

Evaluate the propylthiouracil on thyroid, liver and kidney functions in male rabbits

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Abstract

This work was conducted to investigate the effect of Propylthiouracil thyroid kidney and liver functions in male rabbits. Fifteen (15) rabbits were divided into three groups: a control group, which received tap water only, a low-dose group that received 50 mg/kg oral propylthiouracil and a high-dose group, which received 100 mg/kg oral propylthiouracil. Rabbits were dosed daily for three weeks. After the three-weeks period, the rabbits were sacrificed and blood samples were collected for hormonal and biochemical analysis. Showed changes in liver enzymes as a result of liver tissue damage. Propylthiouracil caused an increase in creatinine concentration, alkaline phosphatase levels, and liver enzyme levels. PTU treatment had no significant effect on the mean urea concentration level. In view of the changes summarized, the increase or decrease in this parameter arises from the reduction in the level of thyroid hormones which, in turn, affect most body tissues.

Keywords: Hypothyroidism, Propylthiouracil, PUT, liver, kidney, Thyroid hormones.

تأثير قصور الغدة الدرقية الناجم عن البروبيل ثيوراسيل على وظائف الكلى والكبد في ذكور الأرانب

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الملخص:

تم إجراء هذه ادراسة لمعرفة تأثير قصور الغدة الدرقية على وظائف الكلى والكبد في ذكور الأرانب. الطريقة تم تقسيم خمسة عشر (15) أرانبًا إلى ثلاث مجموعات: مجموعة ضابطة، تلقت ماء الصنبور فقط، ومجموعة جرعة منخفضة تلقت 50 مجم / كجم من بروبييل ثيوراسيل عن طريق الفم ومجموعة جرعة عالية، والتي تلقت 100 مجم / كجم من بروبييل ثيوراسيل عن طريق الفم. بعد فترة الثلاثة أسابيع، تم التضحية بالأرانب وتم جمع عينات الدم للتحليل الهرموني

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والكيميائي الحيوي. أظهرت النتائج تغيرات في إنزيمات الكبد نتيجة تلف أنسجة الكبد. تسبب عقار Propylthiouracil في زيادة تركيز الكرياتينين ومستويات الفوسفاتيز القلوية ومستويات إنزيمات الكبد. لم يكن للمعالجة بـ PTU أي تأثير معنوي على متوسط مستوى تركيز اليوريا. الخلاصة في ضوء التغييرات التي تم تلخيصها ، فإن الزيادة أو النقص في هذه المعلمة تنشأ من انخفاض مستوى هرمونات الغدة الدرقية والتي بدورها تؤثر على معظم أنسجة الجسم.



Introduction

Thyroid hormones (THs) (thyroxine and triiodothyronine, T₄, and T₃) govern lipid and carbohydrate metabolism and are required for different physiological activities like growth, development, and reproduction [1]. They regulate the rate of tissue oxygen consumption, which controls the body's metabolism rate.

Hypothyroidism is defined by a decrease in the serum level of thyroid hormones (T₄) and (T₃) due to impaired thyroid hormone production and secretion. Hypothyroidism is classified into two types: primary and secondary (central) hypothyroidism. Primary hypothyroidism is caused by a thyroid gland problem. Primary hypothyroidism can be caused by autoimmune thyroiditis, iodine shortage, thyroidectomy, and the use of certain medicines, such as thionamides, lithium, and iodine-containing pharmaceuticals. Clinical hypothyroidism or subclinical hypothyroidism are the two basic types [2, 3].

Weight gain, a decrease in resting energy expenditure, decreased gluconeogenesis, and lipolysis are all symptoms of this illness. Obesity and lipid metabolism problems, which are components of metabolic syndrome, can be caused by thyroid dysfunction [4]. Hypothyroidism impairs triglyceride clearance and fatty acid oxidation by reducing lipolysis and gluconeogenesis, as well as increasing hepatic triglyceride buildup and low-density lipoprotein reuptake [5].

Antithyroid medications like methimazole and propylthiouracil (6-Propyl-2-thiouracil) (PTU) are one of the antithyroid pharmaceuticals utilized by researchers to treat hyperthyroidism [6]. PTU prevents the thyroid gland from producing fresh thyroid hormones. It works on the periphery by preventing the conversion of T₄ to T₃. It has an influence on thyroid hormones that are stored in the thyroid gland or that circulate in circulation [7]. It was regularly employed to create a hypothyroidism animal model that could be used to test the efficacy of new therapies or medications [8].

The thyroid and renal functions have long been recognized to interact. Thyroid hormones are important in kidney growth and function, and the kidney is generally involved in thyroid hormone metabolism, degradation, and excretion. PTU-induced hypothyroidism can also lead to kidney failure, which can be caused by vasculitis, lupus nephritis, or necrotizing glomerulonephritis with pulmonary bleeding [9]. Renal blood flow, glomerular filtration rate,

water and electrolyte balance, and kidney structure are all affected by hypothyroidism [10]. It also caused hypernatremia and elevated serum creatinine levels [11]. Furthermore, in humans, the increase in serum creatinine levels is reversible [12]. Furthermore, some authors have claimed that an increase in serum creatinine is linked to subclinical hypothyroidism [13].

Thyroid hormones affect hepatic function by regulating the basal metabolic rate of hepatocytes, and the liver, in turn, metabolizes thyroid hormones and regulates their activities. As a result, thyroid failure can disrupt hepatic functions, and hepatic disorders can negatively impact thyroid function [14]. As a result, it's not unexpected that hepatic impairment is widespread among thyroid illness patients [15]. Previous research suggests that rather than cholestasis, PTU-induced hepatotoxicity is likely to be hepatocellular at the level of mitochondrial injury [16]. PTU also promotes lipid peroxidation in the liver, which puts the liver tissue under oxidative stress. On the other hand, there is no specific antidote for hepatic harm caused by PTU, PTU-induced liver failure and death have been reported in some cases [17].

This study aims to investigate the effect of propylthiouracil -induced hypothyroidism on the physiological variables of kidney and liver parameters in male rabbits.

Materials and Methods

Animals

Six month old, healthy, Local male rabbits (15), (weighing between 1.5-2.0kg) were obtained from a local breeder and were maintained in individual cages in a room with normal temperature and light/dark cycles. The rabbits were given access to water and food ad libitum. The animals were kept and maintained under normal conditions for four weeks before the experiment.

Chemicals

Propylthiouracil (6-n-propyl-2-thiouracil; PTU), is an antithyroid (goitrogen) agent (Thyrocil tablets from Amoun Pharmaceutical Co., Egypt) was obtained from a local Pharmacy.

Experimental Procedure

The rabbits were weighed and divided randomly into three groups (5 rabbits each): 1- control (received tap water only), 2- low dose group (received 50 mg/Kg of PTU orally), and 3- high

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dose group (received 100 mg/kg PTU orally) [18]. But before receiving the PTU, blood samples were withdrawn from the vein of the ear to determine the levels of TSH, T3, T4 Liver and Kidney function were dosed with PTU for 3 weeks [19]. After the end of the 3 weeks, the rabbits were slaughtered and blood samples were taken from the 3 groups. From each rabbit (8ml) into tubes without EDTA for biochemical and hormonal parameters. The liver was dissected out, weighed and placed in vials containing 10% neutral formalin as a fixative until used for histological studies.

Hormones

T3, T4, and TSH were measured automatically using Elecsys2010 (RD/Hitachi Immunoassay System 2010 from Roche Diagnostics/Hitachi, Japan).

Biochemical parameters

Determination of kidney function

Creatinine concentration was assessed using the method of Murray [20]. The method described by Fawcett and Scott [21]. It was used to determine the concentration of urea in the blood,

Determination of liver function

The activity of alanine aminotransferase (ALT; EC 2.6.1.2) and aspartate aminotransferase (AST; EC 2.6.1.1) were measured according to the method of [22]. The alkaline phosphatase (ALP; EC 3.1.3.1) activity in the serum was assayed by a kinetic method using commercial kits (BioSystems S.A Costa Brava, Barcelona, Spain) according to the International Federation of Clinical Chemistry [23].

Histological Studies

Fixed livers were dehydrated through ascending grades of ethyl alcohol till absolute alcohol (1 hr each) then transferred to xylene (3 changes, 5 minutes each). The specimens were then transferred to a mixture of melted wax and xylene (1:1) in an oven (60°C) for 10 minutes. After that, they were transferred into 3 changes of paraffin wax for 2 hours. Finally, the materials were sectioned at a thickness of 5 microns. Sections were then stained with Harris haematoxylin and counter stained with Eosin [24].

Statistical Analysis

Statistical analysis was performed using a computer run program (GraphPad Prism version 4.00, GraphPad software, San Diego, USA). One way ANOVA followed by Tukey, HSD test was performed to show the statistical significance among the means of the groups. Results were expressed as mean \pm Standard error of the mean (SEM). A P-value below 0.05 was considered to be statistically significant.

Results

The drug PTU is known to lower the levels of thyroid hormones; therefore, it was important to determine the level of these hormones before and after treatment. Figure 1 represents the levels of T3 in the sera of the rabbits before and after treatment with PTU. There were no significant differences between the means of the 3 groups ($P > 0.05$) before treatment. There was no significant difference between the levels of T3 in the serum of the control group before and after treatment with PTU. However, PTU significantly reduced the level of T3 in the low dose- treated group ($P = 0.0371$) and in the high dose-treated group ($P = 0.004$). The levels of T4 are represented in Figure 2. There was no significant difference between the two levels of the control group. However, PTU at 50 mg/kg highly significantly reduced the level of T4 ($P = 0.0008$). The 100 mg/kg dose also significantly reduced the levels of T4 ($P < 0.0001$). The results of the effect of PTU on the levels of TSH are shown in Figure 3. The 50 mg/kg PTU increased significantly the TSH levels ($P = 0.001$). The 100 mg/kg dose also increased significantly ($P = 0.0028$) the levels of TSH.

The effect of PTU on the kidney function tests (Creatinine and Urea) was also studied. Figure 4 represents the result of the effect of PTU on Creatinine. There was no significant difference between the mean of the control group and that of the low dose-treated group ($P > 0.05$). However, there was a significant difference between the mean of the control group and the mean of the 100 mg/kg-treated group ($P = 0.0003$). Also, there was a significant difference between the means of the two treated groups ($P = 0.0177$). As for the concentration of the Urea (mg/dl) there were no significant differences between the means of the 3 groups ($P > 0.05$) (Figure 5).

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Figure 6 represents the effect of the two different doses of PTU on the activity of the enzyme AST. The level of AST (nmol/L) in the serum of the control group increased in the low dose- and high dose-treated rabbit. There was significant difference ($P= 0.013$) between the level of the control group and that of the low dose treated group. Though the level of the enzyme in the serum of the high dose- treated rabbits was higher than that of the control groups, this difference, however, was not statistically significant ($P > 0.05$). There was no significant difference between the level of the low dose treated and that of the high-dose treated rabbits ($p > 0.05$). A Similar trend was observed for the enzyme ALT (Figure 7). There was significant difference between the mean level of the control group and that of the low dose-treated group ($P= 0.0292$). There were no significant differences between the mean level of the control group and that of the high dose- treated group, and between the mean level of the low dose- and that of the high dose treated group ($P > 0.05$).

With concerning to the enzyme ALP (Figure 8), the activity (nmol/L) in the control group increased significantly ($P= 0.0003$) in the high dose-treated rabbits. There was no significant difference between the mean of the control group and that of the low dose treated group. There was significant difference between the means of the two treated groups.

The changes in liver enzymes as result of treatment with PTU could be a result of changes in the tissues of the thin organ. This was confirmed by the changes in histological sections of the liver from the control and treated rabbits (Figure 9, 10, 11). These changes included congestion, dilated hepatic sinusoid, hemorrhage, and necrosis.

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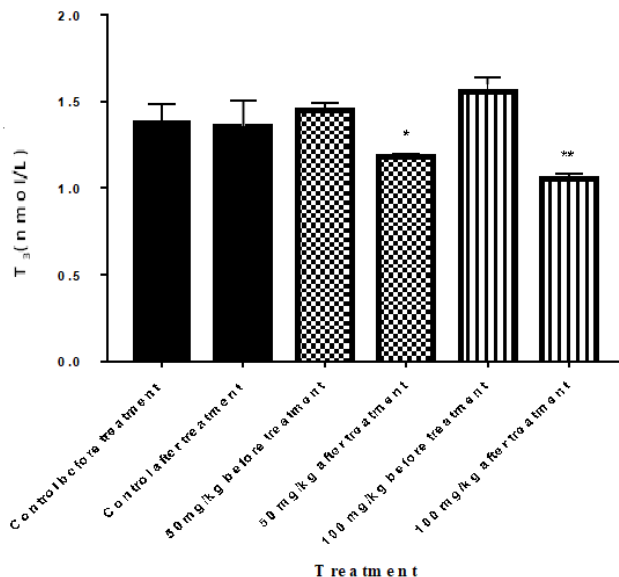


Figure 1: The mean concentrations of T₃ in the sera of the rabbits before and after treatment with PTU. Result are mean ± SEM. Asterisks indicate significant differences before and after treatment within the same group.

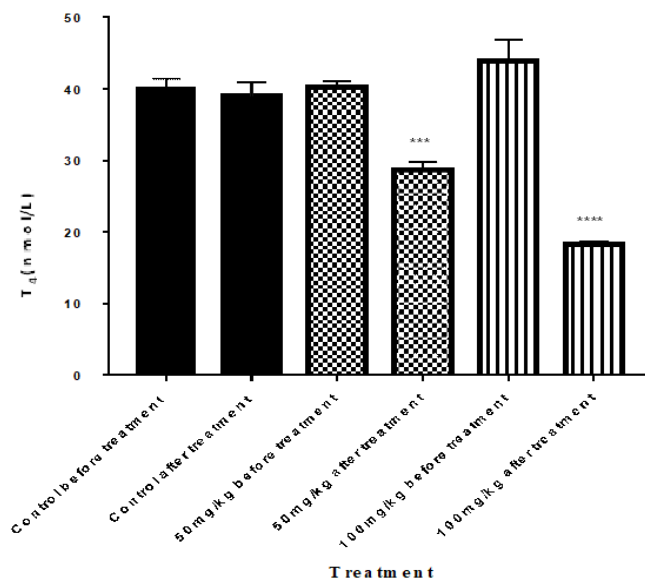


Figure 2: The levels of T₄ in the sera of the rabbits before and after treatment with PTU. Result are mean ± SEM. Asterisks indicate significant differences before and after treatment within the same group.

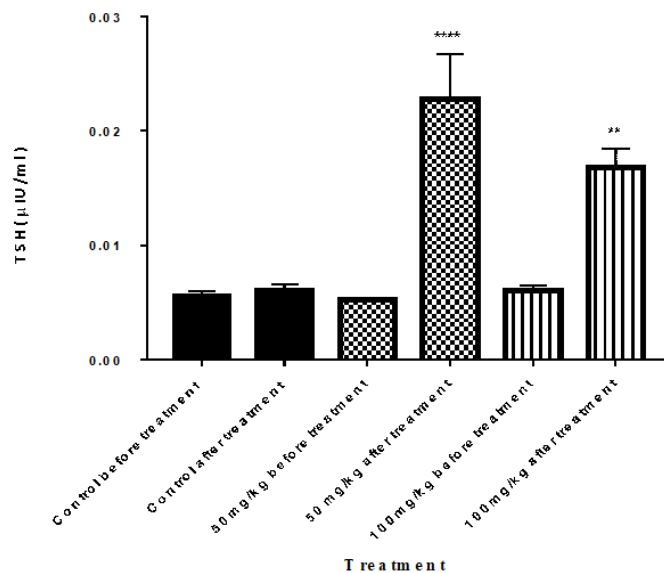


Figure 3: The amount of TSH in the sera of the rabbits before and after treatment with PTU. Result are mean \pm SEM. Asterisks indicate significant differences before and after treatment within the same group.

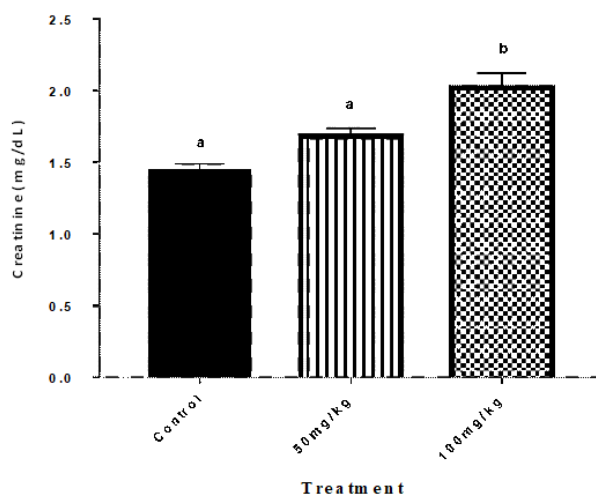


Figure 4: The mean concentrations Creatinine in the sera of the control and PTU-treated rabbits after 3 weeks treatment period. Results are mean \pm SEM. Similar letters indicate no significant differences between the means, while different letters indicate significant differences.

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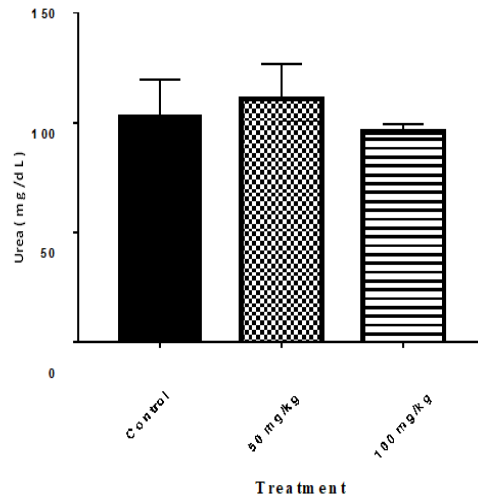


Figure 5: The mean concentrations of urea in the sera of the control and PTU-treated rabbits after 3 weeks treatment period. Results are mean \pm SEM. There were no significant differences between the means.

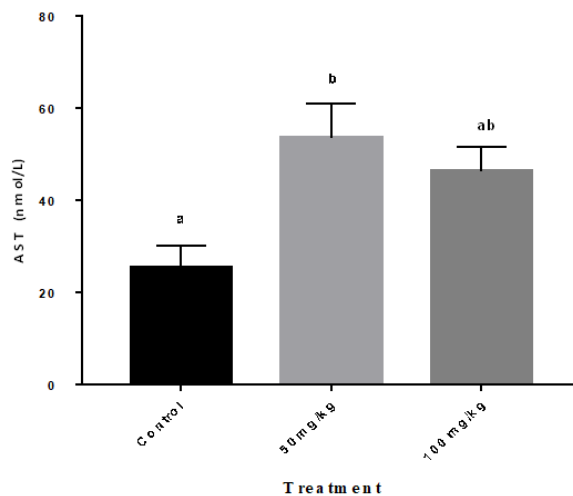


Figure 6: The mean activity of the enzyme Aspartate aminotransferase (AST) in the sera of the control and PTU-treated rabbits after 3 weeks treatment period. Result are mean \pm SEM. Similar letters indicate no significant differences between the means, while different letters indicate significant differences.

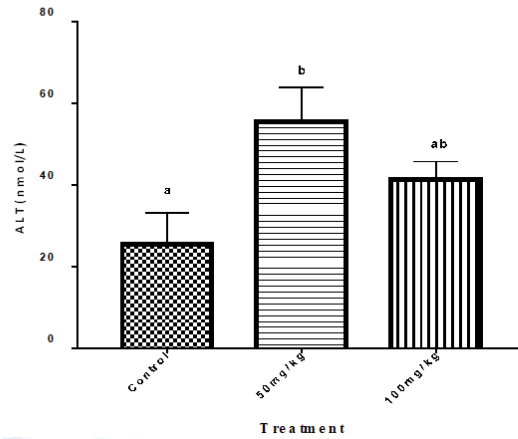


Figure 7: The mean activity the enzyme alanine aminotransferase (ALT) in the sera of the control and PTU-treated rabbits after 3 weeks treatment period. Result are mean \pm SEM. Similar letters indicate no significant differences between the means, while different letters indicate significant differences.

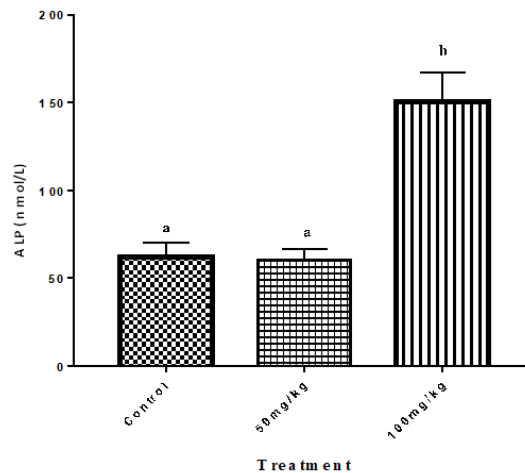


Figure 8: The mean activity of the alkaline phosphatase (ALP) in the serum of the control and PTU treated rabbits after 3 weeks treatment period. Result are mean \pm SEM. Similar letters indicate no significant differences between the means, while different letters indicate significant differences.

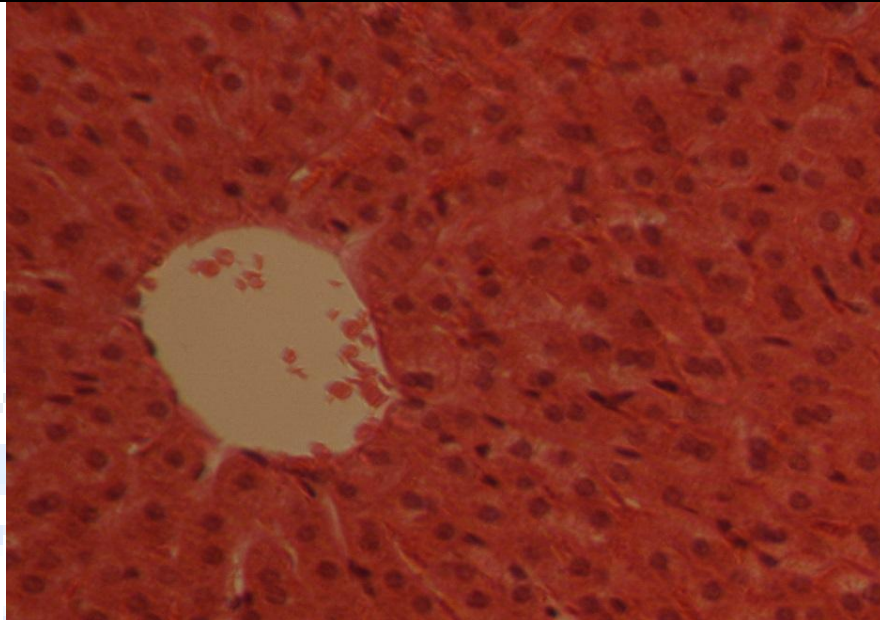


Figure 9: Photomicrograph of a section in the liver of rabbit from control group showing normal structure of hepatic cells and central vein (H & E, X 400).

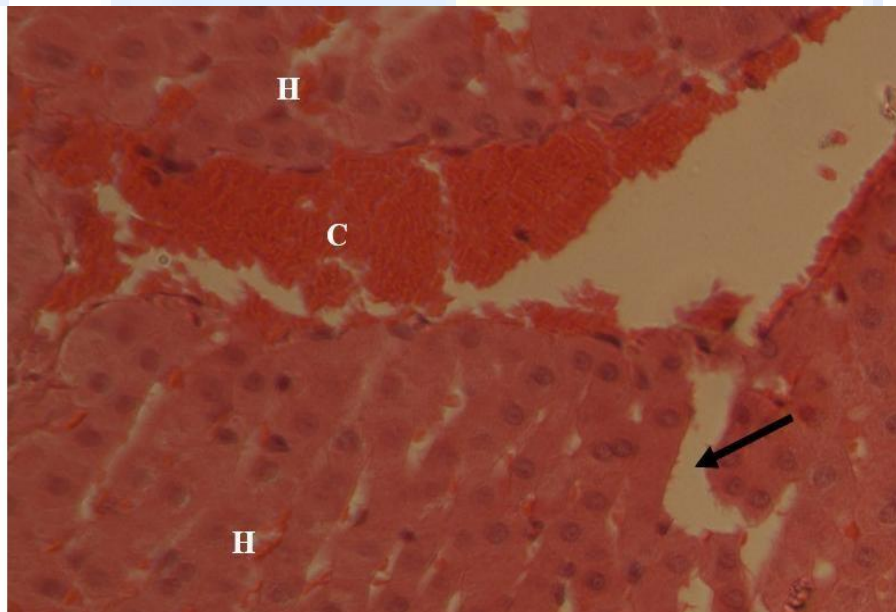


Figure 10 : Photomicrograph of a section in the liver of rabbit treated daily with PTU (50 mg/kg) for 3 weeks showing congestion (C), dilated hepatic sinusoid (Arrow) and haemorrhage (H) (H & E, X 400).

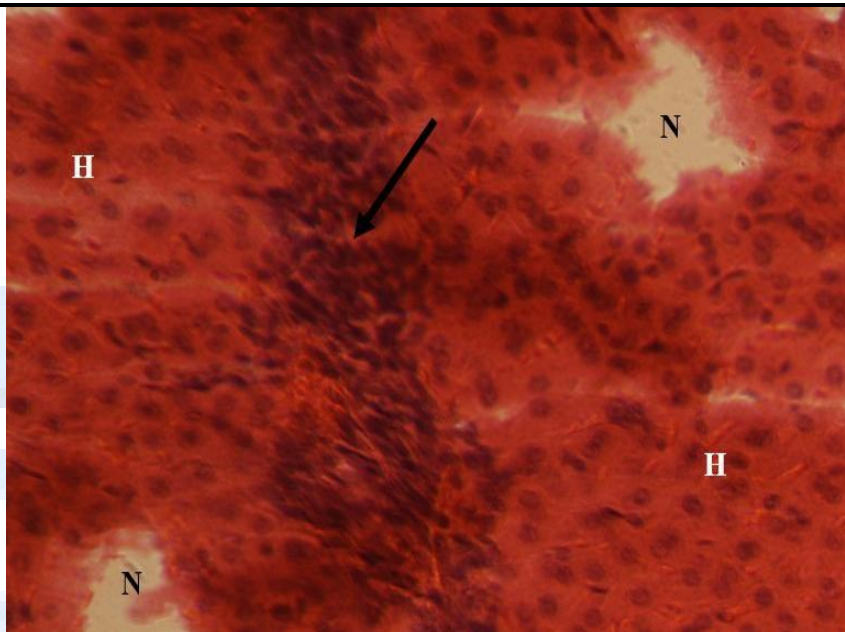


Figure 11: Photomicrograph of a section in the liver of rabbit treated daily with PTU (100 mg/kg) for 3 weeks showing distorted liver architecture with inflammatory infiltration cells (Arrow) and haemorrhage (H) with some necrotic areas (N) (H & E, X 400).

Discussion

This study was conducted to investigate the effect of induced hypothyroidism on liver enzymes and the histological structure of the liver. Hypothyroidism was induced using PTU.

PTU inhibits the production of new thyroid hormones in the thyroid gland. It acts by inhibiting the enzyme thyroid peroxidase, which usually functions to convert iodide to iodine molecule and incorporate the iodine molecule into amino acid tyrosine. Hence, diiodotyrosine (DIT) or moniodotyrosine (MIT) does not get produced, which are the main constituents in the production of T4 and T3 [25].

The kidney function tests (creatinine and urea) were also carried out in animals treated with PTU. In this study, PTU had no significant effect on urea concentration but caused a significant increase in the concentration of creatinine. In rats Salama *et al.* [26] reported significant increases in the concentrations of both creatinine and urea after treatment with PTU. Similar results were also reported by Mohebbati *et al.* [27] and Schmitt *et al.* [28]. Many case reports document increased levels of serum creatinine with hypothyroidism in humans [29]. Thyroid hormones affect renal function by both pre-renal and direct renal

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effects. Pre-renal effects are mediated by the influence of thyroid hormones on the cardiovascular system and renal blood flow (RBF). The direct renal effects are mediated by the effect of thyroid hormones on glomerular filtration rate (GFR), tubular secretory and re-absorptive processes, as well as the hormonal influences on renal tubular physiology [30]. The RBF is reduced in hypothyroidism by decreased cardiac output, increased peripheral vascular resistance [31], intrarenal vasoconstriction [32], reduced renal response to vasodilators [33], and a reduced expression of renal vasodilators such as vascular endothelial growth factor (VEGF) [34].

Liver function enzymes were significantly increased in the animals treated with PTU. In a study to evaluate the effect of thyroid dysfunction on liver function tests, Ajala *et al.* [35] found that hypothyroidism caused a significant increase in the plasma concentrations of liver enzymes activities. Nambiar *et al.* [36] also reported that PTU treatment caused slight increases in serum ALT and ALP in male rats. Another report in rats that were administered PTU for a month described alterations in select hematologic/serum biochemical parameters including increased ALT and AST [37]. Recently, Farrag *et al.* [38] observed hepatic lesions in the form of severe congestion in the central vein and hepatic artery, and hepatocellular necrosis in rabbits treated with PTU. Such lesions were dependent on the doses of PTU.

Karamikhah *et al.* [39] reported that acute exposure to PTU caused damage to the liver of mice as evidenced by the increase in ALT, the occurrence of significant lipid peroxidation, and hepatic glutathione depletion. The mentioned changes were endorsed by histopathological lesions of the liver which were mainly manifested as pre-portal inflammation. The mechanism(s) by which PTU causes hepatic injury is not clear yet [40, 41]. Previous studies suggest that the nature of PTU-induced hepatotoxicity is hepatocellular rather than cholestatic [42]. Some investigations observed the involvement of mitochondrial injury in PTU-induced hepatic damage [43]. The role of metabolism is also indicated to be involved in PTU-induced liver-injury [44]. Moreover, defects in cellular defense mechanisms might be involved in PTU damage.

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Conclusion: In view of the changes summarized, the increase or decrease in these parameters may be attributed to a hypometabolic state which arises from the reduction in the level of thyroid hormones which, in turn, affect most body tissues. Therefore, those who suffer from hypothyroidism should make a routine check to these parameters to make sure that they are in the normal ranges.



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