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The Effect of Exenatide on Thyroid-Stimulating Hormone and Thyroid Volume

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Keywords
Exenatide · GLP-1 analogues · Diabetes mellitus · Thyroid volume · Thyroid-stimulating hormone · Thyroid hormone receptors · Thyroid hormone sensitivity

Abstract
Objective: Glucagon-like peptide-1 (GLP-1) analogues are now widely used for the treatment of type 2 diabetes mellitus (DM). Many binding sites for GLP-1 have been demonstrated in the specific tissue compartments of organs including the brain and thyroid. The aim of this study was to investigate the effect of exenatide treatment on thyroid-stimulating hormone (TSH) and thyroid volume in diabetic patients without thyroid disease. ***Material and Methods:*** The study included 46 diabetic patients without thyroid disease who were receiving exenatide treatment. Comparisons were made of total thyroid volume and serum concentrations of TSH at baseline and after 6 months of follow-up. ***Results:*** Of the 46 patients, 13 were excluded from the study, as they were unable to complete the treatment or left the follow-up process. After 6 months of exenatide treatment, the serum TSH concentration decreased significantly (from 2.3 [0.7–5.4] to 1.8 mIU/L [0.3–4.2], $p = 0.007$). There were no significant differences in thyroid volume (11.6 ± 9.0 vs. 12.1 ± 8.8 cm^3, $p = 0.19$), free thyroxine (fT4), free tri-iodothyronine (fT3), and calcitonin levels before and after treatment. Thyroid volume was not affected by decreased TSH level (p: = 0.141) or a reduction in body mass index (BMI) ($p > 0.05$), and no correlation was detected between variation in TSH level and change in BMI ($p > 0.05$). ***Conclusions:*** Exenatide treatment for 6 months significantly decreased serum TSH concentration but did not affect thyroid volume in diabetic patients without thyroid disease.

Introduction

Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted from L cells in the ileum in response to food intake [1]. GLP-1 has beneficial effects such as increasing glucose-dependent insulin secretion, suppressing glucagon release, delaying gastric emptying, and increasing saturation, all of which make it useful in the treatment of type 2 diabetes mellitus (DM) [2, 3]. Exenatide is a GLP-1 analogue consisting of 39 amino acids, with 53% amino acid homology to GLP-1 which is used in the treatment of DM [4]. GLP-1 receptors are classic G-protein coupled receptors and show 93% homology between rats

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and humans [5, 6]. Studies on rats and humans have shown that GLP-1 receptors are expressed in specific tissue compartments of the pancreas, gastrointestinal tract, brain, lung, heart, kidney, and thyroid [7–11]. Although GLP-1 analogues have very beneficial effects in the treatment of DM, investigation of GLP-1 receptors in the rat and human thyroid gland has shown that there may be potential different effects on the thyroid gland. To the best of our knowledge, there is no study in the literature evaluating the effect of exenatide treatment on thyroid gland volume and thyroid-stimulating hormone (TSH). The aim of this study was to investigate the effect of exenatide treatment on TSH level and thyroid gland volume.

Material and Method

Patient Selection

This was a single-center, prospective trial on diabetic subjects without thyroid disease. The study included 46 patients receiving DM treatment between 2016 and 2017 at our institution. All those included in the study were patients aged 18–65 years, with a body mass index (BMI) >35, who were receiving 2 oral antidiabetic treatment agents because of the national health care system reimbursement conditions for exenatide in Turkey. Patients whose treatment had been changed in the last 6 months were not included in the study. Patients with a history of thyroid disease or surgery, abnormal thyroid function tests, positive thyroid antibody, or pathological findings on ultrasonography (US) were also excluded from the study. The study subjects were prescribed a standard hypocaloric diabetic diet and regular standard aerobic exercise under the supervision of a dietician who monitored them at 3-monthly intervals. Exenatide at a dose of 5 μg twice a day was started for all patients, and after 4 weeks, the dose was increased to 10 μg twice daily.

Clinical, Biochemical, and Hormone Measurements

Baseline demographic data, clinical characteristics, duration of diabetes, comorbidities, and concomitant medications were recorded for all study subjects. Weight, height, and BMI were measured and recorded for all patients before enrollment and at the end of the study. All patients underwent a biochemical and hormone examination before and after the study, including fasting plasma glucose (FPG), post-prandial glucose (PPG), glycated haemoglobin (HbA_{1c}), thyroid function tests, thyroid antibodies, and calcitonin. All blood samples were drawn at 8 a.m. HbA_{1c} was measured using the high-performance liquid chromatography (HPLC) method. Thyroid function tests, thyroid antibodies, and calcitonin were measured with an automated direct chemiluminescent immunoassay (Beckman Coulter, CA, USA). TSH levels in the range of 0.38–5.33 mIU/L were considered normal, and normal ranges for free thyroxine (fT4; 7.72–16.1 pmol/L) and free tri-iodothyronine (fT3; 3.5–6.1 pmol/L) were also detected. The reference range for anti-thyroglobulin (anti-Tg) and anti-thyroid peroxidase (anti-TPO) was 0–40 and 0–35 IU/mL, respectively. For calcitonin, a level <5 ng/L was considered normal.

Thyroid US was performed using high-resolution B-mode ultrasound images (EUB 7000 HV; Hitachi, Tokyo, Japan) with a 13-MHz linear array transducer. All of these examinations were performed by one of the authors (M.E.S.). The volume of thyroid adenoma was calculated using the Brunn model formula: length × thickness × width × 0.479 [12].

Statistical Analysis

Statistical analyses were performed using SPSS software v13.0 (SPSS, Chicago, IL, USA). For data that conformed to the normal distribution, descriptive statistics were expressed as mean ± standard deviation (SD) and percentages. All continuous non-normal distributed variables were expressed as median (range) values. The parameters were compared from baseline to 6 months using the paired samples *t* test for normally distributed variables and the Wilcoxon test for variables not showing a normal distribution. Correlations were analyzed using Pearson's and Spearman's correlation analyses. $p < 0.05$ was considered statistically significant.

Results

Initially, 46 diabetic patients (35 females and 11 males) without thyroid disease were enrolled in the study. A total of 13 were excluded from the study for various reasons: dropping out of follow-up ($n = 4$), high blood glucose, the need for intensive insulin treatment ($n = 4$), angioedema ($n = 1$), drug eruption ($n = 1$), abdominal pain ($n = 1$), diarrhoea ($n = 1$), and severe weakness ($n = 1$).

The remaining 33 patients comprised 28 females and 5 males with a mean age of 52 ± 10 years and a mean duration of diabetes of 9 years. The characteristics of the 33 patients evaluated are presented in Table 1.

After 6 months of exenatide treatment, a significant decrease was determined in the mean weight (from 107 ± 16.5 to 101 ± 17 kg, $p < 0{,}001$) and BMI (from 42 ± 5 to 40 ± 5, $p < 0.001$) of the patients. A significant decrease from the baseline values was determined for HbA_{1c} (from 76 ± 16 to 63 ± 17 mmol/mol, $p < 0.001$), FPG (from 10.4 [5.82–23.2] to 8.54 [3.8–16.9] mmol/L, $p = 0.009$) and PPG (from 16 ± 4 to 13.2 ± 3.6 mmol/L, $p = 0.022$).

Thyroid Functions, Calcitonin, and Thyroid Volume

Serum TSH, fT3, fT4, anti-TPO, anti-Tg, and calcitonin levels were measured before and after 6 months of treatment. Thyroid US was performed before starting treatment and at the end of the study (Table 1).

After 6 months of exenatide treatment, the mean serum concentration of TSH decreased significantly (from 2.3 [0.7–5.4] to 1.8 [0.3–4.2] mIU/L, $p = 0.007$), but there was no significant change in fT4 and fT3 concentrations (11.8 ± 1.3 vs. 11.7 ± 2.6 pmol/L [$p > 0.05$] and 4 ± 0.1 vs. 4.1 ± 0.2 pmol/L [$p > 0.05$], respectively). In the correla-

Table 1. Clinical, laboratory, and thyroid US characteristics of the study subjects before and after exenatide therapy

	Baseline	6 months	*p*
Age, years	52±10		
Female/male, *n*	28/5		
Weight, kg	107±16.5	101±17	*<0.001*
BMI	42±5	40±5.0	*<0.001*
FPG, mmol/L	10.4 (5.82–23.2)	8.54 (3.8–16.9)	*0.009*
PPG, mmol/L	16±4	13.2±3.6	*0.022*
HbA_{1c}, mmol/mol	76±16	63±17	*<0.001*
TSH, mIU/L	2.3 (0.7–5.4)	1.8 (0.3–4.2)	0.007
fT4, pmol/L	11.8±1.3	11.7±2.6	0.747
fT3, pmol/L	4±0.1	4.1±0.2	0.715
Thyroid volume, cm^3	11.6±9.0	12.1±8.8	0.19
Anti-TPO, IU/mL	0.8 (0–35.9)	0.7 (0–40.0)	0.290
Anti-TG, IU/mL	0.8 (0–20.0)	0.9 (0–63.0)	0.076
Calcitonin, ng/L	2 (2.0–3.8)	2 (2.0–17.6)	0.242

Non-normally distributed variables are presented as median (range) and variables with a normal distribution are presented as mean ± SD. US, ultrasonography; BMI, body mass index; FPG, fasting plasma glucose; PPG, post-prandial glucose; TSH, thyroid-stimulating hormone; fT4, free thyroxine; fT3, free triiodothyronine; Anti-TPO, anti-thyroid peroxidase; Anti-TG, anti-thyroglobulin.

tion analysis, no relationship was detected between variation in TSH level and change in BMI ($p = 0.556$).

No statistically significant change in thyroid volume was observed at the end of the study (11.6 ± 9.0 cm^3 at baseline vs. 12.1 ± 8.8 cm^3 at the end of the study, $p = 0.19$). No relationship was found between the decrease in TSH and thyroid volume ($p = 0.141$), and the thyroid volume was not affected by the reduction in BMI ($p = 0.418$).

No new ultrasound findings were detected at the end of the treatment, and there was no increase in calcitonin levels (2 [2–3.8] vs. 2 [2–17] ng/L, $p = 0.242$).

In all the patients, thyroid auto-antibodies were confirmed to be negative before treatment, and there was no change in anti-TPO and anti-Tg levels after 6 months of exenatide treatment.

Discussion

In this observational study, we evaluated the effect of exenatide on thyroid volume and TSH in DM patients without thyroid disease. The results demonstrated that 6 months of exenatide treatment did not change thyroid volume but decreased the TSH level.

The presence of GLP-1 receptors in many tissues and organs other than β cells can cause different and unexpected effects [7, 13]. The determination of GLP-1 receptors in the human thyroid gland has raised concerns that long-term GLP-1 receptor agonist treatment may lead to C-cell hyperplasia and medullar thyroid cancer [7, 11]. In the literature, it has been documented that, in addition to C cells, thyroid follicular cells in inflammation, cellular hyperplasia, or tumorigenesis conditions may be aberrantly expressed GLP-1 receptors; this demonstrated the need for observational studies on the effects of long-term GLP-1 receptor activation on the thyroid [11, 14]. A retrospective analysis, which reported that 4.7 times more thyroid cancers are seen with exenatide than control antidiabetic drugs, supports these studies [15].

The results of our study showed no statistically significant increase in thyroid volume after 6 months of exenatide treatment. This finding can be attributed to the fact that normal thyroid follicular cells do not express the GLP-1 receptor and C cells comprise only 0.1% of the total mass of the human thyroid gland [16]. TSH has been recognized as the main but not the only proliferation factor for thyroid cells [17, 18]. The decreased TSH concentration and weight loss had no effect on the thyroid volume in our study subjects. Despite the decreased TSH level and reduced BMI, the insignificant increase in thyroid volume indicates that long-term studies are needed to examine the effect of exenatide on thyroid volume. The relatively short duration of exenatide treatment and absence of a control group were limitations of this study.

Previous studies have demonstrated GLP-1-specific binding sites on the pituitary. These GLP-1-binding sites mean that GLP-1 agonists may have a potential effect on pituitary function [19–22]. Beak et al. [20] demonstrated specific binding sites for GLP-1 on membranes of rodent thyrotrope cells and reported that GLP-1 agonists and antagonists show a high affinity to these binding sites.

Another interesting result of our study was that exenatide significantly reduced the TSH level without altering the fT4 and fT3 levels. The increased biological activity of TSH can be hypothesized as a possible mechanism of stable fT4 and fT3 levels despite the decreased level of TSH. The other possible mechanism could be that exenatide may increase the sensitivity of the hypothalamus or the pituitary gland to the thyroid hormone negative feedback or else increase the number of receptors on the hypothalamus or pituitary gland. Another explanatory hypothesis could be that exenatide may increase the sensitivity of the thyroid cells to the action of TSH. The absence of an increase in thyroid auto-antibodies following treatment

with exenatide indicates that exenatide did not affect thyroid autoimmunity, at least in this short period. It seems that the effect of exenatide on TSH and thyroid must be independent of autoimmunity.

There are conflicting results in the literature about the effect of weight loss on TSH level. Some studies on obese patients have shown that markedly reduced BMI (30%) after bariatric surgery had no effect on TSH level [23, 24]. In this study, we also found no correlation between TSH and BMI variations in the correlation analyses, showing that the variation in TSH level appears to be independent from the BMI change. Therefore, the decrease in TSH concentration can be considered to be an effect of exenatide. Malendowicz et al. [25] also demonstrated that exenatide had the effect of lowering TSH concentration in rats. In their study, administration of GLP-1 to the rats reduced TSH level at an insignificant level, while administration of Exendin, a GLP-1 receptor agonist, caused a robust and sustained inhibitory effect on blood TSH concentration in the rats [25].

Some studies have investigated the effect of metformin on TSH. Metformin was also found to decrease TSH levels without changing fT4 and fT3 levels, regardless of changes in BMI [26, 27]. The effects of both drugs on TSH may be related to a common mechanism associated with changes in insulin sensitivity [28, 29]. The detailed mechanism and clinical outcomes of this effect need to be clarified in further studies.

At the end of the study, there was no increase in the mean calcitonin levels of the patients; this is compatible with the findings in the literature [30, 31]. Calcitonin level was seen to have slightly increased in the 6-month period only in 2 patients, and these levels remained stable at the 1-year follow-up. In addition, there were no new ultrasound findings in these 2 patients during the treatment period.

Conclusion

Exenatide, which is a GLP-1 agonist, was observed to have a lowering effect on the TSH level without altering fT4 and fT3 levels in patients without thyroid disease or autoimmunity. Exenatide treatment had no effect on thyroid volume or calcitonin levels. Further long-term studies with more patients are needed to clarify the association between GLP-1 agonists and TSH as well as the clinical outcomes of the decreased TSH level.

Statement of Ethics

The study was approved by the Ethics Committee of our institute. All participants were informed about the research protocol, and they declared their voluntary attendance by signed written consent.

Disclosure Statement

The authors have no conflicts of interest to declare.

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