

Ameliorative Effect of Ghrelin on Thyroxin Hormones and Body Weight in Hyperthyroidism Male rats

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Abstract

The study's objective is to evaluate the enhanced effect of the ghrelin on the body weight and thyroid hormones in male rats after inducing hyperthyroidism by L-thyroxin. The rats (95 males) were split into two groups. The first group consisted of 25 male rats that were given normal saline for 30 days S.C and set as a control group. While the remainder of the animals were given levothyroxine 500g/kg subcutaneously for 30 days to induce hyperthyroidism. after induction the divided into 4 groups as followe ,the first one was the control group that mentioned previously, the second group was male rats were given normal saline for 30 days S.C, the third group was male rats were given ghrelin at a dose of (0.5nmol/100µl saline) for 30 days S.C, and the fourth group was male rats (1nmol/100µl saline) for 30 days S.C. The fifth group consisted of hyperthyroidism male rats that was given ghrelin at a dosage of (2nmol/100µl saline) for 30 days S.C. The results of final weight and weight gain are presented showed no significant difference in initial weight within all groups that were observed, while a significant decrease in final body weight in hyperthyroidism group compared with control group. On the other hand, the results revealed a significant decrease in body weight gain in male rats have hyperthyroidism compared with the control group. While the results observed a significant increase final body weight and body weight gain in all treated rats with ghrelin as compared with hyperthyroidism group. On other hand, the effect of hyperthyroidism on serum TSH, T3, and T4 concentrations revealed that the hyperthyroidism group had a significant rise in serum T3 and T4 concentrations when compared to the control group. While no significant drop in serum TSH concentration was observed in all hyperthyroidism groups handled with ghrelin (0.5, 1 and 2 nmol) as compared to the hyperthyroidism group, a significant decrease in serum T3 and T4 level was observed in all hyperthyroidism groups treated with ghrelin in comparison to the group of hyperthyroidism. Ghrelin peptide hormone and it has been shown to have potential effects on the body weight and thyroid hormone.

Keywords: Hyperthyroidism, ghrelin, Levothyroxine, Thyroxin, rats

Introduction

Hyperthyroidism is a clinical condition defined by high serum concentrations of thyroxine (T4), triiodothyronine (T3), or both, as well as a restriction of serum thyroid-stimulating hormone (TSH) concentrations [1], which results in metabolic formation and acceleration of the production of free radicals to induce changes in the activity of antioxidant enzymes. Weight loss despite increased hunger, palpitation, agitation, tremors, dyspnea, fatigability, diarrhea, or enhanced gastrointestinal motility are all symptoms of hyperthyroidism. A patient having hyperthyroidism often has signs and symptoms consistent with this condition of elevated metabolic activity [2-3].

Ghrelin is a kind of human growth hormone (GH) Secretagogue is now recognized as a pleiotropic and ubiquitous hormone engaged in a variety of metabolic activities such as appetite control and weight regulation, glucose metabolism, obesity, reproduction, memory, learn, and reward-related pathways [4-5]. Ghrelin lowers inflammation by significantly suppressing the production of inflammatory cytokines and lowering oxidative stress in a variety of organs [6].

Ghrelin receptor engages with one another in many different organs, includes the stomach, pituitary, digestive system, and thyroid [7]. According to the enzyme ghrelin O-acyltransferase, acyl ghrelin (AG) is the major active isoform in the cytoplasm (GOAT) [8], Desacyl-ghrelin (DAG) was once assumed to be an inactive form of ghrelin. DAG has been linked to a variety of additional effects, but identifying potential alternative DAG receptors is crucial for understanding its distinct modes of action [9]. The different of ghrelin receptors sites

offers that ghrelin has a number of natural activities [10]. It reduces energy expenditure as well as TSH secretion. Previous study has shown that ghrelin lowers pituitary-thyroid nerve center activity [11-12-13]. Ghrelin has also been shown to stimulate desire via the neuropeptide Y (NPY) and agouti related protein pathways, while decreasing T3 and T4 synthesis [11-13]. Likewise, studies have shown that ghrelin can expand the development chemical delivery [14], gastric discharging rate; hunger and body weight and furthermore invigorate the emission of adrenocorticotrophic chemical and restraint of thyroid chemical fixations[15].

Materials and Methods

The present investigation was done at Basrah University/ Veterinary Medicine College. The study comprises two experiments a total of ninety five adult male rats (12 weeks old, weighing (250-300g) were used male rats were kept for adaptation period of one month.

Experimental design

First Experimental (hyperthyroidism-induce in male rat):- The rats were separated into two main groups: the first (Control group) consisted of 20 male rats. Normal saline was used to treat the control group, second group (positive group) (hyperthyroidism-induce in male rat): All the experimental animals were administered with L-thyroxine 500µg/kg body weight S/C daily for one month.

Second Experimental: After 30 days scarified ten male rats from each groups to confirm induction of hyperthyroidism. the From experiment one were divided into five main groups, each of 15 rats. control group of first experiment were administrated of s.c injection of 100 µl saline (served as control) for 30 days, second group hyperthyroidism-

induced rats administrated s.c injection of 100 µl saline (served as positive control) for 30 days, third group hyperthyroidism-induced rats were administrated Ghrelin (0.5nmol/100µl saline) s.c injection for 30 days, fourth group hyperthyroidism-induced rats were administrated Ghrelin (1nmol/100µl saline) s.c injection for 30 days, fifth group hyperthyroidism-induced rats were administrated Ghrelin (2nmol/100µl saline) s.c injection for 30 days.

Body weight and measurement of weight gain: The rats' weight was measured before and after the experiment.

At the end of the treatment ten rats from each group were sacrificed, then the samples of blood were collected from inferior vena cava of the heart and the organ thyroid gland were collected and preserved in 10% formalin for histological examination [16].

Hormonal Aanalysis: TSH, T4, and T3 levels in serum samples were determined using the (ELISA) method and the Elabscience kit[17].

Statistical Analysis

It was performed by single direction covariance (ANOVA) test and t-test. Utilizing SPSS (measurable bundles for the sociologies) program V. 21.[18] .

Results

Impact of hypthyroidism on body weight and body weight gain in male rats.

Table (1) shows that there was no significant ($P>0.05$) difference in beginning body weight between groups detected, however there was a significant ($P<0.05$) drop in final body weight in the hyperthyroidism group compared to the

control group. The results, on the other hand, demonstrated a substantial ($P<0.05$) reduction in body weight increase in hyperthyroid male rats in comparison to the control group.

Effect of Hyperthyroidism on Serum TSH, T₃ and T₄ Concentration in Male Rats.

Table (2) depicts the effect of hyperthyroidism on serum TSH, T₃, and T₄ concentrations, demonstrating that there was a significant ($P\leq 0.05$) rise in serum T₃ and T₄ concentrations in the hyperthyroidism group as compared to the control group. When compared to the control group, the hyperthyroidism group had a substantial ($P\leq 0.05$) drop in blood TSH concentrations.

Ghrelin's Effect on Final Weight and Weight Gain in Male Rats Having Hyperthyroidism Male Rats.

The data of body weight and body weight gain in Table (3) showed a substantial ($P\leq 0.05$) decrease in the last body weight and body weight gain of the hyperthyroidism group when compared with the control, while the results revealed a significant ($P\leq 0.05$) increase in the final body weight and body weight gain in all treated rats with ghrelin when compared with the hyperthyroidism group that the final body weight and body weight gain when treated with ghrelin in all groups.

Effect of Ghrelin on serum TSH, T₃ and T₄ in Hyperthyroidism Adult Male Rats.

Table (4) shows the impact of ghrelin on serum TSH, T₃ and T₄ levels. There's a significant ($P\leq 0.05$) decrease in serum TSH concentration of the hyperthyroidism group and all treated groups with ghrelin when compared to the control group, but no significant in serum TSH concentration was noticed in all hyperthyroidism groups treated

with ghrelin (0.5, 1 and 2 nmol) when compared to hyperthyroidism group.

Table (4) also shows that the hyperthyroidism group had a significant ($P \leq 0.05$) rise in serum T3 and T4 concentrations when compared to the control group, whereas the hyperthyroidism groups treated with ghrelin (0.5, 1 and 2 nmol) had a significant ($P \leq 0.05$) drop in serum T3 and T4 levels when compared to the hyperthyroidism group alone. There were no significant ($P \leq 0.05$) differences in serum T3 level in either of the ghrelin (1 and 2 nmol) treated groups when compared to the control group, but there was a significant ($P \leq 0.05$) increase in serum T3 in the hyperthyroidism group treated with ghrelin (0.5 nmol) when compared to the control group and other hyperthyroidism groups treated with ghrelin (1 and 2 nmol). In addition, no significant ($P > 0.05$) differences in serum T4 concentration were observed in both hyperthyroidism groups treated with ghrelin (0.5 and 1 nmol) in comparison to the control

group, while a significant ($P > 0.05$) decrease in serum T4 was

observed in the hyperthyroidism group treated with ghrelin (2 nmol) in comparison to the control group.

In contrast, a substantial ($P > 0.05$) drop in serum T4 was found in the hyperthyroidism group handled with ghrelin (2 nmol) when compared to the hyperthyroidism group treated with ghrelin (0.5 nmol). There were no significant ($P > 0.05$) variations in blood T4 concentrations between the hyperthyroidism group treated with ghrelin (2 nmol) as compared to the hyperthyroidism group treated with ghrelin (1 nmol). Also, no significant ($P > 0.05$) difference was noticed in serum T₄ concentrations of hyperthyroidism group treated with ghrelin (1 nmol) in comparison to the hyperthyroidism group treated with ghrelin (0.5 nmol).

Table 1: Impact of Hypthyroidism on body weight and body weight gain in male rats. (mean±SD) N=10.

Parameters	Body weight (g)		
	Initiate weight(g)	Final weight (g)	weight gain(g)
control group	273.68± 9.80a	293.62±24.66a	20.78±4.83a
Hyperthyroidism group	273.31± 6.57a	268.00± 18.26b	6.44±1.98 b

Significant differences at the ($P \leq 0.05$) level are denoted by values in tiny letters.

Table 2: Effect of Hyperthyroidism on Serum TSH, T₃ and T₄ Concentration in Male Rats.(mean±SD) N=10.

Parameter	TSH (μIU/ml)	T ₃ (ng/ml)	T ₄ (μg/dl)
Control	0.12±0.007a	1.29±0.34b	4.80±0.08b
Hyperthyroidism	0.03±0.012b	2.82±0.20a	6.25±0.80a

Significant differences at the (P≤0.05) level are denoted by values in tiny letters.

Table 3: Ghrelin's Effect on Final Weight and Weight Gain in Male Rats Having Hyperthyroidism Male Rats. (mean±SD) N=10.

Parameter	Initial body weight(g)	Final body weight (g)	Gain body weight (g)
Control	295.50±14.59 a	310.50±15.40 a	14.00±1.26 a
Hyperthyroidism	268.00±3.62 b	271.75±4.92 b	7.33±1.03 b
Hyper+(0.5 nmmol) GHR	267.62±4.17 b	290.37±3.20 a	13.66±0.98 a
Hyper+ (1 nmmol) GHR	266.50±4.53 b	291.37±2.61 a	13.58±0.91 a
Hyper+(2nmmol) GHR	268.00±2.07 b	294.00±3.85 a	13.91±1.02 a
LSD	7.34	7.44	1.24

Significant differences at the (P≤0.05) level are denoted by values in tiny letters.

Table 4: Effect of Ghrelin on Serum TSH, T₃ and T₄ in Hyperthyroidism Adult Male Rats. (mean±SD) N=10.

Parameter	TSH (μIU/ml)	T3 (ng/ml)	T4 (μg/dl)
Control	0.17±0.018a	1.17±0.05c	4.90±0.12b
Hyperthyroidism	0.07±0.024b	2.66±0.38a	6.26±0.49a
Hyper+(0.5GHR)	0.07±0.029b	2.05±0.15b	5.12±0.33b
Hyper+ (1 GHR)	0.06±0.027b	1.39±0.17c	4.81±0.29bc
Hyper+(2 GHR)	0.07±0.029b	1.20±0.04c	4.44±0.34c
LSD	0.10	0.24	0.40

Significant differences at the (P≤0.05) level are denoted by values in tiny letters.

Histopathological Analysis

Thyroid gland

Control rats' thyroid glands looked to have standard structure, with typical follicles (TF) of varied sizes walled by a singular epithelial cell layer and laden with emulsified colloid (C) surrounded by conventional parafollicular cells (PF), as shown in Fig. (1). Hyperthyroidism rats produced by thyroxine, on the other hand, displayed histological alterations such as disrupted and fused thyroid follicles (DF) and vacuolated cytoplasm (V) in the follicular cells, as seen in Fig (2). Whereas the histological section of the thyroid gland of hyperthyroidism rats treated with ghrelin (0.5nmol/100μl saline) showed virtually standard structure consisting of varied sizes of thyroid follicles brimming with emulsified colloid and typical parafollicular cells (Fig (3)). Furthermore, as shown in Fig. 4, thyroid sections from hyperthyroidism rats treated with ghrelin

(1nmol/100μl saline) revealed typical follicles packed with emulsified colloid. Eventually, the thyroid gland of hyperthyroidism pretreated with ghrelin (2nmol/100μl saline) group displays a virtually standard structure and presence, the gland consisting largely of follicles brimming with emulsified colloid and bordered by parafollicular cells, as seen in Fig. (5).

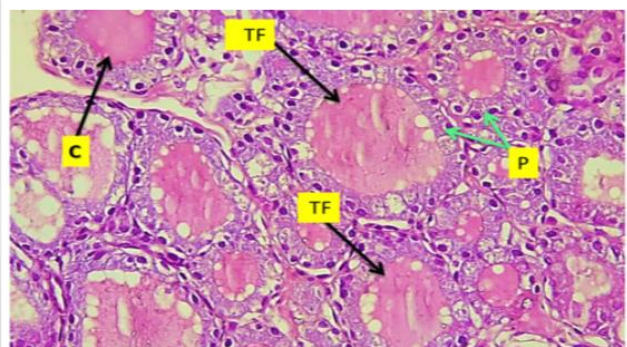


Fig. (1) Thyroid of control rat. Showing normal architecture of different sizes thyroid follicle (TF) filled with homogenized colloid (C) surrounded by normal parafollicular cells (P). (Hematoxylin-Eosin stain) 40X.

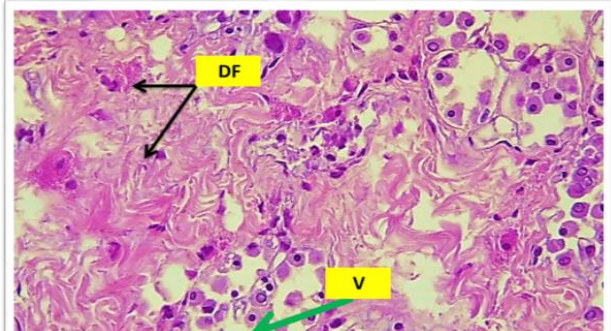


Fig. (2) thyroid gland in hyperthyroidism male rats group. The section shows disturbed and fused thyroid follicles (DF) (Black arrow) and vacuolated cytoplasm (green arrow) can be observed in the follicular cells. (Hematoxylin-Eosin stain) 40X.

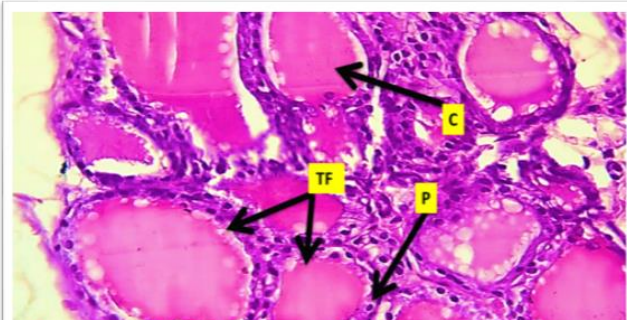


Fig. (3) thyroid of hyperthyroidism male rats treated with ghreline (0.5nmol/100µl saline). Showing normal thyroid follicles filled with homogenized colloid (C), surrounded by normal parafollicular cells (P). (Hematoxylin-Eosin stain) 40X 40X



Fig. (4) of hyperthyroidism male rats treated with ghreline (1nmol/100µl saline). Showing normal thyroid follicles filled with homogenized colloid (C), surrounded by normal parafollicular cells (P). (Hematoxylin-Eosin stain) 40X.

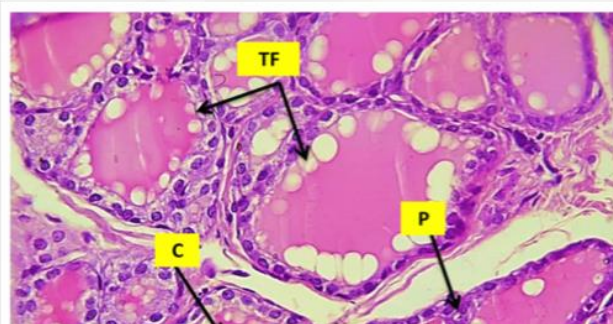


Fig. (5) hyperthyroidism male rat treated with ghreline (2nmol/100µl saline). Showing normal thyroid follicles filled with homogenized colloid (C), surrounded by normal parafollicular cells (P). (Hematoxylin-Eosin stain) 40X.

Discussion

The results show that adult male rats treated with thyroxin (500µg/kg b.w/day) for 30 days had a substantial decrease in the ultimate weight and weight growth, in comparison to the control group. The findings agreed with those of Kim *et al.*, [19] and Ros-Prego *et al.*, [20]. There are several theories regarding it. Hyperthyroidism prompts an expanded basal energy consumption that prompts weight reduction because of a decline in the body's fit and fat mass [21]. When compared to the hyperthyroid group, ghrelin had a better influence on body weight and weight growth in all treatment groups. These findings are consistent with those of Delporte [22] and Akalu *et al.* [23]. Anti-ghrelin antibodies were found to enhance energy expenditure in laboratory mice [24], this demonstrates ghrelin's role in energy regulation by increasing caloric intake while decreasing energy utilization [25]. The ghrelin receptors are an essential thermogenesis controller [26]. Ghrelin alerting through these receptors reduce thermogenesis, which reduces expenditure of energy [23, 27]. In addition to decreased thermogenesis, ghrelin reduces energy expenditure by lowering locomotory action [28] and decreasing the function of the thoughtful sensory system (SNS), notably in brown fat tissue (BAT) [29]. Ghrelin stimulates preadipocyte separation, adipogenesis, inhibits adipocyte death, and irritates lipolysis in rats [28]. Ghrelin promotes increased adiposity causes weight growth in the body [30, 31] in a method that is not dependent on food [32]. Ghrelin has been demonstrated to activate particular brain areas for its function in the control of food-related behaviors [33], such as the hypothalamic arcuate (ARC), where agouti-related peptide (AgRP)/ neuropeptide Y (NPY) neurones convey a negative valence signal [34], and the VTA, which contains dopamine

cells that signal reward. Ghrelin reduces energy expenditure in young healthy women, according to a research [35]. In mice, recombinant proghrelin stimulates food consumption during the photoperiod by going to act on a receptor that has not been identified specific from GHSR1a, but it does not cause weight gain. It reduces respiratory rest, resulting in rise in fat utilization and energies consumption, that is in contrast to the impact of acyl ghrelin [36]. Our analysis of this result could be the ghrelin led to the reduction of thyroxine hormone and thus led to a decrease in basal energy expenditure and an increase in fat mass in the body hyperthyroidism led to increase T3 and T4 while decrease TSH, this result agreement with several investigators [37, 38, 39, 40]. This hyperthyroid state saw here was additionally upheld by the diminished body weight gains and is reliable with the expanding in catabolic movement depicted in hyperthyroidism [41, 42]. When compared to the hyperthyroidism group, ghrelin considerably lowered thyroid hormone concentrations while having no effect on TSH. These data imply that ghrelin may influence the hypothalamus-pituitary-thyroid (HPT) axis. In actuality, a recent study in male rats found that after an intracerebroventricular infusion of ghrelin or a placebo every 24 hours for 5 days, pituitary thyroid stimulating hormone cells were more reasonable and TSH plasma levels were lower, and as a result, thyroid follicles were less dynamic and thyroxin (T4) plasma levels were lower compared to placebo-treated rats [43]. Furthermore, after 20 minutes, a ghrelin injection intraventricular (ICV) infusion resulted in considerably lower TSH plasma levels than a placebo treatment [44]. Ghrelin, on the other hand, showed no influence on TSH levels in investigations on canines (15-16) and humans (17-45). Furthermore, hexarelin, a synthetic GHS-R agonist, was reported to lower TSH after a

solar dose within 2 hours [46]. Despite this, hexarelin had no long-term effect on TSH levels [46]. Other evidence suggests that ghrelin plays a control function of the HPT axis: ghrelin-restricting destinations, perhaps unique to the GHS-R, have been discovered in the human thyroid [48, 49]. Ghrelin also increased in vitro TSH-induced rat thyrocyte development [50] while decreasing cell multiplication in human thyroid cancer cell lines [49]. Our findings are consistent with those of Kordi and Khazali [51], who found that intraventricular infusion of 5 nmol ghrelin substantially lowered plasma levels of T3 and T4. In the arcuate core, ghrelin creates an amalgamation of Agouti and neuropeptide Y. [14, 52]. It is also known that Agouti and neuropeptide Y immunoreactive axons densely innervate the neurons that secrete thyrotropin-releasing hormone (TRH) in the hypothalamic paraventricular nucleus (PVN). Furthermore, exogenous intraventricular (ICV) or PVN injections of Agouti or neuropeptide Y significantly pauses HPT action [53, 54]. As a result, ghrelin may impede thyroid function by increasing Agouti or neuropeptide Y. Also, Agouti has been shown to behave as an endogenous antagonist or inverse agonist at melanocortin receptors on TRH neurons. Several studies have revealed that arcuate alpha-melanocyte-stimulating hormone (α -MSH) neurons densely innervate PVN TRH neurons. As a result, there is a significant increase in TSH and thyroid chemical levels following ICV or paraventricular infusion of α -MSH [54, 55, 56]. Thus, we may expect ghrelin to have an inhibitory influence on the HPT axis, at least partially, due to a rise in Agouti levels and its antagonist action on α -MSH receptors. It has been postulated that localized ghrelin inhibits GABA firing from (gamma aminobutyric acid) Agouti or neuropeptide Y neurons in the nerve center. Inhibiting GABA release is included in the activation of CRF neurons (corticotropin releasing factor) and the increase of

corticotropin releasing hormone (CRH) from the hypothalamus [57]. Because CRH and cortisol have an inhibitory effect on plasma T3 and T4, [58, 59], inhibitory impact of ghrelin on thyroid may be somewhat causes of its stimulatory impact on nerve center -pituitary-adrenal axis.

Barington *et al.*, [60] the impact of ghrelin on the thyroid could be because of an energy saving technique in which the orexigenic impact of ghrelin along with the decreased metabolism prompts a less catabolic state. This is as per the reverse connection between thyroid chemicals and ghrelin found in patients with hyperthyroidism [61, 62] just as the repressing impact of ghrelin on the HPT axis shown in several in vivo studies [43, 44, 63].

Conclusions

Ghrelin peptide hormone produce by different tissues and it has been shown to have potential effects on the body weight and thyroid hormone which may be due to the direct effects on the hypothalamus-pituitary-thyroid axis.

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Conflict of Interest: The authors state that there is no conflict of interest.

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التأثير التحسيني لهرمون الكرتين على هرمونات الغدة الدرقية ووزن الجسم في ذكور الجرذان المصابة بفرط نشاط الغدة الدرقية

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الخلاصة

الهدف من الدراسة هو تقييم التأثير المعزز للكرتين على وزن الجسم وهرمونات الغدة الدرقية في ذكور الجرذان بعد احداث فرط نشاط الغدة الدرقية بواسطة ليفوثايروكسين(L-T4).تم تقسيم الفئران (95 ذكور) إلى مجموعتين. تتكون المجموعة الأولى من 25 ذكور جرذان تم إعطاؤهم محلول ملحي طبيعي لمدة 30 يوماً تحت الجلد وتم تعيينهم كمجموعة سيطرة. بينما تم إعطاء باقي الحيوانات ليفوثايروكسين 500 جم / كجم تحت الجلد لمدة 30 يوماً للاستحداث فرط نشاط الغدة الدرقية. بعد الاستحداث تم تقسيمهم إلى 4 مجموعات على النحو التالي ، المجموعة الأولى كانت المجموعة السيطرة التي ذكرت سابقاً ، المجموعة الثانية كانت ذكور الجرذان أعطيت محلول ملحي طبيعي لمدة 30 يوماً تحت الجلد ، المجموعة الثالثة كانت ذكور الجرذان أعطيت الجريلين بجرعة (0.5 نانومول / 100 ميكرو لتر من محلول ملحي) لمدة 30 يوماً تحت الجلد ، والمجموعة الرابعة كانت ذكور الجرذان المصابة بفرط نشاط الغدة الدرقية والتي تم اعطاؤها الكرتين بجرعة (1 نانومول / 100 ميكرو لتر من محلول ملحي) لمدة 30 يوماً تحت الجلد المصابة بفرط نشاط الغدة الدرقية والتي تم اعطاؤها الجرذان المصابة بفرط نشاط الغدة الدرقية والتي تم إعطاؤها الجريلين بجرعة (2 نانومول / 100 ميكرو لتر من محلول ملحي) لمدة 30 يوماً تحت الجلد. أظهرت نتائج عدم وجود فرق معنوي في الوزن الأولي في جميع المجموعات التي تمت ملاحظتها ، بينما انخفض وزن الجسم النهائي في مجموعة فرط نشاط الغدة الدرقية معنويًا مع مجموعة السيطرة. من ناحية أخرى ، أوضحت النتائج انخفاض معنوي في زيادة وزن الجسم لدى ذكور الجرذان المصابة بفرط نشاط الغدة الدرقية مقارنة بمجموعة السيطرة. بينما لوحظت النتائج زيادة معنوية في وزن الجسم النهائي وزيادة وزن الجسم في جميع الفئران المعالجة بالكرتين مقارنة بمجموعة فرط نشاط الغدة الدرقية. من ناحية أخرى ، أظهر تأثير فرط نشاط الغدة الدرقية على تراكيز TSH و T3 و T4 في الدم أن مجموعة فرط نشاط الغدة الدرقية لديها ارتفاع معنوي في تراكيز T3 و T4 في المصل بالمقارنة مع المجموعة السيطرة ام هرمون TSH قد انخفض في مجموعة فرط نشاط الغدة الدرقية مقارنة بمجموعة السيطرة. بينما لم يلاحظ انخفاض معنوي في تركيز هرمون TSH في الدم في جميع مجموعات فرط نشاط الغدة الدرقية التي تم التعامل معها مع الجريلين (0.5 ، 1 و 2 نانومول) مقارنة بمجموعة فرط نشاط الغدة الدرقية ، لوحظ انخفاض كبير في مستوى T3 و T4 في المصل في جميع مجموعات فرط نشاط الغدة الدرقية المعالجة بالكرتين بالمقارنة مع مجموعة فرط نشاط الغدة الدرقية. هرمون جريلين هو الببتيد وقد ثبت أن له تأثيرات على وزن الجسم وهرمون الغدة الدرقية.