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Assessment of Vitamin D and Parathyroid Hormone in Type 2 Diabetes Mellitus

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Abstract

Background: **Vitamin D deficiency has been proposed as a risk factor for diabetes mellitus type 2(DM type 2). Insulin receptor gene expression and insulin secretion are modulated by vitamin D, indicating their role in the pathogenesis and development of DM type 2. Furthermore, elevated PTH levels may play a role in the etiology of metabolic syndrome (MS), through an association with its individual components or via insulin resistance.** ***Aim:*****This study aimed to investigate the role of vitamin D and parathyroid hormone in glycemic control of DM type 2.** ***Materials and Methods:*** **The study included 90 participants: 60 patients diagnosed as DM type 2 and 30 healthy age and sex-matched subjects as control. All studied subjects underwent full history taking and complete physical examination. Laboratory tests included fasting blood sugar (FBS), HbA1c, lipid profile, vitamin D and parathyroid hormone serum levels.** ***Results:*** **As regard 25(OH) vitamin D levels, 78.33% of patients were deficient or insufficient, compared to 20% of control subjects that were deficient or insufficient. 25(OH) vitamin D levels showed a significant negative correlation with age (p= 0.002), weight (p=0.0001), BMI (p=0.0001) , FBG (p=0.0001), HbA1C (p=0.0001) and TG (p=0.002). Along with a significant positive correlation with HDL-C (p= 0.0001). PTH levels showed a significant negative correlation with HDL-c (P= 0.0001), 25(OH) vitamin D (P=0.001), in addition to a significant positive correlation with weight (P=0.0001), BMI (P=0.0001), FBG (P=0.005) and HbA1c (P=0.0001).** ***Conclusion*****: Not only vitamin D but also parathyroid hormone may play a role in glycemic control in patients with DM Type 2**

Keywords: *Vitamin D deficiency, Insulin receptor gene, metabolic syndrome*

Introduction

Vitamin D regulates calcium absorption in the small intestine and acts with parathyroid hormone (PTH) to mediate bone mineralization and maintain calcium homeostasis in the blood. Studies have demonstrated a relationship between low vitamin D levels and many diseases; probably due to an anti-inflammatory and immune-modulating properties[(1)]. Abundance of Vitamin D receptors (VDR) that are present in the nucleus of different tissues all over the body could explain the multiple extraskeletal functions of vitamin D specially the metabolic implications[(2)]. Vitamin D deficiency has been pro-

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posed as a risk factor for diabetes mellitus type 2(DM type 2)[3,4]. Higher plasma vitamin D has been shown to be related with a lower risk for the development of diabetes mellitus in high risk patients[5]. Insulin receptor gene expression and insulin secretion are modulated by vitamin D, indicating its role in DM type-2 pathogenesis and development[6]. Vitamin D deficiency has been described in the metabolic syndrome (MS)[7]. Low levels of 25(OH) Vit. D and elevated PTH levels may have a role in the etiology of MS, through an association with its individual components or *via* insulin resistance[8]. An inverse relationship was found between Vit. D levels and both fasting blood glucose concentrations[9], and adiposity[10]. Secondary hyperparathyroidism may increase the risk of development of MS components, including hypertension[11], obesity[10,12], and diabetes[13]. 25(OH) Vit. D levels were found to be negatively correlated with glycosylated hemoglobin (HbA1C) levels in DM type 2 patients[22]. However, the effect of PTH levels on glycemic control in DM type 2 patients still not proved. Previous studies performed on Vit. D or PTH alone yielded conflicting results, reflecting the importance of assaying both Vit. D and PTH in diabetic patients. The aim of this study was to assess the role of both 25(OH) Vitamin D and PTH levels in the glycemic control of Egyptian patients with diabetes mellitus type 2.

Subjects and Methods

Subjects

The present study was carried out on patients attending the outpatient clinics in the Specialized Medical Hospital, Mansoura University in the period from May 2015 to February 2016. The study included 90 participants: 60 patients diagnosed as DM type 2 with a mean age (44.07±7.07 year) and male to female ratio 27/33 and 30 healthy age and sex-matched subjects as the control group with a mean age (41.3±6.6 year) and male to female ratio 10/20. Exclusion criteria included Subjects with chronic renal failure, heart failure, metabolic bone diseases, thyroid diseases, parathyroid diseases, Cushing's syndrome, intestinal malabsorption, taking calcium or vitamin D replacement therapy. The 60DM type 2 patients included in the study were on treatment either diet only or diet and oral anti-diabetic drugs. All studied subjects underwent full history taking and a complete physical examination. The study was approved by the Research Ethics Committee (REC) for experimental and clinical studies at Faculty of Medicine, Mansoura University, Mansoura, Egypt. All MS patients and control subjects signed informed consent forms.

Methods

Anthropometrical measurements:

Height measurements were done using a measuring tape. Weights were measured using a digital balance, and then body mass index (BMI) was calculated as body weight divided by height squared (kg/m^2).

Sampling

After an overnight fast, a venous blood sample was withdrawn from all studied subjects under complete aseptic

conditions. Two ml blood was delivered into an EDTA tube chilled on ice; plasma was rapidly separated in a cooling centrifuge at 4°C (and immediately used for analysis of intact PTH. One ml was added to the EDTA tube for immediate assaying of HbA1C. The remaining blood was added into a plain tube without anticoagulant, left for 10 minutes at room temperature to clot, then centrifuged and serum was separated and each sample was divided into two aliquots, one for immediate measurement of FBG, TG, CA and HDL-c and the other aliquot was stored at-20°C until the time of assay of 25 (OH) vitamin D.

Laboratory assessment

FBG, HDL-C and TG were measured enzymatically on the same day immediately after separation of the serum using (Cobas Integra 400 plus). HbA1C was assayed as an index of metabolic control on a DCA 2000 analyzer, fast ion exchange resin (Roche Diagnostic, Germany). Ca levels were measured using commercially available kit supplied by Human (Germany). Parathyroid hormone (PTH) was measured using Immune Assay with chemilumancent substrate using the IMMU-LITE supplied by Siemens (USA). Serum 25 (OH) Vit. D levels were measured using Enzyme-linked immuneso-rbent assay (ELISA) kit supplied by *(DRG, Inc. Marburg, Germany)*. Although 1,25-dihydroxy Vit. D is the active form, it is widely accepted that the measurement of circulating 25 (OH) D provides better information on the patients Vit. D status and allows its use in the diagnosis of hypovitaminosis D[14]. Deficient/Insufficient subjects were defined as those with levels less than 30ng/ml, while the sufficient ones were those with levels greater than 30ng/ml.

Statistical Analysis

The statistical analysis of data was conducted by using the SPSS (statistical package for social science) program (SPSS, Inc, Chicago, IL) version 17. Data were first tested by Kolmogorov-Smimov test for distribution of data. The description of the data was done in the form of mean ± SD for quantitative data. For comparison between two groups; student t-test was used. Pearson correlation was done to detect association between variables. A chi-squared test was used for non-parametric data. Linear regression analysis was done for some variables.

Results

Both study groups were matched regarding their age and sex (p =0.08 and p=0.09 respectively) table (1). Table (1) illustrates anthropometric measures and biochemical parameters in the studied subjects. There were statistically significant differences between the two studied groups as regard weight, BMI, FBG, HbA1C, TG, HDL-c and PTH (p: 0.017, 0.0001, 0.001, 0.0001, 0.0001, 0.010 and 0.001 respectively). In the present study, as regard 25(OH) vitamin D levels, 78.33% of patients were deficient/ insufficient, compared to 20% of control subjects that were deficient/insufficient. Table (2) shows Correlation between the studied parameters and 25(OH) vitamin D and PTH levels.25(OH) vitamin D levels showed a statistically significant

negative correlation with age (r= -0.321, p= 0.002) ,weight (r= -0.538, p=0.0001), BMI (r= -0.579, p=0.0001) , FBG (r= -0.490, p=0.0001), HbA1C (r= -0.490, p=0.0001) and TG (r= -0.329, p=0.002) and a statistically significant positive correlation with HDL-C(r= 0.495, p= 0.0001). PTH levels showed a statistically significant negative correlation with HDL-c (r= -0.275, P= 0.0001), 25(OH) vitamin D (r= -0.638, P=0.001) and a statistically significant positive correlation with weight (r= 0.455, P=0.0001), BMI (r= 0.434, P=0.0001), FBG (r= 0.296, P=0.005) and HbA1c (r= 0.373, P=0.0001) Table (2). Linear regression analysis was done for variables that have positive and negative correlations with HbA1C, representing the glycemic control, and it revealed that in this study, only weight, height and FBG can be used as independent factors that can assess glycemic control of patients with DM type2.

Table 1: Anthropometric measures and biochemical parameters in the studied subjects

Parameter	DM type2 (N=60)	Control (N=30)	P value
Age (year)	44.07±7.07	41.33±6.6	0.081
Gender (Male/female)	27/33	10/20	0.092
Weight (Kg)	90.3±12.1	65.7±5.6	0.017*
Height (cm)	160.8±5.7	166.5±7.1	0.221
BMI(kg/m^2)	35.5±2.9	23.7±1.2	0.000*
FBG (mg/dl)	113.4±29.2	93.7±4.1	0.001*
HbA1C (%)	8.13±1.2	5.8±0.19	0.000*
TG (mg/dl)	167.2±47.7	99.3±7.0	0.000*
HDL-C (mg/dl)	42.6±3.95	48.2±2.3	0.010*
Ca (mg/dl)	9.8±0.4	9.4±0.5	0.235
25(OH) vitamin D(ng/ml)	19.9±13.5	42.1±12.5	0.848
PTH (pg/ml)	61.6±16.2	47.3±7.5	0.001*

Data are presented as Mean ± SD, p* is significant if ≤ 0.05.BMI: body mass index, FBG: fasting blood glucose, HbA1C: glycated haemoglobin , TG: triglycerides, HDL-C: high density lipoprotein- cholesterol, PTH: parathyroid hormone.

Discussion

The main function of vitamin D is the elevation of plasma calcium and phosphate levels for bone health. However, vitamin D receptors (VDR) are found in almost all the body tissues regulating gene transcription of many inflammatory factors and immune cell expression, thus contributing to chronic disease prognosis, recovery, or mortality [2]. Vitamin D has been shown to be related to the development of diabetes mellitus type 2 and MS[3,7,15,16]. In the present study, as regard 25(OH) vitamin D levels, 78.33% of patients were deficient/insufficient, compared to 20% of control subjects that were deficient/insufficient. Statistically, 25

(OH) vitamin D levels showed no significant difference between the two studied groups (p= 0.848). So, vitamin D deficiency was more prevalent in the patient group than the control group as it is a cross-sectional study. Interestingly, an inverse relationship was found between FBG and glycosylated hemoglobin (HbA1C) levels and 25(OH) vitamin D levels in the patient group. These results are consistent with those by Athanassiou et al., who reported that, more patients with DM type 2 had vitamin D deficiency and insufficiency than the healthy control group, in which, in their diabetic 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 and 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. In addition to the inverse relationship between HbA1C levels and 25(OH) vitamin D levels that was observed by the same study, implying the role of vitamin D in glucose control in DM type 2[17].

Table 2: Correlation between the studied parameters and 25(OH) vitamin D and PTH levels

parameter	25(OH) vitamin D		PTH	
	R	p	r	P
Age (year)	-0.321	0.002*	0.174	0.100
Weight (Kg)	-0.538	0.000*	0.455	0.000*
Height (cm)	0.069	0.516	-0.108	0.312
BMI (kg/m^2)	-.579	0.000*	0.434	0.000*
FBG (mg/dl)	-0.266	0.011*	0.296	0.005*
HbA1C (%)	-.490	0.000*	0.373	0.000*
TG (mg/dl)	-0.329	0.002*	0.204	0.054
HDL-c (mg/dl)	0.495	0.000*	-0.275	0.009*
Ca (mg/dl)	-0.143	0.177	0.093	0.381
25 (OH) vit. D (ng/ml)			-0.638	0.000*

p* is significant if ≤ 0.05.BMI: body mass index, FBG: fasting blood glucose, HbA1C: glycated haemoglobin , TG: triglycerides, HDL-C: high density lipoprotein- cholesterol.

Another study carried out on Indian population revealed that the prevalence of severe vitamin D deficiency was significantly more in patients with DM type 2 compared with healthy controls (16.2% in DM type 2 patients and 2.5% in healthy controls)[18]. This study also observed that, 25(OH) vitamin D had a significant negative correlation with FBG and HbA1C[18]. The present study results are in accord with Lau et al., had reported that vitamin D levels may be inversely related to HbA1C levels in gestational DM[19]. Alzaim and Wood added that adequate vitamin D intake may be related to a lower risk for the gestational DM development[20].Hurskinen et al., observed an inverse association between 25(OH) vitamin D levels and fasting insulin, fasting glucose and 2- hour glucose tolerance test glucose results[21].

Moreover, Kayaniyil et al., found a significant inverse association between baseline 25(OH) vitamin D and fasting blood glucose at follow up[22]. These results can be explained by the essential role of vitamin D in the normal release of insulin in response to glucose and in the maintenance of glucose tolerance as VDRs are expressed in the beta cells of the pancreas, in addition to the presence of vitamin D–dependent calcium-binding proteins (DBP) in the pancreatic tissue[23].

Table 3: Linear regression analysis of the parameters that correlated to HbA1C

Parameter	HbA1C	
	B	p
Age (year)	0.025	0.131
Weight (kg)	0.038	0.006
Height (cm)	- 0.089	0.0001
BMI (kg/m^2)	0.027	0.540
FBG (mg/dl)	0.015	0.001
TG (mg/dl)	0.005	0.097
HDL-c (mg/dl)	0.008	0.842
Ca (mg/dl)	- 0.017	0.057
PTH (pg/ml)	-0.005	0.522

p* is significant if ≤ 0.05.BMI: body mass index, FBG: fasting blood glucose, HbA1C: glycated haemoglobin , TG: triglycerides, HDL-C: high density lipoprotein- cholesterol, PTH: parathyroid hormone.

Vitamin D effect on insulin secretion may be via increasing the intracellular calcium concentration by non-selective voltage-dependent calcium channels causing cleavage of proinsulin to insulin[24]. Moreover, calcium is necessary for bete cell glycolysis, which plays a role in signalling circulating glucose concentration and also stimulates insulin synthesis by activating protein synthesis in the pancreatic islets[25]. Therefore, vitamin D deficiency may be related to impaired insulin secretion in DM type 2. Indeed, as vitamin D stimulates insulin receptor expression[26], vitamin D deficiency may be related with insulin resistance (IR)[27]. Besides the previous effects of Vitamin D, it also regulates nuclear Peroxisome proliferative activated receptor (PPAR) that has an important role in the insulin sensitivity[28]. A deficiency of that vitamin is associated with increased inflammation as it decreases the expression of pro-inflammatory cytokines involved in insulin resistance (IR)[29]. In contrast to the previous results, a study on Japanese population observed 70% prevalence of vitamin D deficiency without any difference in 25(OH) vitamin D levels between DM type 2patients and healthy controls[30]. In addition to two reports from United States reporting higher mean value of 25(OH) vitamin D in DM type 2 patients as well as in controls[31,32]. These different results suggest that, vitamin D levels in patients with D M type 2 patients vary according to ethnicity or some other unknown reasons[18]. The current study reported significantly higher PTH levels in the diabetic group than the control group, this can explained by the increased percentage of vitamin D deficiency in diabetic patients than in controls. An inverse correlation between PTH levels and HDL-c, with direct associations between PTH levels and weight, BMI, FBG and HbA1c were also observed in this study. The direct correlation between PTH levels and HbA1c indicates its role in the glycemic control of the diabetic

patients. Similarly, Reis et al. found that elevated PTH levels were associated with an increased prevalence of metabolic syndrome (MS) and this association was not explained by age, season, major lifestyle factors, diabetes, renal function, or 25(OH) vitamin D concentrations[33]. Insulin resistance is widely proposed as the mechanism underlying the MS, the recent link between PTH and MS in may be explained by insulin resistance, high blood pressure, hyperglycemia and low HDL-cholesterol[33,34]. Hjelmesæth et al. reported that, the serum PTH level was an independent predictor of MS in a series of 1,017 consecutive morbidly obese women and men with MS. This study revealed an inverse correlation between 25(OH) vitamin D and PTH similar to our results, but, it did not find any significant association be tween 25(OH) vitamin D levels and MS[35]. Similar to our results that revealed correlations between vitamin D deficiency/insufficiency with high PTH levels and HbA1c implying their effects on glucose metabolism**,** Kramer and co-workers. demonstrated that, the coupling of both vitamin D deficiency/insufficiency with higher PTH levels was associated with declining insulin sensitivity and beta-cell function and rising glycemia over time in a cohort of women in the 1st year postpartum. While both vitamin D and PTH alone were independently associated with some of the outcomes[36]. Previous studies have suggested an association of integrated assessment of vitamin D/PTH with glucose metabolism[37,38].

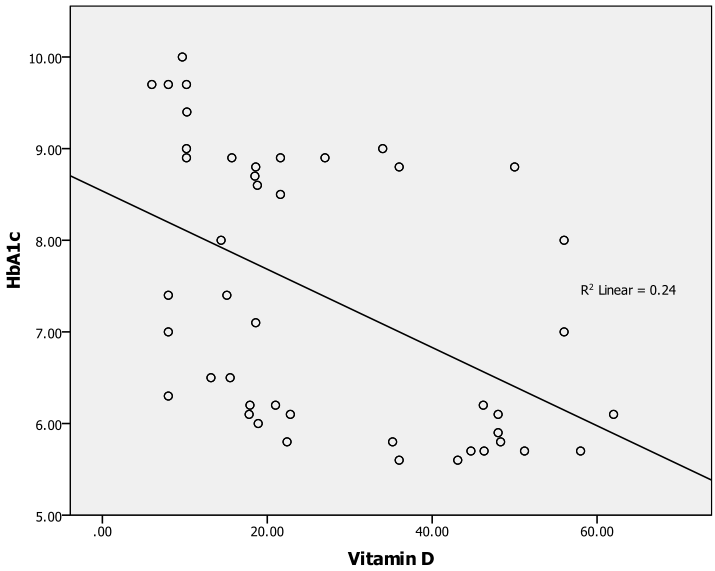

Figure 1: Correlation between HbA1c and vitamin D levels

Stanley et al. demonstrated that the ratio of PTH to vitamin D was associated with insulin sensitivity and highly sensitive C reactive protein hsCRP[37]. Moreover, Alemzadeh and colleagues showed an association of PTH to vitami D ratio with presence of MS[38]. Kramer et al[36]. showed that PTH status needs to be considered when eval uating the associations of vitamin D

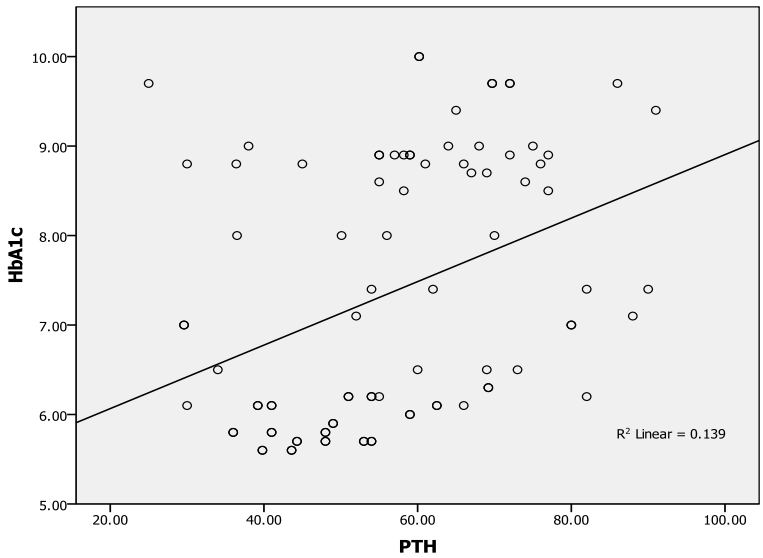

Figure 2: Correlation between HbA1C and PTH levels

status with glucose homeostasis; it reported that glucose metabolism is only adversely affected when circulating 25(OH) vitamin D decreases to a level that causes PTH to rise, reflecting a true vitamin D deficiency

Conclusion

Not only vitamin D but also parathyroid hormone may play a role in glycemic control in patients with Type 2 Diabetes Mellitus. Study limitations: the cross-sectional design of the current study and the small sample size makes it difficult to find a cause-effect relationship, Moreover further investigations are needed to evaluate vitamin D/PTH axis.

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