Relationship between Insulin Resistance "Leptin to Adiponectin Ratio" and Vitamin D in Patients with Type 2 Diabetes

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ABSTRACT

Introduction: Vitamin D deficiency has been known as a major problem in the world, and it possibly plays a role in pathogenesis and insulin resistance in type 2 diabetes. One of the indices of evaluation of insulin resistance is the ration of Leptin to Adiponectin. Leptin and Adiponectin are two of the important adipo-cytokines secreted from adipose tissue, which play a major endocrine role in the body. The aim of this study was finding the relationship between Leptin and Adiponectin ratio with serum level of vitamin D in patients with type 2 diabetes. **Materials and methods:** In this cross-sectional study, 40 patients with type 2 diabetes (20 men and 20 women) and vitamin D deficiency were selected randomly. Demographic and clinical characteristics including age, body mass index, fasting blood glucose, hemoglobin A1C, fat profile and serum Leptin levels and Adiponectin, and vitamin D were measured. Then, the relationship between vitamin D level and Leptin, Adiponectin and the ratio of Leptin to Adiponectin was evaluated. **Results:** This study showed that there was no statistically significant relationship between serum vitamin D level and Leptin and Adiponectin levels. Also, there was no significant relationship between HbA1c and vitamin D levels, Adiponectin and insulin resistance (Leptin / Adiponectin ratio) with cholesterol levels, but there was a significant relationship between Leptin levels with BMI. With increasing levels of Leptin, BMI also increased. There was also a significant relationship between vitamin D levels and fasting blood glucose levels. Finally, the results of this study showed a significant relationship between insulin resistance and body mass index, with insulin resistance increasing with BMI. **Conclusion:** In the present study, no significant relationship between serum level of vitamin D with Leptin and Adiponectin levels and ratio of Leptin to Adiponectin (insulin resistance) was observed. Also, there was no connection between patients' clinical parameters with vitamin D level, insulin resistance, Leptin and Adiponectin levels, but there was a relationship between vitamin D level with fasting blood sugar, insulin resistance with BMI and Leptin with BMI.

Key Words: *Vitamin D, Type 2 diabetes, Leptin, Adiponectin, Leptin to Adiponectin ratio.*

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INTRODUCTION

Diabetes Mellitus is a relatively common disease, and nearly 6% of the population of United States has been found to have some degree of glucose metabolism disorders [1]. In the last century, many studies have been done on Leptin and Adiponectin. Adiponectin have good potential to be used in the treatment of obesity, vascular and metabolic diseases, and other diseases. Also, predicting the risk of type 2 diabetes, using high concentration of Adiponectin, has made it possible to be used as a biomarker for the success of individual therapies

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and prevention of disease progression [2]. Today, much attention has been paid on the role of different Adipokines and their relation to various diseases, including inflammatory diseases, cardiovascular diseases and metabolic diseases, including diabetes [3]. A lot of research has been done on the relationship between Leptin / Adiponectin and insulin resistance, with different results [3]. Inoue et al. (2006) and Inoue et al. (2005) measured the ratio of Leptin to plasma Adiponectin for clinical evaluation of insulin resistance in metabolic diseases [4, 5], which was more sensitive than the basal concentration of each adipocytocaine Leptin or Adiponectin in healthy individuals [6]. In addition, Zaletel pointed out that adipocytokine ratio in assessing adult metabolic hemostasis, was more effective than other HOMA-IR, QUICKI insulin resistance indexes [7]. Recent convincing evidence of the role of vitamin D deficiency in the pathogenesis of insulin resistance and insulin secretion disorders with the potential for involvement in type 2 diabetes has been confirmed [8, 9]. The mechanism of this relationship has not been fully understood. Some cross-sectional studies have suggested that vitamin D deficiency can play a role in worsening insulin resistance [9]. In various studies, the direct effect of vitamin D has been observed in the deterioration of insulin resistance and secretion, which enhanced the risk of developing type 2 diabetes [9, 10]. Today, many observational studies have shown that there is a correlation between vitamin D levels in obese young people and glucose homeostasis, but they have not shown a significant correlation between 25-hydroxyvitamin D concentration and insulin resistance / insensitivity [9]. The LAR method (Leptin to Adiponectin Ratio) is an index for insulin resistance with sensitivity similar to that of HOMA-AD [11]. Both of these have had a good potential for predicting the risk of cardiovascular diseases in this population, which was due to the role of Leptin as an atherogenic indicator, and Adiponectin as an anti-anergic indicator was also realized [11]. The aim of this study was finding the relationship between Leptin and Adiponectin ratio with serum level of vitamin D in patients with type 2 diabetes.

MATERIALS AND METHODS:

The target population of type 2 diabetics was over 18 years of age and suffering from vitamin D deficiency, of which 40 were selected by simple random sampling. Demographic and clinical characteristics including age, body mass index, fasting blood glucose, hemoglobin A1C, and fat profile were measured. Serum levels of Leptin, Adiponectin and 25 hydroxyvitamin D were measured using ELISA kits. Finally, insulin resistance was obtained by dividing serum Leptin levels into Adiponectin in patients. Then, the relationship between vitamin D and Leptin ratios on Adiponectin and each of these adipocytocoins were investigated separately. Regarding the number of data, the Kolmogorov-Smirnov test was a large sample, Shapiro-Wilkes test was used to evaluate the normal variables. The distribution of the values of all variables other than vitamin D in patients was abnormal (P-value <0.05).

Based on the data distribution, Spearman test was used to examine the correlation between insulin resistance parameters and other paraclinical findings with vitamin D levels. There was a significant relationship between P-value <0.05. All the analyses were performed using SPSS software version 21. This study was approved by the Ethics Committee of the University, and the code was TBZMED.REC.1394.1200.

RESULTS:

The average age of patients participating in this test was 55.37 years, with a minimum age of 29 years and a maximum age of 78 years (table 1). In terms of body mass index, 23% of patients were normal, 47% overweight, 15% obesity class 1, 12% obesity class 2 and 3% morbid obesity. Sixty five percent of the patients had insufficient vitamin D levels. The rest of the patients suffered from vitamin D deficiency.

Demographic and paraclinical characteristics of type 2 diabetic patients have been shown in table 1.

Table 1- Demographic and paraclinical characteristics of diabetic patients

Age (years)	55.37 ± 10.59
BMI (kg /m^2)	28.9 ± 521
FBS (mg/dL)	146.025 ± 43.04
HbA1c (%)	7.21 ± 0.63
Triglycerides (mg/dL)	151.25 ± 79.06
Cholesterol (mg/dL)	158.45 ± 32.12
HDL (mg/dL)	49.55 ± 11.96
Leptin (ng/mL)	17.30 ± 10.48
Adiponectin (mg/L)	1.72 ± 1.63

The results of Spearman correlation test showed that there was no relationship between vitamin D level and blood cholesterol, BMI and hemoglobin A1c levels in type 2 diabetic patients. But the relationship between vitamin D levels and fasting blood glucose was significant and direct (Table 2). Spearman test showed that BMI had a direct and significant relationship with Leptin levels (Table 2), so that with increasing BMI, Leptin levels also increased, but there was no correlation between Leptin levels with blood cholesterol, fasting blood glucose and hemoglobin

A1c in type 2 diabetic patients. According to the results of Spearman correlation test, there was no statistically significant relationship between Adiponectin level and blood cholesterol, BMI, fasting blood glucose and hemoglobin A1c in type II diabetic patients. Spearman correlation test showed that there was no statistically significant relationship between insulin resistance (level of Leptin to Adiponectin) and blood cholesterol, fasting blood glucose and hemoglobin A1c in type 2 diabetic patients, but with increasing body mass index, an increasing trend in resistance level Insulin was found to be statistically significant.

Table 2- Spearman correlation between Vit. D, Leptin and LAR with BMI and FBS

Parameters	Vit. D	Leptin	LAR
BMI	-	0.516 P value =0.001	0.428 P value = 0.006
FBS	0.337 P value = 0.0034	-	-

DISCUSSION:

The results of this study showed no significant relationship between vitamin D level and insulin resistance. Considering that all of the patients suffered from vitamin D deficiency, and serum vitamin D levels were below 30 ng / ml, and as there was no control group in this study, it was not possible to achieve a comparative result compared to the patients without vitamin D deficiency. Banerjee et al., studying 77 patients with type 2 diabetes and 73 pre-diabetic patients and 52 healthy controls (control group), showed that those who had a 25 (OH) D level of less than 10 ng / ml had more insulin resistance. In this study, there was a reverse relationship between the levels of 25 (OH) D and insulin in diabetic and pre-diabetic patients. The results of the study found that vitamin D deficiency was associated with the increased insulin resistance and poor control of blood glucose and systemic inflammation [12]. In the study, serum Adiponectin level was significantly lower in diabetic and pre-diabetic subjects compared to the controls. Adiponectin has been thought to play a key role in insulin circulation and metabolism. Research results have shown that Adiponectin had anti-diabetic, anti-atherogenic, and anti-inflammatory effects [13], although its exact role in the development of diabetes remained uncertain. It has also been observed that low levels of 25 (OH) D and Adiponectin were associated with an increased risk of obesity and insulin resistance [14]. Recent studies have shown that direct relationship between levels of 25 (OH) D and Adiponectin levels varied in different BMIs, and increased with an increase in BMI [15, 16]. In this study, there was a significant linear relationship between Adiponectin level and 25 (OH) D level and serum, Adiponectin reduction had a linear inverse relationship with serum insulin and insulin resistance by HOMA-IR method in diabetic and pre-diabetic patients [16]. Although in the current study, there was no significant or linear relationship between vitamin D and Adiponectin levels. Several researches have shown that people who are obese tend to have lower levels of 25 (OH) D than their normal population. According to a study, deficiency of 25 (OH) D was seen in 85% of obese people [17]. In the general population, this figure was 30% to 50% [18]. In a study by Al Masri et al. (2017) on 158 adults with an average BMI of 35.15, the percentage of people with 25 (OH) D deficiencies was 47%. This percentage difference could be due to the latitude of the place of residence and the different range of obesity. In this study, 25 (OH) D levels in obese non-insulin-resistance individuals were similar to insulin-resistance obese people [19]. In a study by Heshmat et al., (2011), it was shown that plasma levels of 25 (OH) D in healthy obese were higher than insulin-resistant obese people [20]. This study showed that there was no relationship between vitamin D level and insulin resistance in subjects with moderate obesity [20]. As in the present study, there was no relationship between insulin resistance and vitamin D levels. A study by Mathieu et al. (2015) indicated that vitamin D deficiency was a potential risk factor for type II diabetes mellitus, which was consistent with the results of the current studies [21]. Several mechanisms for linking vitamin D and type 2 diabetes have been arranged, and these mechanisms were related to diabetes in three ways: the effect of vitamin D on insulin secretion, the resistance of peripheral tissues to insulin and inflammation, and vitamin D to diabetes [22]. Vitamin D modified the function of renin-angioneunin system by reducing the renin gene expression and inhibiting angiotensin receptors. Increasing the activity of this system contributed to insulin resistance, inflammation, and blood pressure. The proposed mechanism was that vitamin D deficiency was associated with an increase in parathyroid hormone, which was associated with increased lipogenesis, obesity, and insulin resistance [23].

CONCLUSION:

The results of this study showed that there was no significant correlation between insulin resistance, Leptin and Adiponectin levels in vitamin D deficiency and type 2 diabetic patients. Also, there was no significant relationship between insulin resistance and laboratory parameters. However, there was a significant correlation with body mass index. On the other hand, there was no significant correlation between the level of vitamin D and

laboratory parameters and BMI except for fasting blood glucose. In this study, there was a significant direct relationship between Leptin and BMI.

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Compliance with ethical standards

Conflict of interest

All authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

Ethical approval

The study protocol was approved by the Ethics Committee of Tabriz University of Medical Sciences, Tabriz, Iran. The current study was performed according to the Institutional Committee for the Protection of Human Subjects, which was adopted by the 18th World Medical Assembly, Helsinki, Finland and its later amendments.

Informed consent

Written informed consents were obtained from the patients and controls.

Abbreviations:

BMI: Body Mass Index
HOMA-IR: Homeostatic Model Assessment of Insulin Resistance
HEGC: Hyperinsulinemic Euglycemic Glucose Clamping
IR: Insulin Resistance
LAR: Leptin to Adiponectin ratio
QUICKI: Quantitative Insulin Sensitivity Check Index

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