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Effect of Altered Thyroid Status in the Domestic Rabbit (*Lepus cuniculus*) on Thermoregulation, Heart Rate and Immune Responses

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Abstract: Fifteen Male rabbits were used to study the effects of thyroid status on thermoregulation, body weight (BW), heart rate (HR) and immunological responses. Hyperthyroidism was induced by subcutaneous injection of thyroxine (T4) (30 µg/ kg BW /day) while hypothyroidism was induced with oral administertion of carbimazole (CBZ) (30 mg/ animal/day). The treatments were administered for 28 days. Animals receiving (T4) and (CBZ) and the control group were immunized each with a single intravenous dose of sheep red blood cells (SRBCs) at day 16. Serum samples were obtained from blood samples collected from the rabbits at days 0, 4, 8 and 12 after immunization and haemagglutination antibody titres were determined. (T4) increased rectal temperature, respiratory rate, heart rate, total leukocyte count and antibody titre, while (CBZ) resulted in a decrease in these parameters compared with control values. (T4) decreased (BW) and increased spleen, heart and liver weights, while (CBZ) increased (BW), spleen, heart and liver weights compared with control values.

Key words: Rabbits · Thyroid status · Thermoregulation · Heart rate · Body weight · Internal organs and Immunity

INTRODUCTION

Scientific evidence supports an essential role for thyroid hormones in thermogenesis of mammals [1]. Generaly, in homeothermic species the thyroid hormone acquires a role in metabolic regulation by increasing oxygen consumption and stimulation of enzymes involve in metabolic reglation [2-4]. The hormones increase energy expenditure by activating Na+- K+ ATPase, promoting mitochondrial biogenesis [5, 6] and by accelerating ATP turnover [7].

Thyroid hormones play a major role in the cardiovascular system such as regulation of heart rate (HR). Hypothyroidism in animal models is manifested in low HR and in contrast, hyperthyroidism is associated with tachycardia [8]. Thyroid hormones increase peripheral oxygen consumption and substrate requirements which cause a secondary increase in cardiac contractility [9]. Also thyroid hormones maintain inotropic and chronotropic effects on cardiac function [10].

Thyroid hormones have important influences on immunological response of mammals. Various studies have indicated that the thyroid hormones have immunomodulatory effects in mammals [11-13]. The administration of thyroid hormones to normal animals induces leukocytosis [11].

Many studies indicated that thyroidectomy and hypothyroidism are associated with suppression of both humoral and cellular immune responses and spleen and lymph node involution [11, 14-16]. Thyroidectomy in rats caused reduction in peripheral lymphocytes and suppression of humoral and cellular immune responses [17]. It has been indicated [18] that severe hypothyroidism caused a reduction in circulating concentration of lymphocytes in rats. Also it has been reported [19] that dwarf mice had impaired immune response to sheep red blood cells (SRBCs) due to thyroid hormones deficiency.

In mammals exposed to tropical environment, high thermal load reduces metabolic heat production due to decreased thyroid hormones secretion and feed intake and causes immunosuppression and increases disease susceptibility [20]. Also consumption of cyanogenic foods has been considered as one of the etiological factors for the persistence of endemic goitre [21].

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Accordingly, the objective of this study was to adopt a rabbit model to investigate the effect of alteration in thyroid status on thermoregulation, heart rate, body weight and immunological responses under summer conditions.

MATERIALS AND METHODS

Experimental Animals and Management: Fifteen local breed adult healthy male rabbits with a mean body weight of 1.66 ±0.10 Kg were used in the study. The study was conducted at the animal house of the Department of Physiology during September-October, 2006 (mean ambient temperature (Ta): 32.25±0.55°C, mean relative humidity (RH): 35%.). The animals were subjected to thorough clinical examination and they were given an anthelmintic injection (Ivomec: 0.02 ml/kg BW: Alpha Laboratories Ltd, India) and antibacterial injection (Oxytetracycline: 7.5 mg/kg BW: Alpha Laboratories Ltd, India). The experimental animals were housed in an animal room in individual cages, provided with adequate ventilation under natural light- dark photoperiod. The animals were kept for an adaptation period of 2 weeks. The animals were fed fresh lucerne (*Medicago sativa*) (CP:162.7 g/Kg; ME: 7.1 MJ/Kg) and sorghum grains (CP: 132.3 g/Kg; ME:14.4 MJ/Kg) and allowed free access to tap water.

Experimental Design: The animals were randomly assigned to three groups of 5 animals each. Group A served as control; group B animals received daily 30 µg/kg BW of sodium L-thyroxine (T4, Eltroxin, Glaxo Wellcome, Germany.) injected subcutaneously to induce hyper thyroidism; and group C animals received daily an oral dose of 30 mg/ animal of the antithyroid drug carbimazole (CBZ, Neomercazole, Roche products Ltd., England.) to induce hypothyroidism. The treatments were continued for 28 days.

Physiological Investigations: During the experimental period, the rectal temperature (T_r) was measured by a digital clinical thermometer (Hartman – United Kingdom). The tip of the thermometer was inserted to a depth of approximately 4 cm into the rectum and (Tr) was measured with an accuracy of ± 0.1°C. The respiratory rate (RR) was measured by visually counting the nose movements for one minute using a stopwatch. The heart rate (HR) was obtained by monitoring the heart sounds for one minute using a stethoscope. The measurements were done every 3 days. During the experiments, the animals were weighed to the nearest ±1.0 g using a traditional balance (Every-United Kingdom). At the end of the experimental period, the animals were sacrificed by intravenous injection of sodium pentobarbital and the thyroid gland, spleen, heart and liver were carefully dissected, isolated and weighed to the nearest ± 0.01g using an electronic digital balance (Equipment Co. Ltd, England). The histological investigation of thyroid gland was done by a standard method [22]. The total leukocyte count (TLC) was determined using the haemocytometer [23].

Immunological Measurements: Haemagglutination test was used to determine antibody production in response to sheep red blood cells (SRBCs) according to the standard methods [24, 25]. Blood was collected from the jugular vein of a healthy male sheep using a heparinized tube. The blood was centrifuged at 3000 r.p.m. for 15 min and plasma was removed by Pasteur pipette. Then the packed red blood cells were washed three times using sterilized normal saline (0.9% NaCl). A suspension of 10% of (SRBCs) was prepared using sterilized normal saline. At day 16 after the beginning of treatments of rabbits with thyroxine and carbimazole, 3 ml of 10% of (SRBCs)suspension was injected into the jugular vein of each rabbit using disposable syringes. Serum samples were obtained from blood samples collected from the rabbits at days 0, 4, 8 and 12 after immunization. Then haemagglutination antibody titres were determined. The sera were activated by keeping in water bath at 56ºC for 30 min. Then haemagglutination test was performed using U-bottomed plastic microtitre plates and microtitre pipettes [25].

Statistical Analysis: The experimental data were subjected to standard methods of statistical analysis using statistical analysis system [26]. Analysis of variane (ANOVA) test as factorial completely randomized design was used to examine the effect of the thyroid status on thermoregulation, heart rate and body weight, organs weight, total leukocyte count and immunity response of rabbits. The experimental data are expressed as mean values ± standard deviation (SD). The separation of means was done by Duncan Multiple Range Test.

RESULTS

Rectal Temperature (T_r): Fig. 1 shows that the initial (T_r) values of rabbits ranged from 39.8 to 40.1 °C. The group of rabbits receiving (T4) had higher and the group receiving (CBZ) had lower (T_r) values compared to the control group (Fig. 1). The group receiving (T4) had

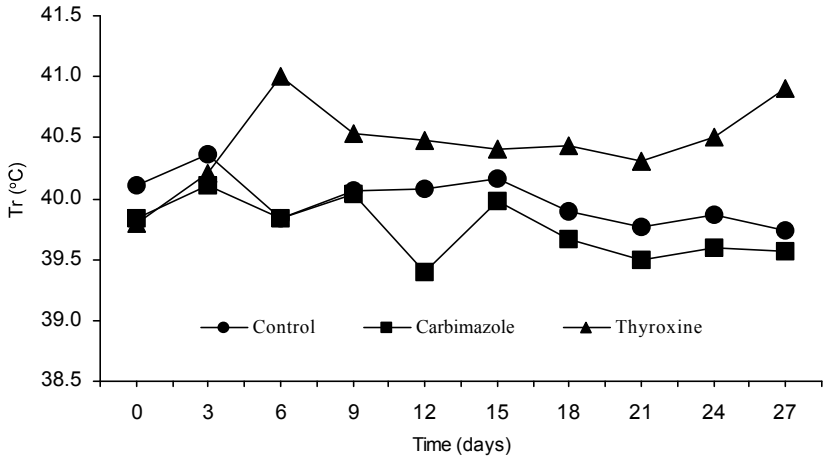

Fig. 1: Effect of thyroid status on rectal temperature (Tr) in male rabbits

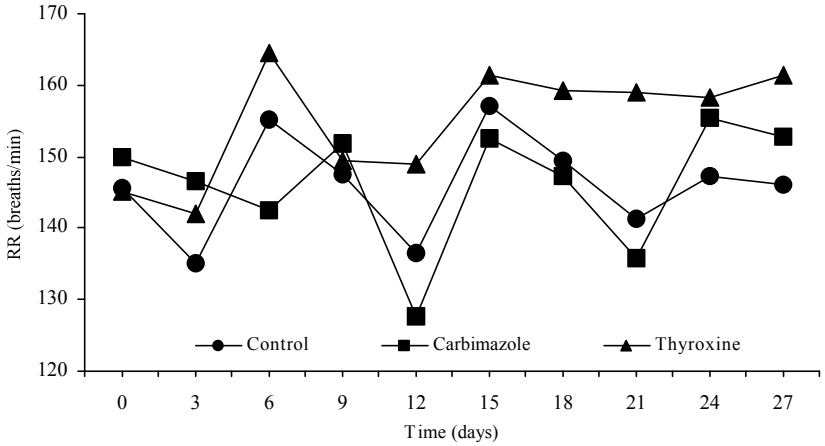

Fig. 2: Effect of thyroid status on respiratory rate (RR) in male rabbits

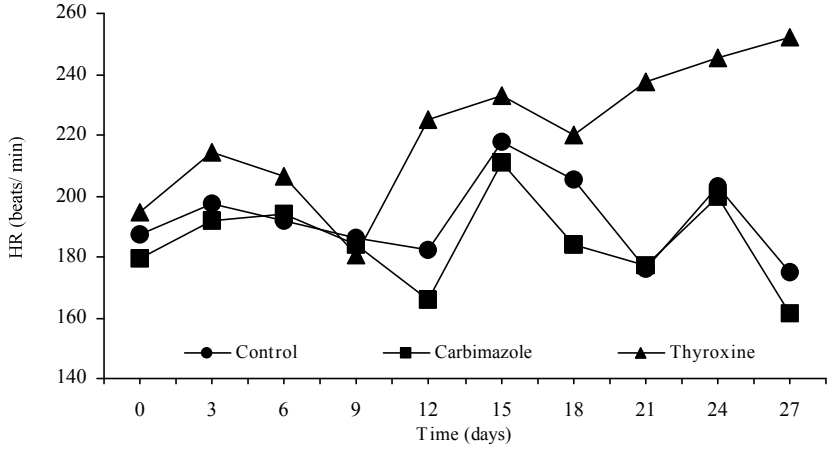

Fig. 3: Effects of thyroid status on heart rate (HR) in male rabbits

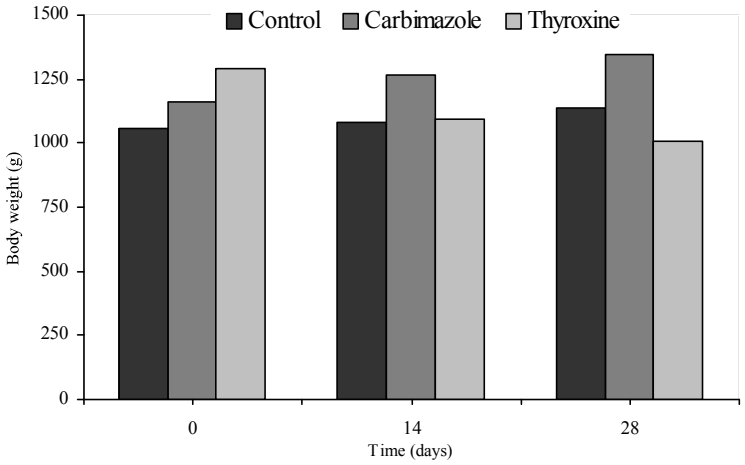

Fig. 4: Effect of thyroid status on body weight (BW) in male rabbits

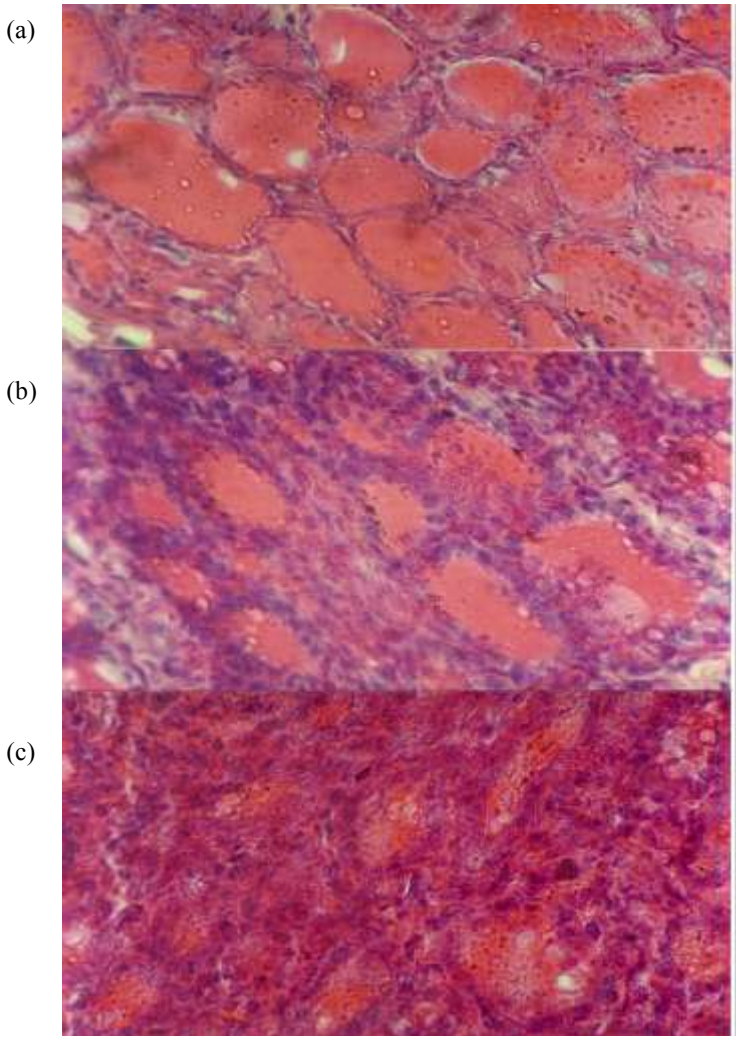

Fig. 5: Histological features of the thyroid gland in (a) T4 treated (hyperthyroid), (b) normal (euthyroid) and (c) CBZ treated (hypothyroid) rabbits

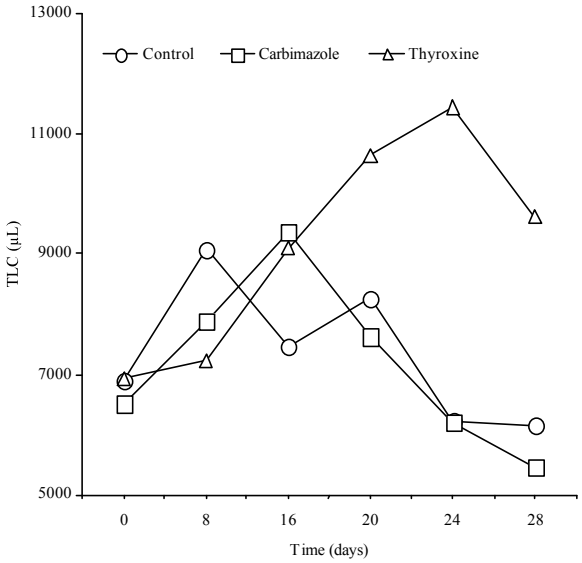

Fig. 6: Effects of thyroid status on total leukocyte count (TLC) in male rabbits

significantly higher (T_r) values compared with control group at days 18 and 21 (P< 0.01) and days 24 and 27 (P< 0.05). The group receiving (CBZ) had significantly lower (T_r) values compared with the control at day 12 (P< 0.05).

Respiration Rate (RR): Fig. 2 indicates that the initial values of (RR) of rabbits ranged from 145 to 150 breaths /min. The general pattern indicates that the group of rabbits receiving (T4)had higher and the group receiving (CBZ) had lower (RR) values compared to the control group. The (T4) group had significantly (P< 0.05) higher (RR) value compared with the control group at day 21.

Heart Rate (HR): The initial values of (HR)of rabbits ranged from 178 to 194 beats/min (Fig. 3). The group of rabbits receiving (T4) had higher and the group receiving (CBZ) had lower (HR) values compared to the control group. The group receiving (T4) had significantly higher (HR)value than the control and (CBZ) treated group at days 12, 21, 24 and 27 (P< 0.01, P< 0.001, P< 0.001 and P< 0.0001, respectively).

Body Weight (BW): Fig. 4 depicts that the initial mean BW of rabbits ranged from 1.05 to 1.29 Kg. Generally, the (T4)treated group had lower mean (BW) and (CBZ) treated group had higher mean (BW) compared to the respective control group values. The (T4) group had significantly (P< 0.05) lower mean (BW) at day 28 compared with (CBZ) values.

Weights of Internal Organs: Table 1 shows the results of the effects of thyroid status on the mean weights of internal organs (thyroid gland, spleen, heart and liver). The (CBZ) treated group had significantly (P< 0.01) higher mean thyroid gland weight than the control and (T4) treated group values. Fig. 5 shows the histological features of the thyroid gland of control and (T4) and (CBZ) treated groups. The gland of the group receiving

Table 1: Effect of thyroid status on organ weight in male rabbits

Organ	Control	(CBZ)	(T4)	LS
Thyroid gland (mg)	90.0^{b}±10	130^{a}±15	80.0^{b}±4.0	**
Spleen (mg)	304^{a}±12	335^{a}±01	356^{a}±02	NS
Heart (g)	3.81^{a}±1.22	5.76^{a}±0.98	4.64^{a}±1.26	NS
Liver (g)	26.72^{a}±4.58	42.32^{b}±2.63	35.10^{ab}±5.63	**

LS: Level of significance **: P<0.01
NS: Not significant

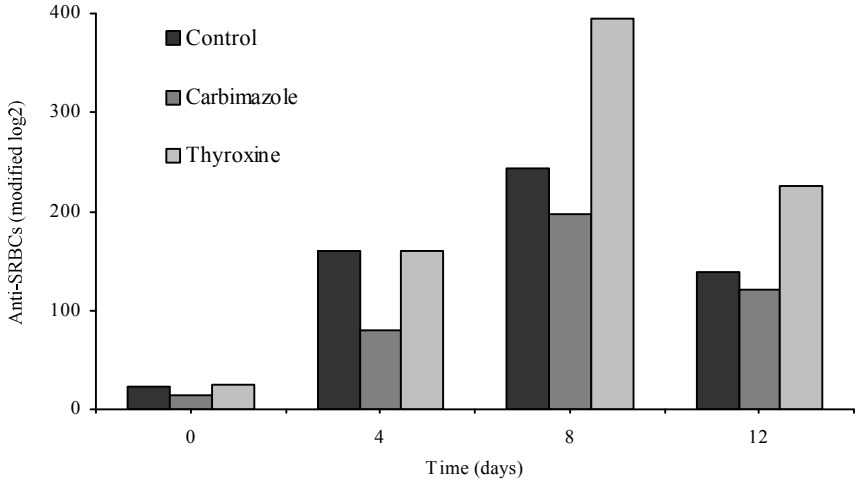

Fig. 7: Effect of thyroid status on antibody production in male rabbits

(T4) showed flattened epithelial cells and accumulation of large amount of colloid in thyroid follicles compared to control group. The group receiving (CBZ) showed decrease in size of follicles and in the amount of colloid compared to control group.

There was no significant difference in the mean spleen and heart weight as related to the thyroid status. However, both (T4) and (CBZ) treated groups had higher spleen weight compared with the control group and the mean weight was higher for (T4) group compared to (CBZ) group. The (T4) and (CBZ) groups had higher heart weight values compared to the control value and the mean weight was higher for (CBZ) group compared to (T4) group. Both (CBZ) ($P< 0.01$) and T4 treated groups had higher mean liver weight compared with control group.

Total Leukocyte Count (TLC): Fig. 6 shows that the initial values of (TLC) of rabbits ranged from 6.5 to 6.9 ($x10^3/\mu L$). The (T4) group had significantly higher (TLC) at days 20 and 28 ($P< 0.05$) compared to the (CBZ) group and at day 24 ($P< 0.01$) compared with control group.

Antibody Production: Fig. 7 shows the effects of thyroid status on antibody production in response to (SRBCs). Generally, the antibody titres increased in the control and the (T4) and (CBZ) treated groups until day 8 and then declined. At day 4, the (T4) treated group had higher and (CBZ) group had lower values of antibody titre compared with the control group. At day 8, the (T4) group had marked but not significantly higher antibody titre compared with the control and the (CBZ) treated group. At day 12, the antibody production decreased in all groups, but the (T4) treated group maintained higher antibody titre compared with both the control and CBZ treated groups.

DISCUSSION

The higher rectal temperature (T_r) of (T4) treated rabbits (Fig. 1) is clearly related to the calorigenic effect of exogenous (T4) which maintains a critical role in the control of body temperature by stimulation of thermogenesis and regulation of cellular metabolism [27]. Thyroid hormones increase (O_2) consumption and stimulate the activity of enzymes involved in metabolic regulation [3]. Some of the calorigenic effect of (T4) is due to metabolism of fatty acids as well as increase in the activity of the membrane bound Na^+-K^+ ATPase in many tissues [28]. The thyroid hormones also increase dissociation of (O_2) from haemoglobin by increasing the concentration of 2, 3 –Diphosphoglycerate in erythrocytes [29]. The decrease in (T_r) of the group of rabbits receiving (CBZ) (Fig. 1) is related to decrease in the levels of thyroid hormones and consequent reduction in energy expenditure. It has been noted [1] that lack of thyroid hormones reduces energy expenditure which leads to a marked decrease in cold tolerance of humans.

The higher value of (RR) obtained with (T4) (Fig. 2) is attributed to the increase in metabolic rate which increases the utilization of (O_2) and the formation of (CO_2); these effects activate the mechanisms that increase the rate and depth of respiration [30]. Also it could be attributed to thermally stimulated increase in pulmonary ventilation that augmented evaporative heat loss. In rabbits exposed to high ambient temperature, the increase in metabolic heat production leads to an increase in respiratory evaporative water loss by panting [31]. The rabbits increased respiratory water loss by increasing (RR) in order to dissipate the internal heat.

The increase in (HR) with (T4) treatment (Fig. 3) is consistent with the physiological effects of thyroid hormones on cardiovascular system which include lowering of systemic vascular resistance, increase of cardiac output and increase in blood volume [10]. The force of contraction of the heart muscle is influenced by thyroid hormones directly [32]. The increase in metabolic heat production may increase the (HR) and cardiac output in order to increase blood flow to the skin and facilitate heat dissipation. It has been indicated [33] that the increase in (HR) in hyperthyroidism resembles a state of increased adrenergic activity, despite normal or low serum concentrations of catecholamines. Klein and Levey [34] noted that (T3) increases cardiac output by increasing tissue oxygen consumption. The haemodynamic changes typical of hypothyroidism are opposite to those of hyperthyroidism [35]. Capasso *et al.* [36] reported that hypothyroidism was associated with a decrease in (HR) in rabbits and rats.

The decrease in mean BW associated with exogenous (T4) (Fig. 4) is related to an increase in metabolic rate and negative nitrogen balance associated with stimulation of protein catabolism. It has been indicated [32] that the increase in basal metabolic rate (BMR) by thyroid hormones is usually associated with mobilization and degradation of protein and lipids in tissues, depletion of the body stores of fat and body weight loss. In hyperthyroidism, if the food intake is not increased, catabolism of endogenous protein and fat stores leads to body weight loss [37]. Previous investigations demonstrated that thyroid hormones caused reduction in

(BW) via an increase in metabolic rate in rats [38, 39]. Hyperthyroidism in humans led to an increase in (BMR) and negative nitrogen balance and hypothyroidism was associated with decrease in (BMR) and slightly positive nitrogen balance [40].

The changes indicative of thyroid status were manifested by the alterations in the mean weight of thyroid gland (Table 1) and the histological features (Fig.5). The mean weight of thyroid gland was higher in (CBZ) treated group of rabbits and it was lower in (T4) treated group compared to the control values (Fig. 5). The changes in the mean weight of thyroid gland were associated with modification in the histological features. Injection of (T4) led to a decrease in the height of follicular cells and an increase in the amount of colloid in thyroid follicles, whereas administration of (CBZ) resulted in an increase in the height of follicular cells and a decrease in the amount of colloid in thyroid follicles (Fig. 5). Impairment of thyroid hormone synthesis by (CBZ) stimulated feedback mechanism regulation, led to a compensatory rise in (TSH) level, which in turn caused hypertrophy and hyperplasia of thyroid follicular cells and, ultimately, enlargement of thyroid gland.

The decrease in thyroid weight in (T4) treated group obtained in the present study is attributed to depression of thyroid function caused by a decrease in the rate of secretion of (TSH), which in turn causes hypotrophy of thyroid follicles. A decrease in thyroid gland activity was expressed in flattening of epithelium and accumulation of large amount of colloid in thyroid follicles of common vole treated with thyroxine [41].

In the current results, the mean weights of the vital internal organs were affected by thyroid status (Table 1). The weight of the spleen increased in (CBZ) and (T4) treated groups compared with the control group. This pattern could be associated with the general gain in (BW) in (CBZ) treated group of rabbits. The higher spleen weight obtained for the (T4) treated group could be related to the influence of thyroid hormones on the immune system and enhancement of the proliferation of lymphoid organs. It has been reported [42] that (T3) induced hyperthyroidism was associated with increase in spleen weight and hypothyroidism induced by propylthiouracil (PTU) did not influence the spleen weight in rats.

The increase in heart weight of (T4) treated group is attributable to the effect of thyroid hormones on the myocardium. Thyroid hormones maintain inotropic and chronotropic effects on cardiac function and increase the heart rate in order to secure sufficient blood flow. A combination of these effects may lead to hypertrophy of the heart muscle. Thyroid hormone administration led to a significant increase in heart weight in rats [43, 44]. The increase in heart weight in CBZ treated rabbits (Table. 1) is likely to be associated with the reported gain in body weight (Fig. 4) and the decrease in (HR) (Fig. 3).

The weight of the liver was increased in both (CBZ) and (T4) groups compared with control. The higher liver weight obtained for (CBZ) treated rabbits is related to a decrease in the level of thyroid hormones and metabolism and the reported body weight gain (Fig.4). Glycogen represents the principal storage form of carbohydrate in the mammalian body, mainly in the liver. The higher weight of the liver in (T4) treated group of rabbits, could be related to an increase the rate of absorption of carbohydrate from the gastrointestinal tract [32]. Kaneko [45] indicated that (T4) improves the intestinal glucose absorption along with glucose turnover. Also thyroid hormones influence glucose kinetics in the body. Thyroxine might decrease the capacity for insulin–stimulated hepatic glycogen storage in monogastric species, resulting in a reduced hyperglycaemic response to glucagon [46].

The increase in (TLC) in (T4) treated group (Fig.6) may be attributed to the effect of (T4) on the bone marrow as exogenous (T4) enhanced the bone marrow and led to an increase in myelopoiesis in mice [47]. The higher (TLC) with (T4) may also be related to lymphatic tissue proliferation. The total T-lymphocyte cells and spleen weight increased in rats injected with (T3) [42]. The decrease in (TLC) in the (CBZ) treated group may be attributed to a decrease in the level of thyroid hormones. Similarly, chemically induced hypothyroidism and thyroidectomy led to reduction in (TLC) in rats [17, 11]. The decrease in (TLC) with (CBZ) may also be attributed to a decrease in the weight and cellularity of lymphoid organs due to the immunosuppressive effects of (CBZ). (CBZ) treatment in humans was shown to be associate with a decrease in (TLC) [48].

The results indicate that the antibody production in response to sheep red blood cells (SRBCs) increased in (T4) treated group and it decreased in (CBZ) treated group (Fig.7). Thyroid hormones stimulate the humoral immunity and exogenous (T4) stimulates proliferation of lymphoid tissues. Filteau and Woodward [49] reported that (T3) increased antibody titres in malnourished mice, but had no effect on well nourished mice. The (CBZ) induced decrease in antibody production in the present study is consistent with the finding [50] that hypothyroidism induced by (PTU) treatment for 30 days decreased the antibody production in rats.

CONCLUSION

The rabbit model can be adopted for investigations of effects of alteration of thyroid status in mammals. Chemical control of thyroid function influences thermoregulation, heart rate, body weight and immunological responses. Further research is warranted to elucidate mechanisms involved in body weight and immunological changes associated with thyroid status. Also future studies should examine the humoral immunity in relation to hyper- and hypothyroidism in relation to thermal environment.

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