Research Article

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Vitamin d status and glucose hemostasis among Saudi type 2 diabetic patients

Abstract

Background: Type 2 diabetes mellitus (T2DM) and vitamin D deficiency are now considered a health problem worldwide that is strongly associated with cardiovascular mortality.

Objective: This study was to investigate the possible relationship between vitamin D status and glucose hemostasis among Saudi type 2 diabetic patients.

Material and Methods: One hundred sixty nine Saudi obese T2DM patients (116 females and 53 males) with body mass index (BMI) ranged from 30 to 36Kg/m^2 and the mean of diabetes chronicity was 12.47±3.16years treated with oral hypoglycemic agents e.g. metformin and/or pioglitazone were selected from the out-patient diabetic clinic of the King Abdulaziz Teaching Hospital, Jeddah, Saudi Arabia. Initially, a physician at King Abdulaziz University Hospital examined all participants; their medical history was taken to collect information about general condition, physical activity and current medications. Exclusion criteria included smokers, kidney insufficiency, congestive heart failure, pregnant female patients, hepatitis and respiratory failure. All participants were enrolled in three groups according to 25-OHD levels: vitamin D deficiency group (A) 25-OHD level <20ng/ml, vitamin D deficiency group (B) 25-OHD level=20–30ng/ml and normal vitamin D group(C) 25-OHD level >30ng/ml.

Results: Regarding glucose hemostasis, results revealed significantly higher values of QUICKI in group (C) compared to subgroup (A) and group (B) in addition to lower values of serum insulin, HOM-IR and HBA1c in subgroup (C) compared to group (A) and group (B). While there was significant difference between groups. Moreover, the 25-OHD showed a strong direct relationship with QUICKI and a strong inverse relationship with serum insulin, HOM-IR and HBA1c in the three groups (P<0.05).

Conclusion: There is an association between glucose hemostasis and vitamin D among Saudi type 2 diabetic patients.

Keywords: glucose hemostasis, insulin resistance, type 2 diabetes, obesity, vitamin d deficiency

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Introduction

Type 2 diabetes mellitus (T2DM) is a common health problem affects about 285million and expected to reach 438million by 2030 worldwide,[1–3] Stroke and cardiovascular disorders may be induced by T2DM.[3–4] In addition, vitamin D deficiency is a worldwide epidemic health related problem[5,6] which play an important role in T2DM development[7] cardiovascular disease (CVD) and mortality.[8–10] Vitamin D deficiency may have a role in T2DM pathogenesis.[11–15]

Deficiency of vitamin D level is usually associated with abdominal obesity, hypertension, and dyslipidemia.[16] Body fat is a repository for vitamin D, a fat-soluble vitamin.[17] Vitamin D that is deposited in adipose tissue is biologically inactive; thus, individuals with an increased body mass index are often vitamin D deficient, in addition aging, dark skin and limited exposure to sun light and heavy clothes are additional risk factors for deficiency of vitamin D.[18] However, about 40% of adults have vitamin D deficiency.[19]

Type 2 DM is a multifactorial disease characterized by chronic hyperglycemia, altered insulin secretion, and insulin resistance. It can be also defined by impaired glucose tolerance (IGT) that results from islet β cell dysfunction, followed by insulin deficiency in skeletal muscle, liver and adipose tissues.[18] Evidence suggests a link between vitamin D deficiency and T2DM.[19] It has been postulated that vitamin

D has an influence on glycemic control.[20] Pancreatic beta cell function may be affected by the existence of specific vitamin D receptors in the beta cells.[21] Additionally, vitamin D is essential for pancreatic β cells insulin secretion regulation and calcium absorption.[22] It is thought that vitamin D stimulates glucose transport and preventing systemic inflammation.[23,24]

Although there are evidences support role of vitamin D on glucose metabolism,[25–30] there is contradicted finding in other studies as the *Sadiya and colleagues* reported that six months of supplemental intake of vitamin D3 did not associated with improvement in glycemic control in T2DM patients.[31] Therefore, the aim of this study was to investigate the possible relationship between vitamin D status and glucose hemostasis among Saudi type 2 diabetic patients.

Material and methods

Subjects

One hundred sixty nine Saudi obese T2DM patients (116 females and 53 males) with body mass index (BMI) ranged from 30 to 36Kg/m^2 and the mean of diabetes chronicity was 12.47±3.16years treated with oral hypoglycemic agents e.g. metformin and/or pioglitazone were selected from the out-patient diabetic clinic of the King Abdulaziz Teaching Hospital, Jeddah, Saudi Arabia. Initially, a physician at

King Abdulaziz University Hospital examined all participants; their medical history was taken to collect information about general condition, physical activity and current medications. Only participants have fasting blood sugar levels more than 5.6mmol/L or random blood sugar level more than 7.8mmol/L (impaired blood sugar) were included in this study and were further checked for type 2 diabetes mellitus as per recent American Diabetes Association criteria i.e. fasting blood sugar ≥7.0mmol/L or post-prandial blood sugar ≥11.1mmol/L [2h plasma glucose 11.1mmol/L during an oral glucose tolerance test] and glycosylated hemoglobin (HbA1c%)>6.5%.[32] Exclusion criteria included smokers, kidney insufficiency, congestive heart failure, pregnant female patients, hepatitis and respiratory failure. All participants were enrolled in three groups according to 25-OHD levels: vitamin D deficiency group (A) 25-OHD level <20 ng/ml, vitamin D deficiency group (B) 25-OHD level=20–30ng/ml and normal vitamin D group(C) 25-OHD level >30ng/ml. The Ethical Committee of the Faculty of Applied Medical Sciences, King Abdulaziz University, approved this study. All participants signed a written informed consent.

Measurements

In all subjects, clinical and anthropometric data were collected at the time of enrollment. Independent assessors who were blinded to group assignment and not involved in the routine treatment of the patients performed clinical evaluations and laboratory analysis. Body mass index (BMI) was calculated on the basis of weight (kilograms) and height (meters), and subjects were classified as normal weight (BMI 18.5–24.9kg/m^2), overweight (BMI 25–29.9kg/m^2), and obese (BMI ≥30kg/m^2). In addition, between 07:30 and 09:00, after an overnight fast of 12h fasting blood sample was drawn.

Serum concentrations of 25-hydroxyvitamin D (25-OHD): Measurement of 25(OH) vitamin D for all patients and controls were done by the commercial kit RIA (Elisa Kit; DiaSorin, Stillwater, MN, USA). Vitamin D deficiency was defined as a 25-OHD level of less than 20ng/ml. Vitamin D levels between 20 and 30ng/ml are termed 'insufficient'. Vitamin D levels greater than 30ng/ml are termed 'optimal'.[33,34]

Serum glucose, insulin and insulin resistance tests: Plasma glucose concentration and insulin were determined (Roche Diagnostics GmbH, Mannheim, Germany) using commercially available assay kits. Insulin resistance was assessed by homeostasis model assessment (HOMA-IR). HOMA-IR=[fasting blood glucose (mmol/l)-fasting insulin(mIU/ml)]/22.5.[35]

However, insulin sensitivity was assessed by The quantitative insulin-sensitivity check index (QUICKI) using the formula: QUICKI=1/[log(insulin)+log(glucose)].[36] All serum samples were analyzed in duplicates.

Statistical analysis

Statistical analysis of data was performed using SPSS (Chicago, IL, USA) version 17. Quantitative variables were described as mean±SD. qualitative variables were described as number and percentage. The Fisher's exact test used in the compression of non-parametric qualitative data and Mann–Whitney test was used to compare nonparametric qualitative data. While the one way ANOVA (analysis of variance) was used to compare more than two groups as regard a quantitative variable, P<0.05 was considered significant. However, the degree of correlation between serum insulin, HBA1c, HOM-IR, QUICKI and 25-OHD was calculated with Pearson's correlation coefficients (r).

Results

Participants were divided into three groups; group (A) included 82 female and 39 male patients has vitamin D deficiency (25-OHD<20ng/ml), group (B) included 19 female and 8 male has vitamin D deficiency (25-OHD=20-30ng/ml) and group (C) included 15 female and 6 male patients has normal vitamin D (25-OHD level >30ng/ml). Comparison between patients' groups regarding baseline variables showed that: there was no statistically significant difference between the three groups as regards all variables except uric acid the study groups showed significant differences (P=0.017). Regards the fasting blood sugar, it was found to be more in group (A) alone than in group (B) and group (C) (p=0.013). In addition, the raised postprandial blood sugar level was found to be more in group (A) than in the group (B) and group (C) with statistically significant difference between the three groups (p=0.008) (Table 1). Regarding glucose hemostasis, results revealed significantly higher values of QUICKI in group (C) compared to subgroup (A) and group (B) in addition to lower values of serum insulin, HOM-IR and HBA1c in subgroup (C) compared to group (A) and group (B). While there was significant difference between groups (Table 2). Moreover, the 25-OHD showed a strong direct relationship with QUICKI and a strong inverse relationship with serum insulin, HOM-IR and HBA1c in the three groups (Table 3) (P<0.05).

Table 1 Comparison between Patients' groups regarding baseline variables

Variable	Group (A) (25-OHD<20Ng/Ml)	Group (B) (25-OHD=20-30ng/Ml)	Group (C) (25-OHD Level >30Ng/Ml)	P Value
Age	54.56±6.27	56.18±5.93	52.72±7.11	0.83
Sex(Male: Female)	39(32%):82(68%)	8(29%):19(71%)	6(28%):15(72%)	0.076
BMI(kg/m^2)	32.14±4.18	30.95±3.13	31.28±2.67	0.125
Diabetes duration	12.15±3.17	11.43±3.62	11.12±4.16	0.084
Uric acid	5.37±1.21	4.25±1.32	3.89±1.15	0.017*
HDL-c(mg/dl)	41.26±7.18	43.14±8.13	47.24±10.22	0.145
LDL-c(mg/dl)	121.31±14.19	110.57±12.26	102.18±11.27	0.316
FBS(mg/dl)	188.16±32.42	142.29±25.12	121.74±19.23	0.013*
PPS (mg/dl)	273.24±46.35	208.14±37.21	167.48±24.66	0.008*

BMI, body mass index; HDL-c, high-density lipoprotein cholesterol; LDL-c, low--density lipoprotein cholesterol; FBS, fasting blood sugar: PPS, postprandial blood sugar; (*) indicates a significant difference between groups, P<0.05

Table 2 Comparison between Patients' groups regarding serum insulin, HBA1c, HOM-IR and QUICKI

Variable	Group (A) (25-OHD<20Ng/Ml)	Group (B)(25-OHD = 20-30Ng/Ml)	Group(C)(25-OHD Level >30Ng/Ml)	P Value
Insulin(mU/L)	15.74±3.68	13.65±3.14	12.31±2.94*	0.013*
HBA1c(%)	9.26±2.45	8.52±1.81	7.18±1.75*	0.024*
HOMA-IR	5.97±1.62	5.13±1.46	4.12±1.17*	0.016*
QUICKI	0.127±0.05	0.152±0.07	0.189±0.08*	0.032*

HBA1c, glycosylated hemoglobin; HOMA-IR, homeostasis model assessment-insulin resistance (HOMA-IR) index, QUICKI, the quantitative insulin-sensitivity check index; (*) indicates a significant difference between groups, P<0.05

Table 3 Correlation coefficient (r) of 25-OHD, serum insulin, HBA1c, HOM-IR and QUICKI in the three groups

	Group (A) (25-OHD<20Ng/Ml)	Group (B) (25-OHD =20-30Ng/Ml)	Group (C) (25-OHD Level >30Ng/Ml)
Insulin(mU/L)	-0.512*	-0.733**	-0.716**
HBA1c(%)	-0.726 **	-0.528*	-0.583*
HOMA-IR	-0.642 **	-0.641**	-0.525*
QUICKI	0.635 *	0.715**	0.611**

Discussion

Vitamin D deficiency plays an important role in development of T2DM[37] and its cardiovascular complications.[38] We detected a significant negative correlation between plasma vitamin D and each of insulin levels, FPG, HOMA-IR and HbA1c levels in all studied groups. Our results were in harmony with *Schuch et al.*,[39] *Mukhopadhyaya et al.*,[40] *Bid et al.*[41] However, *National Health and Nutrition Survey 2001-2006* was conducted to examine the combined impact of vitamin D insufficiency and obesity on insulin sensitivity and T2DM.[42] It was found that obese subjects with low level of vitamin D had a 32.13-fold increase in insulin resistance versus the 19.9-fold increase in insulin resistance noted in obese individuals with adequate vitamin D levels. However, there was not a statistically significant relationship between the 2 factors and diabetes. The investigators concluded that the weaker association with T2DM than insulin resistance might be because insulin resistance is the mechanism in which vitamin D impacts diabetes.[48] Our results revealed that both fasting blood sugar and postprandial blood sugar were statistically significant higher among obese T2DM patients with deficiency in vitamin D than obese T2DM patients with optimal vitamin D levels. Moreover, glucose hemostasis parameters correlated with the 25-OHD in the three groups (P<0.05). Several previous studies demonstrated a direct relationship between insulin sensitivity and circulating vitamin D level.[44–46] While, Pirgon et al.[47] reported that level of 25(OH)D was decreased among 87 obese adolescent with or without nonalcoholic fatty liver disease that was negatively correlated with HOMA-IR and also with and with alanine aminotransferase that indicates low insulin sensitivity associated with insufficient vitamin D status.[47] Also, *Jung et al.*[48] enrolled 257 T2DM patients with microvascular complication included retinopathy, nephropathy and diabetic peripheral neuropathy and categorized them into 3 groups according to the vitamin D status and proved that low level of 25-OHD was associated with increased risk of diabetic peripheral neuropathy in male T2DM patients and increased risk of diabetic nephropathy in female T2DM patients.[48] However, *Alissa et al.*[49] enrolled 300 postmenpausal Saudi women in a cohort study for possible association between metabolic syndrome and 25-OHD deficiency, they found an inverse relationship between 25-OHD and triglycerides and fasting blood glucose and diastolic blood pressure, which indicate an association between decreased level of 25-OHD and metabolic syndrome.[49] Similarly, *Mackawy and Badawi*[50] investigated the possible role of Vitamin D in insulin resistance and systemic inflammation in 130 patients with T2DM; they conducted genetic analysis for vitamin D receptors gene polymorphisms in addition to biochemical analysis and suggested an interaction between vitamin D receptors gene polymorphisms and HOMA-IR, insulin, vitamin D, interleukin-6, body mass index and waist circumference.[50]

In the other hand previous studies proved that supplementation of vitamin D improves insulin sensitivity as *Elseweidy et al.*[51] reported that Vitamin D supplementation alleviated insulin resistance and hyperinsulinemia as result of activation of insulin receptor phosphorylation in diabetic rat model received 20% fructose in drinking water for 45 days to induce diabetes.[51] However, *Osati et al.*[52] enrolled 210 subjects with vitamin D deficiency who were assigned into two group where the first group received supplemental vitamin D and the second group received placebo treatment for two months, they found that corrected deficiency of vitamin D improved insulin sensitivity and maintained serum glucose at the normal level along with low serum insulin level.[52] While, *Calvo-Romero and Ramiro-Lozano*[53] stated that vitamin D supplementation of 16,000 IU for 48days improved indices of insulin resistance (HOMA-IR and QUICKI) in 28 T2DM patients.[53] Moreover, *Jamka et al.*[54] conducted a meta-analysis on 11 clinical trials that had 1181 subjects received vitamin D supplementation, 7 studies reported reduction in blood glucose level, serum insulin and HOMA-IR; whereas, 2 studies reported no significant changes.[54]

The possible mechanisms of improved insulin sensitivity a result of vitamin D supplement may include inhibition of inflammatory cytokines release and improved insulin receptor expression and/or proteins of the insulin-signaling cascade.[55] Moreover, vitamin D may directly enhance binding of 1,25(OH)2vitD to the vitamin D receptor that expressed in the β cells of the pancreas[56,57] or indirectly through its regulation of calcium as secretion of insulin from the β cells is a calcium dependent process.[58] Moreover, the major limitations of the present study is only Saudi obese T2DM patients enrolled in the study, so the value of this study only related only to Saudi subjects, also small sample size in the three groups may limit the possibility of generalization of the findings in the present study. Finally, within the limit of this study, there is an association between glucose hemostasis and vitamin D among Saudi type 2 diabetic patients.

Acknowledgments

Conflict of interest

Author declares that there is no conflict of interest.

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