The effects of low thyroid hormone levels on the formation of stress gastritis: an experimental study on the rats

Stres gastriti oluşumunda düşük tiroit hormon düzeylerinin etkisi: Sıçanlar üzerinde deneysel bir çalışma

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BACKGROUND

The aim of this study was to investigate the effect of low circulating thyroid hormone levels on the development of acute stress gastritis in rats.

METHODS

Sixty adult Sprague-Dawley rats were divided into six groups: Control group, surgically thyroidectomized group, stressed group, surgically thyroidectomized + stressed group, surgically thyroidectomized + T_4 + stressed group, and surgically thyroidectomized + T_3 + stressed group. Damage to the gastric mucosa was studied using millimetric acetate papers on photographs enlarged 3.5 times and the number and the size of the lesions was recorded.

RESULTS

Acute stress gastritis was significantly increased in stress + surgically thyroidectomized rats as compared to rats that were only put under stress (group III) (stress gastritis scores; group IV: 44, group III: 16, $p<0.001$). The stress gastritis score in group VI was significantly decreased compared to rats in group IV (stress gastritis scores; group VI: 10, group IV: 44, $p<0.001$).

CONCLUSION

Low circulating thyroid hormone levels in rats increased the development of stress gastritis. This effect could be prevented by thyroid hormone replacement therapy.

Key Words: Euthyroid sick syndrome; hypothyroidism; low serum triiodothyronine; low T3 sick syndrome; rats, Sprague-Dawley; stress gastritis; trauma.

AMAÇ

Bu çalışmanın amacı, sıçanlarda akut stres gastritis gelişmesinde düşük serum tiroit hormon düzeylerinin etkisini araştırmaktır.

GEREÇ VE YÖNTEM

Altmış erişkin Sprague-Dawley cinsi sıçan onarlı altı gruba ayrıldı: Kontrol grubu, cerrahi tiroidektomi grubu, stres grubu, cerrahi tiroidektomi + stres grubu, cerrahi tiroidektomi + T_4 + stress grubu ve cerrahi tiroidektomi + T_3 + stres grubu. Gastrik mukoza hasarının sayı ve büyüklüğü milimetrik asetat kağıdı kullanılarak 3,5 kez büyütülmüş fotoğraf üzerinde belirlendi.

BULGULAR

Sadece stres altında olan sıçanlar (grup III) ile karşılaştırıldığında cerrahi tiroidektomi + stres grubunda (grup IV) akut stres gastriti, belirgin olarak artmıştı (stres gastriti skorları; grup IV: 44, grup III: 16, $p<0,001$). Grup IV'teki sıçanlarla karşılaştırıldığında stres gastriti skorunun grup VI'da belirgin olarak azaldığı gözlendi (stres gastriti skorları; grup VI: 10, grup IV: 44, $p<0,001$).

SONUÇ

Sıçanlarda düşük serum tiroit hormon düzeyleri stres gastritinin gelişmesini artırmakta ve bu etki, tiroit hormon replasman tedavisi ile önlenebilmektedir.

Anahtar Sözcükler: Düşük T3 hasta sendromu; düşük serum triiyodotironin; hipotiroidi; ötiroid hasta sendromu; sıçan, Sprague-Dawley cinsi; stres gastriti; travma.

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Stress gastritis and resulting acute upper gastrointestinal bleeding are serious concerns when evaluating critically ill patients. Euthyroid sick syndrome (ESS), characterized by low serum 3,5,3'-triiodothyronine (T3) with normal L thyroxine levels, is associated with a wide variety of disorders including sepsis, malignancy, and AIDS.[1-5] A clinical correlation has been observed between ESS patients and patients suffering from bleeding due to stress gastritis.[6] However, the relationship between gastrointestinal function and hypothyroidism is still unclear.

The aim of this study was to investigate the effects of low thyroid hormone levels on the development of stress gastritis and to determine the effect of thyroid hormone replacement therapy on stress gastritis.

MATERIALS AND METHODS

The subjects for the experiment were adult male Sprague-Dawley rats weighing 300-350 g. The animals were randomly divided into six groups, each containing 10 animals:

Group I: Control group (C) (n=10);

Group II: Surgically thyroidectomized group (ST) (n=10);

Group III: Stressed group (S) (n=10);

Group IV: Surgically thyroidectomized plus stressed group (ST + S) (n=10);

Group V: Surgically thyroidectomized plus T_4 plus stressed group (ST + T_4 + S) (n=10);

Group VI: Surgically thyroidectomized plus T_3 plus stressed group (ST + T_3 + S) (n=10);

Group I: The rats in this group were allowed free access to food (prepared pellet feed) and water and were kept in the same environment as the other animals. They were sacrificed after 8 weeks. Following sacrifice, thyroid hormone levels were measured and the stomachs of the rats were removed, opened and examined (Fig. 1a).

Group II: The rats in this group were surgically thyroidectomized and sacrificed after 8 weeks. In thyroidectomy; after anesthesia, the rats were positioned to supine. Collar incision was done. Thyroid was found in environment of trachea. The thyroidectomy was done with 22 gauge needle. Thyroid was dissected slowly, slightly and totally with needle. Then the wound was sutured with absorbable sutures.[7] The stomachs were examined and the serum thyroid hormone and calcium levels were measured (Fig. 1b).

Group III: The rats in this group were stressed by starvation + mobility restriction before sacrifice. Their stomachs were examined and the serum thyroid hormone levels were measured (Fig. 1c).

Group IV: The rats in this group were surgically thyroidectomized. Eight weeks after the operation, these animals were subjected to starvation and mobility restriction. The rats were then sacrificed. Their stomachs were examined and the serum thyroid hormone and calcium levels were measured (Fig. 1d).

Group V: The rats in this group were surgically thyroidectomized. Eight weeks after surgery, they were treated with a T_4 dissolved tablet solution of 1600ng/100gr body weight/day via the orogastric route for seven days.[5] At the end of the seven days, starvation and mobility restriction were applied and the animals were sacrificed. The stomachs were examined and the serum thyroid hormone and calcium levels were measured (Fig. 1e).

Group VI: The rats in this group were surgically thyroidectomized. Eight weeks later they were treated with a T_3 dissolved tablet solution of 0.4 microg/100gr body weight/day via the orogastric route, divided into two equal daily doses for seven days.[5] At the end of the seven days, starvation and mobility restriction were applied and the rats were sacrificed. Their stomachs were examined and the serum thyroid hormone and calcium levels were measured (Fig. 1f).

Diethyl ether was used to anesthetize the rats and bilateral total thyroidectomy was performed. To prevent the possibility of parathyroid disorder, 1% calcium gluconate was added to their water at postoperative 8th week (in the group V and VI, 9th week).

The stressors applied to the animals were starvation and mobility restriction. The animals were starved in their cages for 24 hrs (free access to water was allowed), followed by mobility restriction for 24 hrs. The anterior extremities of the rats were covered with tape and fastened to a wooden plate with a thumbtack through the tips of the tape.

The posterior extremities were taped and fastened together onto the plate.

At the end of the stress period diethyl ether was used to anaesthetize the animals.

Blood samples were taken from their hearts and stored at -20 °C in order to measure serum T_3, T_4, TSH and calcium levels. Immediately after the rats were sacrificed, the stomachs were rapidly removed, opened along the greater curvature and gently washed with 0.9% NaCl solution. Photographs of the stomachs were taken and they were put in 10% formalin solution.

Damage to the mucosa was studied using millimetric acetate papers on photographs enlarged 3.5 times, and the number and the size of the lesions was recorded. Scores were calculated according to the system suggested by Cioli et al.[6] In this system, punctiform lesions were lesions <1 mm in length; small lesions were 1 to 2 mm in length, and large lesions were >2 mm of length (Table 1).

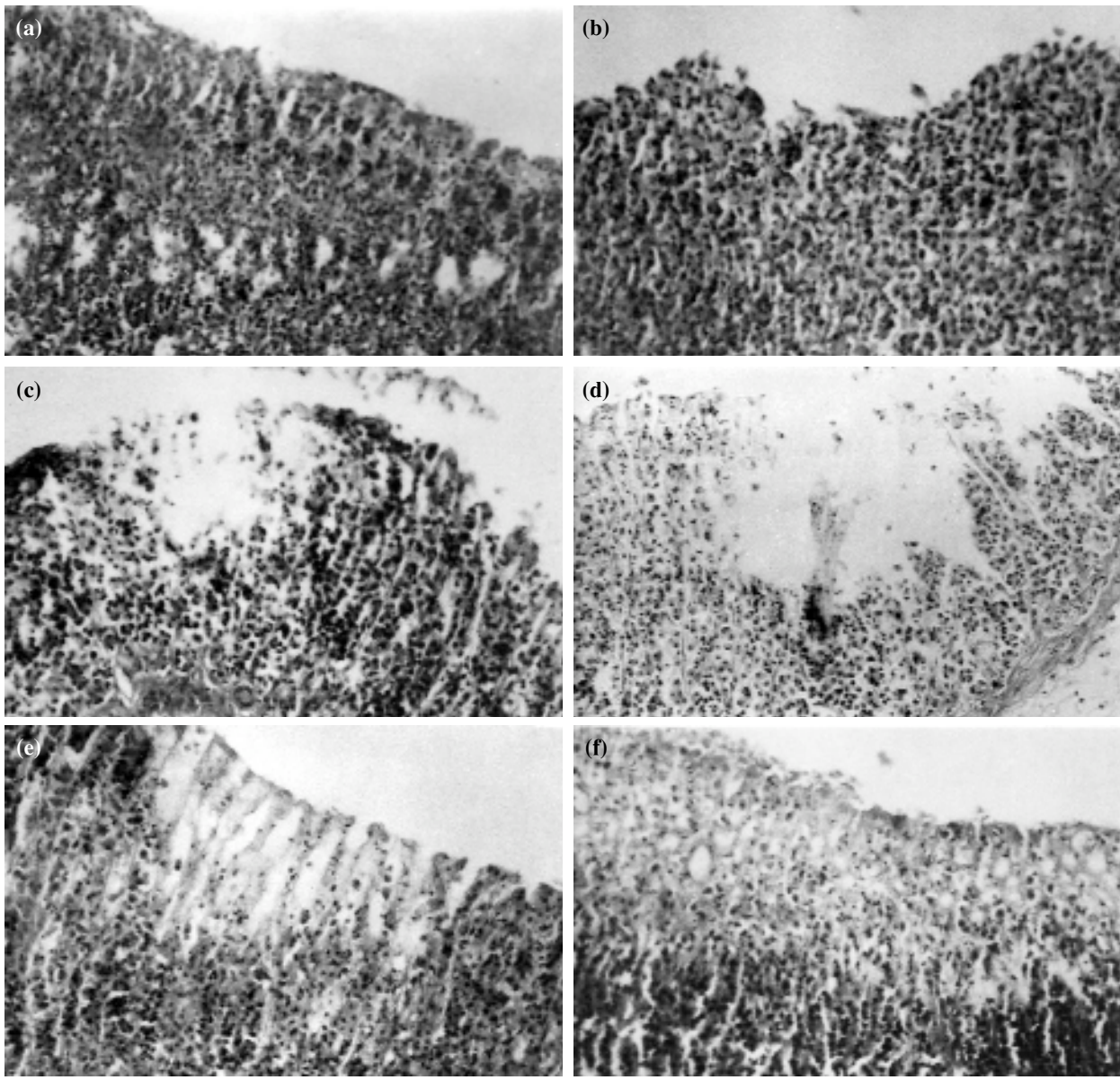

Fig. 1. The microscopic views of the rat's stomach in **(a)** the control group (H-E, 4x10), **(b)** the surgical thyroidectomy group (H-E, 4x10), **(c)** the stress group (H-E, 4x10), **(d)** the surgical thyroidectomy + stress group (H-E, 4x10), **(e)** the ST + T_4 + stress group (H-E, 4x10), **(f)** the ST + T_3 + stress group (H-E, 4x10).

Table 1. Lesion scores of the rat stomachs

Score 0	0-3 punctiform lesions
Score 1	3-10 punctiform lesions
Score 2	More than 10 punctiform lesions
Score 3	1-3 small lesions
Score 4	More than 3 small lesions or one large lesion
Score 5	More than 1 large lesions

Thyroid tissue samples were surgically removed and studied in pathology laboratories. A histopathological analysis of the stomach was made and photographs were taken.

We used the Orion Diagnostica (Espoo, Finland) coated tube T_3 and T_4 test procedures (based on radioimmunoassay techniques) to measure serum T_3 and T_4 levels. We used the Farmos Diagnostica (Espoo, Finland) coated tube TSH - IRMA test procedure (based on the principles of a non-competitive immunoradiometric assay) to measure serum TSH levels.

The study was designed and conducted according to the guidelines of the Helsinki Declaration and the International Guiding Principles for Biomedical Research Involving Animals. It was approved by the local ethical committee.

Statistical analysis was performed using Kruskall Wallis variance analysis test, Chi square test and median test technique. The Kruskall Wallis variance analysis test and Chi square test were used for comparing the differences of the groups. Median Test Technique was used to compare the rank of the differences of the groups.

RESULTS

The mean stress gastritis scores of the control group and the ST group were 0±0. In the control group the mean serum T_3 and serum T_4 levels were 1.85±0.49 nmol/L and 62.1±12.35 nmol/L respectively. In the ST group the same mean levels were 0.24±0.13 nmol/L and 8.7±3.47 nmol/L respectively.

In the stress group the mean serum T_3 and serum T_4 levels were 0.90±0.12 nmol/L and 29.2±7.11 nmol/L respectively. The mean stress gastritis score was 1.6±1.07. In the ST plus stress the mean serum T_3 and serum T_4 levels were 0.46±0.18 nmol/L and 11.9±3.45 nmol/L respectively. The mean stress gastritis score of this group was 4.4±0.51. This group had the highest mean stress gastritis score.

In the ST plus T_4 plus stress group the mean serum T_3 and serum T_4 levels were 5.57±0.96 nmol/L and 188.2±10.89 nmol/L respectively. The mean stress gastritis score of this group was 1.8±1.13.

In the ST plus T_3 plus stress group the mean serum T_3 and serum T_4 levels were 3.06±0.93 nmol/L and 11.6±2.76 nmol/L respectively. The mean stress gastritis score of this group was 1±0.47.

Stress gastritis score was “0” in control and surgical thyroidectomy group. The most highest stress gastritis score was 3 in stress group. Only one rat score was “0”. The most highest score was in surgical thyroidectomy + stress group. Surgical thyroidectomy + T_4 + stress and surgical thyroidectomy + T_3 + stress groups were compared with surgical thyroidectomy + stress group, stress gastritis scores were down significantly in T_4 and T_3 replacement groups. Table 2 has the total number of stomach mucosal lesions and the scores of all experimental groups.

Using the Kruskall Wallis variance analysis test a significant difference was found between groups IV, V and VI. Thyroid hormone replacement therapy was considered to be useful (Table 3: The effects of stress, thyroidectomy and thyroid hormone replacement on the development of stress gastritis in rats.).

Table 2. Totally number and score of the stomach mucosa lesions in all the experimental groups

Lesions	C	ST	S	ST + S	ST +T_4 + S	ST + T_3 + S
Punctiforms (<1 mm)	5	6	44	0	42	67
Small lesions (1-2 mm)	0	0	4	21	6	0
Large lesions (>2 mm)	0	0	0	11	0	0
Total scores of the lesions	0	0	16	44	18	10

Table 3. The effects of stress, thyroidectomy, and thyroid hormone replacement on the development of stress gastritis in rats

Group	Stress	ST	Replacement T_3	Replacement T_4	T_3 nmol/L	T_4 nmol/L	Total stress gastritis scores
I	–	–	–	–	1.85±0.49	62.1±12.35	0
II	–	+	–	–	0.24±0.13	8.7±3.47	0
III	+	–	–	–	0.90±0.12	29.2±7.11	16
IV	+	+	–	–	0.46±0.18	11.9±3.45	44
V	+	+	–	+	5.57±0.96	188.2±10.89	18
VI	+	+	+	–	3.06±0.93	11.6±2.76	10

N=10, All of the group.

Analysis using the Median test technique found that group IV had the highest significant difference in terms of gastritis scores ($p<0.001$). It was followed by the score differences of group V ($p<0.01$), group III ($p<0.001$) and group VI ($p<0.001$). The scores of the first and second groups were zero.

DISCUSSION

Low T_3 levels in the circulation has been shown to correlate with the severity of the underlying disorders and with the prognosis.[8,9] ESS is a manifestation of hypothalamic-pituitary dysfunction, and in view of current evidence should be treated with appropriate replacement therapies.[10,11]

Metabolic depression brought about by hypothyroidism has been associated with a decrease in oxidant production and with protecting tissues from lipid peroxidation.[12-15] It has been claimed that in disorders other than thyroid disorders, the reduction of serum T_3 levels is due to reduction of thyroid secretion, reduction in the transformation of peripheral T_4 into T_3, increase in T_3 concentration in tissues, increase in T_3 metabolism, or several combinations of these factors.[16] In euthyroid sick syndrome, peripheric 5 monodeiodinaz activity may be reduced. TSH secretion and transformation of T_4 into T_3 is inhibited as a result of increased glucocorticoids due to stress, and reverse T_3 formation is increased.[17-19] The reduction of total T_4 levels in severe illnesses could result from several factors, such as a modification in serum thyroxin binding proteins, an increase in T_4 catabolism, a reduction of T_4 release from the thyroid[16,18,20,21] and the inhibition of TSH secretion for any of several reasons. Endoscopic studies reported that the surface erosion was 86-100% in patients with a risk of developing stress gastritis.[22] Actually, the incidence of severe upper gastrointestinal bleeding as a consequence of stress gastritis is low, but the mortality is high when they are seen together. For this reason it is more important to prevent stress gastritis than to treat it.[23,24] The relationship between gastrointestinal function and hypothyroid status is unclear. Increased development of stress gastritis in hypothyroidism could be due to reduced metabolism, hypogastrinemia, or the reduced trophic effect of thyroxin on the gastrointestinal mucosa.[25] Thyroid hormones are essential for the continuity of metabolism. Johnson showed that gastrin had a trophic effect on the gastric mucosa,[26,27] and it has been shown that T_4 hormone has a smaller trophic effect on the gastrointestinal mucosa.[28] In cases of absent or insufficient thyroid hormone, the metabolic rate decreases and this decreased can cause a decreased in the rate of cell repair or renewal. As a result, there would be more damage and tissue destruction. During stress, insufficient amounts of thyroid hormone could negatively affect cell formation.[29] In this study, decreased metabolic rate was observed in surgically thyroidectomized, and surgically thyroidectomized + stress group rats. These rats were hypoactive. Their hairs were decreased.

Many studies have shown that hypothyroidism significantly increases stress gastritis.[25,30] Our study only showed a significant difference in the stress gastritis scores of the stressed group and the ST plus stress group. In the ST plus stress group, the stress gastritis score was approximately three times that of the stressed group. Furthermore, in this study the gastrin levels of the ST group were not measured since the stress gastritis score was zero. If

the stress gastritis score in this group was greater than zero, the gastrin levels would have been measured based on suspicion of hypogastrinemia together with hypothyroidism. It has been shown that T_4 hormone is less trophic for the gastrointestinal mucosa. Our study showed that T_4 does not have a trophic effect on the stressed group in which the T_4 hormone was found to be low.

Money et al. stated that in rats a low serum T_3 level increases the risk of stress gastritis and this effect can be reduced through thyroid hormone replacement therapy.[25] Kaynaroğlu and Gökçe stated in their experimental study that in rats, the reduction in thyroid hormones following thyroidectomy increased stress gastritis significantly.[30] In severely ill patients the question of whether to use thyroid hormone replacement therapy to reduce morbidity and mortality is still unresolved. Although some experimental studies emphasize the necessity of hormone administration, others do not. Researchers advocating the former suggest that positive results are obtained by this treatment. On the other hand, researchers advocating the latter suggest that in seriously ill patients, the body adapts to the situation with low metabolism and less energy usage.[18,25,29,31] In this study it was observed that low serum thyroid hormone levels due to total thyroidectomy increased the formation of stress gastritis in rats under stress and this effect could be prevented through thyroid hormone replacement therapy.

The presence of a 'low T_3 syndrome' in the setting of nonthyroidal illness has long been recognized with the recommendation being to observe and not treat with thyroid hormone replacement therapy. That approach has recently been challenged in the setting of critical cardiac illness. Research demonstrating that thyroid hormone therapy may improve hemodynamic parameters has rekindled interest in the use of thyroid hormone therapy in critical illness.[10,32-34]

In conclusion, low thyroid hormone levels increase stress gastritis, and the affect of low thyroid hormone levels can be decreased by thyroid hormone replacement therapy. More experimental studies are needed to explain the development of stress gastritis when thyroid hormone levels are low. Finally, more comparative studies are needed to determine the utility of administrating thyroid hormones to stress gastritis patients.

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