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Does insulin resistance in type 2 diabetes alter vitamin D status?

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ABSTRACT

Aims: Data on changes of vitamin D due to insulin resistance are conflicting. We assessed vitamin D concentrations and parameters of glycemia and mineral homeostasis in patients with insulin resistant type 2 diabetes and in matched normal controls.

Methods: Sixty-nine patients with type 2 diabetes and 60 matched normal control subjects were studied. After an overnight fast, blood was collected for measuring the parameters of glycemia (glucose, insulin and HbA1c), mineral profile (corrected calcium, phosphate and alkaline phosphatase), total 25(OH) vitamin D and parathyroid hormone (PTH) levels.

Results: Patients had significantly elevated fasting glucose ($P = 0.0001$), insulin ($P = 0.0003$) and HbA1c ($P = 0.0005$) than the controls had. They had significantly raised calculated insulin resistance compared with control subjects ($P = 0.0001$). Patients and controls had similar levels of serum corrected calcium and ALP, whereas serum phosphate was significantly lower in the patients compared with controls ($P = 0.001$).

Patients and controls had similar levels of 25(OH)D, but the levels of 25(OH)D in both were in the deficiency range. Intact PTH was similar in the patients and controls. Levels of 25(OH)D did not demonstrate any relation with fasting insulin, insulin resistance, or HbA1c, but correlated negatively with intact PTH ($r = -0.4$, $P = 0.02$).

Conclusion: This study demonstrated prevalent vitamin D deficiency in insulin resistant type 2 diabetic and normal subjects. Insulin resistance did not influence the status of vitamin D.

1. Introduction

Vitamin D deficiency is now considered a public health problem around the world. In 2008, it was estimated that 1 billion individuals presented with vitamin D insufficiency or deficiency [1] and the number is increasing with the progression of years.

Recent evidence suggested that vitamin D is involved in several mechanisms in addition to bone metabolism [2]. Its role in abnormal glucose metabolism as well as in type 2 diabetes has been demonstrated [3,4]. Some authors indicated

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Table 1 – Clinical characteristics of patients with type 2 diabetes and controls.

Variable	Patients	Controls	P value
Number	69	60	
Males	25	20	
Females	44	40	
Age (years)	41 ± 1	40 ± 1	NS
BMI (kg/m^2)	32.0 ± 0.7	31.4 ± 1.5	NS

Values are mean ± SEM.
BMI, body mass index; NS, not significant.

that vitamin D deficiency may predispose to glucose intolerance, altered insulin secretion and type 2 diabetes [5], either through a direct action via vitamin D receptor (VDR) activation or indirectly via calcemic hormones and also via inflammation [6].

Several population-based cross-sectional studies have been published showing inverse associations between 25(OH)D and undiagnosed diabetes risk, including two large national surveys [7,8], but this study design provides only moderate evidence regarding causation because of the simultaneous measurement of 25(OH)D and diabetes status. On the other hand, the epidemiology of vitamin D status seems to be inverse to that of diabetes, since blood levels of 25(OH)D decline with age and are lower in populations with increased skin pigmentation, such as African Americans and South Asians, and in people with obesity, while diabetes increases with age and obesity and is higher in these ethnic groups [9]. Furthermore, it has been postulated that low vitamin D status predicts hyperglycemia and hyperinsulinemia [10,11].

Due to the fact that data on vitamin D status in Kuwaiti subjects with insulin resistant type 2 diabetes are not known, we have conducted this study to assess levels of vitamin D in Kuwaiti subjects with insulin resistant type 2 diabetes and in matched normal control subjects. The relationship of vitamin D with parameters of glycemia in particular insulin resistance was then explored.

2. Subjects and methods

2.1. Subjects

Sixty-nine patients with insulin resistant type 2 diabetes mellitus and 60 normal control subjects were included in the study. The patients and controls were matched for ethnic group, age, gender and body mass index (Table 1). Patients were included in the study if they have no other known illness were not taking other medications than their anti-diabetic therapy. Controls were healthy subjects who were not taking any medication in the past 12 months, and had no known family history of diabetes mellitus. The study protocol was approved by the Local Ethics Committee and patients gave informed written consent. We have calculated that enrolling the above sample of patients and controls would achieve 80% power to detect a difference in vitamin D level between the two groups.

2.2. Study design

After 12-h of an overnight fast, subjects' height and weight were taken followed by blood collection for the measurement of parameters of glucose homeostasis (serum glucose, insulin and HbA1c), mineral profile (serum corrected calcium, phosphate, alkaline phosphatase), total 25(OH) vitamin D level, and parathyroid hormone level. Routine complete blood count, liver profile, and renal profile were also measured.

2.3. Analytical methods

All collected blood samples were transferred on ice container immediately, centrifuged at 2500 rpm at 4 °C for 15 min and the supernatants were stored at minus 70 °C until analysis. Fasting glucose was measured by an enzymatic colorimetric test using an automatic colorimeter (Hitachi Boehringer Mennheim 717). Insulin was measured by radioimmunoassay. Total 25(OH) vitamin D level was measured using chromosystems reagent kit that allows its determination on a simple isocratic high performance liquid chromatography (HPLC) system with UV detection (Chromosystems Instruments & Chemicals GmbH, Munich, Germany). Intact parathyroid hormone (iPTH) was measured by chemiluminescent immunoassay (Access Immunoassay systems, Beckman Coulter intact PTH kit, High Wycombe, UK)

The inter-assay and intra-assay Coefficients of Variation (CV) respectively were 7.0 and 7.8% for insulin (at 30.7 mU/l), 3.3 and 3.0% for total 25(OH)D (at 3.8 nmol/l), and 5.8 and 2.6% for iPTH (at 1.3 pmol/l). Hemoglobin, packed cell volume, white cell count, platelets, and liver and renal functions were measured by routine laboratory techniques.

Insulin resistance (IR) was calculated from the following equation:

$$\mathrm{IR} = \frac{\text{Fasting insulin(mU/L)} \times \text{Fasting glucose(mmol/L)}}{22.5}$$

This equation constitutes the homeostasis model assessment estimate of IR that has been validated by comparison with results of glucose clamp studies [12].

Glycemic control in the patients was labeled excellent if HbA1c is ≤6.5%, good-to-very good if HbA1c is between (8% ≥ HbA1c > 6.5%) and poor if HbA1c is >8%.

WHO reference ranges for 25(OH) vitamin D were used for defining vitamin D states as normal if the level is >75 nmol/l, insufficient if it is between 50 and 75 nmol/l, and deficient if it is <50 nmol/l [13].

2.4. Statistical analysis

Data are expressed as mean ± standard error of the mean or median (range). Data in patients and controls were compared using Mann–Whitney U test or Student's unpaired t test as appropriate. Correlation between variables was sought using Spearman's rank correlation coefficient (rho). Non-normally distributed variables were normalized by log-transformation prior to analysis. P level of less than 0.05 was considered statistically significant.