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Vitamin D and glycemic control in diabetes mellitus type 2

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Abstract

Objectives: The extraskeletal effects of vitamin D have attracted considerable interest. Vitamin D deficiency appears to be related to the development of diabetes mellitus type 2 and the metabolic syndrome. Vitamin D may affect glucose homeostasis, vitamin D levels having been found to be inversely related to glycosylated hemoglobin levels in gestational diabetes mellitus. In addition, vitamin D appears to protect from the development of gestational diabetes mellitus. The aim was to study levels of 25-hydroxy vitamin D₃ [25(OH)D₃] and the relationship between 25(OH)D₃ levels and glycemic control in patients with diabetes mellitus type 2.

Methods: Glycosylated hemoglobin (HbA_{1c}) and 25(OH)D₃ levels were measured in a group of 120 diabetes mellitus type 2 patients. The same measurements were performed in a group of 120 control subjects of the same age and sex. 25(OH)D₃ was measured by radioimmunoassay and glycosylated hemoglobin (HbA_{1c}) was measured by high-performance liquid chromatography.

Results: 25(OH)D₃ levels were lower in the diabetes mellitus type 2 patients than in the control group, being 19.26 ± 0.95 ng/ml and 25.49 ± 1.02 ng/ml, in the patient and control groups, respectively ($p < 0.001$, Student's *t*-test). 25(OH)D₃ levels were found to be inversely associated with HbA_{1c} levels in the diabetic patients ($p = 0.008$, $r^2 = 0.058$, linear regression). 25(OH)D₃ levels were found to be inversely associated with HbA_{1c} when the patient and control groups were analysed together ($p < 0.001$, $r^2 = 0.086$).

Conclusions: Vitamin D levels appeared to be lower in diabetes mellitus type 2 patients than in the control group, vitamin D levels being related to glycemic control in diabetes mellitus type 2. These findings may have therapeutic implications as cautious vitamin D supplementation may improve glycemic control in diabetes mellitus type 2.

Keywords: diabetes mellitus type 2, glycemic control, vitamin D

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Introduction

Vitamin D is a hormone related to skeletal integrity [Holick, 2011]. Recently, the extraskeletal effects of vitamin D have raised considerable interest [Holick, 2008, 2010]. Vitamin D deficiency appears to be related to the development of diabetes mellitus type 2 [Pittas *et al.* 2007, 2010, 2012; Mitri *et al.* 2011; Chagas *et al.* 2012, Lim *et al.* 2013]. Mild to moderate vitamin D insufficiency has been proposed as a risk factor for type 2 diabetes [Pittas *et al.* 2007]. Higher plasma vitamin D has been shown to be related with a lower risk for the development of diabetes

mellitus in high risk patients [Pittas *et al.* 2012]. Vitamin D deficiency has been described in the metabolic syndrome [Kayaniyil *et al.* 2013], specific vitamin D receptor gene polymorphisms having been found to be related to components of the metabolic syndrome [Schuch *et al.* 2013]. Moreover, vitamin D seems to affect glucose homeostasis, vitamin D levels having been found to be inversely related to glycosylated hemoglobin levels in gestational diabetes mellitus [Lau *et al.* 2011]. In addition, vitamin D deficiency seems to be related with an increased risk for the development of gestational diabetes mellitus [Aghajafari

et al. 2013; Wei *et al.* 2013]. We hypothesized that vitamin D deficiency may be prevalent in a population of diabetes mellitus type 2 patients and that vitamin D may be related to glucose control in this group of patients.

The aim was to study levels of 25-hydroxy vitamin D₃ [25(OH)D₃] and the relationship between 25(OH)D₃ levels and glycemic control in patients with diabetes mellitus type 2.

Methods

To test the hypothesis that 25(OH)D₃ levels may be lower in a cohort of diabetes mellitus type 2 patients and that 25(OH)D₃ levels may be related to glucose control in this group of patients, 25(OH)D₃ and HbA_{1c} levels were measured in diabetes mellitus type 2 patients and controls. In a group of 120 consecutive diabetes mellitus type 2 patients, aged 25–82 years, mean age 56.8 ± 1.1 years, 25(OH)D₃ levels and glycosylated hemoglobin (HbA_{1c}) levels were measured. The study population consisted of 120 diabetes mellitus type 2 patients from the area of Athens and Pireaus. The study was conducted over a period of a year during the winter and spring. The same measurements were performed in a group of 120 normal subjects of the same sex and age, who served as controls. The cohort of 120 diabetes mellitus type 2 patients included in the study were on treatment either with diet only or with diet and oral antidiabetic drugs. The study was approved by the ethics committee of Metaxa Hospital.

Levels of 25(OH)D₃ were measured by radioimmunoassay (RIA) in a two-step procedure. The first step involved rapid extraction of 25(OH)D and other hydroxylated metabolites from serum or plasma with acetonitrile. Following extraction, the treated samples were assayed by competitive RIA using an antibody with specificity to 25(OH)D. The sample, antibody and tracer were incubated for 90 min at 20–25°C. Phase separation was accomplished after 20 min incubation at 20–25°C with a second antibody precipitating complex. To reduce nonspecific binding, buffer was added after this incubation prior to centrifugation. The sensitivity of the assay was < 1.6 ng/ml. The recovery was approximately 100% for 25(OH)D₃. Within and between batch precision was $< 12\%$ and $< 11\%$, respectively.

Levels of HbA_{1c} were measured by high-performance liquid chromatography (HPLC), with a

within run coefficient of variation of 0.78%, a between run coefficient of variation of 0.52% and a total precision of 1.16%. HbA_{1c} was chromatographically separated on a cation exchange cartridge. The method utilizes principles of ion-exchange liquid chromatography. Samples were automatically diluted and injected into the analytical cartridge. A programmed buffer gradient of increasing ionic strength was delivered to the cartridge, where the hemoglobins were separated based on their ionic interactions with the cartridge material. The separated hemoglobins then passed through the flow cell of a filter photometer.

Statistical evaluation of the results was performed using the statistical package SPSS19. Student's *t*-test was used to compare the patient group with the control group. Regression analysis was performed to analyse the relationship between HbA_{1c} and 25(OH)D₃ levels. In order to test normality of the parameters involved in regression analysis, histograms of regression standardized residuals and *p*-*p* plots of regression standardized residuals were performed. A chi-squared test was performed to compare the number of subjects with vitamin D deficiency and insufficiency within the patient and control groups.

Results

HbA_{1c} levels were higher in the group of diabetes mellitus type 2 patients than in the control group, HbA_{1c} levels being $7.2 \pm 0.18\%$ and $5.1 \pm 0.05\%$ in the patient and control groups, respectively ($p < 0.001$, Student's *t*-test) (Table 1). In the group of diabetes mellitus type 2 patients, 25(OH)D₃ levels were lower than in the control group, 25(OH)D₃ levels being 19.26 ± 0.94 ng/ml and 25.48 ± 1.02 ng/ml in the patient and control group, respectively ($p < 0.001$) (Table 1).

In the group of diabetes mellitus type 2 patients, 21 of 120 (17.5%) as opposed to 7 of 120 (5.8%) in the control group had vitamin D deficiency, 25(OH)D₃ levels ≤ 10 ng/ml (chi-squared test, $p = 0.0089$). In the group of diabetes mellitus type 2 patients, 76 of 120 (63.3%) as opposed to 28 of 120 (23.3%) in the control group had vitamin D insufficiency, 25(OH)D₃ levels < 20 ng/ml (chi-squared test, $p < 0.0001$) (Table 1).

25(OH)D₃ levels were found to be inversely associated with HbA_{1c} levels in the group of diabetic type 2 patients ($p = 0.008$, $r = 0.058$, linear regression analysis) (Figure 1). When the analysis was

Table 1. 25(OH)D₃ (ng/ml) (mean ± SEM), HbA_{1c} (%) (mean ± SEM) in the diabetes mellitus type 2 patients (n = 120) and controls (n = 120) and statistical significance (Student's *t*-test), number and percentage of subjects with 25(OH)D₃ deficiency and insufficiency [25(OH)D₃ ≤ 10 ng/ml and < 20 ng/ml] in the patient and control groups and statistical significance (chi-squared test).

Subjects	HbA _{1c} (%) mean ± SEM	25(OH)D ₃ (ng/ml) mean ± SEM	25(OH)D ₃	
			≤ 10 ng/ml	< 20 ng/ml
Patients	7.2±0.18	19.26±0.94	21 (17.5%)	76 (63.3%)
Controls	5.1±0.05	25.48±1.02	7 (5.8%)	28 (23.3%)
Statistical significance	<i>p</i> < 0.001	<i>p</i> < 0.001	<i>p</i> = 0.0089	<i>p</i> < 0.0001
25(OH)D ₃ , 25-hydroxy vitamin D ₃ ; HbA _{1c} , glycosylated haemoglobin; SEM, standard error of the mean.

Figure 1. Inverse association between 25(OH)D₃ (ng/ml) and HbA_{1c} (%) in diabetes mellitus type 2 patients, (*p* = 0.008, *r*² = 0.058, linear regression analysis).
25(OH)D₃, 25-hydroxy vitamin D₃; HbA_{1c}, glycosylated haemoglobin.

performed in the complete population studied, diabetes mellitus type 2 patients and controls, it was found that 25(OH)D₃ levels were inversely associated with HbA_{1c} levels (*p* < 0.001, *r*² = 0.086) (Figure 2).

Discussion

In the present study, lower 25(OH)D₃ levels were observed in a cohort of diabetes mellitus type 2 patients than in a control group and an inverse relationship was observed between glycosylated hemoglobin levels and 25(OH)D₃ levels in the patient group, implying that 25(OH)D₃ levels may affect glucose control in diabetes mellitus type 2. Interestingly, an inverse relationship was found between vitamin D levels and glycosylated hemoglobin in the whole population studied, diabetes mellitus type 2 patients and controls when

analysed together. It appears that vitamin D may be related to glucose control in diabetes mellitus type 2. In addition, statistically significantly more diabetes mellitus type 2 patients than the control population had vitamin D deficiency and insufficiency.

Vitamin D is related to bone metabolism, being a secosteroid synthesized in the skin by the action of ultraviolet irradiation from the sun. The extraskeletal effects of vitamin D are currently the focus of research efforts [Rosen *et al.* 2012]. The relationship of vitamin D with the immune system is being intensely discussed. It has been shown that vitamin D induces immune tolerance [Weiss, 2011], vitamin D deficiency being related to the development of autoimmune diseases, such as multiple sclerosis [Ho *et al.* 2012; Holmøy *et al.* 2012, Weinstock-Guttman *et al.* 2012],

Figure 2. Inverse association between 25(OH)D₃ (ng/ml) and HbA_{1c} (%) in the whole population studied, diabetes mellitus type 2 patients and controls ($p < 0.001$, $r^2 = 0.086$, linear regression analysis). 25(OH)D₃, 25-hydroxy vitamin D₃; HbA_{1c}, glycosylated haemoglobin.

rheumatoid arthritis [Cutolo *et al.* 2007; Haga *et al.* 2013] and diabetes mellitus type 1 [Hyppönen *et al.* 2001]. Recently, the relationship between vitamin D and diabetes mellitus type 2 and the metabolic syndrome has been debated [Palomer *et al.* 2008; Tai *et al.* 2008; Maxwell and Wood, 2011; Mezza *et al.* 2012; Lim *et al.* 2013]. Vitamin D has been shown to be related to glucose metabolism and the development of diabetes mellitus type 2 and the metabolic syndrome [Pittas *et al.* 2007; Mezza *et al.* 2012; Lim *et al.* 2013; Kayaniyil *et al.* 2013].

In a cross-sectional analysis of a general population sample in eastern Finland, an inverse association was observed between 25(OH)D₃ levels and fasting insulin, fasting glucose and 2 h glucose tolerance test glucose results [Hurskainen *et al.* 2012], implying that low serum 25(OH)D₃ may be associated with impaired glucose metabolism. In a recent study, an inverse association of insulin resistance with 25(OH)D₃ levels was observed which was principally found at 25(OH)D₃ levels between 16 and 36 ng/ml [Heaney *et al.* 2013]. In a nested case-control study conducted among 608 women with newly diagnosed type 2 diabetes, higher plasma 25(OH)D₃ concentration was associated with lower risk of type 2 diabetes in women [Pittas *et al.* 2010]. In a prospective observational study with a mean follow up of 2.7 years, higher plasma 25(OH)D₃ assessed repeatedly was associated with a lower risk of incident diabetes in high-risk patients [Pittas *et al.* 2012]. In a prospective study in high risk Asian subjects, 25(OH)D₃ deficiency was associated with a higher risk for the development of type 2 diabetes

mellitus. In a longitudinal study of the determinants of insulin resistance and the metabolic syndrome, a significant inverse association of baseline 25(OH)D₃ with fasting glucose at follow up was observed [Kayaniyil *et al.* 2013]. In a large cohort study of older adults involving 7791 subjects, initially diabetes-free, serum 25(OH)D levels were inversely associated with incident diabetes in women but not in men [Schöttker *et al.* 2013].

Previous studies have shown that low vitamin D ingestion may be related with a higher risk for the development of diabetes mellitus type 2 and the metabolic syndrome [Liu *et al.* 2005; Pittas *et al.* 2006].

In the present study, lower 25(OH)D₃ levels were observed in diabetes mellitus type 2 patients than in controls. In an earlier study, vitamin D deficiency was found to be related to a higher risk for insulin resistance and the metabolic syndrome [Chiu *et al.* 2004]. In a study involving 8421 participants from the National Health and Nutrition Examination Survey III (NHANES III), significantly lower levels of 25(OH)D were observed in the subjects with metabolic syndrome than in those without it [Ford *et al.* 2005]. In a study in postmenopausal women, fasting glucose levels were found to be negatively correlated with serum 25(OH)D [Need *et al.* 2005].

In the present study, vitamin D levels were found to be negatively correlated with glycosylated hemoglobin levels. The correlation persisted even after outliers were excluded. Recent work has shown that vitamin D levels may be inversely

related with glycosylated hemoglobin levels in gestational diabetes mellitus [Lau *et al.* 2011]. In addition, it has been suggested that adequate vitamin D intake may be related with a lower risk for the development of gestational diabetes mellitus [Alzaim and Wood, 2013].

Vitamin D receptors have been found in pancreatic beta cells [Johnson *et al.* 1994], which additionally have been found to express the enzyme 1- α -hydroxylase [Bland *et al.* 2004]. Vitamin D facilitates the secretion of insulin from pancreatic beta cells, thus appearing to regulate insulin secretion [Bourlon *et al.* 1999; Zeitz *et al.* 2003]. Therefore vitamin D deficiency may be related to impaired insulin secretion in diabetes mellitus type 2. In addition, as vitamin D stimulates the expression of the insulin receptor [Maestro *et al.* 2000], vitamin D deficiency may be related with insulin resistance [Talaie *et al.* 2013].

Based on these results it would be physiologically correct to recommend vitamin D supplementation to improve glucose control in type 2 diabetes mellitus patients [Osei, 2010]. Accordingly, vitamin D has been administered to patients with diabetes mellitus type 2 [Borissova *et al.* 2008; Al-Daghri *et al.* 2012; Heshmat *et al.* 2012; Breslavsky *et al.* 2013]. However, these studies have not shown consistent results. In some studies vitamin D supplementation was found to improve glucose control in diabetes mellitus type 2 [Borissova *et al.* 2008; Al-Daghri *et al.* 2012], while in others no such effect was observed [Heshmat *et al.* 2012; Breslavsky *et al.* 2013]. In a randomized controlled trial, the administration of 2000 international units (IU) cholecalciferol daily for 16 weeks was found to improve beta cell function in adults at high risk for diabetes [Mitri *et al.* 2011]. In addition, vitamin D was administered to type 2 diabetics with nephropathy and was found to ameliorate albuminuria [Huang *et al.* 2012]. At a molecular level vitamin D appears to reduce oxidative stress [Salum *et al.* 2013].

The present study has several limitations. It is an observational study and therefore no conclusion can be made as far as any cause and effect relationship is concerned between vitamin D deficiency and diabetes mellitus type 2. In addition, 25(OH)D₃ was chosen as a marker of vitamin D deficiency, as currently recommended. However, vitamin D circulates in several forms in the blood and its active form is 1,25(OH)₂D₃. As such, more studies are needed using finer tools for the

determination of vitamin D deficiency in the human and in particular, in diabetics. More studies are also needed with vitamin D supplementation and long-term observation of glucose control in diabetes mellitus type 2.

Having discussed these results the hidden relationship between vitamin D deficiency and various diseases remains to be unravelled [Chagas *et al.* 2012]. Vitamin D may be related to autoimmunity as well as to metabolic diseases [Holick, 2012]. In addition, recent work has been set forward which discusses the relationship of vitamin D with adipose tissue. It appears that vitamin D may affect adipogenesis [Ochs-Balcom *et al.* 2011; Landrier *et al.* 2012], thus modulating energy expenditure in adipose tissue. These new findings may explain why the administration of vitamin D to patients with diabetes mellitus and the metabolic syndrome appears to have contradictory results.

The findings presented herein have therapeutic implications. In patients with diabetes mellitus type 2, normal levels of vitamin D in the blood may facilitate glucose control. In addition, in people with a tendency to develop diabetes mellitus type 2, optimal levels of vitamin D within the blood may retard the clinical development of diabetes mellitus type 2.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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