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ARAŞTIRMA / RESEARCH

Evaluation of physical and vital signs and the effect of carnosine in experimental hyperthyroidism

Deneysel hipertiroidide fiziksel ve vital bulguların ve karnozinin etkisinin değerlendirilmesi

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Abstract

Purpose: This study aims to investigate the effects of experimental hyperthyroidism and carnosine which is known to have antioxidant properties on physical and vital findings in rats, and to determine the relationship between these parameters and free T3 (FT3) levels.

Materials and Methods: Rats were analyzed in 7 groups (each containing 12 animals); control (CONT), hyperthyroidism-1 (T:10-day L-thyroxine (L-T4) administration), hyperthyroidism-2 (T-T: 20-day L-T4 administration), Carnosine (10 day carnosine administration), Hyperthyroidism-1 + Carnosine (T-C), Hyperthyroidism-2 + Carnosine (T-TC), and Carnosine + Hyperthyroidism-1 (C-T). In order to create a hyperthyroidism model, L-thyroxine (L-T4) doses of 300 µg/kg rat weight/day and carnosine doses of 300 µg/kg rat weight/ day were intraperitoneally (ip) administered to the rats.

Results: After 10 and 20 days of thyroxine administration, FT3 levels (T:3.64±0.51pg/mL, T-T: 4.06±0.91pg/mL) and body temperature (T:37.1±0.3oC, T-T: 37.6±0.3oC), significantly increased while body weight decreased (T:240.7±22.0g, T-T:263.0±28.7g). Carnosine administration only prevented the increase of FT3 levels, but had no effect on other parameters.

Conclusion: The increased FT3 levels observed with L-T4 administration were consistent with the physical and vital findings, but carnosine administration did not reflect the expected effects on the physical findings observed in the hyperthyroid condition.

Keywords:. Hyperthyroidism, body temperature, heart weight, body weight, carnosine.

Öz

Amaç: Bu çalışmada, deneysel hipertiroidinin ve antioksidan özelliği bilinen karnozinin ratların fiziksel ve vital bulgular üzerine etkilerinin araştırılması; ve bu parametreler ile serbest T3 (FT3) seviyeleri arasındaki ilişkinin belirlenmesi amaçlandı.

Gereç ve Yöntem: Ratlar; her biri 12 rattan oluşan (n=12) kontrol (CONT), hipertiroidi 1 (T), hipertiroidi 2 (T-T), Hipertiroidi-1 + Karnozin (T-C), Hipertiroidi-2 + Karnozin (T-TC), Karnozin (C) ve Karnozin + Hipertiroidi-1 (C-T) olmak üzere yedi gruba ayrıldı. Ratlarda hipertiroidi modeli oluşturmak için intraperitoneal (ip) olarak rat ağırlığı/gün başına 300 µg/kg L-tiroksin (L-T4) ve karnozinin etkilerinin belirlenmesi için rat ağırlığı/gün başına 300 µg/kg dozunda karnozin (ip) uygulandı.

Bulgular: 10 ve 20 günlük tiroksin uygulaması ile FT3 düzeylerinin (T:3.64±0.51pg/mL, T-T: 4.06±0.91pg/mL) ve vücut sıcaklığının (T:37.1±0.3oC, T-T: 37.6±0.3oC) anlamlı şekilde arttığı, vücut ağırlığının (T:240.7±22.0g, T-T:263.0±28.7g) azaldığı tespit edildi. Karnozin uygulamasının etkileri incelendiğinde, sadece profilaktik uygulamada FT3 düzeylerinin yükselmesini engellediği, diğer parametreler üzerinde iyileştirici etkisinin olmadığı görüldü.

Sonuç: L-T4 uygulamasıyla gözlenen artmış FT3 düzeylerinin elde edilen fiziksel ve vital bulgularla uyumlu olduğu ancak karnozin uygulamasının hipertiroidik tabloda gözlenen fiziksel bulgular üzerinde beklenen etkileri yansıtmadığı tespit edildi.

Anahtar kelimeler: Hipertiroidi, vücut sıcaklığı, kalp ağırlığı, vücut ağırlığı, karnozin

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INTRODUCTION

Hyperthyroidism, in its most general definition, is known as the increase of L-3,5,3',5'-tetraiodothyronine (T4) and L-3,5,3'-triiodothyronine (T3) levels in plasma as a result of overactivity of the thyroid gland. T3 and T4 are the main thyroid hormones that are derived from tyrosine amino acids, have a 4'-hydroxy diphenyl ether structure, contain iodine atoms in their phenolic rings, and show biological activity[1,2]. Thyroid hormones, which are important regulators of gene expression, accompany many metabolic processes such as cell growth, development, homeostasis and differentiation as a result of their interactions with their receptors[3].

Free radicals are formed as a result of oxidative cell metabolism and play a role in some cellular processes. These radicals are in balance with antioxidants and thus the organism is protected from their damaging effects. However, in pathological conditions, including hyperthyroidism, this balance is disrupted and oxidative stress occurs[4].

It is thought that treatment with antioxidants can be helpful because free oxygen radicals increase in patients with hyperthyroidism thus, weakening the antioxidant system[5,6].

Carnosine, an endogenous dipeptide composed of β-alanine and L-histidine, is found naturally in the skeletal muscles, brain, and heart of an organism. It can be taken through diet or can be directly synthesized in glial cells and myocytes by carnosine synthase. Acid-base buffer activity, metal chelation, and antioxidant/antitoxic activities of carnosine have been demonstrated [7].

Thyroid hormones, which are known to affect various mitochondrial functions such as energy homeostasis, thermogenesis, oxygen consumption, oxidative phosphorylation, and proton leakage, cause an increase in body temperature and weight loss, and also affect cardiac weight through different mechanisms[8]. Thus, it has also been recommended in experimental studies in the literature to use physical and vital signs, such as serum/plasma free T4 (FT4)[9] and free T3 (FT3)[10] levels as well as body weight (BW)[9-11], heart weight/BW ratio (HW/BW)[9,10] and body temperature (BT) values[11-14] to diagnose hyperthyroidism.

Although hyperthyroidism has been investigated in different ways mentioned in the literature, no study has been found in which all these vital signs were evaluated together in terms of both the development of hyperthyroidism and the effectiveness of carnosine.

In this study, it was aimed to examine the effect of L-thyroxine applied to rats to induce hyperthyroidism and carnosine applied individually or together with L-thyroxine on physical and vital signs, and also to compare the relationship between these parameters and FT3 levels.

MATERIALS AND METHODS

Animals and treatment

In one way ANOVA study, sample size of 12 for 7 groups whose means are to be compared. Total sample of 84 subjects achieved 95% power to detect differences among the means versus the alternative of equal means using an F test with a 0,05 significance level.

The study group consisted of 84 male Wistar rats that were 90-110 days old and weighed 200-310 g. During the study, the rats were kept at normal room temperature (22±1°C) and humidity on a 12-hour light/dark cycle and were fed with standard pellet feed and tap water. In order to adapt them to the environment, the rats were taken into the same experimental environment at least one week before the study.

Seven groups, each containing 12 animals, were randomly formed: the Control (CONT), Hyperthyroidism-1 (T), Hyperthyroidism-2 (T-T), Carnosine (C), Hyperthyroidism-1 + Carnosine (T-C), Hyperthyroid-2 + Carnosine (T-TC), and Carnosine + Hyperthyroid-1 (C-T).

L-T4 (89405; Fluka) was administered to the rats intraperitoneally (*ip*) at a dose of 300 μg/kg rat weight/day and was applied to the T group for 10 days and to the T-T group for 20 days to mimic the hyperthyroid state. Carnosine (100936; MP Biomedicals), on the other hand, was administered at a dose of 300 mg/kg rat weight/day for 10 days alone in the C group; for 10 days after 10 days of L-T4 administration to the T-C group. Carnosine was administered simultaneously with the 10-day L-T4 administration following the 10-day L-

T4 administration to the T-TC group. In the C-T group, carnosine was administered for 10 days after the 10-day L-T4 administration. 0.01M NaOH for L-T4 and saline for carnosine were used as solvents. Animals in the control group were given only solvent agents for 10 days.

Determination of plasma concentrations of thyroid hormones

FT3 levels in the initial and final plasma samples of the rats were determined using the rat FT3 kit (Cusabio Tech., Catalog No: CSB-E05076r) using the ELISA method.

Measuring the physical and vital signs

After the administration, to investigate the physical and vital signs in the hyperthyroid state, the body weight (BW) and rectal body temperature (BT) of the rats were measured and recorded during the study. The rectal body temperature of rats was measured with a clinical thermometer by entering 4 cm from the rectum [15]. BW and BT were measured on the first, 10th, and 20th days of the study. In addition, at the end of the study, the hearts taken from the rats under ketamine hydrochloride (Ketalar-Pfizer®, 80 mg/kg body weight)/xylazine hydrochloride (Rompun-Bayer®, 10 mg/kg body weight) anesthesia were weighed, and HW/BW ratios were calculated.

In this study, in accordance with the "Guideline for the Care and Use of Laboratory Animals", animal rights are protected. This study was supported by Erciyes University, Turkey Scientific Research Projects (Project number: TSD-10-3080) and approved by Erciyes University Experimental Animals Ethics Committee (dated 13.01.2010, meeting number 1, decision no: 10/1). The study was carried out in Erciyes University Experimental Research and Application Center and Research Biochemistry Laboratory, Kayseri, Turkey.

Statistical analysis

Statistical analyzes were carried out with the computer package program "SPSS 15.0 for Windows". The compliance of the data to normal distribution was checked with the Shapiro-Wilk test. The data were presented as mean ± standard deviation. İnitial and final fT3 levels compared with paired t-test. In-group analyzes, 1st, 10th and 20th days were performed using the Friedman test and paired t-test, and between-group analyzes were performed using the ANOVA and post-ANOVA tests. In all statistical comparisons, the significance level was accepted as $p<0.05$.

RESULTS

Two rats in each of the T, T-T, and C groups, and one rat in each of the T-C, T-TC, and CONT groups could not complete the study due to intracardiac blood draws to determine baseline plasma FT3 levels.

When evaluated in terms of hyperthyroidism formation, there was no difference in plasma FT3 levels between the groups at the beginning, while a significant increase at the end of the application in the T and T-T groups compared to the baseline and control values which in turn confirmed the formation of hyperthyroidism with L-T4 at the applied dose and time. However, although there was a numerical increase, no significant difference was observed between the T and T-T groups. It was observed that the CONT, C, and C-T groups did not differ from the initial values, while plasma FT3 values were higher in the T-C and T-TC groups compared to the baseline (Table 1).

In the in-group comparisons made to determine the effects of the administrations on body weight, similar results were obtained regarding the decrease in body weight in all groups except the significant increases in the CONT and C groups at the end of the 10th day. At the end of the 20th day, it was observed that the body weights in the T-T and T-C groups were significantly higher than the measurements made on the 10th day, and decreased significantly in the C-T group. It was found that the body weights of the rats in the T-T, T-TC, and C-T groups decreased significantly on the 20th day compared to the 1st day, and increased significantly in the T-C group compared to the initial values.

In the comparisons between the groups, it was seen that there was no significant difference in the body weights of the rats on the 1st and 10th days. It was observed on the 20th day of the application that the body weights of the rats in the T-C group were higher than the body weights of the rats in the T-TC and C-T groups (Table 2).

Table 1. Initial and final plasma FT3 values of the rats

	Plasma FT3 (pg/mL)		
GROUP	N	Initial	Final
CONT	11	2.13 ± 0.39	2.16 ± 0.27
T	10	2.54 ± 0.59	3.64 ± 0.51◊,*
T-T	10	2.48 ± 0.19	4.06 ± 0.91◊,*
T-C	11	2.19 ± 0.45	3.43 ± 0.82◊,*
T-TC	11	2.35 ± 0.21	4.46 ± 1.30◊,*
C	10	2.13 ± 0.40	2.04 ± 0.6a,b,c,d
C-T	12	2.36 ± 0.64	2.06 ± 0.36 a,b,c,d

Control (CONT), Hyperthyroidism-1 (T), Hyperthyroidism-2 (T-T), Carnosine (C), Hyperthyroidism-1 + Carnosine (T-C), Hyperthyroid-2 + Carnosine (T-TC), and Carnosine + Hyperthyroid-1 (C-T).
Significant results were obtained with the comparison of the *: CONT; a: T; b: T-T, c: T-C, and d: T-TC groups with the other groups. Significant findings were found in the comparisons within groups: ◊: comparison result of days initial-final.

Table 2. Change of rat body weights during the study

GROUP	**n**	**Day 1**	**Day 10**	**Day 20**
CONT	11	271.8 ± 42.1	278.7 ± 41.9♦	-
T	10	253.5 ± 19.7	240.7 ± 22.0♦	-
T-T	10	272.7 ± 31.1	256.6 ± 30.8♦	263.0 ± 28.7◊,●
T-C	11	275.4 ±2 0.8	260.4 ± 13.3♦	282.5± 14.7◊,●
T-TC	11	266.8 ± 27.4	248.0 ± 24.8♦	245.4 ± 22.3 ●,c
C	10	285.8 ± 41.1	286.5 ± 41.1	-
C-T	12	265.7 ± 24.3	262.0 ± 24.7♦	247.3 ± 21.0 ◊,●,c

Control (CONT), Hyperthyroidism-1 (T), Hyperthyroidism-2 (T-T), Carnosine (C), Hyperthyroidism-1 + Carnosine (T-C), Hyperthyroid-2 + Carnosine (T-TC), and Carnosine + Hyperthyroid-1 (C-T).
Significant findings were found in the comparisons within groups: ♦: comparison result of days 1-10; ●: comparison result of days 1-20; and ◊: comparison result of days 10-20. Significant findings in comparisons between groups were obtained by comparing c: T-C group with the other groups were also found.

Table 3. Change of rat rectal body temperature (BT) by time

		Rectal body temperature values (°C)		
GROUP	n	Day 1	Day 10	Day 20
CONT	11	36.5 ± 0.1	36.6 ± 0.3	-
T	10	36.3 ± 0.3	37.1 ± 0.3♦	-
T-T	10	36.2 ± 0.4	37.3 ± 0.4♦,*	37.6 ± 0.3●
T-C	11	36.1 ± 0.3	37.0 ± 0.4♦	36.9 ± 0.3●,b
T-TC	11	36.3 ± 0.3	37.6 ± 0.3♦,*,c	37.8 ± 0.3●,c
C	10	36.3 ± 0.4	36.8 ± 0.3♦,d	-
C-T	12	36.3 ± 0.3	36.9 ± 0.3♦,d	37.6 ± 0.3●,c

Control (CONT), Hyperthyroidism-1 (T), Hyperthyroidism-2 (T-T), Carnosine (C), Hyperthyroidism-1 + Carnosine (T-C), Hyperthyroid-2 + Carnosine (T-TC), and Carnosine + Hyperthyroid-1 (C-T).
Significant results were obtained with the comparison of the *: CONT; a: T; b: T-T, c: T-C, and d: T-TC groups with the other groups. Significant findings were found in the comparisons within groups: ♦: comparison result of days 1-10; ●: comparison result of days 1-20; and ◊: comparison result of days 10-20.

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Table 4. HW and HW/BW values of the study groups

GROUP	n	HW (g)	HW/BW(mg/g)
CONT	11	0.77 ± 0.10	2.56 ± 0.83
T	10	0.94 ± 0.10	3.90 ± 0.22*
T-T	10	1.05 ± 0.09*	4.03 ± 0.39*
T-C	11	0.91 ± 0.09	3.23 ± 0.25[b]
T-TC	11	0.98 ± 0.11*	4.00 ± 0.19*,[c]
C	10	0.85 ± 0.17	2.96 ± 0.39[a,b,d]
C-T	12	0.96 ± 0.12	3.88 ± 0.41*,[c]

Control (CONT), Hyperthyroidism-1 (T), Hyperthyroidism-2 (T-T), Carnosine (C), Hyperthyroidism-1 + Carnosine (T-C), Hyperthyroid-2 + Carnosine (T-TC), and Carnosine + Hyperthyroid-1 (C-T).
Significant results were obtained with the comparison of the *: CONT; a: T; b: T-T, c: T-C, and d: T-TC groups with the other groups.

The body temperature of the rats in the control group did not change during the application. However, when examining the study groups, it was seen that there was a significant increase in body temperature in all groups except the carnosine-only (C) group. At the end of the 20th day, it was observed that the body temperature of the rats in the T-T and C-T groups was higher than that on the 10th day, and there was no statistically significant difference in the T-C and T-TC groups. In the comparisons made within the group for the 1st and 20th days, it was observed that the body temperature of the rats in all groups increased (Table 3).

Only the T-T and T-TC groups had significantly higher values than the control group in terms of heart weights, while the other groups did not differ from each other and the control group.

When evaluated in terms of HW/BW ratios, it was observed that HW/BW ratios increased in both T and T-T groups however, HW/BW ratios, which did not change compared to the control with carnosine administration, were still higher in the T-TC and C-T groups. HW and the HW/BW of rats are shown in Table 4

DISCUSSION

The physiological effects of thyroid hormones generally result from the transcription of many nuclear genes that cause an increase in the metabolic rate of tissues basal oxygen consumption, and heat production. As a result, thyroid hormones can cause an increase in the metabolism of up to 100%, which results in increased heart rate, cardiac output, and decreased systemic vascular resistance[16]. Furthermore, while increasing the forced thermogenesis as a result of stimulation of various metabolic pathways, it may specifically affect certain mechanisms, such as Na/K-ATPase, and the Ca^{2+} cycle in the muscles, in keeping the body temperature constant. Considering all these effects of thyroid hormones on the organism, it can be concluded that BW, BT, and HW/BW measurements in hyperthyroidism can be used to evaluate the degree of hyperthyroidism.

Additionally, hyperthyroidism is accompanied by an increase in the ratio of pro-oxidant / antioxidant, and as a result, secondary pathologies to hyperthyroidism such as liver damage due to oxidative stress and heart failure may occur[17]. There are many studies in the literature showing the use of various antioxidant agents to support the treatment. However, although its beneficial effects in different pathologies have been shown[18], no study has been founded regarding the effectiveness of carnosine on the organism in the case of hyperthyroidism. For this purpose, in this experimental model, it was aimed to investigate the relationship between FT3 levels with physical and vital signs, and the effect of carnosine on hyperthyroidism through those parameters.

Plasma FT3 levels of the study groups were taken into account in demonstrating the presence of hyperthyroidism. However, despite the formation of hyperthyroidism was confirmed with the FT3 levels, the fact that there was no statistically significant difference between the T-T and T groups even though there was a numerical increase in the T-T group compared to the T group, suggests that there was no linear response during the L-T4 administration period and that the fastest response occurred at the beginning. Similarly, Moulakakis et al. reported that serum FT3 levels, measured by increasing the administration time by a multiple of 4, increased only 1.6 times in rats with hyperthyroidism formed with L-T4[11].

When the effects of carnosine administration which were demonstrated with FT3 levels were examined, it was observed that only the C-T group (pre-L-T4 carnosine administration) was similar to the control, but carnosine administered after/during L-T4 administration (T-C/ T-TC group) did not affect plasma FT3 levels. The fact that it has been reported that carnosinase activity is decreased in hypothyroidism[19] may suggest increased plasma carnosinase activity in hyperthyroidism. As a result, it is possible to say that the degradation of carnosine, which is added to the environment later, accelerates, so its effectiveness in a prophylactic application may have decreased in combination with L-T4.

Although no study investigating the efficacy of carnosine in the case of hyperthyroidism was found in the literature, other studies have reported that when the effects of various antioxidants on plasma FT3 levels increased in hyperthyroidism status, FT3 levels that increase in hyperthyroidism have not been affected by vitamin E and curcumin administration alone, but that they have decreased with the Vit E/curcumin combination[13], caffeic acid phenethyl ester application[20] and also *Bupleurum falcatum* L.[21] in a dose-dependent manner.

In the literature, the effect of hyperthyroidism in reducing body weight associated with oxidative stress in adipocytes[21], increased thermogenesis and increased serum adiponectin levels[22], and increased basal metabolic rate[23] has been supported by different experimental models[10, 11]. Similarly, in this study, the body weight showed a significant decrease on the 10th-day in the T and T-T groups, which were shown to develop hyperthyroidism. However, the fact that on the 20th day BW values in the T-T group were still low compared to the 1st-day values, but higher than the 10th-day values, can be thought to be due to the negative feedback effect of plasma FT3 levels on the hypothalamus and pituitary gland[24], which increased further towards the 20th day of the application. . The change in FT3 levels measured in these groups also reflects this situation.

Considering the FT3 levels change between groups in this study, although it was shown that the administration of carnosine before L-T4 prevented hyperthyroidism, weight loss was also observed in these animals. Furthermore, a significant increase in body weight is observed in the T-C group, despite high FT3 levels. Considering these results, it can be said that the change in FT3 levels and body weight cannot always coincide.

It has been reported that BT values generally increase in hyperthyroid rats[11-14]. It was observed in this study that although there was no difference between the groups in terms of baseline values, the BT values gradually increased with thyroxine administration and there was a significant increase in the T and T-T groups at the end of the 10th day. Additionally, it was observed that the BT values continued to increase with thyroxine administration, increasing significantly at the end of the 20th day compared to the baseline and 10th day.

Huh et al., who reported an increase (4.3%) in BT values with combined T3: T4 administration (ip, 3 days 300 μg/kg body weight/day) at a ratio of 1:4 in rats[13], suggested that oxidative stress induced by thyroid hormone can be determined indirectly by increased BT values. However, in this study, it was observed that the administration of carnosine, which can be used as an antioxidant, before (C-T), during (T-TC), or after (T-C) administration of L-T4 did not cause a change in body temperature. Even the administration of carnosine alone caused an increase in body temperature. Supporting these results, it has been demonstrated that during intense muscle activity, carnosine is released from the muscles into the bloodstream in small amounts, regulating the sympathetic nervous system that innervates brown adipose tissue and thus, particularly high doses of carnosine[25] increase body temperature.

One of the recommended physiological parameters that can be used to decide whether experimental hyperthyroidism has developed in rats is the heart weight which is evaluated either alone[26,27] or by proportioning to body weight[8-10]. It is known that there is an obvious cause-and-effect relationship between heart hypertrophy and thyroid hormone levels. It has been emphasized that decreased heart tissue GLUT4 levels secondary to SOR levels increasing in hyperthyroid conditions, increased basal metabolic rate and cellular respiration, and suppressed Cu/Zn-SOD activity may be responsible for hypertrophic heart tissue[28]. Heckmann and Zimmer[29] and Craig et al.[30] showed that the true and relative heart weights (HW/BW) in hyperthyroidic rats significantly increased as a result of increased cardiac activity due to excess thyroid hormone. Although it contains methodological differences, it can be said that the effect of hyperthyroidism created in this study on HW and HW/BW values yielded similar results with the studies in the literature. It has been reported that the HW/BW ratio increased in

hyperthyroid conditions can be partially prevented by antioxidants such as melatonin[28], and Vit E[13].

In this study, the fact that the significant increase in HW indicating cardiac hypertrophy was observed only in the T-T group given thyroxine for 20 consecutive days can be explained by more pronounced cardiac findings at lower TSH levels[31]. However, the demonstration that hypertrophy could not be prevented by adding carnosine for 10 days (T-TC group) seems to be consistent with the still high FT3 levels in the same group. The fact that hypertrophy secondary to hyperthyroidism could not be prevented in the presence of carnosine may also be due to the insufficient dose of carnosine administrated, on the other hand, considering that pathological hypertrophy is irreversible[32], it may be thought that it will not be very informative in evaluating the possible positive effects on heart tissue.

In conclusion, it can be said that although hyperthyroidism can be associated with BW, BT, HW, and the HW/BW ratio, it does not reflect FT3 levels exactly. It can be said that it is important to monitor FT3 values in terms of determining hyperthyroidism, especially in experimental models to be made in the future. The fact that the effects of carnosine administration are independent of FT3 levels can be interpreted as the effects of hyperthyroidism on different tissues may be related to various other ways, especially with oxidative stress.

However, this study also has limitations, the oxidative situation can be evaluated more clearly by adding analyzes that will show oxidative stress and antioxidant activity, which were not included in this study in order not to become confusing. In addition, larger-scale studies are needed for clinical use of the findings.

Yazar Katkıları: Çalışma konsepti/Tasarımı: FD, CY, İG, GŞS; Veri toplama: FD, CY, İG; Veri analizi ve yorumlama: FD, CY, İG, GŞS; Yazı taslağı: FD, CY, İG, GŞS; İçeriğin eleştirel incelenmesi: FD, CY, İG, GŞS; Son onay ve sorumluluk: FD, İG, GŞS, CY; Teknik ve malzeme desteği: FD, CY, İG; Süpervizyon: FD, CY, İG, GŞS; Fon sağlama (mevcut ise): yok.
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