EVALUATION OF LEPTIN LEVEL AND VITAMIN D RELATIONSHIP IN OBESE PATIENTS

Obez Hastalarda Leptin Düzeyinin ve D Vitamini İlişkisinin Değerlendirilmesi

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ÖZET

Amaç: Adiposit kaynaklı hormon olarak bilinen Leptin, beslenme ve enerji homeostazinda önemli rol oynamaktadır. Leptin, reseptörleri aracılığıyla merkezi veya periferik kompleks biyolojik etkileri düzenler. Obezite ve ilişkili Leptin direncini bağlayan mekanizmalar büyük ölçüde belirsizliğini korumaktadır. Ayrıca vitamin D'nin kalsemik olmayan etkileri, glikoz metabolizmasının hormonal regülasyonu ve adipokinlerin yağ dokusu ile sentezi üzerinde perspektif rol oynar. Çalışmamızın amacı, vitamin D düzeylerinin obezite üzerindeki rolünü ve obez hastalarda D vitamini farklılaşması sırasındaki Leptin düzeylerinin aktivitesini göstermektir.

Gereç ve Yöntemler: Vitamin D düzeylerini analiz etmek için 40 obez ve sağlıklı hasta bu çalışmaya dâhil edildi. Düşük vitamin D düzeyi görülen bireylerde, 4 hafta vitamin D tedavisi uygulandı. Leptin ölçümü için tüm deney gruplarından kan alındı.

Bulgular: D vitamini düzeyi düşük olan hasta grubunda, Leptin ekspresyonunun azaldığı görülürken; D vitamini takviyesi sırasında, obez hastalarda Leptin seviyeleri anlamli duzeyde artmıştır. Bu, Leptinin, vitamin D düzeyi ile doğrudan ilişkisi olan obeziteyi tespit etmek için önemli bir belirleyici olduğu anlamına gelir.

Sonuç: Bu sonuçlar serum vitamin D seviyelerinin arttırılmasının Leptin duyarlılığında iyileşme sağladığını göstermektedir. Gelecekteki klinik denemeler test edilmelidir. Vitamin D değişikliği, Leptin salgılanmasına bağlı obezite için tanısal bir faktör olabilir.

Anahtar Kelimeler: *Beden Kitle Indeksi; Leptin Ekspresyonu; Obezite; Vitamin D*

ABSTRACT

Objective: Adipocyte-induced hormone Leptin, nutrition and energy play an important role in homeostasis. Leptin regulates central or peripheral complex biological effects through its receptors. The mechanisms linking obesity and associated Leptin resistance remain largely unclear. Also noncalcaemic effects of vitamin D, perspective role is played on hormonal regulation of glucose metabolism and synthesis of adipokines by fat tissue. The aim of our study is to show the role of vitamin D levels on obesity and the activity of Leptin levels during vitamin D differentiation on obese patients.

Material and Methods: Fourty obese and healthy patients were included this research to analyze vitamin D levels. While seen low-vitamin D level in individuals, 4 weeks vitamin D treatment has been completed. Whole experimental groups were taken blood for Leptin measurement.

Results: Our findings were indicated that Leptin expression was decreased when vitamin D level in low. However, during vitamin D uptake, Leptin levels in obese patients were increased correlated to deficiency. That means, Leptin is known significant marker to detect obesity which has direct relation with vitamin D level.

Conclusion: These results highlight that reduction serum vitamin D levels leads to improved Leptin sensitivity. Future clinical trials should be tested vitamin D alteration might be diagnostic factor for obesity treatment to Leptin secretion.

Keywords: *Body Mass Index; Leptin Expression; Obesity; Vitamin D Level*

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INTRODUCTION

Obesity, a complex and multifactorial disease that negatively affects health, is the second most important cause of preventable deaths after smoking which is described by the World Health Organization as 'excessive fat accumulation to risk health'. Obesity is defined as an excess body weight for the body in a way that is simply defined, but this simple definition is not only related to body size, but also associated with an etiologically complex phenotype associated with excess fat or body fat that can manifest metabolically. According to research data of health ministry, obesity rate was report 23.9 % in women, 15.2 % in men and 19.6 % as an average value in Turkey. We are facing each day with this increasing problem and fat tissue rising adversily threat health. If the process continues as it is now, by 2030, about 38 % of the adult population in the world will be overweight and another 20 % will be obese (1). Obesity chronic disease (disability, depression, type 2 diabetes, cardiovascular disease, certain cancers) greatly increases the risk of morbidity (2). Fat tissue involved in many metabolic events is not just a storage organ but an endocrine organ that can secrete more than 250 different peptides/proteins (3). Zhang et al. has been first described Leptin as a hormone in the 16 kDa molecular weight released from adipocytes and in the protein structure that regulates the energy balance in the body from 167 amino acids. (4). Later, it was understood that Leptin was released as a stimulant factor from adipocytes and interacted with the hypothalamus, which is an antiobesity factor that regulates many metabolic processes including central nervous system immunity, endocrine system and energy balance in reproductive system (5). Leptin is structurally similar to cytokine family interleukin 6 (IL-6), interleukin 12 (IL-12), interleukin 15 (IL-15), prolactin, granulocyte colony regulating factor and growth hormone (6). The blood-brain barrier passes through a saturable transport system. Serum levels range from 1-10 ng/ml. Leptin has peripheral and central effects after expression. It stimulates the hypothalamus with central effect and regulates the release of the hypothalamus-pituitary-adrenal axis (HPA) hormones, bone growth, appetite and autonomic nervous system exits. Peripherally, it accelerates basal metabolism, affects the differentiation of reproductive functions, hematopoiesis, pancreatic-β cell functions and insulin secretion, thymic generation of T-cells and helper T cells (TH1) in lymph nodes and pro-angiogenic effect for endothelial cells (7).

Leptin secretion is directly related to adipose tissue mass and nutritional status. The levels are positively correlated with the best body mass index and body fat ratio. Leptin levels in women are higher than in men. Leptin release has diurnal rhythm and is lowest in the morning when peaking at night (8). As the lipid deposits in the body increase, Leptin secretion in the adipocytes increases accordingly. In cases where the fat deposits are diminished, Leptin is stored in the vesicles in a manner that is ready to release as an acute response (9). The reason for the higher level of Leptin secreted in obese patients compared to healthies is due to not invasion the blood brain barrier or to resistance of Leptin receptors (10).

Obesity is also associated with vitamin D deficiency (11). Vitamin D is a steroid-based prohormone produced mainly by the action of ultraviolet light from 7-dehydrocholesterol in human skin. Vitamin D deficiency is recognized as a global problem. In our country, it has been determined that the deficiencies and insufficiency are high. Among the causes of deficiency; inadequate sunlight exposure, nutritional deficiency, diseases preventing absorption, drugs, liver and kidney diseases, metabolic deficiencies (12).

In some observational studies have been shown that the relationship between low serum 25(OH) D levels and obesity, diabetes mellitus and metabolic syndrome. There is strong evidence that active vitamin D modulates intracellular ionized calcium signaling in adipocytes, inhibits uncoupling protein-2 (UCP-2) protein, reduces lipolysis and increases lipogenesis. It is thought that excess body fat preserves the metabolites of vitamin D and that cholecalciferol produced by the skin or taken through the diet is partially retained by body fat before it is transported to the liver for the first hydroxylation (13). Most data demonstrating the relationship between vitamin D and obesity are observational. On the other hand, some experimental data showed that vitamin D deficiency might support increased adipocytosis by promoting increased parathyroid hormone levels and increased calcium flow to adipocytes, thus suggesting increased

increased lipogenesis (14, 15). For this reason, our study is aimed to determine the relationship between vitamin D and obesity referring to the connection between Leptin levels put forward more concrete of future alternative treatments for obesity.

MATERIAL and METHODS

The study was conducted in 40 obese and healthy patients, 20 females and 20 males, ranging in age from 18 to 65 years. Ethics committee approval and patient informed consent were obtained from Duzce University Medical Faculty Clinical Research Ethics Committee (2017/90). Patients were separated groups according to BMI> over 30 as obese, BMI <25 below as normal group for evaluation.

Blood samples were collected and vitamin D were analyzed in the same time interval. Then re-arrange experimental groups with low and normal vitamin D levels. Samples were centrifuged at 3000 rpm for 15 minutes at 4 C were separated for colorimetric measurements.

In the second phase of the study, patients with lower levels of vitamin D were grouped and vitamin D supplementation was performed for 4 weeks. After this treatment, which was applied to patients in synchronized time, vitamin D and Leptin levels were measured again. Serum samples were analyzed with commercial Enzyme Linked Immunosorbent Assay kit (Sunred, 201-12-1560). Designated test groups normal-obese patients and lowest vitamin D- normal vitamin D parameters were interpreted by comparing changes of Leptin levels.

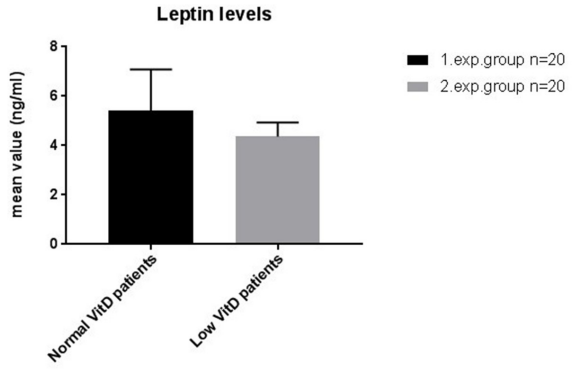

Figure 1. The comparison of average Leptin levels with groups of low and normal D vitamin levels

Statistical analysis

Continuous variables of basic characteristics and comparison data are given as mean and plus minus standard deviations and compared with one way annova test at 95 % confidence interval. p value was accepted as significant difference below 0.05. Groups with vitamin D deficiency were compared with pair sample t test in terms of Leptin levels before and after treatment. The nominal values were compared with the cross table chi square test.

RESULTS

The correlation between Leptin, vitamin D level was performed by Pearson correlation test. Pearson correlation index values above 0.5 were considered as significant positive correlations, and -0.5 were considered as index negative negative relationships.

Changes in the expression level of Leptin protein in patients with normal and low vitamin D levels were shown in Figure 1. Considering with Table 1, Leptin level was seen 5.42 ± 1.66 ng/mL with normal vitamin D individuals although 4.36 ± 0.57 ng/mL in low vitamin D patients.

There was a moderate correlation between the increase in vitamin D levels and the increase in Leptin levels in patients with vitamin D deficiency (pearson correlation index 0.497) (Table 2, Figure 2).

In addition, vitamin D treatment showed a significant increase in Leptin levels compared to before treatment. (p <0.001) (Figure 3).

Thus, Leptin levels are significantly increased with vitamin D treatment in individuals with low vitamin D.

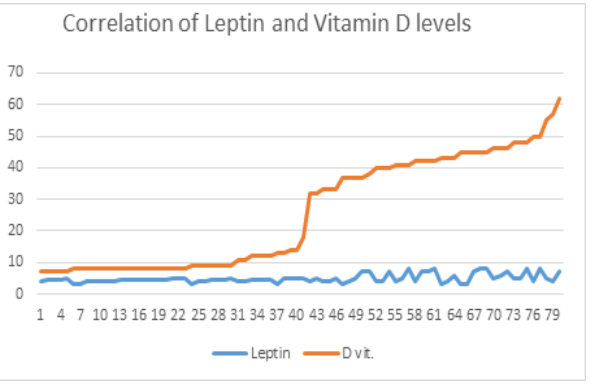

Figure 2. The comparison of Leptin levels and D vitamin

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Tablo 1. The comparison of Leptin levels at the persons with Low and normal D vitamins

	Normal vitamin D (n:20)	Low vitamin D (n:20)	p
Leptin levels	5.42 ± 1.66	4.36 ± 0.57	<0.001

*They were analyzed by One Way ANNOVA test

Tablo 2. Leptin Levels changes with D vit therapy in the patients with low D vitamin

Leptin Levels Before Therapy	Leptin Levels After Therapy	Paired Sample Test	Paired Sample correlation
4.37 ± 0.57	9.85 ± 3.50	P<0.001	0.497

DISCUSSION

Leptin expression is not only exerted by adipose tissue, but also by other tissues and organs, and has pleiotropic effects on a wide variety of cell types, such as other cytokines. The previous researches aim of investigating effects of Leptin deficiency was investigated in blood samples taken from mice and obese people. Leptin levels are found higher in obese people, caused a concept called Leptin resistance. Although obesity in the mouse Leptin receptor gene mutation cannot be detected in humans, obese people also have Leptin resistance. It is unclear whether is currently playing a role in the development of obesity (16). Thus obesity observed in humans does not originate solely from the absence of Leptin. Another reason why Leptin is not effective in obesity is resistance to itself. In order to overcome Leptin resistance, a higher level of Leptin is required, which leads to more Leptin release than fat tissue, more Leptin release leads to an increase in fat tissue that produces more (17).

There is a positive correlation between Leptin level and body mass index (BMI) in obese women and men, but not in normal weight. Although serum Leptin levels are three times higher in obese mice, Leptin transport is three times lower than normal. This result indicates that Leptin resistance is responsible for 100% of the transport disorder in BBB (18). Obesity, defined as BMI> 30 kg / m2, is reported to be associated with low vitamin D levels in some studies. Findings from human and animal studies have revealed that the main cause of obesity is caused by disorders of transport of serum Leptin from BBB (19).

Leptin is a hormone that is effective on the whole body by acting not only an anti-obesity factor that controls body weight and feeding through the central system, but also plays a critical role in the regulation of osteogenesis, hematopoiesis, angiogenesis and glucose balance, immunity and gastrointestinal system. It has been understood that stimulant factors such as Leptin, adiponectin, omentin, TNF-α and interleukin-6, which are secreted from adipose tissue, play important roles in various metabolic processes (20). Adipokines, especially Leptin, adiponectin and omentin, which increase insulin sensitivity and regulate energy balance, are suggested to be used alone or in combination with other medicines for the treatment of obesity, diabetes. Identification of the mechanisms of action of Leptin and other such signaling molecules is also important for diagnosis and treatment of multifunctional diseases.

On the other hand, previous researches indicate that low vitamin D levels lead to obesity is a stronger perspective. Most studies investigating the relationship between vitamin D and obesity are cross-sectional. Lipogenesis has been shown to suppress lipogenesis in cases where the passage of Ca to the fat cell increases. In the study by Shi et al. was emphasized that with the nongenomic effect of vitamin D receptor-mediated 1.25(OH)2D3 administration, the dose of Ca was significantly increased in dose-dependent fat tissue and this effect played a role in obesity (21).

In a study of obese children, a 5 ng/ml increase in serum 25 (OH) D3 was shown to be associated with a 1 kg/m2 reduction in BMI. On the other hand, there are also reports that a 1 kg/m2 decrease in BMI is accompanied by a decrease in 25 (OH) D3 levels (22). Vitamin D deficiency, which is a public health problem, is a condition in which serum 25-hydroxyvitamin D [25 (OH) D] is less than 20 ng / mL (50 nmol / L) and is common in the presence of obesity, especially in young people (23). A hypothesis, dietary or skin-synthesized vitamin D is a potential mechanism to limit the cutaneous vitamin D synthesis by reducing bioavailability, reducing or accumulating in large body fat sections, and decreasing exposure to sun UV radiation and decreasing out-door activity (24).

Vitamin D deficiency, insulin resistance (IR), Leptin and adiponectin can potentially contribute to obesity-related complications with potential interactions

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between cytokines. Several studies on adolescent vitamin D status and IR have shown lower concentrations of circulating Leptin and adiponectin in black adolescents or in sun-rich climates (25).

In a study of thirty patients aged 60 years and older with type 2 diabetes mellitus and diabetic foot complication, 14 patients received vitamin D3 and 16 patients received placebo treatment. Some parameters such as Leptin were measured. Vitamin D3 supplementation was found to significantly increase serum Leptin levels (26).

In another study, 47 randomized, placebo-controlled diabetic patients were divided into two groups: Group 1 received daily oral support with vitamin D at a daily dose of 1000 U / day for 12 months. Group 2 was given placebo capsules. Blood levels of Leptin and a group of parameters were measured. After 12 months, Leptin did not change in both groups during treatment period in patients receiving vitamin D (27).

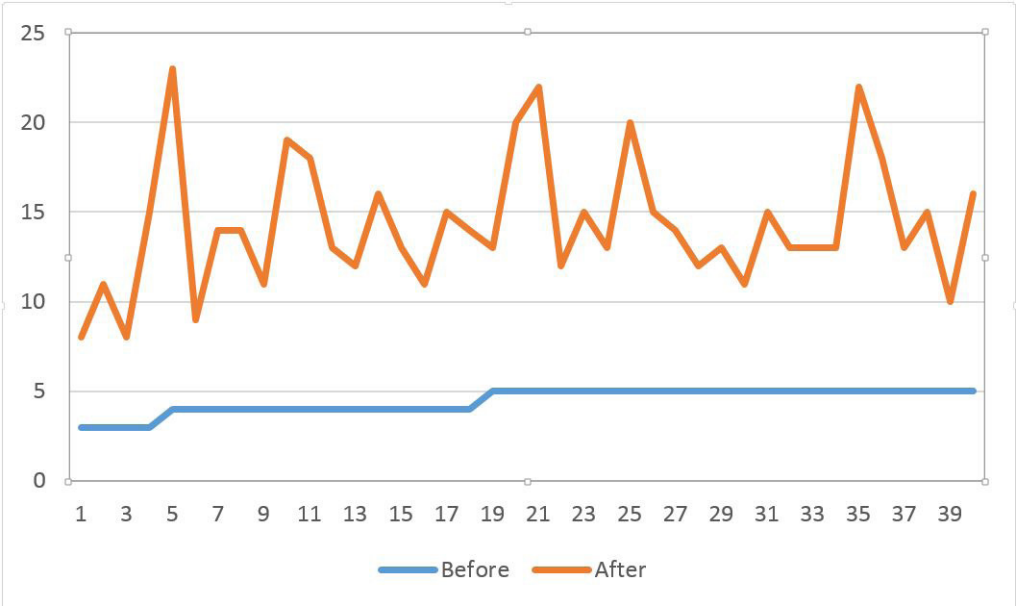
In our study, we have a total of 40 obese people with low and normal levels of vitamin D. Our datas showed that Leptin levels were significantly lower in obese patients than normal vitamin D individuals (indicated in Table. 1, Figure: 1 and Figure 2). We also found that serum Leptin levels were increased significantly when vitamin D supplementation was low in individuals with vitamin D uptake (Table 2). Our findings are consistent with previous studies.

An increase in adiposity, dyslipidemia and decreased insulin secretion together with vitamin D deficiency suggest that deficiency is a potential cause of obesity, but it is an optimistic idea to prevent obesity by increasing vitamin D levels.

SONUÇ

Epidemiological data were reviewed with vitamin D deficiency or insufficiency, there was found that is an inverse relationship between 25 (OH) D3 levels and all elements of metabolic syndrome in human. This requires for prospective randomized controlled studies investigating the cause-effect relationship between vitamin D and obesity, whether vitamin D deficiency causes obesity or lack of vitamin metabolism due to obesity development process. Determination of relationship vitamin D and Leptin levels which is an important role in obesity patients will lead to alternative and effective method of vitamin D supplementation instead of traditional ways on obesity treatments.

Figure 3. Serum Leptin levels after vitamin D treatment in experimental group of low vitamin D



Alteration of Leptin levels after vitamin D therapy in low level Vitamin D patients

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