MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2013; 19: 264-268
DOI: 10.12659/MSM.883880

Received: 2012.09.28
Accepted: 2012.11.15
Published: 2013.04.12

25-OH-Vitamin D and procalcitonin levels after correction of acute hyperglycemia

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Source of support: This work was supported by the Hacettepe University Scientific Research and Developmental Office (010D02101002)

Background: Hyperglycemia is a common complication of diabetes melitis (DM) and in the absence of metabolic decompensation is a common finding in the Emergency Department (ED). We aimed to evaluate the 25 OH Vit D [25(OH) D] and procalcitonin (PCT) levels during hyperglycemia and after normalization of blood glucose.

Material/Methods: The study included 88 patients over the age of 18 years who presented with acute hyperglycemia at the Hacettepe University Department of Emergency Medicine. Euglycemia was obtained within 6–12 hours and serum samples were taken from patients on admission and 6 hours after normalization of blood glucose. Along with plasma glucose, plasma 25(OH)D and PCT levels were measured using ELISA.

Results: There were 88 (45 males) patients, with a median age of 60.0±13.9 years. Serum 25(OH)D levels increased in all patients after normalization of blood glucose, and serum PCT levels decreased in the whole group. This decrease was independent of type of diabetes or presence of infection.

Conclusions: We demonstrated an increase in 25(OH)D after normalization of blood glucose, and a decrease in PCT in patients with hyperglycemia. This effect was independent of the type of diabetes and presence of infection. Further studies are needed to evaluate the faster link between metabolic abnormalities, vitamin D, PCT, and inflammation.

Key words: hyperglycemia • procalcitonin • 25-OH-Vitamin D

Full-text PDF: http://www.medscimonit.com/download/index/idArt/883880

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Background

Diabetes mellitus (DM) is increasing word-wide [1]. Hyperglycemia is frequently encountered in patients with DM who are admitted to the Emergency Department (ED) [2].

Vitamin D (Vit D) is known to play a role in many diseases. Hypovitaminosis D is associated with falls, fracture risk, cardiovascular disease, hypertension, cancer, and diabetes; an optimum level of Vit D is perhaps necessary for protection from these diseases [1,2]. Many studies have evaluated the association between Vit D and DM [3,4]. A large systematic review including 8 observational studies and 11 randomized controlled trial concluded that Vit D may play a role in the pathogenesis of type 2 diabetes [5]. Short-term supplementation with cholecalciferol improved B-cell function and had a regional effect on attenuating the rise in HbA1c [5]. Most studies have focused on long-term mutual interactions of DM and Vit D.

Infections are frequent causes of hyperglycemia. Procalcitonin (PCT), a propeptide of calcitonin, is an important host response biomarker indicating infection and its prognosis [6]. It may also increase in other clinical situations such as trauma, pancreatitis, cardiogenic shock, and drug hypersensitivity syndrome [7,8].

Until now no study has evaluated the effect of acute glycemic changes on Vit D or PCT levels. We evaluated 25 OH Vit D [25(OH)D] and PCT levels during hyperglycemia and after normalization of blood glucose.

Material and Methods

Patients

Eighty-eight adult patients admitted to the Hacettepe University ED with acute hyperglycemia (blood glucose ≥300 mg/dl) were included. Age, sex, height, weight, type of the diabetes, and treatment were recorded, as well as comorbid diseases, the reason for hyperglycemia, and the presence of ketonuria and acidosis. All patients were stabilized and plasma glucose control was obtained with intravenous hydration and intravenous crystalline insulin infusion. Euglycemia was obtained within 6–12 hours and serum samples were taken from the patients on admission and 6 hours after normalization of blood glucose. Along with plasma glucose, plasma 25(OH)D and PCT levels were measured.

Methods

25(OH)D was measured with direct ELISA (ImmunDiagnostiK, Bensheim, Germany) with intraassay variation and interassay variation of 7%. PCT was measured with ELISA (Wuhan EIAAb Science Co Ltd, China). This study was approved by the ethics committee of Hacettepe University (HEK 09/177-107). All patients gave written informed consent. This study was supported by the Hacettepe University Scientific Research and Developmental Office (010D02101002).

Table 1. Clinical and laboratory parameters of patients at admission.

Sex	43 female/45 male
Age (years)	60.00±13.9
Height (cm)	165.3±13.2
Weight (Kg)	76.88±16.88
BMI (kg/m^2)	27.34±4.7
Presence of Hypertension	46 (52.3%)
Presence of Coronary Heart Disease	25 (28.4%)
Smoking	12 (13.6%)
Type 1 DM	20 (22.4%)
Type 2 DM	54 (61.4%)
New onset DM	14 (15.9%)

BMI – body mass index; DM – diabetes mellitus Data is presented as n % or mean ±SD.

Statistical analyses

Statistical analyses were carried out using the SPSS® software package, version 15.0 (SPSS Inc., Chicago, IL, USA) for Windows®. Numerical variables are shown as mean (range) and categorical variables are shown as frequencies and percentages. The Mann-Whitney *U* test and Kruskal-Wallis test were used to determine differences in numerical variables between groups, and the χ^2 test was used to determine differences between categorical variables. A *P* value of ≤0.05 was considered to be statistically significant.

Results

The mean age of patients (45 males, 43 females) was 60±13.9 (17–85) years. Clinical and laboratory parameters are presented in Table 1. Fourteen patients had diagnosis of DM on admission. One patient was on dietary control only, 37 patients were on oral antidiabetic drugs, 5 patients used basal insulin and oral anti-diabetic drugs, and 31 patients used insulin twice daily.

The most common reason for hyperglycemia was noncompliance with medications (45.5%) and 27% of patients had

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Table 2. The change in 25(OH)D and PCT levels before and after treatment in whole group.

	Before treatment	After treatment	p
PCT (pg/ml)	237.55±213.11	174.68±193.71	<0.001
25(OH)D (nmol/L)	30.71±22.73	70.58±40.39	<0.001

infections. Urinary tract infection was detected in 9, upper respiratory tract infection was seen in 2, pneumonia in 8 and diabetic foot ulcer was present in 7 patients. Four patients had acute coronary syndrome and 6 patients had acute stroke together with hyperglycemia. Ketonuria was detected in 26 patients and acidosis was present in 10 patients.

Serum 25(OH)D levels increased and serum PCT levels decreased in all patients after normalization of blood glucose in the whole group (Table 2).

Pretreatment 25(OH)D and PCT levels were similar between patients with and without infection. Post-treatment 25(OH)D levels were higher in patients with infection (p=0.026). Both parameters decreased in both groups after treatment (Table 3).

Excluding the patients with sudden onset DM, only pretreatment 25(OH)D level was higher in type 2 diabetes; post-treatment 25(OH)D values and pre- and post-treatment PCT levels did not show any difference according to diabetes type (p=0.031, 0.629, 0.974 and 0.900, respectively). PCT decreased significantly in type 1 diabetes patients, whereas 25(OH)D increased significantly in patients with type 2 diabetes (Table 4).

Table 3. Comparison of serum PCT and 25(OH)D before and after treatment in patients with or without infection.

	Before treatment	After Treatment	P
Infection (+)			
PCT (pg/ml)	198.79±135.28	129.86±75.95	<0.001
25(OH)D (nmol/L)	33.99±28.28	85.31±47.6	0.001
Infection (–)			
PCT (pg/ml)	196.2±134.35	134.68±81.25	<0.001
25(OH)D (nmol/L)	29.34±20.06	64.40±35.58	<0.001

Table 4. Comparison of serum PCT and 25(OH)D before and after treatment in patients according to diabetes type.

	Before treatment	After Treatment	p
Type 1 DM			
PCT (pg/ml)	202.78±107.36	134.41±60.81	<0.001
25(OH) (nmol/L)	20.67±14.31	65.85±33	<0.001
Type 2 DM			
PCT (pg/ml)	194.55±150.83	131.67±89.05	<0.001
25(OH) (nmol/L)	32.9±23.27	71.04±43.39	<0.001

Discussion

The results of the present study demonstrated that 25(OH)D levels were increased after normalization of blood glucose in patients with diabetes, whereas PCT levels were decreased. Both effects were independent of the type of diabetes and presence of infection.

Previous studies have shown an overall trend for an inverse correlation between levels of 25(OH)D and type 1 and type 2 diabetes. Vit D levels were found to be correlated negatively with HOMA-IR and 2-h glucose levels [9]. Most of the human studies investigating the association between Vit D status and DM are either cross-sectional, which focuses on the effect of hypovitaminosis D, or supplementation trials with regular Vit D as protection against development of diabetes [10–12]. Although there are some contradictory results, higher baseline 25 (OH) D was found to predict better β-cell function in the PROMISE study, and diabetes was also found to be associated with low levels of 25(OH)D, but there was no conclusion about the exact mechanism related to Vit D and diabetes [13–16].

Regulation of Vit D is far more complicated than a simple loop that is limited to parathyroid and calcium. The majority of 25 (OH)D is found in plasma, but some is stored in fat and fat-free mass [17]. Findings of studies on the regulation of 25-hydroxylation have not been completely consistent. The half-life of Vit D is reported to change at between 10–40 days [18]. For Vit D to be active it must first be hydroxylated by several cytochrome P450 isoforms. 25-hydroxylation in the liver is little affected by Vit D status, but CYP27A1 expression in the intestine and kidney is reduced by 1,25(OH)2D [19,20]. Insulin decreases CYP27A1 expression through an unknown mechanism [21]. It also potentiates the capacity of PTH to increase the expression of 25(OH)D3 24 hydroxylase [22]. The acute change in 25(OH) D levels may be related to administration of exogenous insulin. Pancreatic insulin secretion is impaired in Vit D-deficient rats [23]. It is also evident that $1,25(OH)_2$ regulates β cell function. It affects insulin secretion by regulating intracellular levels of calcium, increasing β cell resistance to apoptosis and increasing its replication [24]. Vit D receptor

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ablation showed abnormal increases in islet renin angiotensin system components, which indicates that the interaction between the islet cells and Vit D is much more complicated than previously assumed [25].

This increase may also reflect a release from stored form or a decrease in metabolism. Limn et al. demonstrated a release of 25(OH)D from adipose tissue after Roux-en-Y gastric bypass surgery [26].

This increase in 25(OH)D that we documented might reflect a mechanism that becomes active during acute metabolic complications. Persistence of this change independent of diabetes type or presence of infection suggests that hyperglycemia itself was the triggering problem. The higher levels of 25(OH)D in patients with infection may be a reflection of the active role of Vit D in immune response [27].

Vit D also acts as an immunomodulator, which is supported by the presence Vit D receptors (VDR) on many different cells, including those of the immune system [28–30]. It is clear that immune signaling controls local Vit D metabolism and, in turn, the 1,25 D-bound VDR modulates immune system function. There is an interplay between Vit D signaling and signaling through different classes of pattern recognition receptors in the production of antimicrobial peptides during innate immune responses to microbial infection [31]. Vit D modulates cytokine response, decreases proinflammatory cytokines, upregulates antimicrobial peptide trigger B lymphocyte apoptosis, and activates T lymphocytes [32].

The absence of differences in PCT levels and a decrease in PCT levels after treatment of hyperglycemia in patients without infection is a quite interesting finding. PCT levels, a marker of bacterial infections, is being used in algorithms in which PCT levels are used for antibiotic decisions in patients with respiratory tract infections and sepsis [33,34]. The most likely explanation might be the presence of subtle infection, but there is no documented cut-off level for hyperglycemic patients that might be used as a reflection of infection. Administration of anti-microbial therapy did not have any effect on PCT levels. Hyperglycemia itself may have triggered the release of PCT, as in other inflammatory conditions in which high levels of PCT are reported [35].

This is the first study documenting an increase in Vit D levels and a decrease in PCT during acute hyperglycemia. The relative heterogeneity of the group might be a limitation of this study, and the presence of diabetic complications might also have affected the responses.

Conclusions

We demonstrated an acute response of 25(OH)D in patients with acute hyperglycemia. Further studies are needed to evaluate the faster link between metabolic abnormalities, Vit D, PCT, and inflammation.

Declaration of interest

There is no conflict of interest.

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