

Effect of a Randomised Controlled Vitamin D Trial on Insulin Resistance and Glucose Metabolism in Patients with Type 2 Diabetes Mellitus

Authors

F. Strobel^{1*}, J. Reusch^{1*}, M. Penna-Martinez^{1*}, E. Ramos-Lopez¹, E. Klahold¹, C. Klepzig², J. Wehrle³, H. Kahles^{1*}, K. Badenhoop^{1*}

Affiliations

¹ Division of Endocrinology, Diabetes and Metabolism, Department of Internal Medicine I, Goethe-University Hospital, Frankfurt am Main, Germany

² Diabetes Outpatient Clinic Offenbach and Frankfurt am Main, Germany

³ Pharmacy of the Goethe-University Hospital, Frankfurt am Main, Germany

Key words

- diabetes
- vitamin D
- metabolism
- HbA1c
- C-peptide
- insulin

received 22.04.2013
accepted 26.09.2013

Bibliography

DOI <http://dx.doi.org/10.1055/s-0033-1358453>

Published online:

November 6, 2013

Horm Metab Res 2014;

46: 54–58

© Georg Thieme Verlag KG

Stuttgart · New York

ISSN 0018-5043

Correspondence

Dr. M. Penna-Martinez

Division of Endocrinology,

Diabetes and Metabolism

Department of Internal

Medicine I

Goethe-University Hospital

Frankfurt am Main

Theodor-Stern-Kai 7

60590 Frankfurt am Main

Germany

Tel.: +49/69/6301 83977

Fax: +49/69/6301 83343

Marissa.Penna-Martinez@

gu.de

Abstract



The aim of our study was to investigate the influence of a 6-month vitamin D supplementation in patients with noninsulin-requiring type 2 diabetes mellitus. We included 86 patients in a placebo-controlled, randomised, double-blind study. During 6 months patients received Vigan-tol oil once a week corresponding to a daily dose of 1904 IU or placebo oil, followed by 6 months of follow-up. At start and at 3-month intervals 25OHD, PTH, body mass index, HbA1c, insulin, C-peptide, and homeostasis model assessment-index were measured. The primary outcome was a change in fasting blood glucose and insulin levels. After 6 months of therapy, the verum group's 25OHD had increased to a median of 35 ng/ml in comparison to the placebo group (median 20 ng/ml, $p < 10^{-6}$). PTH tended to decrease in the

verum group (25.5 pg/ml vs. 35.0 pg/ml, $p = 0.08$). After 6 months of therapy, 31 patients (78%) achieved a 25OHD concentration of > 20 ng/ml. Their HbA1c was significantly lower at baseline ($p = 0.008$) and after therapy ($p = 0.009$) than in patients with 25OHD below 20 ng/ml. C-Peptide, insulin, and HOMA-index did not change significantly in the verum group but fasting insulin was positively correlated with 25OHD concentrations after 6 months of therapy in both groups. There were no significant effects of vitamin D with a daily dose of 1904 IU on metabolic parameters in type 2 diabetes. However, the correlative findings of this study suggest a link of the 25OHD status and metabolic function in type 2 diabetes. Whether vitamin D therapy with higher doses can improve glucose metabolism needs to be investigated in follow-up trials.

Introduction



According to the International Diabetes Federation, more than 300 million people worldwide are currently affected by diabetes mellitus (<http://www.idf.org/diabetesatlas/5e/the-global-burden>). A further increase of diabetes prevalence is expected, in particular due to the growing population in developing countries, the increasing industrialisation, urbanisation, and life style changes [1,2]. Diabetes pathophysiology is believed to result from environmental factors on a genetic background, but the causal genes remain complex and exert low hazard risk ratios [3]. The prevalence of type 2 diabetes (T2D) is influenced by multiple environmental factors, one of them may lie in the vitamin D system [4]. During recent years, vitamin D (VD), mainly known for its effects on bone and mineral metabolism, is growingly perceived as a pleiotropic

endocrine regulator [5]. The active form of VD, $1\alpha,25(\text{OH})_2\text{D}$ or calcitriol, is synthesised from precursor cholesterol by metabolic steps in skin, liver, and kidney. The primary metabolite, 25OHD, is the most abundant form of VD in blood and therefore established for measuring VD status. Various studies have shown an association of VD status and T2D [6]. Low 25OHD is found more often in patients with T2D [7,8] and correlates with a higher risk for T2D [6,9,10]. Furthermore, the 25OHD serum concentration is negatively associated with components of the metabolic syndrome, such as obesity, hyperglycaemia [11–13], and high body mass index (BMI) [9,14–16]. Finally, many studies confirmed an inverse correlation between 25OHD and parameters of insulin resistance: fasting glucose, glucose tolerance, insulin levels, and homeostasis model assessment-index (HOMA-I) [17–24]. In addition, interventional studies showed beneficial effects of VD on glucose status, insulin sensitivity, and insulin resistance [25–27].

*Equal contribution.

However, other investigations did not confirm these findings. They showed neither an association between VD and components of the metabolic syndrome [28–30] nor an influence of VD on glucose metabolism and T2D [31–33]. These studies are difficult to compare due to heterogeneous cohorts and differing outcome parameters. Furthermore, the effects of VD on metabolism have mainly been studied in nondiabetics. In addition intervention times varied greatly and patients were treated with very different doses of VD or even combinations of VD and calcium. Therefore, the aim of our study was to investigate the influence of a 6-month VD supplementation of 1904 IU/d on the metabolism in patients with noninsulin-requiring T2D and to find out how many of the treated individuals would normalise their VD status. Hereby we defined VD deficiency as 25OHD concentrations <20 ng/ml, VD insufficiency >20 ng/ml and <30 ng/ml, the latter being the threshold for VD sufficiency. For group comparisons we divided the verum or placebo treated patients into those with 25OHD levels <20 ng/ml (deficient) or >20 ng/ml (not deficient; encompassing insufficient and sufficient) [34].

Subjects and Methods

We invited patients with T2D from the city and region of Frankfurt am Main, Germany, to participate in the study. Out of 101 interested individuals, we recruited 86 patients in a randomised, double-blind, placebo-controlled trial: patients with diagnosed T2D aged 18–80 years without VD supplementation for at least 3 months before baseline. Patients who took bisphosphonates, calcimimetics, glucocorticoids, phenytoin, glycosides, or benzodiazepines, or in which therapy with one of these drugs was planned during study time were excluded. Further exclusion criteria were carcinomas, HIV infection, psychiatric diseases affecting participation, renal or hepatic dysfunction, hypercalcaemia, nephrolithiasis, and sarcoidosis. Women were only included if they were not pregnant or breast-feeding and, if premenopausal, with effective double barrier contraception.

At baseline all participants were randomised into parallel groups (50% placebo, 50% verum). Study time was 12 months for each patient. During the first 6 months the verum group's patients received 20 drops Vigantol oil once a week, corresponding to a daily dose of 1904 IU/d. The placebo group's patients received placebo oil consisting of medium chain triglycerides once a week. This was followed by 6 months of follow-up. Study visits were at 3-month intervals. At each visit body weight, BMI, and blood pressure were recorded. Laboratory investigations included calcium, phosphate, fasting glucose, and HbA1c. Furthermore, 25OHD concentrations and 1,α-25OHD were measured by ¹²⁵I-radioimmunoassay. PTH, insulin, and C-peptide were measured by a solid-phase chemiluminescence immunometric assay. Finally the homeostasis model assessment-index (HOMA-I) was calculated by using the formula: $HOMA-I = \text{fasting insulin } (\mu\text{U/ml}) \times \text{fasting glucose } (\text{mg/dl}) / 405$.

Main outcome parameters of the trial were changes in blood glucose and insulin levels with HOMA-I over the course of treatment by either verum or placebo. Power calculations indicated that 82 subjects (half treated by verum and half by placebo) will suffice to have more than 80% power in order to detect a true difference in the means of 1.25 difference for HOMA-I. The calculations were performed by using the program Power and Sample Size Calculations 3.0. [35].

Table 1 Baseline characteristics of patients; age and duration are medians.

Characteristics	All patients	Verum	Placebo
n	86	43	43
Age (range, years)	60 (30–78)	61 (36–78)	60 (30–78)
Men	48	24	24
Women	38	19	19
Duration of DM (range, years)	3 (1–4)	2 (1–4)	3 (1–4)

Statistical analysis

For statistical analyses, we used the software program BiAS for windows version 9.08. Group comparisons were conducted by using the nonparametric Wilcoxon-Mann-Whitney U-test and the Kruskal-Wallis test. Correlations were measured by using Spearman's rank correlation coefficient. A p-value of <0.05 was determined as significant, ≤0.11 as a trend. All vitamin D levels were adjusted according to the season of blood collection by linear regression using a linear model. These calculations were done by using R software package that is freely available: Frequently asked questions are available from: <http://CRAN.R-project.org/doc/FAQ/R-FAQ.html>.

Results

Baseline characteristics

The median age of the patients (38 women, 48 men) was 60 years with a median diabetes duration of 6–10 years. The patients' baseline characteristics are shown in **Table 1**. Out of 86 recruited, 72 patients completed the full study, 39 in the verum and 33 in the placebo group, with 4 patients missing the follow-up period of the last 6 months. The drop-out of 14 patients was not related to medical but personal reasons. These 14 individuals did not differ from the others for the investigated parameters (data not shown). At baseline all patients (n=86) showed a VD deficiency with median 25OHD concentration of 11.90 ng/ml.

Clinical and biochemical parameters over the trial period

After 3 months of VD therapy, the verum group's (n=40) 25OHD concentration had increased to 37.3 ng/ml, after 6 months of therapy the verum group's (n=40) 25OHD had increased to a median of 35 ng/ml, significantly higher than in the placebo group (median 20 ng/ml, $p < 10^{-6}$, **Table 3**). After VD therapy 37/40 (93%) patients of the verum group achieved 25OHD levels of >20 ng/ml, but only 29/40 (73%) reached 25OHD concentration in the sufficient range (>30 ng/ml).

In contrast, the placebo group showed VD deficiency through the entire study period. In addition the 25OHD concentrations varied with the seasonal timing of study visits in both groups (**Fig. 1**) that had started in summer/autumn in most patients. Highest 25OHD concentrations were measured in summer (placebo) and in autumn (verum), lowest in winter (placebo) and in spring (verum) when patients were in the follow-up phase (data not shown).

The PTH tended ($p=0.08$) to decrease more in the verum group until the end of therapy ($\Delta=9.50$ pg/ml). No association between PTH and any other parameter was seen. Both, calcium and phosphate were always in the normal range and nearly constant during the study period. All patients showed calcium levels between

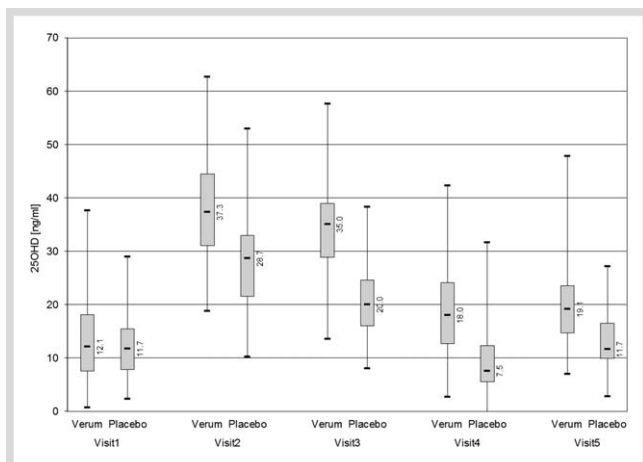


Fig. 1 Median 25OHD concentrations in verum and placebo group.

2.39 and 2.43 mmol/l and phosphate levels between 3.40 and 3.60 mg/dl.

The study failed to demonstrate a significant effect on the main outcome parameters blood glucose or insulin levels. Neither fasting glucose nor HOMA-1 or HbA1C were significantly affected by the intake of Vigantol, nor were there any changes in systolic blood pressure, or body weight. The median systolic blood pressure during whole study time was 140 mm Hg in all patients. The verum group's median body weight was 90.4 kg, their fasting glucose 121 mg/dl. In the placebo the median body weight was 83.9 kg, the median fasting glucose 116 mg/dl.

25 OHD status indicates metabolic control in T2D patients

In all patients we observed that 25OHD and BMI were inversely related (► **Table 2, 4**) particularly at 6 months of therapy or placebo: those patients with 25OHD levels of <20 ng/ml had a median BMI of 33 in comparison to those having achieved a

25OHD (ng/ml) [#]	Baseline values (all patients n = 86)				
	≤ 20		> 20		p
	Median	Range	Median	Range	
PTH (pg/ml)	42	4.5–92	34	9.3–103	0.352
Body weight (kg)	87.1	55.5–140.1	85.3	60–127	0.808
BMI (kg/m ²)	30.6	21.1–44.1	28.6	21.8–41.5	0.246
Systolic blood pressure (mm Hg)	140	110–180	141	110–190	0.548
Fasting glucose (mg/dl)	119	69–224	117	90–166.9	0.693
HbA1c (mmol/mol Hb)	52	34–75	48	41–54	0.008
Insulin (μU/ml)	6.8	2–41	7.7	2–32	0.969
HOMA-index (μU/ml × mg/dl)	2.0	0.3–14	1.8	0.6–11.3	0.908
C-Peptide (ng/ml)	1.9	0.6–6.8	2.2	1.6–4.6	0.504
25OHD (ng/ml) [#]	After 6 months of therapy (all patients n = 77)				
	≤ 20		> 20		p
	Median	Range	Median	Range	
PTH (pg/ml)	32	16.1–81	27	3.5–74	0.152
Body weight (kg)	87.2	61.8–131.5	85.4	56–139	0.816
BMI (kg/m ²)	33.0	23–44.4	29.9	21.6–41.5	0.098
Systolic blood pressure (mm Hg)	140	117–170	140	100–201	0.932
Fasting glucose (mg/dl)	118.0	87–170	121.0	60–182	0.874
HbA1c (mmol/mol Hb)	54	42–81	50	30–64	0.009
Insulin (μU/ml)	4.8	2–19	7.8	2–80.2	0.111
HOMA-index (μU/ml × mg/dl)	1.2	0.4–5.8	2.2	0.4–8.6	0.202
C-Peptide (ng/ml)	1.8	0.6–4.5	2.2	0.2–9.5	0.259

[#]Adjusted for season of blood collection

Table 2 Parameters before and after 6 months of VD-therapy in all study subjects classified according to their 25OHD concentration, which were adjusted for season of blood collection.

	Verum		Placebo		p
	Median	Range	Median	Range	
25OHD (ng/ml) [#]	35	13.6–57.6	20	8–38.3	< 10 ⁻⁶
PTH (pg/ml)	25.5	7.8–67	35	3.5–81	0.080
Body weight (kg)	90.4	56–139	83.9	60–131.5	0.524
BMI (kg/m ²)	30.5	21.6–41.5	31.1	22.5–44.4	0.856
Systolic blood pressure (mm Hg)	140	100–201	140	117–160	0.955
Fasting glucose (mg/dl)	121	84–178	119.5	60–182	0.624
HbA1c (mmol/mol Hb)	51	30–64	51	38–81	0.681
Insulin (μU/ml)	7.5	2–80.2	5.6	2–27	0.749
HOMA-index (μU/ml × mg/dl)	1.9	0.4–7.8	1.5	0.4–8.6	0.821
C-Peptide (ng/ml)	2.4	0.2–9.5	1.9	0.4–6.2	0.553

[#]Adjusted for season of blood collection

Table 3 Outcome measures after 6 months of therapy (Visit 3).

	Baseline values		After 6 months of therapy (all patients n = 77)					
	All patients (n = 86)		All patients		Verum		Placebo	
	rho	p	rho	p	rho	p	rho	p
PTH (pg/ml)	-0.19	0.081	-0.20	0.078	-0.11	0.488	-0.08	0.645
Body weight (kg)	-0.10	0.373	0.01	0.941	-0.11	0.483	-0.13	0.447
BMI (kg/m ²)	-0.26	0.015	-0.14	0.216	-0.18	0.271	-0.35	0.040
Systolic blood pressure (mm Hg)	0.03	0.799	0.00	0.993	-0.10	0.558	0.19	0.273
Fasting glucose (mg/dl)	0.04	0.740	0.01	0.946	-0.18	0.282	-0.03	0.854
HbA1c (mmol/mol Hb)	-0.23	0.038	-0.19	0.089	-0.19	0.245	-0.31	0.064
Insulin (μU/ml)	-0.12	0.265	0.23	0.041	0.11	0.492	0.41	0.013
HOMA-index (μU/ml × mg/dl)	-0.10	0.357	0.19	0.106	-0.01	0.954	0.36	0.030
C-Peptide (ng/ml)	-0.06	0.616	0.20	0.074	0.14	0.398	0.17	0.311

25OHD concentrations were adjusted for season of blood collection

Table 4 Correlation of parameters with 25OHD before and after 6 months of VD therapy.

25-OH-D level of >20 ng/ml with a median BMI of 29.9; $p=0.098$).

Over all study visits the lowest HbA1c levels were seen in patients with 25OHD of >20 ng/ml. HbA1c was 4 mmol/mol Hb ($p=0.008$; **Table 2**) lower at baseline and 4 mmol/mol Hb ($p=0.009$; **Table 2**) lower after VD therapy than in patients with 25OHD of <20 ng/ml. Highest HbA1c ($p=0.009$) by a median of 54 mmol/mol was seen in patients with 25OHD of ≤ 20 ng/ml at the end of therapy. As depicted in **Table 2** all patients with 25OHD of >20 ng/ml showed higher C-peptide (2.2 ng/ml vs. 1.8 ng/ml) and higher insulin (7.8 μU/ml vs. 4.8 μU/ml, $p=0.11$) after VD therapy, but this was not significant. However 25OHD concentrations correlated significantly with the BMI at baseline in all patients and after 6 months of therapy in the placebo group. Furthermore fasting insulin was positively correlated with 25OHD after 6 months of therapy in both groups (**Table 4**).

Discussion and Conclusion

Vitamin D deficiency or insufficiency is highly prevalent and this observation is more profound in patients with type 2 diabetes [36, 37]. This global epidemic has been described in several populations of all age groups and evoked interest into the effects of controlled vitamin D supplementation as opposed to uncontrolled self-ingestion as an alimentary component. It is now widely held that vitamin D has multiple extra-skeletal effects, some of which affect metabolism and the endocrine pancreas [38]. In an animal model active vitamin D can increase islet insulin secretion upon glucose stimuli [39].

Whether vitamin D can also affect the human β -cell has been subject to several studies, including interventional trials. A meta-analysis of vitamin D supplementation of patients with type 2 diabetes has recently summarised 15 trials that had included patients for a controlled intervention with vitamin D, its metabolites and placebo, and studied fasting glucose, HbA1c as well as parameters of insulin resistance [40]. The conclusion of their summary was that insufficient evidence supported a recommendation for vitamin D supplementation for improving glucose metabolism or insulin action in patients with diabetes or prediabetes. However, those studies had used both low vitamin D doses as well as higher ones, had been performed on heterogeneous cohorts, and did not address all potential confounders. Furthermore vitamin D acts on several cells and tissues including immunity. Hereby anti-inflammatory effects may indirectly improve cardiovascular and metabolic health in

patients with diabetes [38]. Since vitamin D's immune effects may vary between individuals with variants in their vitamin D system genotypes, intervention trials are needed to address pharmacogenomic differences for potential therapeutic stratification [41].

Our study shows a significantly lower HbA1c with improving 25OHD status. Furthermore, this randomised, placebo-controlled intervention study with nearly 2000 IU cholecalciferol per day demonstrates that insulin levels correlate significantly after 6 months of VD although the underlying insulin resistance persisted. Although the trial failed to meet endpoints for improved insulin and C-peptide secretion as well as HOMA-index, the correlation of BMI, HbA1c, insulin levels, and the vitamin D status suggests that glucose homeostasis may be positively regulated by vitamin D. The paradox observation that differences were more significant at 6 months of therapy in the placebo group suggests that either the chosen dose is insufficient or that other factors regulate vitamin D's metabolic effects. A recent placebo-controlled trial with 47 diabetic patients and a lower daily dose (1000 IU/d) demonstrated no metabolic effects but a nonsignificant increase in adiponectin and a significant improvement of aortic stiffness [42].

Physiologic and metabolic improvement may be due to direct or indirect VDR-mediated musculoskeletal, hepatic or effects on pancreatic β -cell secretion. Since β -cells express the VDR, some of their pathways involved in insulin secretion are subject to VD actions such as metabolic processing, stress response and DNA repair, as well as epigenetic regulations. These mechanisms have recently been elucidated by microarray analysis of buffy coat cells from a small randomised double-blind clinical trial using 2000 IU VD/d [43].

Since vitamin D dosing appears to be safe in this population of preadipose and obese individuals higher VD doses are needed to optimise VD status in more than half of patients. Interventional studies with higher study numbers and higher VD doses are required to verify these findings. However, this study illustrates potential metabolic benefits of VD therapy in type 2 diabetes.

Acknowledgements

Vigantol oil was provided by Merck KGaA. We thank Dr. Ulrike Hostalek for continuous support. KB received a grant based on the EU-FP7 program (NAIMIT, grant agreement No. 241447).

Conflict of Interest



The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

References

- Guariguata L, Whiting D, Weil C, Unwin N. The International Diabetes Federation diabetes atlas methodology for estimating global and national prevalence of diabetes in adults. *Diabetes Res Clin Pract* 2011; 94: 322–332
- Guariguata L. By the numbers: new estimates from the IDF Diabetes Atlas Update for 2012. *Diabetes Res Clin Pract* 2012; 98: 524–525
- Andersson EA, Allin KH, Sandholt CH, Borglykke A, Lau CJ, Ribel-Madsen R, Sparso T, Justesen JM, Harder MN, Jorgensen ME, Jorgensen T, Hansen T, Pedersen O. Genetic risk score of 46 type 2 diabetes risk variants associates with changes in plasma glucose and estimates of pancreatic beta-cell function over five years of follow-up. *Diabetes* 2013; 62: 3610–3617
- Pittas AG, Nelson J, Mitri J, Hillmann W, Garganta C, Nathan DM, Hu FB, Dawson-Hughes B. Plasma 25-hydroxyvitamin D and progression to diabetes in patients at risk for diabetes: an ancillary analysis in the Diabetes Prevention Program. *Diabetes Care* 2012; 35: 565–573
- Van Belle TL, Gysemans C, Mathieu C. Vitamin D and diabetes: the odd couple. *Trends Endocrinol Metab* 2013 [Epub ahead of print]
- Pittas AG, Lau J, Hu FB, Dawson-Hughes B. The role of vitamin D and calcium in type 2 diabetes. A systematic review and meta-analysis. *J Clin Endocrinol Metab* 2007; 92: 2017–2029
- Hintzpetter B, Mensink GB, Thierfelder W, Muller MJ, Scheidt-Nave C. Vitamin D status and health correlates among German adults. *Eur J Clin Nutr* 2008; 62: 1079–1089
- Isaia G, Giorgino R, Adami S. High prevalence of hypovitaminosis D in female type 2 diabetic population. *Diabetes Care* 2001; 24: 1496
- Mattila C, Knekt P, Mannisto S, Rissanen H, Laaksonen MA, Montonen J, Reunanen A. Serum 25-hydroxyvitamin D concentration and subsequent risk of type 2 diabetes. *Diabetes Care* 2007; 30: 2569–2570
- Pittas AG, Dawson-Hughes B, Li T, Van Dam RM, Willett WC, Manson JE, Hu FB. Vitamin D and calcium intake in relation to type 2 diabetes in women. *Diabetes Care* 2006; 29: 650–656
- Ford ES, Ajani UA, McGuire LC, Liu S. Concentrations of serum vitamin D and the metabolic syndrome among U.S. adults. *Diabetes Care* 2005; 28: 1228–1230
- Hyyponen E, Boucher BJ, Berry DJ, Power C. 25-hydroxyvitamin D, IGF-1, and metabolic syndrome at 45 years of age: a cross-sectional study in the 1958 British Birth Cohort. *Diabetes* 2008; 57: 298–305
- Parikh SJ, Edelman M, Uwaifo GI, Freedman RJ, Semega-Janneh M, Reynolds J, Yanovski JA. The relationship between obesity and serum 1,25-dihydroxy vitamin D concentrations in healthy adults. *J Clin Endocrinol Metab* 2004; 89: 1196–1199
- Lagunova Z, Porojnicu AC, Lindberg F, Hexeberg S, Moan J. The dependency of vitamin D status on body mass index, gender, age and season. *Anticancer Res* 2009; 29: 3713–3720
- McGill AT, Stewart JM, Lithander FE, Strik CM, Poppitt SD. Relationships of low serum vitamin D3 with anthropometry and markers of the metabolic syndrome and diabetes in overweight and obesity. *Nutr J* 2008; 7: 4
- Rueda S, Fernandez-Fernandez C, Romero F, Martinez de OJ, Vidal J. Vitamin D, PTH, and the metabolic syndrome in severely obese subjects. *Obes Surg* 2008; 18: 151–154
- Alvarez JA, Ashraf AP, Hunter GR, Gower BA. Serum 25-hydroxyvitamin D and parathyroid hormone are independent determinants of whole-body insulin sensitivity in women and may contribute to lower insulin sensitivity in African Americans. *Am J Clin Nutr* 2010; 92: 1344–1349
- Cheng S, Massaro JM, Fox CS, Larson MG, Keyes MJ, McCabe EL, Robins SJ, O'Donnell CJ, Hoffmann U, Jacques PF, Booth SL, Vasan RS, Wolf M, Wang TJ. Adiposity, cardiometabolic risk, and vitamin D status: the Framingham Heart Study. *Diabetes* 2010; 59: 242–248
- Chiu KC, Chu A, Go VL, Saad MF. Hypovitaminosis D is associated with insulin resistance and beta cell dysfunction. *Am J Clin Nutr* 2004; 79: 820–825
- Forouhi NG, Luan J, Cooper A, Boucher BJ, Wareham NJ. Baseline serum 25-hydroxy vitamin d is predictive of future glycemic status and insulin resistance: the Medical Research Council Ely Prospective Study 1990–2000. *Diabetes* 2008; 57: 2619–2625
- Kayaniyl S, Vieth R, Retnakaran R, Knight JA, Qi Y, Gerstein HC, Perkins BA, Harris SB, Zinman B, Hanley AJ. Association of vitamin D with insulin resistance and beta-cell dysfunction in subjects at risk for type 2 diabetes. *Diabetes Care* 2010; 33: 1379–1381
- Liu E, Meigs JB, Pittas AG, McKeown NM, Economos CD, Booth SL, Jacques PF. Plasma 25-hydroxyvitamin d is associated with markers of the insulin resistant phenotype in nondiabetic adults. *J Nutr* 2009; 139: 329–334
- Scragg R, Sowers M, Bell C. Serum 25-hydroxyvitamin D, diabetes, and ethnicity in the Third National Health and Nutrition Examination Survey. *Diabetes Care* 2004; 27: 2813–2818
- Zhao G, Ford ES, Li C. Associations of serum concentrations of 25-hydroxyvitamin D and parathyroid hormone with surrogate markers of insulin resistance among U.S. adults without physician-diagnosed diabetes: NHANES 2003–2006. *Diabetes Care* 2010; 33: 344–347
- Pittas AG, Harris SS, Stark PC, Dawson-Hughes B. The effects of calcium and vitamin D supplementation on blood glucose and markers of inflammation in nondiabetic adults. *Diabetes Care* 2007; 30: 980–986
- Sabherwal S, Bravis V, Devendra D. Effect of oral vitamin D and calcium replacement on glycaemic control in South Asian patients with type 2 diabetes. *Int J Clin Pract* 2010; 64: 1084–1089
- von Hurst PR, Stonehouse W, Coad J. Vitamin D supplementation reduces insulin resistance in South Asian women living in New Zealand who are insulin resistant and vitamin D deficient – a randomised, placebo-controlled trial. *Br J Nutr* 2010; 103: 549–555
- Hjeltneseth J, Hofso D, Aasheim ET, Jessen T, Moan J, Hager H, Roislien J, Bollerslev J. Parathyroid hormone, but not vitamin D, is associated with the metabolic syndrome in morbidly obese women and men: a cross-sectional study. *Cardiovasc Diabetol* 2009; 8: 7
- Lippi G, Montagnana M, Targher G, Guidi GC. Vitamin D, parathyroid hormone levels, and the prevalence of metabolic syndrome in community-dwelling older adults: response to Reis et al. *Diabetes Care* 2007; 30: e135
- Snijder M, van DR, Visser M, Deeg D, Seidell J, Lips P. To: Mathieu C, Gysemans C, Giulietti A, Bouillon R (2005) Vitamin D and diabetes. *Diabetologia* 48: 1247–1257. *Diabetologia* 2006; 49: 217–218
- Avenell A, Cook JA, MacLennan GS, McPherson GC. Vitamin D supplementation and type 2 diabetes: a substudy of a randomised placebo-controlled trial in older people (RECORD trial, ISRCTN 51647438). *Age Ageing* 2009; 38: 606–609
- de Boer IH, Tinker LF, Connelly S, Curb JD, Howard BV, Kestenbaum B, Larson JC, Manson JE, Margolis KL, Siscovick DS, Weiss NS. Calcium plus vitamin D supplementation and the risk of incident diabetes in the Women's Health Initiative. *Diabetes Care* 2008; 31: 701–707
- Luo C, Wong J, Brown M, Hooper M, Molyneaux L, Yue DK. Hypovitaminosis D in Chinese type 2 diabetes: lack of impact on clinical metabolic status and biomarkers of cellular inflammation. *Diab Vasc Dis Res* 2009; 6: 194–199
- Holick MF. Vitamin D deficiency. *N Engl J Med* 2007; 357: 266–281
- Dupont WD, Plummer WD Jr. Power and sample size calculations. A review and computer program. *Control Clin Trials* 1990; 11: 116–128
- Joergensen H, Gall MA, Schmedes A, Tarnow L, Parving HH, Rossing P. Vitamin D levels and mortality in type 2 diabetes. *Diabetes Care* 2010; 33: 2238–2243
- Grimnes G, Emaus N, Joakimsen RM, Figenschau Y, Jessen T, Njolstad I, Schirmer H, Jorde R. Baseline serum 25-hydroxyvitamin D concentrations in the Tromso Study 1994–95 and risk of developing type 2 diabetes mellitus during 11 years of follow-up. *Diabet Med* 2010; 27: 1107–1115
- Badenhoop K, Kahles H, Penna-Martinez M. Vitamin D, immune tolerance, and prevention of type 1 diabetes. *Curr Diab Rep* 2012; 12: 635–642
- Cheng Q, Li YC, Boucher BJ, Leung PS. A novel role for vitamin D: modulation of expression and function of the local renin-angiotensin system in mouse pancreatic islets. *Diabetologia* 2011; 54: 2077–2081
- George PS, Pearson ER, Witham MD. Effect of vitamin D supplementation on glycaemic control and insulin resistance: a systematic review and meta-analysis. *Diabet Med* 2012; 29: e142–e150
- Rose K, Penna-Martinez M, Klahold E, Karger D, Shoghi F, Kahles H, Bayer M, Hintermann E, Pfeilschifter JM, Badenhoop K, Ramos-Lopez E, Christen U. Influence of the vitamin D plasma level and vitamin D-related genetic polymorphisms on the immune status of patients with type 1 diabetes: a pilot study. *Clin Exp Immunol* 2013; 171: 171–185
- Breslavsky A, Frand J, Matas Z, Boaz M, Barnea Z, Shargorodsky M. Effect of high doses of vitamin D on arterial properties, adiponectin, leptin and glucose homeostasis in type 2 diabetic patients. *Clin Nutr* 2013 [Epub ahead of print]
- Hossein-Nezhad A, Spira A, Holick MF. Influence of vitamin d status and vitamin d3 supplementation on genome wide expression of white blood cells: a randomized double-blind clinical trial. *PLoS One* 2013; 8: e58725