwe WE, Williams PF, Caterson ID, Harrison LC, Turtle JR** 1983 Calcium-dependence of insulin receptor phosphorylation. Biochem J 214:361–366
114. **Zemel MB, Shi H, Greer B, Dirienzo D, Zemel PC** 2000 Regulation of adiposity by dietary calcium. FASEB J 14:1132–1138
115. **McCarty MF, Thomas CA** 2003 PTH excess may promote weight gain by impeding catecholamine-induced lipolysis-implications for the impact of calcium, vitamin D, and alcohol on body weight. Med Hypotheses 61:535–542
116. **Levy J** 1999 Abnormal cell calcium homeostasis in type 2 diabetes mellitus: a new look on old disease. Endocrine 10:1–6
117. **Riachy R, Vandewalle B, Kerr Conte J, Moerman E, Sacchetti P, Lukowiak B, Gmyr V, Bouckenooghe T, Dubois M, Pattou F** 2002 1,25-dihydroxyvitamin D3 protects RINm5F and human islet cells against cytokine-induced apoptosis: implication of the antiapoptotic protein A20. Endocrinology 143:4809–4819
118. **Gysemans CA, Cardozo AK, Callewaert H, Giulietti A, Hulshagen L, Bouillon R, Eizirik DL, Mathieu C** 2005 1,25-Dihydroxyvitamin D3 modulates expression of chemokines and cytokines in pancreatic islets: implications for prevention of diabetes in nonobese diabetic mice. Endocrinology 146:1956–1964
119. **van Etten E, Mathieu C** 2005 Immunoregulation by 1,25-dihydroxyvitamin D3: basic concepts. J Steroid Biochem Mol Biol 97:93–101
120. **D'Ambrosio D, Cippitelli M, Cocciolo MG, Mazzeo D, Di Lucia P, Lang R, Sinigaglia F, Panina-Bordignon P** 1998 Inhibition of IL-12 production by 1,25-dihydroxyvitamin D3. Involvement of NF-κB downregulation in transcriptional repression of the p40 gene. J Clin Invest 101:252–262
121. **Pittas AG, Joseph NA, Greenberg AS** 2004 Adipocytokines and insulin resistance. J Clin Endocrinol Metab 89:447–452
122. **Rabinovitch A, Suarez-Pinzon WL, Sooy K, Strynadka K, Christakos S** 2001 Expression of calbindin-D(28k) in a pancreatic islet β-cell line protects against cytokine-induced apoptosis and necrosis. Endocrinology 142:3649–3655
123. **Kadowaki S, Norman AW** 1984 Pancreatic vitamin D-dependent calcium binding protein: biochemical properties and response to vitamin D. Arch Biochem Biophys 233:228–236
124. **Christakos S, Barletta F, Huening M, Dhawan P, Liu Y, Porta A, Peng X** 2003 Vitamin D target proteins: function and regulation. J Cell Biochem 88:238–244

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.