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The effect of coenzyme Q10 on blood plasma nitric oxide and total antioxidant capacity levels in hypothyroidism-induced rats

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ABSTRACT

In this study, the effect of coenzyme Q10 (CoQ10) on nitric oxide (NO) and total antioxidant (TAS) capacity in rats for which experimentally hypothyroidism was induced through PTU was investigated. A total of 32 healthy male Wistar Albino rats weighing 300-350g, approximately 12 weeks old, were used as animal material in the study. . Rats were divided into 4 experimental groups as control (K), Coenzyme Q10 (C), Hypothyroidism (H), and Coenzyme Q10 + Hypothyroidism (CH). During the trial period of three weeks, 3mg CoQ10 (10mg/kg/day) was dissolved in 0.3 ml of maize oil and intraperitoneally administered for each animal in group C. In group H, PTU has added to drinking water daily at a weight/volume (w/v) ratio of %0.05. In the HC group, coenzyme Q10 was administered intraperitoneally and PTU was administered with drinking water at a rate of %0.05. TT4, TT3, and TSH levels were determined in serum samples and NO and TAS levels in plasma samples. In the present study; the highest plasma NO level among the groups was determined in group H ($p<0.05$) and there was no significant difference between other groups (H, C, HC) ($p>0.05$). The plasma TAS value of group H was found to be significantly higher than the same value in the K, C and HC groups ($p<0.05$). The plasma TAS level in group C had no difference from the same value in the HC group ($p>0.05$), although it was higher than the same value of group K ($p<0.05$). As a result, it was found to cause oxidative stress in hypothyroidism-induced rats with a particular increase in plasma NO levels, and CoQ10 was found to be effective in normalizing the increased plasma NO level due to hypothyroidism.

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Introduction

One-third of the world's population lives in the region where iodine deficiency is present, and its effects on the neurological development of fetuses and children in cases where iodine deficiency is severe are well known (Zimmermann, 2009). Moreover, the possible effects of iodine deficiency during pregnancy on the cognitive development of fetus have also been increasingly recognized in recent years (Bath et al., 2013). Changes in food and agricultural practices since the 1950s have caused iodine deficiency to come back to the agenda even in countries where iodine was previously believed to be sufficient, including some developed countries (Taylor et al., 2014). Hypothyroidism, also known as a condition in which the thyroid gland is unable to produce as many hormones as necessary, can be caused by the thyroid gland (primary hypothyroidism), the pituitary gland (secondary hypothyroidism), or the hypothalamus

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(tertiary hypothyroidism) (Schmid et al., 2006). The most common cause of primary hypothyroidism is severe iodine deficiency (Taylor et al., 2018).

The thyroid hormones, thyroxine (T4) and triiodothyronine (T3) play a critical role in growth and development and regulate the basic metabolic processes that affect almost every organ system in adults (Biondi & Cooper, 2019). Thyroid hormones affect metabolic processes, especially due to changes in ATP metabolism. ATP production, along with other related processes including apoptosis triggering, redox signalling, and intracellular Ca+2 regulation, is primarily driven by mitochondria (Scheffler, 2011). In this respect, hypothyroidism is known to reduce oxygen consumption and promote low metabolism, which causes impairments in hemodynamic, heart and kidney function, as well as lipid metabolism (Franco et al., 2011). Whether T3 and T4 regulate the expression of various membrane-associated respiratory enzymes and metabolite transporters in mitochondria is still controversial.(Paradies et al., 1994; Scheffler, 2011; Schönfeld et al., 1997). Hypothyroidism also affects the expression of mitochondrial proteins from the respiratory chain and decreases coenzyme Q10 (CoQ10) levels, as well as the antioxidant capacity of mitochondria (Fernández-Vizarra et al., 2008; Venditti et al., 2003).

CoQ10 is a fat-soluble vitamin-like compound that can be found in any cell, acting as a coenzyme in enzymatic reactions that occur during energy production in cells (Stocker, 2007). CoQ10, also known as 'Ubiquinone', is found in all tissues in the body, even if its amount is variable, and has a role in all oxidative reactions (Saini, 2011). CoQ10 plays an important role in electron transport and ATP synthesis in mitochondria. There may also be a decrease in the amount of CoQ10, as oxidative damage may occur in patients with both hyperthyroidism and hypothyroidism (Mancini et al., 2011). CoQ10 plays a very important role in the body since it is involved in ATP synthesis and is essential for the health of every tissue and cell in the body. It also has an important antioxidant function (Santoro, 2020).

Considering that hypothyroidism is a serious problem in our country and throughout the world in the case of experimentally hypothyroidism-induced rats, the extent to which CoQ10 will affect blood plasma thyroid hormone levels and levels of nitric oxide and total antioxidant capacity parameters planned to be investigated to contribute to the relevant information.

Materials and Methods

Animal Material: In the study, a total of 32 healthy male Wistar Albino rats, approximately 12 weeks old, weighing 300-350 g, obtained from S.Ü Experimental Medicine Research and Administration Center were used. In the experiment, which included a 10-day adaptation and 3-week main study period, the rats were provided with suitable living conditions in the form of 22 + -2ºC room temperature, \ 50% + -10 relative humidity and 12/12 night and daylight period. In the study, the average amount of water that rats can drink daily (average 50 ml/day/rat) was determined and their water was refreshed daily. The animals were fed with standard rat feed ad libitum.

During the research period, rats hosted in 8 separate cages and 4 in each cage were divided into 4 trial groups: control (K), coenzyme Q10 (C), hypothyroidism (H) and Coenzyme Q10+ hypothyroidism (CH).

Control Group (K): no administration was made to the animals in this group, and during the study, their feed was given as ad libitum, while daily drinking water was given in a determined amount.

Coenzyme Q10 Group (C): rats in this group were administered intraperitoneally during the trial, dissolving in 0.3 ml of maize oil, approximately 3mg CoQ10 (TCI, C1971) (10mg/kg/day) per animal according to their alive weight (Singh et al., 2000).

Hypothyroidism Group (H): 6-N-propyl-2-thiouracil (PTU) (brand; SIGMA p3755) was added to drinking water daily at a rate of \%0.05 weight/volume (w/v) during the trial to induce hypothyroidism in rats (Das & Chainy, 2001).

Hypothyroidism + Coenzyme Q10 Group (HC): animals in this group were intraperitoneally administered coenzyme Q10 dissolved in maize oil in the amount of 10mg/kg/day during the trial.%0.05 PTU was added to drinking water.

At the end of the administration period, blood was taken separately and in sufficient quantities from rats in groups to EDTA and serum tubes with cardiac puncture under general anaesthesia performed with 70 mg/kg ketamine + 5 mg/kg Rompun. Blood samples were centrifuged at +4 ºC at 3500 rpm to obtain plasma (Hettich Rotina 35 R). Serum and plasma samples were stored at -20 °C until they were analyzed. The obtained serum samples of total thyroxine, total triiodothyronine, Thyroid Stimulating Hormone (TSH); Nitric Oxide (NO) and Total Antioxidant Capacity (TAC) levels were determined from plasma samples. The lives of the blood-drawn animals were ended by cervical dislocation, which was

The research was approved by the animal experiments Ethics Committee of Selcuk University Experimental Medicine Practice and Research Center on 28.12.2018 with decision no.2018-49.

From the serum samples taken, TSH, TT4 and total TT3 levels were measured by Kemuliminescence measurement method in Abbot Architect i2000 analyzer, Abbott kits were used for measurements Plasma nitric oxide (Cayman, 780001) and total antioxidant capacity (Tas, Red Assay Diagnostics®) levels of animals in trial groups were determined by the spectrophotometric method by reading absorbency values under commercial kit prospectuses using Biotek brand LX800 model Elisa device and Cayman brand test kits (Messerah et al., 2011) (Messarah et al. 2010).

Statistical analysis of the data obtained at the end of the research SPSS 18.0 (SPSS, Inc. Chicago, IL, USA) was performed using. Variance analysis was performed to determine the importance of the differences between the trial groups, and Duncan multiple comparison tests were performed for posthoc analyses.

Results

In the study, serum thyroid-stimulating hormone (TSH), total thyroxine (TT4) and triiodothyronine levels (TT3) and plasma nitric oxide (NO) and total antioxidant capacity (TAS) values were determined in all four groups are shown in Table 1.

Considering the TSH, TT4 and TT3 values in the study, it is seen that PTU administration causes hypothyroidism in the hypothyroid (H) and hypothyroid + coenzyme Q10 (HC) groups. Serum TSH levels in the H and HC groups were higher ($p < 0.05$) than the control (K) and coenzyme Q10 (C) groups (Table 1), and serum TT4 and TT3 values, which are the main thyroid hormones affecting tissues, were both H and TT3. The lower amount of rats in HC groups compared to other groups confirms this (Table 1).

The highest mean serum TT4 and TT3 levels recorded among the trial groups in the study were observed in Group K, which was significant ($p<0.05$) compared to those of other groups (C, H and HC). While there was no difference between the H and HC groups in terms of these values ($p>0.05$), serum TT4 and TT3 levels in Group C were lower than in Group K ($p<0.05$) and higher than in the H and HC groups ($p<0.05$) (Table 1).

The highest mean serum recorded among the trial groups in the study was observed in group K, which was significantly higher ($p<0.05$) than those of other groups (C, H and HC). While there was no difference between H and HC groups in terms of these values ($p>0.05$), serum TT4 and TT3 levels in group C were lower ($p<0.05$) than in group K, and higher than in H and HC groups ($p<0.05$) (Table 1).

When plasma NO levels were taken into account, it was found that the highest value among groups was in group H with hypothyroidism ($p<0.05$), while plasma NO levels did not differ significantly among other groups (H, C, HC) ($p>0.05$) (Table1).

In the study, it was determined that the plasma TAS value of group H was considerably higher than the same value in the K, C and HC groups ($p<0.05$). The plasma TAS level in group C was recorded as showing no significant difference ($p>0.05$) than in the HC group, although the K group had higher amounts ($p<0.05$) than the same value (Table 1).

Discussion

Since thyroid hormones affect the metabolic activities of a living thing, the development and growth of tissues, and the rate at which nutrients are used to provide energy, (Mortezaee et al., 2019; Pascual & Aranda, 2012), when the secretion of the thyroid hormones decreases, the functions of almost all systems in the body are affected, metabolic activities are disrupted and hypothyroidism occurs (Hall & Hall, 2020).

Table 1. Serum means TSH, TT_4, TT_3 levels and NO and TAS values for all groups.

	Control	Hypothyroidism	Coenzyme Q10	Hypothyroidism + CoQ10
TSH (µIU/ml)	$2.45 \pm 0,055^{b}$	23.28 ± 2.17^{a}	1.80 ± 0.42^{b}	18.82 ± 1.33^{a}
TT_4 (µg/dl)	2.41 ± 0.07^{a}	0.26 ± 0.14^{c}	2.08 ± 0.12^{b}	0.12 ± 0.01^{c}
TT_3 (ng/ml)	0.33 ± 0.18^{a}	0.02 ± 0.003^{c}	0.20 ± 0.05^{b}	0.02 ± 0.01^{c}
NO (µM)	51.5 ± 3.62^{b}	87.1 ± 6.24^{a}	57.5 ± 6.93^{b}	64.0 ± 4.14^{b}
TAS (mmol/l)	9.47 ± 0.85^{c}	15.87 ± 0.68^{a}	12.91 ± 1.33^{b}	10.42 ± 0.94^{bc}

CoQ10 = coenzyme Q10, TSH =thyroid-stimulating hormone, TT_4 = total thyroxine, TT_3 = triiodothyronine levels, NO = nitric oxide, TAS = total antioxidant capacity .

In experimental studies conducted to investigate the effects of hypothyroidism, various anti-thyroid agents that inhibit thyroid hormone synthesis are used. Among these, one of the most widely used is propylthiouracil (PTU). PTU acts by inhibiting the activation of iodine and its binding to tyrosine by inhibiting the tyrosine peroxidase enzyme in the thyroid gland, by preventing the binding of monoiodotyrosine and diiodotyrosine to each other, and by inhibiting the conversion of T4 to T3 with deiodinase inhibition in the periphery. (Cooper et al., 1983). In this study, PTU was administered to rats in the H and HC groups, and it was determined that PTU administration induced hypothyroidism in animals in these groups (Table 1).

According to the findings obtained in the study, the increase in serum TSH level ($p<0.05$), decreased TT4 and TT3 levels ($p<0.05$) in the H and HC groups administered in PTU compared to groups K and C experimentally shows that hypothyroidism was induced.

CoQ10 is a powerful antioxidant in all cells, with electron carrier properties in the electron transport chain. It is synthesized in the body under normal physiological conditions and the amount is sufficient for the body. But various diseases, ageing and degenerative processes can lead to an insufficient amount of CoQ10 synthesized in the body(Bhagavan et al., 2007; Quiles et al., 2020; Sawashita et al., 2020). Therefore, its increasing use as a food supplement is becoming more and more common and is the subject of scientific research in this direction (Gholnari et al., 2018; Jorat et al., 2019; Lee et al., 2012).

CoQ10 can also be used frequently in some endocrinological disorders (Mancini et al., 2011). Since thyroid hormones have common biosynthesis pathways through CoQ10 and tyrosine amino acid, it is common for tight interactions between the hormones of the endocrine glands in question and CoQ10 (Sayıner & Kısmalı, 2016). Metabolic stress caused by a slowing basal metabolic rate in the case of hypothyroidism and an increased basal metabolic rate in the case of hyperthyroidism affects all systems of the body (Venditti & Di Meo, 2006). In cases where metabolic stress and free radical production increased, CoQ10 was found to decrease. (Bhagavan & Chopra, 2006). Therefore, concerning thyroid health, it is thought that CoQ10 supplementation in a controlled manner may be beneficial in people with both hyperthyroidism and hypothyroidism (Saini, 2011).

Different findings in various studies on the effect of CoQ10 on hypothyroidism are notable (Mancini et al., 1989; Mancini et al., 2011; Ogura et al., 1980; Pandolfi et al., 1994; Resch et al., 2002; Saini, 2011). Mancini et al. (1989) report that CoQ10 levels in the blood show a significant inverse relationship with thyroid hormone levels in patients with hyper or hypothyroidism. In another study carried out by the same researchers (Mancini et al. 2011), they noted that due to oxidative damage in patients with both hyperthyroidism and hypothyroidism, there may be a decrease in the amount of CoQ10 that plays an important role in electron transport and ATP synthesis in mitochondria. In comparison to people with hyperthyroidism and hypothyroidism, there are also studies indicating that although serum CoQ10 levels in hyperthyroidism are lower than euthyroidism and hypothyroid subjects, there is no significant difference in hypothyroidism than euthyroidism which reports that the decrease in coq10 level of hyperthyroidism is more than hypothyroidism, on the other hand, it has been emphasized that oxidative stress increases in both hyperthyroidism and hypothyroidism, and that negative changes in the enzymatic and non-enzymatic antioxidant system can have a significant impact (Resch et al., 2002)

In this study, the serum TSH, TT4 and TT3 levels of the C group given CoQ10 did not show a significant difference compared to the control group ($p> 0.05$), the serum TSH level in the HC group given CoQ10 with PTU was higher than the control group ($p <0.05$), The low levels of TT4 and TT3 ($p <0.05$) suggested that CoQ10 was not effective in correcting serum TSH, TT4 and TT3 levels due to hypothyroidism under the conditions in this study (Table 1).

The most important production site of free oxygen radicals in cells is mitochondria (Brown & Borutaite, 2012; Di Meo et al., 2016), therefore, it is inevitable that increases and decreases in levels of thyroid hormones affect the production of free oxygen radicals (Chainy & Sahoo, 2020). Because thyroid hormones make significant changes in the activity and number of certain respiratory chain components in the mitochondria in tissues (Guerrero et al., 1999)significant changes in the oxidant and antioxidant systems of the body occur in both hyperthyroidism and hypothyroidism (Hosseini-Zijoud et al., 2016; Mancini et al., 2011; Resch et al., 2002) Increased metabolic rate with the effect of thyroid hormones accelerates electron transport in mitochondria, which increases superoxide production. Superoxide radicals lead to the formation of many other reactive oxygen species (Freinbichler et al., 2011). Thus, the acceleration of all metabolic events in hyperthyroidism leads to lipid peroxidation, increasing

oxidative metabolism (Joshi et al., 2018; Venediktova et al., 2020). In hypothyroidism, since the metabolic rate slows down, oxidative byproducts are also expected to decrease (Joshi et al., 2018; Pereira et al., 1994), in contrast, there are also studies showing increased oxidative stress (Costantini et al., 1998; Yilmaz et al., 2003). In case of hypothyroidism, oxidized lipoproteins in the hydrolysis of lipid peroxide which serum paraoxonase (PON-1) activity recorded when the decrease occurred, hypothyroidism observed in lipid peroxidation, serum PON-1 enzyme activity and an increase in the reduction of LDL cholesterol to undergo oxidation quickly discussed it with (Sarandol et al., 2006). In this study, compared to the control group, the high plasma NO level ($p<0.05$), which is one of the oxidative stress indicators in hypothyroidism induced rats, supports this view (Table 1). Similarly, Verma et al. (2013) in a study conducted in humans, did not record that serum NO levels increased in those with hypothyroidism compared to controls (Verma et al., 2013). In contrast, plasma NO levels are not affected in the case of hypothyroidism (Hermenegildo et al., 2002). These different findings among some studies may be due to differences in tissue and organ sensitivity, measurement methods, animal species and administration methods (Messerah et al., 2011).

CoQ10, which joins the mitochondrial respiratory system as an antioxidant, protects cells and tissues from the harmful effects of free radicals (Cooke et al., 2008). It performs this function by acting as a coenzyme of three mitochondrial enzymes (complex I, II, III) (Littarru & Tiano, 2010). Furthermore, the quinol form of CoQ10 plays a potential antioxidant role by directly suppressing free radicals in the inner membrane of the mitochondria or by reducing the α - tocopherol radical (Kwong et al., 2002). Paunović et al (2017) report that CoQ10 administration strengthens erythrocyte antioxidant capacity by clearing ROS of the toxic effects of cadmium and interrupting lipid peroxidation (Paunović et al., 2017). Gholami et al (2018) CoQ10 supplementation in women with Type 2 diabetes, adiponectin concentrations and the level of MDA including the fall of adiponectin/leptin ratio were effective in increasing observed (Gholami et al., 2018). In Moazen et al (2015), they noted that the concentration of MDA, a marker of oxidative stress, decreased with the administration of CoQ10 (Moazen et al., 2015). Although the plasma NO level of the HC group is dramatically lower than the H Group ($p<0.05$), it can be concluded that CoQ10 administered to hypothyroidism-induced animals is effective in correcting the changing no level due to hypothyroidism (Table 1). In parallel with AL-Megrin et al (2020) declarations that the administration of CoQ10 in rats increases the body's antioxidant capacity (AL-Megrin et al., 2020), in this study, the plasma TAS of Group C given CoQ10 was found to be higher than that of the control group ($p<0.05$). At the same time, the presence of plasma TAS levels in hypothyroidism-induced rats in Group H in the study in higher amounts than rats in groups K, C and HC ($p<0.05$) may indicate that the body's total antioxidant capacity may have increased due to increased oxidative stress in hypothyroidism (Table 1).

Conclusion and Recommendations

There are many studies with different results regarding the effect of hypothyroidism on the oxidant and antioxidant system and the effect of CoQ10 on the correction of oxidative damage that may occur in hypothyroidism. It is thought that different data, which can be found even in the same tissue and parameters in the literature, may depend on the species, age of the animals, and the different administration methods used (addition to drinking water, intraperitoneal or subcutaneous injections, different anti-thyroid drugs, dosage regimen and duration). Therefore, the relationship between hypothyroidism and oxidative stress and the effect of CoQ10 needs to be studied in more comprehensive research.

In this study, plasma NO and TAS parameters examined within the framework of research opportunities also presented information in harmony with some, although they differed from some literature data. Especially when plasma NO and TAS values are taken into consideration, the results obtained indicate that although oxidative stress increases in hypothyroidism, the addition of CoQ10 may be an effective agent in eliminating oxidative stress formed as an antioxidant.

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Conflict of interest

Author has no conflict of interest to declare.

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