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Effect of Vitamin D Deficiency on the Frequency of Lipohypertrophy Occurrence in Patients with Type 2 Diabetes Mellitus Under Injectable Treatment

D Vitamini Eksikliğinin Enjeksiyon Tedavisi Alan Tip 2 Diabetes Mellitus Hastalarında Lipohipertrofi Sıklığına Etkisi

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Abstract

Objective: Lipohypertrophy (LH) is one of the most common treatment-related cutaneous complications of injectable therapies. Although the etiology of LH cannot be clarified, it may be due to the lipogenic effect of insulin or recurrent tissue trauma caused by injections. In this respect, we aimed to evaluate the relationship between vitamin D level and LH. **Material and Methods:** Patients with Type 2 diabetes mellitus aged 18 years or older, who were under insulin and/or exenatide treatment for at least one year were included in this study. The injection sites of the patients were examined by inspection and palpation method. Patients were categorized into two groups according to vitamin D levels as below and above 20 ng/mL. **Results:** A total of 140 patients, including 91 women and 49 men, aged between 20-78 years with a mean age of 54.53±13.89 were included in the study. LH was detected in 91 (65%) of 140 patients. This study demonstrated that there was a significant relationship between gender and LH. Statistically, the frequency of LH was higher in female patients (p=0.001). Further, a relationship between vitamin D levels and LH was also observed (p=0.006). **Conclusion:** Besides calcium metabolism, the effects of vitamin D on lipogenesis are also known. Vitamin D inhibits the differentiation of pre-adipocytes to mature adipocytes. This is the first study showing the relationship between vitamin D and LH in our knowledge.

Keywords: Diabetes mellitus; exenatide; insulin treatment; lipohypertrophy; vitamin D

Özet

Amaç: Lipohipertrofi (LH), enjekte edilebilir tedavilerin, tedaviyle ilişkili en yaygın kutanöz komplikasyonlarından biridir. LH'nin etiyolojisi tam olarak açıklanamasa da, insülinin lipojenik etkisinden veya enjeksiyonun neden olduğu tekrarlayan doku travmasından kaynaklandığı düşünülmektedir. Bu bağlamda D vitamini ve LH arasındaki ilişkiyi değerlendirmeyi amaçladık. **Gereç ve Yöntemler:** En az 1 yıl boyunca insülin ve/veya eksenatid tedavisi kullanan 18 yaş ve üzeri Tip 2 diabetes mellitus tanılı hastalar çalışmaya dâhil edildi. Hastaların enjeksiyon bölgeleri inspeksiyon ve palpasyon yöntemi ile incelendi. Hastalar, D vitamini seviyelerine göre 20 ng/mL'nin altında ve üstünde olmak üzere iki gruba ayrıldı. **Bulgular:** Yaş ortalaması 54.53±13.89 yıl olan 20-78 yaşları arasında 91'i kadın, 49'u erkek toplam 140 hasta çalışmaya dâhil edildi. 140 hastanın 91 (%65)'inde LH saptandı. Bu çalışma, cinsiyet ile LH arasında anlamlı bir ilişki olduğunu göstermekteydi. İstatistiksel olarak kadınlarda LH sıklığının daha fazla olduğu görüldü (p=0.001). D vitamini düzeyleri ile LH arasında da anlamlı bir ilişki vardı (p=0.006). **Sonuç:** Kalsiyum metabolizması üzerindeki etkilerine ek olarak, D vitamininin lipogenez üzerindeki etkileri de bilinmektedir. D vitamini, preadipositlerin olgun adipositlere farklılaşmasını inhibe eder. Bu makale, bilgimiz dâhilinde D vitamini ile LH arasındaki ilişkiyi gösteren ilk çalışmadır.

Anahtar kelimeler: Diabetes mellitus; eksenatid; insülin tedavisi; lipohipertrofi; D vitamini

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Introduction

The occurrence of diabetes mellitus (DM) is increasing worldwide, and the number of patients diagnosed with DM is expected to reach 642 million in 2040 (1). Thirty-five percent of these patients use insulin therapy (2), causing an increase in the cost of both treatment and treatment-related complications. One of the most common cutaneous complications due to incorrect insulin use is lipohypertrophy (LH), and daily insulin requirement is higher in patients with LH than in patients without LH. According to a study by Blanco et al. the increased requirement of insulin due to LH in the Spanish healthcare system was estimated to cost € 122 million per year (3). Besides the treatment cost, the frequency of hypoglycemia is six-times higher, and the glycemic fluctuations are seven-times higher in patients with LH (3). Although the etiology of LH has not yet been clarified, it is thought to be due to the lipogenic effect of insulin or recurrent tissue trauma caused by injections (4). According to the examination method and the examiner, in various studies conducted globally, the frequency of LH was found to be quite variable, between 1.9% and 77% (5). The most significant cause of LH development was found to be insufficient rotation between injection sites (3). In addition, the frequency of injections, the total daily dose of insulin, and the needle length were also found to be associated with LH (6). Further, the fact that there is a large difference in the frequency of LH between these studies and the presence of LH in other subcutaneous treatments other than insulin such as pegvisomant, long-acting exenatide and anti-tumor necrosis factor, suggest that this complication is not related to recurrent trauma only (7). In this respect, we aimed to evaluate the relationship between vitamin D, which is known to play a role in lipogenic effect, and LH.

Material and Methods

Patients who applied at our outpatient clinic between May-August 2019 for routine tests, who had been using insulin and/or exenatide treatment for at least one year, were included in the study. All patients were older than 18 years. The exclusion criteria were evidence of dermatitis and cutaneous disease. The patients were classified according to the body mass index (BMI) classification of the World Health Organization, as, 18.5-24.9 kg/m^2, normal; 25-29.9 kg/m^2, overweight; 30-39.9 kg/m^2, obese; and ≥40 kg/m^2, morbidly obese. The injection sites of the patients were examined by inspection and palpation method, and the LH regions were recorded by the education nurse working in our clinic. Patient data of HbA1c and vitamin D levels determined for routine tests were acquired from the hospital system. Vitamin D analyses were made with liquid chromatography-mass spectrometry API 3200 (ABSCIEX, USA), while HbA1c was measured by glycohemoglobin analyzer (G7 HPLC Analyzer, Tosoh Bioscience, USA). Patients were categorized into two groups according to vitamin D levels as below and above 20 ng/mL. Our study was carried out after the approval of the Ethics Committee of Selçuk University Faculty of Medicine dated 17.04.2019 and numbered 2019/04. Written informed consent was obtained from each patient.

All statistical analyses of the study were performed in SPSS (version 21.0 for Windows) program. The variables were investigated using visual (histograms and probability plots) and Kolmogorov-Smirnov test to determine whether or not they are normally distributed. The categorical variables were expressed as numbers and percentages, whereas continuous variables were summarized as mean with standard deviation, median, and minimum-maximum, wherever appropriate. While investigating, the associations between non-normally distributed variables and their significance were calculated using Spearman's test or Kruskal-Wallis test. A p-value of <0.05 was considered statistically significant.

Results

A total of 140 patients, including 91 women (65%) and 49 men (35%), aged between 20 and 78 years (mean age of 54.53±13.89), were included in the study. Thirteen (9.3%) patients had normal BMI [mean BMI=21.94 (interquartile range; IQR=19.65-24.25)] while 40 (28.6%) patients were overweight [mean BMI=27.6 (IQR=26.4-28.84)], 65 (46.4%) patients were obese [mean value of BMI: 33.97

(IQR 31.6-36.13)] and 22 (15.7%) patients were morbidly obese [mean value of BMI=41.68 (IQR=40.02-44.08)]. When the treatments of the patients were evaluated, 93 (66.4%) patients were receiving insulin, 28 (20%) patients were receiving exenatide twice daily, and 19 (13.6%) patients were receiving insulin+exenatide twice daily. LH was detected in 91 of 140 patients (65%).

While mean HbA1c levels of the patients with LH were 9.43±2.97, the mean HbA1c levels of the patients without LH were 8.42±1.85. Vitamin D levels of 96 (68.5%) patients were less than 20 ng/mL and 44 (31.4%) patients were 20 ng/mL and above. Spearmen's correlation analysis demonstrated a significant negative correlation between levels of vitamin D and the presence of LH (Spearmen's ρ=|-0.2|, p=0.006) (Table 1). Kruskal-Wallis test showed no significant relationship between LH and BMI (p=0.057) (Table 1). This study indicated the absence of significant correlations between types of injectable treatments and the presence of LH (Spearmen's ρ=0.17, p=0.296) (Table 1). There was no correlation between LH and HbA1c levels, and the age of the patients (Spearmen's ρ=|-0.11|, p=0.18, and ρ=0.13, p=0.11, respectively). We also observed a significant relationship between gender and LH. Statistically, the frequency of LH was higher in female patients (Spearmen's ρ=|-0.34|, p=0.001) (Table 1).

Discussion

Vitamin D is one of the primary hormones that play a role in calcium, phosphorus hemostasis, and bone metabolism. Due to the low vitamin D content of foods, the main source of vitamin D endogenous synthesis is through the ultraviolet B rays from cholesterol in the skin (8). Although different vitamin D ranges are used in different studies, generally accepted normal vitamin D levels have been determined as 20-50 ng/mL in a healthy population (9).

In addition to affecting the bone metabolism, vitamin D plays a role in the etiology and progression of many different diseases such as cardiovascular diseases, autoimmune diseases, and malignancies (10-12). In addition to these effects, the effects of vitamin D on lipogenesis are known. In a study performed by Borges et al. on obese mice, vitamin D deficiency was found to increase lipogenesis in the liver, reduce beta-oxidation, and increase the risk of fatty liver disease (13). Vitamin D inhibits differentiation of pre-adipocytes to mature adipocytes by inhibiting characteristic mature adipocyte genes such as peroxisome proliferator-activated receptor-γ, and

Table 1. Relationship between LH and gender, BMI, vitamin D, and the patient's treatment.

	Lipohypertrophy		
	Present	**Absent**	**p**
Gender			
Male	21	28	0.001
Female	70	21	
Body mass index (kg/m²)			
Normal	12	1	0.057
Over-weight	21	19	
Obese	42	23	
Morbid obese	16	6	
Vitamin D (ng/mL)			
<20	55	41	0.006
≥20	36	8	
Patient's treatment			
Insulin	57	36	0.296
Exenatide	22	6	
Insulin+exenatide	12	7	

sterol regulatory element-binding protein-1c (14). Vitamin D has also been shown to be protective against obesity due to its negative effect on adipocytes by increasing dinucleotide concentration and Sirtulin 1 activity to nicotinamide adenine (15). LH is the adipose tissue that appears as a tumor-like swelling at subcutaneous injection sites. Histopathologically, it is seen that the dermal reticular layer consists of mature adipocytes of volume larger than that of normal adipocytes. Some lipid droplets may occur in the periphery of some of the adipocytes in LH tissue, possibly due to the stimulation of lipogenesis (16). This study was planned based on the above-mentioned effects of vitamin D on lipogenesis, and on assessing the relationship between LH and vitamin D, the frequency of LH was found to increase significantly in patients with low vitamin D levels (p=0.006). There are conflicting results on the effects of the replacement of vitamin D on levels of HbA1c and fasting blood glucose in DM patients (17). However, studies showing the positive effects of vitamin D replacement on glycemic control in Type 1 DM patients who were treated with insulin alone (18,19) suggest that this effect of vitamin D may improve LH and exert positive effects on glucose metabolism.

Although the incidence of LH in our country varied in previous studies, the LH rate was 27.4% in a study published in 2018 with 29 different centers, whereas this rate was 48.8% in another study with 215 patients (20,21). In our study, the incidence of LH was found to be 65%. This difference may be due to the low number of patients included in our study; it also indicates that we need more efforts on insulin treatment education in our center.

While no relationship was observed between gender and LH in previous studies, LH was more common in women in our study (3). Contrary to the studies reporting that increased BMI increases the risk of LH, we observed no statistically significant relationship between BMI and LH in our study (6). These conflicting results maybe because of the sample size of our study.

There are some limitations to our study. We focused only on the relationship between vitamin D and LH. The other factors which could affect LH, for example, rotation of the injection site, injection regimen, needle syringe length, etc., needs to be evaluated in this study. Another limitation was, as indicated earlier, the sample size. As the third limitation of the study, we evaluated LH by the inspection and palpation methods. Evaluating the presence of LH by radiological methods would provide more sensitive and specific results.

Conclusion

To our knowledge, this is the first study showing the relationship between vitamin D and LH. Further randomized controlled trials are needed to clarify this relationship. LH is a significant issue that cannot be underestimated considering its negative effects on the frequency of hypoglycemia, quality of life of the patients, glycemic control, and cost of treatment.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Cem Onur Kıraç, Cuma Gönüllü; Design: Cem Onur Kıraç, Cuma Gönüllü, Süleyman Baldane; Control/Supervision: Süleyman Baldane, Levent Kebapçılar; Data Collection and/or Processing: Cem Onur Kıraç, Cuma Gönüllü; Analysis and/or Interpretation: Levent Kebapçılar; Literature Review: Cem Onur Kıraç; Writing the Article: Cem Onur Kıraç, Süleyman Baldane; Critical Review: Süleyman Baldane, Levent Kebapçılar; References and Fundings: Cem Onur Kıraç, Cuma Gönüllü, Süleyman Baldane.

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