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Research Article

Investigation the impact of liraglutide on the thyroid function tests

Liraglutidin tiroid fonksiyon testleri üzerine etkisinin araştırılması

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Abstract

Aim: Liraglutide is a once-daily glucagon-like peptide-1 receptor agonist (GLP-1 RA) which is an incretin hormone secreted from intestinal L cells in response to nutritional intake and stimulates glucose-dependent insulin secretion, decreases hepatic glucagon secretion, slows gastric emptying, provides a feeling of satiety and is the first GLP-1 RA to be indicated for weight loss treatment for obesity. The impact of liraglutide on thyroid function tests is unknown and to the best of our knowledge, there are no studies on this regard. Our aim is to compare thyroid function tests, other biochemical and hemogram parameters before and 6 months after liraglutide treatment.

Material and Methods: The patients, 18-65 years old, who used liraglutide for at least 6 months due to obesity treatment between January 2021 and January 2023 in Burdur State Hospital were included.

Results: There were 51 patients (39 female, 12 male) using liraglutide without thyroid disease during the study period. Twelve patients discontinued liraglutide use before the 6th month of treatment was completed. Weight, body mass index (BMI), fasting plasma glucose (FPG), hemoglobin A1C (HbA1c), low-density lipoprotein (LDL), triglyceride and thyroid-stimulating hormone (TSH) values were significantly lower at the 6th month of treatment. Free thyroxine (FT4) and free triiodothyronine (FT3) values were similar and there was no difference other biochemical and hemogram parameters between before and 6 months after treatment

Conclusion: After 6 months of liraglutide treatment, we found a significant decrease in TSH values and improvement in metabolic parameters, but no change in thyroid hormone levels.

Keywords: thyroid; liraglutide; obesity; thyroid-stimulating hormone (TSH)

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Öz

Amaç: Liraglutid, gıda alımına yanıt olarak intestinal L hücrelerinden salgılanan bir inkretin hormon olan glukagon benzeri peptid-1 reseptör agonistidir (GLP-1 RA). Glukoz bağımlı insülin sekresyonunu uyarır ve hepatik glukagon sekresyonunu azaltır. Ayrıca, mide boşalmasını yavaşlatır ve tokluk hissi sağlar. Obezite tedavisinde kilo verme amaçlı kullanılan ilk GLP-1 RA'dir. Liraglutidin tiroid fonksiyon testlerine etkisi bilinmemektedir ve bilgimiz dahilinde bu konuda herhangi bir çalışma bulunmamaktadır. Amacımız, liraglutid tedavisi öncesi ve tedaviden 6 ay sonrasındaki tiroid fonksiyon testlerini, diğer biyokimyasal ve hemogram parametrelerini karşılaştırmaktır.

Gereç ve Yöntemler: Burdur Devlet Hastanesi'nde Ocak 2021-Ocak 2023 tarihleri arasında obezite tedavisi nedeniyle en az 6 aydır liraglutide kullanan 18-65 yaş arası hastalar çalışmaya alındı.

Bulgular: Çalışma süresince tiroid hastalığı olmayan ve liraglutid kullanan 51 hasta (39 kadın, 12 erkek) vardı. 12 hasta, tedavinin 6. ayı tamamlanmadan liraglutid kullanımını bıraktı. Kilo, vücut kitle indeksi, açlık serum glukozu, hemoglobin A1C (HbA1c), düşük yoğunluklu lipoprotein (LDL), trigliserit ve tiroid uyarıcı hormon (TSH) değerleri tedavinin 6. ayında anlamlı olarak düşüktü. Serbest tiroksin (sT4) ve serbest triiyodotironin (sT3) değerleri benzerdi. Diğer biyokimyasal ve hemogram parametrelerinde tedavi öncesi ve tedaviden 6 ay sonrasında fark yoktu.

Sonuç: Liraglutid tedavisinin 6.ayında, TSH değerlerinde anlamlı azalma ve metabolik parametrelerde düzelme saptadık, ancak tiroid hormon düzeylerinde farklılık yoktu.

Anahtar Kelimeler: tiroid; liraglutid; obezite; tiroid uyarıcı hormon (TSH)

Introduction

Glucagon-like peptide 1 (GLP-1) is an incretin hormone secreted from intestinal L cells in response to nutritional intake and has effects in multiple target organs. GLP-1 stimulates glucose-dependent insulin secretion, decreases hepatic glucagon secretion, slows gastric emptying, provides a feeling of satiety, and limits calorie intake [1].

Endogenous GLP-1 is rapidly degraded by the dipeptidyl-peptidase 4 (DPP-4) enzyme and therefore has a short-term effect. GLP receptor agonists (GLP-1 RAs) have a longer effect as they are resistant to degradation by this enzyme. They stimulate regeneration and proliferation in pancreatic B cells and protect against damage, and provide better glycemic control and weight loss [2]. GLP-1 receptors are not limited to the pancreas, but are present in many human tissues such as stomach, intestines, kidney, lung, thyroid, skin, immune cells, and hypothalamus [3,4]. The most common side effects of GLP-1 RA treatment are related to the gastrointestinal system, such as diarrhea, nausea, vomiting, and abdominal pain [5]. This condition is often self-limiting in most patients and is rarer than 5% in clinical trials. The side effects are usually associated with high doses and decrease with slow dose titration [6].

Obesity is a metabolic disease with an increasing prevalence all over the world and is associated with an increased risk of developing type 2 diabetes mellitus (DM), hypertension (HT), and cardiovascular disease [7]. Liraglutide is a once-daily GLP-1 RA with an extended half-life, approximately 13.1 hours, similar to native GLP-1 with 97% homology [8]. Liraglutide provides weight loss by multiple mechanisms, which slows down gastrointestinal motility, prolongs the absorption time of nutrients, inhibits appetite and creates a feeling of satiety, increases the resting metabolic rate, and decreases the plasma free fatty acid level [9], and also provides cardioprotective and renoprotective effects with its pleiotropic features [10]. Liraglutide is the first GLP-1 RA to be indicated for weight loss treatment for obesity independent of type 2 DM, at a dose of 3.0 mg/day. It is recommended if the body mass index (BMI) is 30 kg/m2 and above or 27 kg/m2 with at least one comorbidity such as DM, HT, and dyslipidemia [11].

GLP-1 receptors are usually expressed in parafollicular C-cells within the thyroid gland [12]. In animal studies, liraglutide has been shown to increase calcitonin levels, a C-cell marker, and may cause hyperplasia and cancer in C-cells at higher doses [13]. Although there are few studies on the effects of exenatide, one of the GLP-1 RAs, on the thyroid gland, there are limited data on this issue for GLP-1 RAs in general. The impact of liraglutide on thyroid function tests is unknown and to the best of our knowledge, there are no studies on this regard in the literature.

Our aim in the present study is to compare thyroid function tests, other biochemical and hemogram parameters before and 6 months after liraglutide treatment and to evaluate possible differences.

Material and Methods

The present study, single-center and retrospective study, was approved by the ethics committee of the Faculty of Medicine of Suleyman Demirel University (Date: 6th March 2023, Approval number: 2023/46) and was carried out in accordance with the Helsinki declaration. The patients, between 18-65 years old, who used liraglutide for at least 6 months due to obesity treatment between January 2021 and January 2023 in Burdur State Hospital were included in the study. Obesity was defined as BMI of 30 kg/m2 and above [11].

Exclusion criteria were any thyroid and pituitary disease and drug use affecting the hypothalamo-pituitary-thyroid axis, history of thyroid surgery, history of radiotherapy to the neck, thyroid antibody positivity, pregnancy, breastfeeding, liver and kidney failure, history of malignancy, and use of liraglutide for less than 6 months.

All participants were followed with a standard hypocaloric diet, exercise program, and on a liraglutide treatment plan, starting with 0.6 mg/day and gradually reaching the target dose of 3 mg/day with weekly dose increases of 0.6 mg.

The age, gender and chronic diseases of the patients were recorded, and height, weight, BMI, fasting plasma glucose (FPG), hemoglobin A1C (HbA1c), lipid values, liver and kidney function tests, hemogram parameters and thyroid-stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3) values before and 6 months after liraglutide treatment were evaluated. Thyroid function tests were measured by the electrochemiluminescence immunoassay (ECLIA) methods (Cobas; Roche Diagnostics, Mannheim, Germany). HbA1c values were measured by high-performance liquid chromatography (HPLC) method. The reference ranges of the thyroid function tests were as follows; TSH values were 0.27-4.20 µU/mL, FT4 values were 0.93-1.97 ng/dL, FT3 values were 2-4.4 pg/mL.

Statistical analysis

Data were analyzed with the IBM SPSS program version 22. The Shapiro–Wilk test was used for data distribution. Normally and non-normally distributed data were shown as mean ± standard deviation and median (quartile 25%-quartile 75%), respectively. For comparison of data before and after 6 months of treatment, paired samples t-test or the Wilcoxon test were used for normally and non-normally distrubution data, respectively. For the correlation analysis, the Pearson or Spearman analysis was used according to the data distribution. P values <0.05 were considered statistically significant.

Results

There were 51 patients (39 female, 12 male) using liraglutide without thyroid disease during the study period. Twelve patients discontinued liraglutide use before the 6th month of treatment was completed. The reasons for discontinuation were nausea (2 patients), abdominal pain (1 patient), constipation (1 patient) and financial conditions (8 patients).

Of the remaining 39 patients, 31 (79.5%) were female and 8 (20.5%) were male, with a mean age of 43.8 ± 13.5 years (range: 19-65 years). Four patients had type 2 DM, 8 patients had HT and 3 patients had coronary artery disease. Metabolic and laboratory parameters before and 6 months after treatment were compared. Weight (97 ± 16 kg vs 88 ± 14 kg, p= 0.001), BMI (38.2 ± 4.8 kg/m2 vs 34.2 ± 4.4 kg/m2, p= 0.001), FPG (102 ± 16 mg/dL vs 92 ± 12 mg/dL, p= 0.001), HbA1c [5.9 (5.3-6.4) % vs 5.4 (5-5.7) %, p= 0.001], LDL (114 ± 29 mg/dL vs 102 ± 30 mg/dL, p= 0.02), triglyceride [151 (106-220) mg/dL vs 115 (98-136) mg/dL, p= 0.001] and TSH values (2.6 ± 1 µU/mL vs 2 ± 0.8 µU/mL, p= 0.02) were significantly lower at the 6th month of treatment. FT4 (1.3 ± 0.2 ng/dL vs 1.3 ± 0.3 ng/dL, p= 0.56) and FT3 (3.2 ± 0.7 pg/mL vs 3.1 ± 0.4 pg/mL, p= 0.44) values were similar and there was no difference other biochemical and hemogram parameters between before and 6 months after treatment. The comparisons of metabolic and biochemical parameters were shown in Tables 1 and 2. The graphs of thyroid function tests was shown in Figure 1.

No significant correlation was found in the correlation analyzes of thyroid function tests and other parameters.

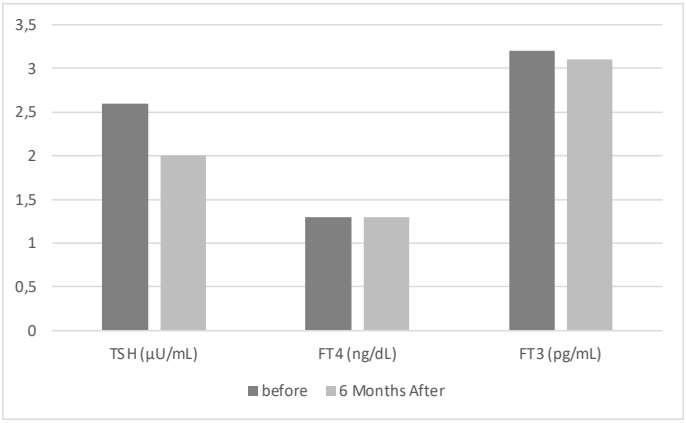

Figure 1. The graphs of thyroid function tests between before and 6 months after liraglutide

TSH: thyroid-stimulating hormone, FT4: Free thyroxine, FT3: Free triiodothyronine

Table 1. The comparison of metabolic parameters between before and 6 months after liraglutide

Variables Reference Range	Before	6 Months After	P value
Weight (kg)	97 ± 16	88 ± 14	0.001
BMI (kg/m2)	38.2 ± 4.8	34.2 ± 4.4	0.001
FPG (70-110 mg/dL)	102 ± 16	92 ± 12	0.001
Hb1Ac (< 5.7%)	5.9 (5.3-6.4)	5.4 (5-5.7)	0.001
LDL (< 130 mg/dL)	114 ± 29	102 ± 30	0.02
HDL (> 40 mg/dL)	49 ± 12	51 ± 14	0.12
Triglyceride (< 150 mg/dL)	151 (106-220)	115 (98-136)	0.001

BMI: Body mass index, FPG: Fasting plasma glucose, Hb1Ac: Hemoglobin A1C, LDL: Low-density lipoprotein, HDL: High-density lipoprotein

Table 2. The comparison of biochemical parameters between before and 6 months after liraglutide

Variables Reference Range	Before	6 Months After	P value
TSH (0.27-4.20 µU/mL)	2.6 ± 1	2 ± 0.8	0.02
FT4 (0.93-1.97 ng/dL)	1.3 ± 0.2	1.3 ± 0.3	0.56
FT3 (2-4.4 pg/mL)	3.2 ± 0.7	3.1 ± 0.4	0.44
Creatinine (0.5-1 mg/dL)	0.7 (0.6-0.8)	0.7 (0.6-0.9)	0.45
ALT (0-55 mg/dL)	22 (17-34)	20 (16-28)	0.13
AST (5-34 mg/dL)	18 (16-23)	14 (11-20)	0.07
WBC (4-10.5x103/µL)	8 (6.6-9.6)	7.7 (6.4-9.4)	0.37
Neutrophil (2-7x103/µL)	4.9 ± 1.4	5 ± 1.8	0.84
Lymphocyte (0.6-3x103/µL)	2.6 (2-3.1)	2.4 (2-3.4)	0.27
Hemoglobin (12-16 g/dL)	14 ± 1.5	14 ± 1.1	0.77
Platelet (140-424x103/µL)	277 ± 76	266 ± 83	0.17

TSH: thyroid-stimulating hormone, FT4: Free thyroxine, FT3: Free triiodothyronine, ALT: Alanine transaminase, AST: Alanine transaminase, WBC: White blood cells

Discussion

In the present study, according to our knowledge for first time in the literature, significant decrease in TSH values was detected 6 months after liraglutide treatment in obese patients without thyroid disease, but there was no change in thyroid hormone values, and as expected, improvement in metabolic parameters was detected.

The presence of GLP-1 receptors has been demonstrated in many cells and systems in the body, and therefore, GLP-1 RAs may have potentially different and unexpected effects in organs other than the pancreas. It is known that long-term use of GLP-1 RAs may cause hyperplasia in thyroid C-cells and possible medullary thyroid cancer (4). In addition, increased GLP-1 receptor expression has been shown in follicular cell-derived hyperplasic and neoplasic conditions [14]. The patients receiving exenatide and oral antidiabetic drug treatment were evaluated retrospectively, and thyroid cancer was found to be 4.7 times higher in the exenatide group [15]. The current data on the relationship between the use of GLP-1 RAs and thyroid cancers are limited and contradictory.

In rodent studies, which were performed using higher doses of liraglutide than in humans, liraglutide was shown to lead C-cell hyperplasia and neoplasia. The possible hypothesis on this issue is the uncontrolled stimulation of C-cells by liraglutide via GLP-1 receptors [13]. The United States food and drug administration (FDA) has placed a medullary thyroid cancer warning for liraglutide [16]. However, this relationship has not been clearly demonstrated in human studies and remains unclear.

Almost all studies on the effects of GLP-1 RA treatment on the thyroid gland are only related to exenatide. Sencar et al. evaluated thyroid function tests and thyroid gland volumes before and 6 months after exenatide treatment in 46 patients with type 2 DM. They found a significant decrease in TSH values, but FT4, FT3 values, and gland volumes were similar [17]. In a similar study design, Koseoglu et al. compared 39 patients with type 2 DM before and 6 months after exenatide treatment. They revealed a significant decrease in TSH values and gland volumes, and there was no change in FT4 and FT3 values. They thought that this decrease in thyroid gland volume was a reflection of the decrease in TSH values. However, they could not reveal a clear mechanism relationship [18]. The study with the largest sample and follow-up period on this regard was revealed by Tee et al. that 112 patients with type 2 DM were prospectively evaluated before and 12 months after exenatide treatment. Like other studies, they found a significant decrease in TSH values and no change in FT4 and FT3 values [19]. In our study, we demonstrated a significant decrease in TSH values at the 6th month of liraglutide treatment and it was the first time in the literature as a GLP-1 RA different from exenatide. Since our present study was retrospective, we could not evaluate thyroid gland volume. There was no change in thyroid hormone levels, similar to exenatide studies. The common result of these

studies, the decrease in TSH values, may be a class effect of GLP-1 RAs. In addition, Koseoglu et al. also revealed a decrease in thyroid gland volume [18]. However, gland volume may also be affected by factors such as age, gender, presence of accompanying nodules, operator dependency [20]. The fact that this issue is inconsistent between the two studies may suggest that there will not be a clear result.

While all participants in the exenatide studies were diabetic and most were on metformin, only 4 (10%) patients in our study had DM. There are studies on the effects of metformin treatment on TSH values. There are studies showing that a decrease in TSH values without a change in thyroid hormone values with metformin treatment and that this situation is independent of the decrease in BMI [21,22]. Although this issue is not clear in the literature, the use of metformin in exenatide studies may also contribute to the decrease in TSH values. However, in our study, the rate of metformin use was very low compared to exenatide studies.

Several theories have been considered as the reason for the decrease in TSH values with GLP-1 RA treatment, especially with regard to exenatide. GLP-1 receptors have also been demonstrated in pituitary tissue and these receptors on pituitary TSH-producing cells in rodents were shown to bind to GLP-1 RAs with high affinity. GLP RAs may lead a decrease in TSH values with an effect at the pituitary level [23]. It has also been suggested that GLP-1 RAs may increase TSH sensitivity to thyroid cells [17]. Another possible mechanism is that GLP-1 RA-related weight loss may affects TSH values [19].

Data on the effects of weight loss on TSH value are contradictory in the literature [24]. There are some studies showing that a significant decrease in BMI values after bariatric surgery performed on obese patients has no effect on TSH values [25]. On the contrary, there are some studies showing that there is an increase in TSH values with weight gain [26] and a decrease in TSH values with weight loss [27]. On the other hand, Sencar et al. and Koseoglu et al. did not find a relationship between TSH values and the decrease in BMI [17,18]. In the study of Tee et al. with more patient participation and longer follow-up period, an independent nonlinear relationship was found between weight loss and decrease in TSH values, and there was no significant change in TSH values in patients without weight loss. They thought that the main reason for the decrease in TSH values was weight loss and that this was due to the change in the sensitivity of the hypothalamus and/or pituitary to thyroid hormones [19].

Liraglutide is an effective treatment in obesity management with its multiple action mechanisms [5]. We found significant improvements in metabolic parameters such as weight, BMI, FPG, HbA1c, LDL, and triglyceride values at 6 months of treatment. 7% and 16% of patients could not complete the 6th month due to gastrointestinal system complaints and treatment cost, respectively. As can be seen, the most important parameter limiting the use of liraglutide is financial conditions.

Our study has some limitations. The number of participants and the follow-up period of the study were relatively small and short. Prospective multicenter studies with longer follow-up periods and follow-up processes after treatment discontinuation may be more enlightening in this regard. Our study may reveal the decrease in TSH values with liraglutide use, but it is lack in terms of establishing any causality between these two conditions.

Conclusion

We evaluated for the first time in the literature, as there were similar studies with exenatide, the effects of liraglutide treatment, which is used for weight loss, on thyroid gland functions before and 6 months after treatment, and we found a significant decrease in TSH values, but no change in thyroid hormone levels. In addition, we found improvement in metabolic parameters such as weight, BMI, serum glucose, HbA1c values, and lipid profile, except HDL. It should be kept in mind that there may be a decrease in TSH values in patients using liraglutide. There is a need for further studies with larger samples, longer follow-up, and a causal relationship to this regard.

Conflict of interest

There is no conflict of interest in this study. There is no financial support for this study.

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