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Original Research

Investigation of the Relationship of Vitamin D, Parathyroid Hormone, Calcium Serum Level, and Insulin Resistance among Obese Individuals

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ABSTRACT

Objective: Several studies have shown that 25-hydroxyvitamin D, parathyroid hormone (PTH), and serum calcium (Ca) may play functional roles with insulin resistance.

Methods: This case–control study included 60 obese individuals with impaired fasting glucose who were compared with 60 non-obese individuals with normal fasting glucose who visited the endocrinology and metabolism department. Fasting plasma glucose, fasting insulin, triglyceride, PTH, and serum 25-hydroxyvitamin D (25(OH)D) were measured from all subjects in the morning after approximately 8 h of fasting using methods with respect to the standard operating procedures. Homeostatic model assessment of insulin resistance (HOMA-IR) was used for determining insulin resistance. The statistical analysis was attained by SPSS.

Results: A lack of association was found between serum 25(OH)D and insulin resistance (HOMA-IR) before and after adjusting PTH, Ca, and various variables either in all participants or after exclusion of participants with HOMA-IR ≤2.5. On the other hand, PTH showed a significant inverse correlation with fasting insulin (p=0.022) and HOMA-IR (p=0.023) after adjusting 25(OH)D, serum Ca, and various variables and exclusion of participants with HOMA-IR ≤2.5.

Conclusion: In the present study, we did not find a relationship between insulin resistance and vitamin D levels. Further studies are needed for clarifying the relationship between insulin resistance and vitamin D levels.

Keywords: Calcium, insulin resistance, obesity, parathormone, vitamin D

INTRODUCTION

25-Hydroxyvitamin D 25(OH)D and parathyroid hormone (PTH) are important physiological regulators of extracellular calcium (Ca) metabolism. The effects of intestinal Ca absorption are elevated by vitamin D (1, 2). In vitro and in vivo studies showed that vitamin D status may play a functional role in glucose homeostasis (3). Associations between low vitamin D and the risk of type 2 diabetes were indicated by many studies (4, 5). On the other hand, there are many studies which support the opposite. 25(OH)D level, insulin resistance, and diabetes in non-Hispanic Whites and Mexican Americans have a common inverse association, but not in non-Hispanic Blacks as observed in a study conducted by the Third National Health and Nutrition Examination Survey (6). A study of Chinese individuals showed that serum 25(OH)D level was inversely related with insulin resistance (7, 8), whereas in a Canadian Cree study, these parameters were found to be not connected with insulin resistance or beta cell function. However, these studies did not present the data on serum Ca, nor did they adjust PTH levels for Ca concentrations as we have done in our study. The objective of the present study was to investigate the relationship of 25(OH)D, PTH, and Ca serum levels with IR among obese individuals with impaired fasting glucose (IFG) compared with non-obese individuals with normal fasting glucose.

METHODS

Subjects

This study was conducted on 60 obese adult individuals with IFG with a body mass index (BMI) ≥30 kg/m^2 as diagnosed by physicians. The mean age of the patients was 47.7 (20-60) years. Patients who had serious disease, pregnant women, or patients who take any medication drugs were excluded from the study. The results of these 60 case study individuals were compared

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with 60 healthy individuals with normal fasting glucose with a BMI <30 kg/m^2 as the control group. The mean age of the healthy individuals was 40.3 (20-60) years. Patients' tobacco use (response set smoker or nonsmoker) and typical alcohol consumption (response set drinking or nondrinker) data were gathered.

Study samples were collected from outpatients attending to Gaziantep University endocrinology and metabolic diseases clinic from October 2016 to January 2017. All participants were informed about the study procedure through a written consent form before participation. The study complied with the Declaration of Helsinki, and the research protocol was approved by Gaziantep University School of Medicine Research Ethics Committee (Decision date: 08.15.2016, Decision no: 2016/238).

A BMI ≥30 kg/m^2 was defined as general obesity (9), whereas the explanation of IFG is according to the current American Diabetes Association guidelines. The explanation of IFG is a serum glucose level of 100-125 mg/dL, and homeostatic model assessment of insulin resistance (HOMA-IR) ≤2.5 was agreed as the natural range for insulin resistance.

After overnight fasting, blood samples were obtained from the subjects by venipuncture in the morning and centrifuged immediately, and serum samples were analyzed directly without storage. In the central laboratory of Gaziantep University, a serum concentration of total Ca and triglyceride (TG) was measured by enzymatic methods, whereas fasting plasma glucose (FPG) was measured by the hexokinase method by an autoanalyzer. Fasting plasma insulin and PTH levels were assayed by the chemiluminescent immunoassay technique by an autoanalyzer.

Insulin resistance was estimated by using HOMA-IR. HOMA-IR was calculated and estimated fasting plasma insulin value (mIU/mL) and the FPG value (mg/dL), given in the same amount and homeostatic model assessment-beta cell function (HOMA2-B%) and homeostatic model assessment-sensitivity (HOMA2-S%) (10).

Statistical Analysis

Anderson-Darling test was done to assess if continuous variables follow normal distribution. If continuous variables followed normal distribution, then mean and standard deviation would be used. However, if they did not follow normal distribution, then median and interquartile range (25%-75%) were used. Discrete variables were used to present the data, chi-square test was used to analyze the discrete variable, and Fisher's exact test was used to analyze the distribution between the two groups (used instead of chi-square for 2×2 table, if total sample <20 and if two or more with expected frequency <5). Two samples t-test was used to analyze the differences in means between the two groups (if both follow normal distribution with no significant outlier). Mann-Whitney U test was used to analyze the differences in the median of the two groups (if they do not follow normal distribution).

Linear regression analysis was performed to assess the relationship between different variables. If one or both of them followed normal distribution, then Pearson regression was used, but if both did not follow normal distribution, then Spearman correlation was used. Scatter plot was used to present the regression analysis, r (correlation coefficient or standardized beta is a representative of magnitude and direction of the relationship), r<0.25 weak, 0.25-0.5 mild, 0.5-0.75 moderate, and >0.75 strong correlation. A negative sign indicates inverse relationship, whereas a positive sign represents direct relationship.

Multiple linear regression analysis was applied by using dummy variables (sex, alcoholic, and smoking) after adjustment of possible confounders (age, sex, BMI, smoking, alcoholic, TG, 25(OH)D, and serum Ca), and the results were shown using partial correlation coefficient (which represents the correlation coefficient after adjustment).

Statistical Package for the Social Sciences (SPSS) 20.0.0 version (SPSS IBM Corp.; Armonk, NY, USA) Minitab 17.1.0, MedCalc 14.8.1, and GraphPad Prism 7.0 software packages were used for statistical analysis. A p value <0.05 was considered to be significant.

RESULTS

In Table 1, regarding the characteristics of the subjects, obese individuals were compared with those with IFG, and the results of the control non-obese subjects were compared with normal fasting glucose subjects with respect to demographic and biochemical parameters.

Table 2 shows the simple regression analysis between serum 25(OH)D versus demographic and biochemical parameters. Significant and inverse correlation between 25(OH)D, BMI, and PTH was found, whereas no correlation with other demographic and biochemical parameters was reported. However, among the control group subjects, there was no correlation between 25(OH)D and various variables (demographic and biochemical parameters) as shown in Table 2.

Table 3 shows the simple regression analysis between serum PTH versus demographic and biochemical parameters. Only serum PTH showed a significant correlation with 25(OH)D (p=0.032, inverse correlation) and with HOMA2-B% (p=0.049). In the control group, there was no correlation between serum PTH and various variables (demographic and biochemical parameters) as shown in Table 3.

Table 4 shows the simple regression analysis between serum Ca level versus demographic and biochemical parameters. Only Ca showed a significant correlation with HOMA2-S% (p=0.008, inverse correlation) in the control group, whereas no correlation was found between serum Ca and various variables (demographic and biochemical parameters) in the case group.

In Table 5, multiple regression analysis was performed on serum 25(OH)D versus IR-related parameters adjusted for PTH, as well as Ca, age, sex, BMI, smoking, and alcohol consumption. No significant correlation was demonstrated between 25(OH)D and IR-related parameters after adjusting these variables in the case

Table 1. Baseline characteristics of the subjects

Variables	Case N=60	Control N=60	p
Age (years)	47.7[a]±9.5[b]	40.3[a]±14.6[b]	0.001 [Sig.]
Sex			0.449
Female	40[c] (66.7%)[d]	36[c] (60.0%)[d]	
Male	20[c] (33.3%)[d]	24[c] (40.0%)[d]	
Smoking			0.461
Nonsmoker	36[c] (60.0%)[d]	32[c] (53.3%)[d]	
Smoker	24[c] (40.0%)[d]	28[c] (46.7%)[d]	
Alcoholic			0.685
No consumption	44[c] (73.3%)[d]	42[c] (70.0%)[d]	
Consumption	16[c] (26.7%)[d]	18[c] (30.0%)[d]	
Height (cm)	161[a]±8[b]	169[a]±8[b]	<0.001 [Sig.]
Weight (kg)	90[a]±11[b]	73[a]±6[b]	<0.001 [Sig.]
BMI (kg/cm^2)	34.3[a]±4.5[b]	25.3[a]±2.5[b]	<0.001 [Sig.]
FPG (mg/dL)	105.1[a]±3.7[b]	89.4[a]±7.0[b]	<0.001 [Sig.]
F.I (mIU/mL)	10.5[e] (6.2–15.5)[f]	8.5e (5.0–14.0)[f]	0.204
25(OH)D (ng/mL)	20.0[a]±9.8[b]	18.9[a]±9.9[b]	0.536
PTH (pg/mL)	44.6[e] (34.0–59.1)[f]	44.9[e] (40.0–60.0)[f]	0.502
S.Ca (mg/dL)	10.0[a]±0.5[b]	9.7[a]±0.5[b]	0.009 [Sig.]
TG (mg/dL)	134.4[a]±9.4[b]	106.5[a]±20.4[b]	<0.001 [Sig.]
HOMA-IR	2.78[e] (1.58–3.92)[f]	1.88[e] (1.14–2.84)[f]	0.015 [Sig.]
HOMA2-B%	83.4[e] (58.1–108.9)[f]	108.5[e] (66.6–131.3)[f]	0.006 [Sig.]
HOMA2-S%	73.0[e] (51.2–120.4)[f]	91.5[e] (55.0–152.5)[f]	0.152

[a]Mean; [b]standard deviation; [c]number; [d]percentage; [e]median; [f]interquartile range
BMI: body mass index; FPG: fasting plasma glucose; F.I: fasting insulin; 25(OH)D: 25-hydroyvitamin D; PTH: parathyroid hormone; S.Ca: serum calcium; TG: triglyceride; HOMA-IR: homeostatic model assessment—insulin resistance; HOMA2-B%: homeostatic model assessment—beta cell function; HOMA2-S%: homeostatic model assessment-sensitivity; Sig.: significant

and control groups. When subjects with HOMA-IR ≤2.5 were excluded and data were reanalyzed, 25(OH)D results were also not significantly correlated with IR-related parameters in either the case or the control group as shown in Table 5.

DISCUSSION

In the present study, serum 25(OH)D had no relationship with insulin resistance (HOMA-IR) occasionally adjusting for PTH, Ca, and various variables either in all participants or after excluding participants with HOMA-IR ≤2.5. There is a modest and inverse association in the middle of serum 25(OH)D and IR, and multiple adjustment was widely reported by studies. Recently, the con-

Table 2. Correlation between 25(OH)D and various variables

	Control		Case	
Variables	r	p	r	p
Age (year)	−0.96	0.467	0.131	0.317
Weight (kg)	0.080	0.544	−0.106	0.421
Height (cm)	−0.047	0.720	0.236	0.069
BMI (kg/m^2)	0.199	0.127	−0.286	0.027 [Sig.]
PTH (pg/mL)	−0.216	0.098	−0.278	0.032 [Sig.]
S.Ca (mg/dL)	0.051	0.700	−0.002	0.991
FPG (mg/dL)	0.078	0.551	−0.015	0.911
F.I (mIU/mL)	−0.118	0.370	0.131	0.319
TG (mg/dL)	−0.014	0.917	−0.094	0.473
HOMA-IR	−0.122	0.393	0.134	0.306
HOMA2-B%	−0.101	0.441	0.081	0.540

BMI: body mass index; FPG: fasting plasma glucose; F.I: fasting insulin; PTH: parathyroid hormone; S.Ca: serum calcium; TG: triglyceride; HOMA-IR: homeostatic model assessment—insulin resistance; HOMA2-B%: homeostatic model assessment—beta cell function; Sig.: significant

Table 3. Correlation between PTH and various variables

	Control		Case	
Variables	r	p	r	p
Age (years)	0.192	0.143	0.022	0.869
Weight (kg)	0.227	0.081	0.180	0.168
Height (cm)	0.101	0.445	−0.009	0.945
BMI (kg/m^2)	0.111	0.398	0.189	0.149
25(OH)D (ng/mL)	−0.216	0.098	−0.278	0.032 [Sig.]
S.Ca (mg/dL)	−0.068	0.603	−0.137	0.298
FPG (mg/dL)	0.036	0.785	0.077	0.561
F.I (mIU/mL)	−0.049	0.709	−0.239	0.065
TG (mg/dL)	−0.122	0.355	−0.069	0.602
HOMA-IR	−0.037	0.779	−0.236	0.071
HOMA-B%	−0.141	0.282	−0.255	0.049 [Sig.]
HOMA-S%	0.247	0.057	0.060	0.647

BMI: body mass index; FPG: fasting plasma glucose; F.I: fasting insulin; S.Ca: serum calcium; TG: triglyceride; HOMA-IR: homeostatic model assessment—insulin resistance; HOMA-B%: homeostatic model assessment—beta cell function; HOMA-S%: homeostatic model assessment-sensitivity; 25(OH)D: 25-hydroyvitamin D; Sig.: significant

centration of 25(OH)D was approximately the same as indicated by the Framingham Offspring Cohort Study (mean=15 ng/mL) and many Chinese studies (n=3262) (20). The Framingham Cohort Study showed that the participants in the highest 25(OH)D tertile had a 12.7% lower HOMA-IR score (p-trend <0.001) than those in the lowest tertile category (7). In other words, other studies showed clearly that 25(OH)D had a relationship with HOMA-IR after adjusting for age, sex, current smoking, BMI, and WC (p<0.001). Meanwhile, a highly important regression coefficient for 25(OH)D as a predictor of HOMA-IR (p<0.01) followed after settlement for multivariables, having and containing BMI, in a study conducted on a Chinese population (8).

Table 4. Correlation between calcium and various variables

	Control		Case	
Variables	**r**	**p**	**r**	**p**
Age (years)	−0.214	0.100	0.123	0.349
Weight (kg)	0.072	0.585	0.056	0.673
Height (cm)	0.029	0.826	0.043	0.742
BMI (kg/m^2)	0.042	0.749	0.028	0.831
PTH (pg/mL)	−0.068	0.603	−0.137	0.298
25(OH)D (ng/mL)	0.051	0.700	−0.002	0.991
FPG (mg/dL)	0.348	0.006	−0.154	0.240
F.I (mIU/mL)	0.177	0.175	0.051	0.696
TG (mg/dL)	0.150	0.254	0.029	0.823
HOMA-IR	0.181	0.167	0.031	0.813
HOMA-B%	0.152	0.248	0.143	0.275
HOMA-S%	−0.342	0.008 [Sig.]	−0.113	0.390

BMI: body mass index; FPG: fasting plasma glucose; F.I: fasting insulin; TG: triglyceride; HOMA-IR: homeostatic model assessment—insulin resistance; HOMA-B%: homeostatic model assessment—beta cell function; HOMA-S%: homeostatic model assessment-sensitivity; 25(OH)D: 25-hydroyvitamin D; Sig.: significant

In this report, the reason behind the lack of an association between 25(OH)D and HOMA-IR is not clear and needs to be debated.

Various possibilities in vitamin D metabolism in our homogenous, ethnically distinct population in comparison with other cohorts previously recorded in the literature have explained the clear loss of influence of 25(OH)D on IR (HOMA-IR) in this study because 1,25-dihydroxyvitamin D3 mediates biological effects by vitamin D receptor binding including facilitating the biosynthetic capacity of B-cells.

A vital role in glucose metabolism has been detected to be attained by the PTH by bringing about insulin resistance (9, 10). The correlations of essential inverse were clear between PTH with fasting insulin (p=0.022) and HOMA-IR (p=0.023) after adjustment of 25(OH)D, serum Ca, and various variables and exclusion of participants in addition to HOMA-IR ≤2.5. The relationship of PTH to insulin resistance stems from data that patients with primary hyperparathyroidism were clear to be at a serious risk of death from coronary artery illness by 1.71-1.85 times which has to be into one's consideration as an additional evidence (11). This result shows that primary hyperparathyroidism has a relationship with insulin resistance (or decreased insulin sensitivity), as the concept between coronary artery illness and insulin resistance is well based (12). Therefore, our study is the same with these reports which depict the relationship between plasma PTH and insulin resistance.

It is common that mechanisms that clearly show the vital role of Ca in IR are also not fully elucidated. Increasing intracellular Ca concentration can affect the movement of glucose mediated by insulin and insulin secretion as it has been proposed by some studies (13, 14).

This study has some limitations. First, its small sample size may have an effect on the association. Second, only subjects who visited Gaziantep University Hospital were investigated, so we cannot generalize these study results to other adult populations. Third, our samples were collected in the winter season (from October 2016 to January 2017), where sunlight is another essential source of plasma 25(OH)D. We did not have an exact measurement of sunlight exposure. We did not provide help for IR

Table 5. Partial correlation coefficients between 25(OH)D and IR-related parameters adjusted for age, sex, BMI, smoking, alcoholic, PTH, and serum calcium

	Control				Case			
	All		HOMA-IR >2.5		All		HOMA-IR >2.5	
Variables	**r**	**p**	**r**	**p**	**r**	**p**	**r**	**p**
FPG (mg/dL)	0.007	0.958	0.007	0.981	−0.029	0.838	−0.047	0.820
F.I (mIU/mL)	−0.211	0.129	−0.360	0.226	−0.005	0.973	0.087	0.674
HOMA-IR	−0.206	0.138	−0.328	0.274	0.001	0.992	0.613	0.104

FPG: fasting plasma glucose; F.I: fasting insulin; HOMA-IR: homeostatic model assessment—insulin resistance; BMI: body mass index; PTH: parathyroid hormone

by hyperinsulinemic euglycemic clamp, a gold standard for the measurement of IR. However, HOMA-IR is highly correlated with the clamp technique.

CONCLUSION

We did not find a relationship between insulin resistance and vitamin D levels. Further studies are needed for clarifying the relationship between insulin resistance and vitamin D levels.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Gaziantep University of School of Medicine (Decision date: 08.15.2016, Decision no: 2016/238).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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