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Incretin levels in patients with hypothyroidism and the evaluation of incretin levels alterations with treatment

Serkan Alemdar¹, Nusret Yilmaz¹, Sebahat Ozdem², Ramazan Sari^{1,*}

Abstract

Background: Incretin hormones may influence the effects of thyroid hormones on insulin secretion, insulin resistance, and glucose metabolism. Thyroid hormones regulate insulin secretion, and the risk of diabetes was found to be associated with thyroid hormones.

Objectives: To determine whether incretin hormones influence the effects of thyroid hormones on insulin resistance and glucose metabolism.

Methods: A total of 26 patients were included in 2 groups consisting of 13 patients with hypothyroidism and 13 healthy controls. Levels of glucose, insulin, glucagon-like peptide 1 (GLP-1), and gastric inhibitory polypeptide (GIP) levels were measured in 0, 30, 60, 90, and 120th min during the oral glucose tolerance test in the control group and before and after thyroxine treatment in the hypothyroid group.

Results: In the hypothyroid group, waist circumference decreased after the euthyroid state was achieved ($P = 0.026$). No statistically significant differences were detected in the GLP-1 and GIP levels at baseline and 30, 60, 90, and 120 min between the hypothyroidism and control groups or after ensuring the euthyroid state in patients with hypothyroidism. Peak GLP-1 levels were observed at 30 min in the control group, whereas peak GLP-1 and GIP levels were detected at 90 min in the hypothyroidism group. After achieving the euthyroid state, peak GLP-1 and GIP levels were detected at 30 min as well.

Conclusion: In patients with hypothyroidism, the incretin hormones, especially the peak response of the incretin system, are significantly affected. Significant changes were observed in the incretin system by correcting hypothyroidism.

Keywords: glucagon-like peptide 1; hypothyroidism; incretins

Thyroid hormones induce a dose-dependent adverse effect on carbohydrate metabolism. For instance, in rats, while low doses of thyroid hormones and insulin increase glycogen synthesis, high doses of thyroid hormones accelerate degradation of liver glycogen to glucose. Thyroid hormones also affect the intestinal absorption rate, adipose tissue, and the intake rate of glucose by the muscles. On the other

hand, thyroid hormones effectively and dose dependently increase the degradation of insulin [1–3]. In the case of thyroid hormone deficiency, the insulin response to glucose was found to be delayed in the oral glucose tolerance test (OGTT), and patients with hypothyroidism showed an increase in insulin sensitivity and a decrease in insulin degradation [4–7].

*Correspondence to: Ramazan Sari, Department of Internal Medicine, School of Medicine, Akdeniz University, Antalya 07058, Turkey, e-mail: rsari@akdeniz.edu.tr

¹Department of Internal Medicine, School of Medicine, Akdeniz University, Antalya 07070, Turkey

²Department of Biochemistry, Akdeniz University, School of Medicine, Antalya 07070, Turkey

The incretin effect is defined as the difference in insulin secretion due to orally given glucose compared to that due to intravenous glucose, which would increase the plasma glucose level by the same amount [8]. This effect related to the intestine is associated with humoral or neural factors that are known as incretin and potentiate insulin secretion after enteral nutrition [9]. The incretin effect is responsible for 50%–70% of the insulin secretion occurring after oral food intake [10]. Glucagon-like peptide 1 (GLP-1) increases the beta cell mass, inhibits the apoptosis of beta cells, increases insulin synthesis and secretion, suppresses glucagon secretion, slows down the gastric drainage, and decreases the intake of food [9, 11–13].

Thyroid dysfunction and diabetes are the 2 most common endocrine disorders, and both these diseases are closely linked with each other [14]. It has been reported that thyroid hormones regulate insulin secretion, and the risk of diabetes was found to be associated with thyroid hormones [15, 16]. Moreover, incretin hormones may influence the effects of thyroid hormones on insulin resistance, insulin secretion, and glucose metabolism.

In this study, our aim was to determine whether incretin hormones influence the effects of thyroid hormones on insulin secretion, insulin resistance, and glucose metabolism. To our knowledge, this is the first study to assess the exchange of incretin hormones before treatment and after ensuring the euthyroid state in patients with hypothyroidism.

Materials and methods

This study included patients with hypothyroidism ($N = 13$) aged above 18 years who attended the Endocrinology Clinic of Akdeniz University Hospital and were kept under regular observation. These patients did not have any illness that would affect glucose and carbohydrate metabolism. Healthy individuals without any illnesses were also included as a control group ($N = 13$). Patients aged <18 years and those diagnosed with diabetes mellitus, had undergone GIS surgery, had shown increased liver function test results for more than 2 times, and had creatinine levels >1.5 mg/dl were excluded from the study. This study was approved by the Akdeniz University Medical Faculty Ethics Committee (approval no. B.30.2.AKD.0.20.05.06/69). Written informed consent was obtained from the patients.

Laboratory evaluations

All the assessments were performed after 12 h of fasting with the consent of the patients. Comprehensive medical

history taking and physical examinations of the patients were performed. After anthropometric measurements, venous blood samples were used for assessing baseline laboratory parameters, including the levels of glucose, creatinine, alanine transaminase, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, hemoglobin A1c, and insulin. Then, an OGTT was performed, in which 75 g of glucose was mixed in 300 ml of water, and the patient was instructed to drink the prepared glucose solution within 5 min. Venous blood samples were obtained for measuring the levels of glucose, insulin, GLP-1 (7–36), and total gastric inhibitory polypeptide (GIP) at 0, 30, 60, 90, and 120 min. Blood samples for GLP-1 and GIP measurements were collected in BD brand (BDÔ P800) special tubes with a special content containing dipeptidyl peptidase-IV, esterase, and other protease inhibitors preventing the degradation of GLP-1 and GIP and centrifuged for 10 min at +4°C and 3000 rpm. Then, the plasma samples were separated and stored at -80°C until analysis.

The homeostasis model assessments of insulin resistance (HOMA-IR) scores of the patients were calculated by the formula $\text{insulin } (\mu\text{U/ml}) \times \text{glucose (mg/dl)} / 405$ [17].

In addition, for patients with hypothyroidism, after ensuring the euthyroid state with thyroxine treatment, the tests were repeated, and the data from hypothyroid and euthyroid states were compared.

Statistical analysis

Statistical analyses were performed using SPSS version 20.0 software. Continuous variables were represented as median and minimum–maximum with mean \pm standard deviation. Categorical variables were expressed as frequency and percentage. One-sample Shapiro–Wilk test was performed to evaluate the normal distribution of the data. The Mann–Whitney test was used for the analysis of independent groups (hypothyroidism group and control group), and Wilcoxon signed ranks test was used for the comparison of the dependent groups (hypothyroid and euthyroid groups). While conducting the statistical analyses, the results were within the confidence interval of 95%, and $P < 0.05$ was considered as statistically significant.

Results

Age, body mass index (BMI), waist circumference, and HOMA-IR scores were similar between the hypothyroidism and control groups ($P > 0.05$). Serum thyroid-stimulating

hormone (TSH) levels were higher in the hypothyroidism group than those in the control group (16.5 ± 10.1 vs 1.99 ± 1.2 IU/ml, $P = 0.001$). The serum TSH level was 2.2 ± 1.9 IU/ml in the hypothyroidism group after treatment. There was no change in the BMI and HOMA-IR scores of the patients with hypothyroidism before treatment and after ensuring the euthyroid state ($P > 0.05$); however, there was a significant decrease in the waist circumference after ensuring the euthyroid state (90.3 ± 11.7 vs 88.6 ± 12.5 cm, $P = 0.026$).

The OGTT results revealed that 2 patients in the hypothyroidism group had impaired glucose tolerance, while 1 subject each in the control group had impaired fasting glucose and impaired glucose tolerance. Regarding the impaired glucose tolerance detected in the 2 patients with hypothyroidism, the condition improved in 1 patient in the euthyroid state, whereas it continued in the other patient. Moreover, in 1 of the patients in the control group, impaired fasting glucose was detected while in the euthyroid state unlike in the state of hypothyroidism.

Plasma glucose and insulin levels were similar in the hypothyroidism and control groups. There was also no change in the plasma glucose and insulin levels in patients with hypothyroidism before and after treatment (Table 1).

GLP-1 levels were increased after the glucose intake with OGTT in both the hypothyroidism and control groups. However, no statistically significant differences were detected in the GLP-1 levels at baseline and 30, 60, 90, and 120 min

between the hypothyroidism and control groups. Peak GLP-1 levels were observed at 30 min in the control group, whereas peak GLP-1 levels were detected at 90 min in the hypothyroidism group (Table 2).

GIP levels were increased after the glucose intake with OGTT in both the hypothyroidism and control groups, with no statistically significant difference observed between the groups. The highest GIP level was detected at 90 min in the control group, whereas in the hypothyroidism group, the highest GIP level was observed at 60 min (Table 2).

After ensuring the euthyroid state in patients with hypothyroidism, GLP-1 levels were found to be increased after the glucose intake with OGTT. However, there was no change in the GLP-1 levels measured in these patients after ensuring the euthyroid state when compared to those before treatment. In the hypothyroidism group, the highest GLP-1 level before treatment was detected at 90 min, whereas the highest GLP-1 level after treatment was detected at 30 min (Table 2).

After ensuring the euthyroid state in patients with hypothyroidism, GIP levels were found to be increased after the glucose intake with OGTT. However, the GIP levels at baseline and 30, 60, 90, and 120 min measured before treatment and after ensuring the euthyroid state in patients with hypothyroidism were found to be similar. In the hypothyroidism group, the highest GIP level was observed at 60 min before treatment, whereas the highest GIP level after treatment was detected at 30 min (Table 2).

Table 1. Plasma glucose and insulin levels in patients in the control group and in patients with hypothyroidism before treatment and hypothyroidism after treatment[†]

Laboratory parameters	Control (n = 13)	Hypothyroidism before treatment (n = 13)	Hypothyroidism after treatment (n = 13)	P (control vs hypothyroidism before treatment)	P (hypothyroidism before vs after treatment)
Glucose levels (mg/dl)					
Baseline	87.46 \pm 6.85	90.30 \pm 3.85	90.38 \pm 7.24	0.143	0.972
30th min	141.65 \pm 40.72	145.92 \pm 22.38	148.15 \pm 26.84	0.343	0.753
60th min	139.47 \pm 45.79	142.84 \pm 27.09	128.30 \pm 28.31	0.663	0.05
90th min	117.01 \pm 25.34	121.69 \pm 34.48	118.61 \pm 30.84	0.939	0.610
120th min	96.60 \pm 30.78	104.92 \pm 31.67	102.89 \pm 29.95	0.555	0.272
Insulin levels (mU/ml)					
Baseline	10.32 \pm 4.79	8.24 \pm 3.31	9.66 \pm 4.51	0.191	0.152
30th min	54.74 (22.99–294.3)	54.14 (23.7–229.6)	56.35 (34.06–243.9)	0.858	0.422
60th min	56.32 (18.53–226.6)	69.95 (23.87–160.7)	53.43 (28.7–146.7)	0.59	0.116
90th min	46.7 (7.9–121.8)	42.75 (8.1–127.1)	42.94 (9.36–208.5)	0.957	0.753
120th min	27.65 (4.87–132.7)	32.08 (7.61–18)	31.34 (6.26–133.5)	0.317	0.249

[†]Results are shown as mean \pm standard deviation for normal distribution and median (minimum–maximum) for abnormal distribution.

Table 2. Plasma GLP-1 and GIP levels in patients in the control group and in patients with hypothyroidism before treatment and hypothyroidism after treatment

Laboratory parameters	Control (n = 13)	Hypothyroidism before treatment (n = 13)	Hypothyroidism after treatment (n = 13)	P (control vs hypothyroidism before treatment)	P (hypothyroidism before vs after treatment)
GLP-1 levels (pg/ml)					
Baseline	3.88 ± 1.54	3.90 ± 1.47	4.12 ± 1.64	0.93	0.67
30th min	5.63 ± 1.74	5.58 ± 1.93	6.01 ± 2.40	0.83	0.51
60th min	4.9 ± 1.7	5.0 ± 2.1	5.16 ± 2.09	0.74	0.59
90th min	4.47 ± 1.73	5.67 ± 1.85	5.53 ± 2.21	0.17	0.64
120th min	3.87 ± 1.52	4.50 ± 1.01	5.04 ± 2.15	0.29	0.15
GIP levels (pg/ml)					
Baseline	44.5 ± 28.9	55.1 ± 18.7	53.4 ± 15.3	0.59	0.74
30th min	81.1 ± 31.9	69.1 ± 22.6	87.1 ± 21.9	0.89	0.19
60th min	85.9 ± 47.0	79.1 ± 32.7	83.6 ± 20.1	0.94	0.14
90th min	96.5 ± 42.7	75.8 ± 26.4	74.2 ± 16.5	0.38	0.62
120th min	64.5 ± 32.9	68.4 ± 33.1	58.0 ± 13.8	0.56	0.54

GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide 1.

Area under the curve (AUC) for GLP-1 (8.7 ± 2.4 vs 8.6 ± 3.1 , $P = 0.65$) and GIP (408.2 ± 139.3 vs 417.5 ± 153.6 , $P = 0.45$) in hypothyroidism and control groups, respectively, did not differ significantly. Reversal of hyperthyroidism to euthyroid status with antithyroid treatment did not induce significant changes in AUCs for incretins: 8.7 ± 2.6 vs 8.9 ± 3.2 , $P = 0.85$, for GLP-1 and 408.2 ± 139.3 vs 415.3 ± 151.9 , $P = 0.67$, for GIP in hypothyroid and euthyroid states, respectively.

Discussion

Thyroid hormones have significant effects on glucose homeostasis. Therefore, a deficiency or an excess of thyroid hormones may induce changes in carbohydrate metabolism [18]. In hypothyroidism-induced rats, transformation of glycogen from glucose was found to be partially inhibited, along with a decrease in glucose transport and phosphorylation stimulated by insulin and disturbances in the phosphorylation of post-receptor insulin signaling proteins [19]. Clinical studies that have investigated insulin resistance in patients with hypothyroidism have reported contradictory results [20–26], which may be attributed to the methods used in the studies, the cause of hypothyroidism, the severity of hypothyroidism, and the different patient populations. Although some studies have reported that insulin resistance increased more specifically in the post-prandial period than in the fasting period in hypothyroidism, a study that was carried out with a control group, 11 women with primary hypothyroidism, and 10 women with a euthyroid state showed that the HOMA-IR index did not differ between the 2 groups [21, 22]. Similarly, in our study, the HOMA-IR score

was not different between the hypothyroidism and control groups [21–23]. Moreover, the HOMA-IR scores of patients in the hypothyroidism group remained unchanged after ensuring the euthyroid state with thyroxine treatment.

In the case of hypothyroidism, studies conducted on carbohydrate metabolism have reported that glucose absorption from the intestines is slower than normal. However, in our study, it was observed that fasting plasma glucose and fasting insulin and C-peptide levels were mostly similar to those in the control groups reported in some studies [22, 26, 27]. However, some studies have reported slightly high insulin and low glucose levels compared to the normal levels [23, 28]. In a study carried out by Nada, fasting glucose values remained unchanged; however, a significant increase in fasting insulin levels was detected in patients with hypothyroidism after ensuring the euthyroid state with treatment [26]. Another study carried out by Gimenez-Palop et al. showed that this increase in insulin levels did not reach a statistically significant difference after treatment [24]. In our study as well, fasting glucose and insulin levels remained unchanged in patients with hypothyroidism after the treatment.

In addition, as mentioned earlier, thyroid hormones are known to regulate insulin secretion, and the risk of diabetes was found to be associated with the level of thyroid hormones [15, 16]. Assuming that thyroid hormones may affect glucose levels and insulin secretion, in the present study, after ensuring the euthyroid state before treatment and with treatment in patients with hypothyroidism, we evaluated the glucose levels and insulin secretion by performing OGTT.

In the case of patients with hypothyroidism, clinical studies related to the insulin response to glucose have shown

contradictory results. The insulin response to an oral glucose load is variable; in some cases, it is observed to be higher than that in the control group, while it is sometimes delayed [22, 23]. Handisurya et al. conducted a study aimed at detecting the changes in glucose metabolism before and after treatment in 11 patients with subclinical hypothyroidism and 12 patients with overt hypothyroidism, and they observed that the glucose-related insulin secretion was impaired, although it improved with treatment [29]. However, some studies have shown that, usually, the OGTT results do not show any abnormality; however, the peak value remained high in the second hour depending on the slowdown in gastric drainage and the delay in absorption [22, 28]. In our study, we detected that the glucose and insulin responses of the patients in the hypothyroidism and control groups were similar when evaluated using OGTT. We also observed that the glucose response to OGTT performed after ensuring the euthyroid state with the treatment in the hypothyroidism group decreased at 60 min. Supporting our study, Hays et al. also showed that the AUC for insulin secretion decreased by ensuring the euthyroid state [30].

As mentioned earlier, the incretin effect is responsible for 50%–70% of the insulin secretion occurring after oral food intake [10]. There are limited studies examining the relationship between thyroid hormones and the incretin system in the literature [16, 30]. Considering the hypothesis that the incretin hormones may also influence the effects of thyroid hormones on insulin secretion, insulin resistance, and glucose metabolism, we evaluated the levels of GLP-1 and GIP by performing OGTT after ensuring the euthyroid state before treatment and with treatment in patients with hypothyroidism. To our knowledge, this is the first study that examined the incretin levels after ensuring the euthyroid state before treatment and with treatment in patients with hypothyroidism.

Studies evaluating the GIP response to baseline and glucose load in patients with hypothyroidism are also limited, and the results obtained are contradictory as well [16, 30]. For instance, in the study conducted by Doong et al. exploring the effect of thyroid hormones on GIP secretion in rats, baseline plasma GIP levels were found to be higher in the hypothyroid rats than those in the euthyroid rats. Following oral glucose load in the euthyroid rats, an increase in the secretion of GIP was detected at 20 min. The circulating GIP levels in the hypothyroid rats remained high from the 45th min to the 90th min compared to those in the euthyroid rats. In addition, the peak GIP response to glucose intake was not observed in thyroidectomized rats [16]. However, in another study in which Hays et al. evaluated the GIP response to oral glucose in patients with hypothyroidism, the GIP response to glucose was observed to be similar in the

hypothyroid and euthyroid groups [30]. In our study, the GIP levels were found to be increased in both the hypothyroidism and control group after the glucose intake with OGTT. However, the GIP response induced by basal and glucose was observed to be similar in both groups. In the literature, the time in which the GIP level peaked with the glucose load varies between 30 min and 90 min. While the highest GIP value was detected at 60 min in the hypothyroidism group in our study, the fact that the highest peak GIP value was detected at 90 min in the control group indicates that hypothyroidism may have an effect on the temporal variation of GIP response to a glucose load.

When the patients with hypothyroidism were evaluated in terms of GIP response after ensuring the euthyroid state with treatment in our study, it was observed that the GIP levels induced by baseline and glucose remained unchanged. Moreover, the fact that the highest peak GIP level was detected at 30 min after treatment, whereas the highest peak GIP level was observed at 60 min in the hypothyroidism group makes us to assume that the GIP response was temporally affected by ensuring the euthyroid state with the treatment.

The incretin effect is significantly dependent on GLP-1 levels. GLP-1 beta increases the cell mass, inhibits the apoptosis of beta cells, increases insulin synthesis and secretion, suppresses glucagon secretion, slows down the gastric drainage, and decreases the food intake [9,11–13]. Upon searching the literature, we did not find any important study examining the relationship between thyroid hormones and GLP-1 levels. In our study, the GLP-1 levels were found to be increased in both the hypothyroidism and control groups after the glucose intake with OGTT; however, no difference was observed in the GLP-1 levels at baseline and after OGTT between the hypothyroidism and control groups. While peak GLP-1 levels were detected at 90 min in the hypothyroidism group, the fact that the peak GLP-1 level was observed at 30 min in a manner that would comply with the results reported in the literature indicates that hypothyroidism caused a delay in the peak GLP-1 response.

In our study, GLP-1 levels measured after ensuring the euthyroid state with the treatment remained unchanged in patients in the hypothyroidism group. Nevertheless, in the hypothyroidism group, the highest GLP-1 level was detected at 90 min before the treatment and the highest GLP-1 level was detected at 30 min after the treatment. This finding makes us to assume that the delayed peak GLP-1 response to OGTT in the hypothyroidism group improved by ensuring the euthyroid state with the treatment.

The most important limiting factors of our study were that we could not evaluate the gastric drainage time and the limited number of patients included in the study. However, important

data regarding the incretin system in patients with hypothyroidism were obtained despite these limitations. In patients with hypothyroidism, it was observed that, in particular, the peak responses of the incretin system hormones were considerably affected and considerable changes occurred in the incretin system with the improvement in hypothyroidism. Further studies with larger populations and calculating the gastric drainage time will contribute toward detecting the changes and the relationships among glucose, insulin, and incretin hormones in patients with hypothyroidism.

Conclusion

In patients with hypothyroidism, the incretin hormones, especially the peak response of the incretin system, are significantly affected. Significant changes were observed in the incretin system by correcting hypothyroidism.

Author contributions. SA and RS contributed substantially to the conception and design of this study. SA, NY, and SO contributed substantially to the acquisition of data. SA, SO, and RS analyzed and interpreted the data. SA and RS drafted the manuscript. NY and SO contributed substantially to its critical revision. All the authors approved the final version submitted for publication and take responsibility for the statements made in the published article.

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