

## Thyroid Hormone Depression During Sepsis

Yücel ARITAŞ<sup>x</sup>, Kadir KAZEZ<sup>xx</sup>, Tahir E. PATIROĞLU<sup>xxx</sup>, Zeki YILMAZ<sup>xxxx</sup>

**Summary:** Thyroid hormone alterations are common following surgery, sepsis and other acute and chronic illnesses. In the present study, thyroid hormone levels are measured in two groups of rats. Group 1, consisted of ten rats, with sepsis induced by cecal ligation and puncture. In Group 2, there were ten control animals underwent laparotomy and manipulation of cecum without ligation or puncture. Thyroid hormone levels were measured preoperatively and fortyeight hours after surgery. Compared with preoperative values, the mean serum T<sub>3</sub> and T<sub>4</sub> concentrations decreased and serum TSH levels increased in postoperative stage in septic group (p<0.01). T<sub>3</sub> and T<sub>4</sub> levels were found lower in septic rats than in control group, in postoperative period (P<0.01). Reduced serum levels of T<sub>3</sub> and T<sub>4</sub> support the concept of a role of thyroid hormone in metabolic alterations in some organs during sepsis.

**Key words:** Thyroid hormones, Sepsis.

Circulating thyroid hormones levels are reduced in critically ill and septic patients and this result may indicate that thyroid hormones are involved in the pathogenesis of altered muscle protein turnover in sepsis (1,3,10). Total cellular and hepatic uptake of thyroxine (T<sub>4</sub>) was increased in septic monkeys (7) and concentrations of triiodothyronine (T<sub>3</sub>) was maintained or increased in kidney and liver tissue during endotoxemia in rats, despite decreased circulating T<sub>3</sub> levels (9).

The purpose of this investigation was to determine the changes in thyroid hormones concentrations during sepsis in rats.

### Material and Methods

This experimental study was performed in two groups of rats weighing 180-200 gr. In Group 1, ten rats were accepted as septic group. Sepsis was induced by cecal ligation and puncture method. In Group 2, ten rats were accepted as control group. Sham operation was performed. Venous blood samples were obtained for each rat, from internal jugular vein before operation. Under light ether anesthesia, laparotomy was performed and the cecum was ligated and punctured twice with an 18-gauge needle in septic group rats. Nonseptic control group rats had sham operation, in which a

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*From The Departments of General Surgery and Pathology, Erciyes University Medical School Hospital, Kayseri-TURKEY.*

*x Professor of General Surgery*

*xx Resident of General Surgery*

*xxx Professor of Pathology*

*xxxx Associate Professor of General Surgery.*

laparotomy was performed and cecum was manipulated but not ligated or punctured. Fortyeight hours later two groups of rats were sacrificed and autopsy was done. Diffuse peritonitis was confirmed in septic rats. Lung biopsies were taken and prepared in Formalin (10 %) for paraffin sections.

Second blood samples were drawn just before death. Toxic granulation was also studied in fresh blood samples for each group of rats.

All blood samples were processed immediately and stored at  $-20^{\circ}$  C for later analysis. Each sample was assayed for total T<sub>3</sub>, T<sub>4</sub> and Thyroid Stimulating Hormone (TSH) using specific radioimmunoassays (Amerlex-m T<sub>3</sub>,T<sub>4</sub> and TSH RIA). Results are presented as Mean  $\pm$  SEM. Data were analyzed by student t-test.

### Results

The preoperative mean value of T<sub>3</sub> was 0.703 ng/ml in control group. Total T<sub>3</sub> values fell following laparotomy to 0.488 ng/ml. These changes are shown in Table I and statistically significant ( $P < 0.01$ ). The changes in preoperative and postoperative serum T<sub>4</sub> levels in control group was not significant (Table I).

Table I. Preoperative and postoperative serum T<sub>3</sub>, T<sub>4</sub> and TSH levels changes in control group

Hormones	n	Preoperative values $\bar{x} \pm \text{SEM}$	Postoperative values $\bar{x} \pm \text{SEM}$	P
T <sub>3</sub> (ng/ml)	10	0.703 $\pm$ 0.039	0.488 $\pm$ 0.035	P<0.01
T <sub>4</sub> ( $\mu$ g/dl)	10	3.54 $\pm$ 0.241	3.27 $\pm$ 0.351	P> 0.05
TSH (MIU/ml)	10	0.112 $\pm$ 0.06	0.158 $\pm$ 0.012	P<0.02

In septic rats, the preoperative mean value of T<sub>3</sub> was 0.702 ng/ml and decreased to 0.302 ng/ml in postoperative period. This reduction is significant ( $P < 0.01$ )(Table II). In this group, serum T<sub>4</sub> levels decreased, but TSH levels increased to statistically significant levels in the postoperative stage (Table II).

Table II. Preoperative and Postoperative serum T<sub>3</sub>, T<sub>4</sub> and TSH levels changes in septic rats.

Hormones	n	Preoperative values x ± SEM	Postoperative values x ± SEM	P
T <sub>3</sub> (ng/ml)	10	0.702 ± 0.32	0.302 ± 0.036	P < 0.01
T <sub>4</sub> (µg/dl)	10	3.43 ± 0.344	0.388 ± 0.061	P < 0.01
TSH (MIU/ml)	10	0.161 ± 0.014	0.263 ± 0.014	P < 0.01

In the septic rats, postoperative serum T<sub>3</sub>, T<sub>4</sub> and TSH values were compared with the control group (Table III). TSH levels were found to be higher (P < 0.01) in septic rats than in control group. But T<sub>3</sub> and T<sub>4</sub> levels were found lower in septic rats (P < 0.01) (Table III).

Table III. Comparison of two groups postoperative serum T<sub>3</sub>, T<sub>4</sub> and TSH levels.

Hormones	n	Control Group x ± SEM	Septic Group x ± SEM	P
T <sub>3</sub> (ng/ml)	10	0.488 ± 0.035	0.302 ± 0.036	P < 0.01
T <sub>4</sub> (µg/dl)	10	3.27 ± 0.351	0.388 ± 0.61	P < 0.01
TSH (MIU/ml)	10	0.158 ± 0.012	0.263 ± 0.014	P < 0.01

In the eight septic rats out of ten, toxic granulation was positive in peripheral blood smears, in postoperative period. There was no abnormality in control group.

Minimal microscopic changes were observed in lung biopsies in both groups of rats. This changes were not characteristic for shock lung.

## Discussion

The marked changes in  $T_3$  and  $rT_3$  (reverse  $T_3$ ) concentrations in association with acute and chronic illness, malnutrition and after surgery have been reported by a number of authors (1,2,4,6,15). Recent studies suggest that the peripheral conversion of  $T_4$  to  $T_3$  is diminished and that increased amounts of the alternative metabolite  $rT_3$  are formed preferentially. The mechanism by which the peripheral production of  $T_3$  is diverted to  $rT_3$  remains uncertain (4,15). It has been suggested that these changes resulted from an increase in cortisol secretion, since similar changes are seen after the administration of large doses of dexamethasone (8). But these changes are not dependent upon a stress-induced increase in cortisol secretion (8).

Similar rises in  $T_4$  and TSH after surgery under halothane anesthesia have also been reported by Oyama and his colleagues (13).

In an experimental study, reduced serum levels of  $T_3$ , but maintained or increased muscle concentrations of the hormone was observed (10). This result suggests that increased  $T_3$  uptake by muscle may be one mechanism of low  $T_3$  syndrome in sepsis. Thus thyroid hormones may be of importance for various metabolic responses to sepsis (10).

In another experimental study, hemorrhagic shock of one hour duration produced alterations in thyroid hormone metabolism in dogs (18). In this investigation, plasma concentrations of total thyroxine ( $T_4$ ) and ( $T_3$ ) were significantly decreased after only 20 minutes of shock (18).

In our study serum  $T_3$  was significantly reduced after the laparotomy in both groups of rats. This observation confirms previous results of a low  $T_3$  syndrome after surgical injury and sepsis (1,3,4,5,9,17). Serum  $T_3$  and  $T_4$  levels were decreased in septic rats more than control group in postoperative period (Table III).

Different mechanisms of reduced circulating levels of thyroid hormones after injury and sepsis were suggested previously, reduced thyroid function (6,16), defective binding of the hormones to carrier proteins (11) and an impaired 5 - deiodination of  $T_4$  to  $T_3$  (11).

Metabolically  $T_3$  is several times more active than  $T_4$ , while  $rT_3$  seems to be biologically inactive (2).

Burr et al. showed a rapid decrease in  $T_3$  levels after surgery with simultaneous increase of  $rT_3$  concentrations and slight fall of  $T_4$  levels (5).

Serum total  $T_4$  levels are unaltered in patients who survive the trauma but are significantly depressed in fatal cases

(12,14). Becker found 84 % mortality in critically ill patients when the total  $T_4$  declined below 3.0  $\mu\text{g/dl}$  (4). Hypothyroxinemia with normal TSH levels was found to be associated with high mortality rate (11,14). In our septic rats, elevated levels of TSH 48 hours after the sepsis is considered a response to decreased levels of  $T_3$  and  $T_4$ .

In a variety of acute and chronic medical illnesses, depressed serum  $T_3$  occurs consistently. Variable total thyroxine ( $T_4$ ) levels have been reported (17,18).

Current techniques are inadequate to establish all factors that contribute to the changes in thyroid hormone concentrations but changes in  $T_4$  and  $T_3$  production rate, alterations in thyroid hormone binding capacity and alterations in cellular uptake, metabolism and degradation have all been implicated by various authors (2, 11).

In conclusion, the current study suggests that thyroid hormones may be of importance for various metabolic responses to sepsis. In future studies, the interection between  $T_3$  and other possible mediators of protein breakdown in sepsis such as some catabolic hormones, would be of interest to elucidate.

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