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Antioxidant Vitamins Status in Wistar Rats with Induced Thyroid Dysfunction

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Authors' contributions

This work was carried out in collaboration between both authors. Author MHY designed the study, wrote the protocol and performed the statistical analysis. Author ZY managed the literature searches and analyses of the study and wrote the first draft of the manuscript. Both authors read and approved the final manuscript.

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ABSTRACT

Oxidative stress plays an important role in the pathogenesis of thyroid disorders. Major effects of thyroid hormones are the acceleration of mitochondrial respiration which is accompanied by excessive production of reactive oxygen species leading to oxidative stress and lipid peroxidation. The current study examined the status of serum antioxidant vitamins A, C, and E in rats with induced thyroid dysfunction. Twenty-one (21) rats were divided into three groups of 7 each: euthyroid (control), hypothyroid and hyperthyroid groups. Hypothyroidism was induced using 6-propyl-2-thiouracil (5 mg/100 g orally); hyperthyroidism was induced by daily intraperitoneal injection of L-thyroxine (0.1 µg/g). At the end of the experiment, rats were fasted for 12 hours and blood samples were collected under chloroform anaesthesia for the estimation of serum total triidothyronine (tT_3), total tetraiodothyronine (tT_4), thyroid stimulating hormone (TSH) and antioxidant vitamins A (retinol), C (ascorbic acid), E (α-tocopherol) using standard techniques. The results indicated significant decrease in tT_3 (0.95±0.06ng/ml), tT_4 (0.54±0.07 µg/dl) and increase TSH (0.13±0.00 µIU/ml) in hypothyroid, while there were significant increase in tT_3 (2.60±0.21 ng/ml), tT_4 (12.91±0.57 µg/dl) and decrease TSH (0.020±0.00 µIU/ml) in hyperthyroid compared

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with euthyroid rats (1.53±0.05 ng/ml, 3.62±0.25 µg/dl and 0.05±0.001 µIU/ml respectively). The serum levels of antioxidant vitamins A (1.77±0.07 µmol/L, 1.20±0.48 µmol/L), C (13.87±2.11 µmol/L, 25.63±1.59 µmol/L), and E (9.30±1.50 µmol/L, 12.34±1.82 µmol/L) were significantly ($p<0.001$) lower in both hypothyroid and hyperthyroid respectively compared with euthyroid rats (2.28±0.07 µmol/L, 44.69±1.62 µmol/L, 44.51±2.96 µmol/L respectively). A significant negative correlation was established between antioxidant vitamin A and tT_3, and also between vitamin E and tT_4 in hyperthyroid rats. The results confirmed the role of oxidative stress in hypothyroidism and hyperthyroidism and underscores the role of antioxidant vitamins A, C and E in delaying the consequence of hypothyroidism and hyperthyroidism or otherwise.

Keywords: Hypothyroidism; hyperthyroidism; antioxidant vitamins; thyroid hormones; rats.

1. INTRODUCTION

The thyroid gland is the body's primary regulator of metabolism and produces hormones necessary for the normal development of body organs. The gland is unique among the endocrine glands because of its size; it is the largest endocrine gland and one of the most responsive organs in the human body [1]. It produces two major hormones triidothyronine (T_3) and tetraiodothyronine or thyroxine (T_4). These hormones are both produced from iodine, an essential mineral and tyrosine, an amino acid [2].

Thyroid disorders are of great importance because most are amenable to medical or surgical management. They include conditions associated with excessive release of thyroid hormones (hyperthyroidism), those associated with thyroid hormone deficiency (hypothyroidism) and those that present as mass lesions of the thyroid [3]. The incidence of thyroid gland diseases also varies with geographical location [1].

Disorders of the thyroid gland are common worldwide [4]. Community based studies in the United Kingdom and North America reported prevalence rates for thyroid dysfunction at about 2–5% of the general population [5,6]. The autoimmune thyroid disorders (Hashimoto's thyroiditis and Graves' disease) account for the vast majority of thyroid dysfunction seen in iodine-replete populations [4]. In contrast, iodine deficiency is the predominant cause of thyroid disease in Africa, and worldwide [7].

Thyroid hormones are modulators of basal metabolic state, protein degradation and oxidative metabolism. Hyper secretion of thyroid hormone has been shown to increase the production of reactive oxygen species (ROS) such as superoxide radical (O_2^-) and hydroxyl radical (OH^-) can induce oxidative damage to cells resulting to oxidative stress [8-11]. Excessive production and/or inadequate removal of ROS or oxidative stress is described as an imbalance between the formation of reactive oxygen/nitrogen species and the rate at which they are scavenged by enzymatic and non-enzymatic antioxidants, such as catalase (CAT), glutathione reductase, glutathione peroxidase (GPX) and superoxide dismutase (SOD), and non-enzymatic antioxidants, such as vitamins C and E, glutathione, transferrin, ferritin, ceruloplasmin and uric acid [9].

Oxidative stress is a deleterious process and has been suggested to play a significant role in the mediation of damage to cellular structures and biomolecules, including nucleic acids, proteins, lipids and membranes [12]. Oxidative stress has been suggested as the mechanism underlying the pathogenesis of a number of human diseases, such as cancer, coronary heart disease, arthritis, diabetes, cataract and degenerative disease [13]. Therefore, maintenance of adequate antioxidant levels is essential to prevent or even manage a great number of disease conditions [14].

There is paucity of knowledge on the status of serum antioxidant vitamins A, C and E in subjects with thyroid dysfunction in the study environment. The current study was undertaken to assess the status of serum vitamins A, C and E status and investigates the relationship between thyroid hormones (tT3, tT4, and TSH) and vitamins A, C and E in rats with induced thyroid dysfunction.

2. MATERIALS AND METHODS

2.1 Chemicals and Reagents

Analytical graded chemicals and reagents were used for this research. L-thyroxine and propylthiouracil (6-propyl-2-thiouracil) were

purchased from Sigma-Aldrich Chemie GmbH, USA. The kits for tT_3, tT_4 and TSH were purchased from Monobind Inc. Lake forest, CA 92630, USA.

2.2 Experimental Animals

A total of 21 male Wistar rats weighing between 100 – 140 g were purchased from National Veterinary Research Institute Vom, Jos, Nigeria. The rats were housed in well aerated cages under hygienic conditions in the Animal House, Faculty of Pharmaceutical Sciences, Usmanu Danfodiyo University, Sokoto. The rats were allowed to acclimatize for a period of 2 weeks before the commencement of the experiment. The rats were grouped into three (3) groups of 7 rats each and were fed pelletized growers feed (Vital®), obtained from Grand Cereal Soil Mills Limited, Jos, Nigeria. They were also allowed access to clean drinking water *ad libitum* throughout the experimental period. Cleaning of the animal cages was carried out daily, and on regular basis. They were maintained in clean metabolic cage-sand, placed in a well-ventilated room conditions with a temperature of 26℃ to 28℃, photoperiods of 12 hours light and 12 hours darkness; humidity of 40% to 60% as described by Aniagu et al. [15]. All the experimental protocols were in compliance with our Institutional Animal Ethics Committee guidelines as well as internationally accepted practices for use and care of laboratory animals as contained in US guidelines (National Institute of Health).

2.3 Experimental Design

The animals were randomly divided into three (3) groups of seven (7) rats each: Euthyroid (control) (group I): untreated receiving daily intraperitoneal injection of 0.9% normal saline solution; hypothyroid (group II): treated with 6-propyl-2-thiouracil and hyperthyroid (group III): treated with L- thyroxine.

2.4 Induction of Hypothyroidism

Hypothyroidism was induced by administering propylthiouracil (PTU; 6-propyl-2-thiouracil) at a dose of 5mg/100g body weight per day through oral route by the use of oral cannula (a feeding needle) for 30 days according to Petrulea et al. [16].

2.5 Induction of Hyperthyroidism

Hyperthyroidism was induced by daily intraperitoneal injection of L- thyroxine (T_4) at a dose of 0.1 µg/g body weight per day for 30 days. The control group received daily intraperitoneal injections of normal saline (0.9%) solution for 30 days [17]. Only rats from groups II and III that have serum TSH ≥ 0.06 µI U/ml were included in the study for further treatment.

2.6 Measurement of Body Weight

The rats in all the groups were weighed using a sensitive balance, once before the commencement of PTU or L- thyroxine (T_4) dosing and once on the day of animals sacrifice.

2.7 Blood Sample Collection and Processing

After 30 days period, the animals were fasted for 12 hours, and were anaesthetized in a glass jar containing wool soaked with chloroform. About five millilitres (5 ml) of blood samples were collected from the animals through cardiac puncture, into clean, plain vacutainer tubes. The samples collected were allowed to clot at room temperature and later centrifuged at 4000 revolution per minute (4000 rpm) for 10 minutes. The sera were then transferred into labelled sterile serum bottles and tightly caped and stored at-20℃ until the time for the estimation of biochemical parameters.

2.8 Estimation of Biochemical Parameters

The serum tT_3, tT_4 and TSH were estimated by ELISA method [18], retinol [19], ascobate acid [20] and α-tocopherol [21] were determined by spectrophotometric method.

2.9 Statistical Analysis

The data obtained were analysed using Microsoft Office Excel 2007 and Statistical Package for Social Sciences (SPSS) version 23. Values were expressed as mean ± SEM. Group comparisons were made using one-way analysis of variance (ANOVA), p value less than or equal to 0.05 ($p \leq 0.05$) was considered as statistically significant.

3. RESULTS

Table 1 shows the initial and final body weight of rats with induced thyroid dysfunction and control. The result indicated significantly decreased ($p<0.05$) body weight in hypothyroid and

hyperthyroid as compared with control (euthyroid) rats.

The administration of 5 mg/100 g PTU to rats (Table 2) significantly (P< 0.05; P< 0.001) decreased serum tT_3 and tT_4 (0.95±0.06 ng/ml and 0.54±0.07 µg/dl respectively) while, serum TSH (0.13±0.00 µIU/ml) significantly (P<0.001) increased in hypothyroid rats compared with control (1.53±0.05 ng/ml, 3.62±0.25 µg/dl and 0.05±0.00 µIU/ml respectively).

Administration of L- thyroxine (0.1 µg/g) to rats (Table 2) significantly (P< 0.001) increased serum tT_3, and tT_4 (2.60±0.21 ng/ml and 12.91±0.57 µg/dl respectively) and significantly (P< 0.001) decreased serum TSH (0.02±0.00 µIU/ml) compared with the control (1.53±0.05 ng/ml, 3.62±0.25 µg/dl and 0.05±0.00 µIU/ml respectively).

Serum antioxidant vitamins A, C and E in rats with induced thyroid dysfunction and control are presented in Table 3. The result indicated significantly (P< 0.001) decreased serum vitamins A, C and E in hypothyroid group (1.77 ± 0.07 µmol/l, 13.87 ± 2.11 µmol/l and 9.30 ± 1.50 µmol/l respectively) and hyperthyroid group (1.20 ± 0.48 µmol/l, 25.63 ± 1.59 µmol/l and 12.34 ± 1.82 µmol/l respectively) compared with control (2.28 ± 0.07µmol/l, 44.69 ± 1.62 µmol/l and 44.51 ± 2.9 µmol/l respectively).

Table 4 shows the correlation between thyroid hormones (tT_3, tT_4 and TSH) and antioxidant vitamins A, C and E in euthyroid rats (control). The result indicated that, with the exception of serum tT_3 which has a significant negative correlation (r = -0.884; P=0.008) with vitamin E, significant correlation was not established between serum antioxidant vitamins (A and C) and thyroid hormones (tT_4 and TSH) in control rats. The correlation between serum tT_3, tT_4, TSH and vitamins A, C and E is presented in Table 5. The result indicated no significant correlation between the thyroid hormones (tT_3, tT_4 and TSH) and antioxidant vitamins (A, C and E) in hypothyroid rats. Significant negative correlation was established between serum vitamin A and tT_3 (r = -0.966; p =0.000) and between serum vitamin E and tT_4 (r = -0.797; p =0.032) hyperthyroid rats (Table 6).

Table 1. Initial and final body weight of Wister rats with induced thyroid dysfunction and controls

Group	(n)	Initial body weight (g)	Final body weight (g)
Group I	7	128.00 ± 1.46	161.57 ± 8.22
Group II	7	129.71 ± 2.08	141.43 ± 2.59
Group III	7	130.86 ± 2.72	136.71 ± 2.99
P-value		>0.05	<0.01
Post-hoc analysis, Bonferroni			
Group I Vs II		P>0.05	P<0.05
Group I Vs III		P>0.05	P<0.05
Group II Vs III		P>0.05	P>0.05

Values are mean ± SEM, n= Number of rats; Group I = Controls; Group II = Hypothyroid; Group III = Hyperthyroid.

Table 2. Serum levels of tT_3, tT_4 and TSH in Wister rats with induced thyroid dysfunction and controls

Group	N	tT_3 (ng/ml)	tT_4 (µg/dl)	TSH (µIU/ml)
Group I	7	1.53 ± 0.05	3.62 ± 0.25	0.05 ± 0.00
Group II	7	0.95 ± 0.06	0.54 ± 0.07	0.13 ± 0.00
Group III	7	2.60 ± 0.21	12.91 ± 0.57	0.02 ± 0.00
P-value		<0.001	<0.001	<0.001
Post-hoc analysis, Bonferroni				
Group I Vs II		P<0.05	P< 0.001	P< 0.001
Group I Vs III		P< 0.001	P<0.001	P< 0.001
Group II Vs III		P< 0.001	P< 0.001	P< 0.001

Values expressed as mean ± SEM; N= Number of subjects; tT_3 = Total triidothyronine; tT_4= Total thyroxine; TSH= Thyroid stimulating hormone; Group I= Controls; Group II= Hypothyroid; Group III= Hyperthyroid

Table 3. Serum antioxidant vitamins A, C and E in Wister rats with induced thyroid dysfunction and controls

Group	N	Vitamin A (µmol/l)	Vitamin C (µmol/l)	Vitamin E (µmol/l)
Group I	7	2.28 ± 0.07	44.69 ± 1.62	44.51 ± 2.96
Group II	7	1.77± 0.07	13.87 ± 2.11	9.30 ± 1.50
Group III	7	1.20 ± 0.48	25.63 ± 1.59	12.34 ± 1.82
P-value		<0.001	<0.001	<0.001
Post-Hoc analysis, Bonferroni				
Group I Vs II		p<0.001	p<0.001	p<0.001
Group I Vs III		p<0.001	p<0.001	p<0.001
Group II Vs III		p<0.001	p<0.01	p>0.05

Values expressed as mean ± SEM; N= Number of subjects; Group I= Control; Group II= Hypothyroid; Group III= Hyperthyroid

Table 4. Correlation between thyroid hormones (tT_3, tT_4 and TSH) and antioxidant vitamins A, C and E in euthyroid group

Antioxidant vitamins	Thyroid hormones		
	tT3 (ng/ml)	tT4 (µg/dl)	TSH (µlU/ml)
Vitamin A (µmol/l)	r = -0.170	r = -0.238	r =0.525
	p =0.715	p =0.628	p =0.226
Vitamin C (µmol/l)	r = -0.830	r = -0.261	r = 0.158
	p =0.859	p =0.571	p =0.735
Vitamin E (µmol/l)	r = -0.884	r = -0.170	r = -0.498
	p =0.008	p =0.715	p =0.256

r = Correlation coefficient; p = p-value; tT_3 = Total triidothyronine, tT_4= Total thyroxine, TSH = Thyroid stimulating hormone

Table 5. Correlation between serum thyroid hormones and antioxidant vitamins A, C and E in Wister rats with induced hypothyroidism

Antioxidant vitamins	Thyroid hormones		
	tT3 (ng/ml)	tT4 (µg/dl)	TSH (µlU/ml)
Vitamin A (µmol/l)	r = -0.359	r = 0.570	r = -0.410
	p =0.429	p =0.181	p =0.361
Vitamin C (µmol/l)	r = -0.178	r = -0.022	r = -0.210
	p =0.703	p =0.962	p =0.652
Vitamin E (µmol/l)	r = -0.302	r = -0.310	r = 0.548
	p =0.510	p =0.499	p =0.203

r = Correlation coefficient; p = p-value; tT_3 = Total triidothyronine, tT_4= Total thyroxine, TSH= Thyroid stimulating hormone, PTU= Propylthiouracil

Table 6. Correlation between thyroid hormones (tT_3, tT_4 and TSH) and antioxidant vitamins A, C and E in Wister rats with induced hyperthyroidism

Antioxidant vitamins	Thyroid hormones		
	tT_3 (ng/ml)	tT_4 (µg/dl)	TSH (µlU/ml)
Vitamin A (µmol/l)	r = -0.966	r = -0.270	r =0.010
	p =0.000	p =0.558	p =0.984
Vitamin C (µmol/l)	r = -0.143	r = 0.184	r = -0.513
	p =0.760	p =0.693	p =0.239
Vitamin E (µmol/l)	r = -0.294	r = -0.797	r = 0.235
	p =0.525	p =0.032	p =0.612

r = Correlation coefficient, p = p-value, tT3 = Total triidothyronine, tT4= Total thyroxine, TSH= Thyroid stimulating hormone

4. DISCUSSION

Thyroid hormones play a critical role in the regulation of oxidative metabolism and therefore contribute in free radical generation [9]. Thyroid hormones regulate the degradation and synthesis of antioxidant enzymes such as superoxide dismutase, glutathione peroxidase and catalase and also non-enzymatic antioxidants such as uric acid, vitamins E and C, glutathione and ferritin. Changes in these enzymatic and non-enzymatic antioxidants affect the redox balance in the body. One of the major effect of thyroid hormones is the acceleration of mitochondrial respiration which is accompanied by excessive production of reactive oxygen species (ROS) leading to oxidative stress and damage to membrane lipids [17].

The current study assessed the status of serum antioxidant vitamins A, C and E in rats with induced-thyroid dysfunction. The study revealed that administration of PTU (5 mg/100 g body weight per day for 30 days) to rats induced hypothyroidism as indicated by a decrease in serum tT_3 and tT_4 levels, and an increase in serum TSH level. The decreased serum levels of tT_3, tT_4 and increased TSH confirmed the establishment of hypothyroid state in rats. Our results are in agreement with the studies of Zbucki et al. [22] and Khalawi et al. [23] who independently reported significant decrease in the plasma concentration of tT_3, tT_4 and significant increase in TSH in experimental hypothyroid rats compared with controls. The results also corroborated with report of Haiying et al. [24] who demonstrated that hypothyroid subjects were diagnosed having plasma concentrations of tT_3 and tT_4 below the normal ranges, and TSH above the normal range.

The mechanism by which PTU induce hypothyroid state in rats could be due to its inhibition of thyroid hormone synthesis by interfering with thyroid peroxidase–mediated iodination of tyrosine residues in the thyroid gland at both steps of iodine organification and iodotyrosine coupling as well as inhibiting the conversion of T_4 to T_3 in extra thyroidal tissues [23,25].

On the other hand, the administration of L-thyroxine at a dose of 0.1 µg/g body weight per day for 30 days to rats induced hyperthyroidism as indicated by an increase in serum tT_3 and tT_4 levels, and a simultaneous decrease in serum TSH level compared with controls. The elevation of serum tT_3 and tT_4 are indicative of hyperthyroidism, while a low serum TSH in the presence of elevated thyroid hormones is logical because secretion of TSH from the anterior pituitary is regulated by negative feedback from the serum free thyroid hormone concentrations [17,26,27]. Hence both hypothyroid and hyperthyroid states in experimental rats were associated with oxidative stress as indicated by significant decrease in the serum levels of vitamins A, C and E.

There was no significant change in the body weight of the rats at baseline. However after 30 days of PTU and L-thyroxine administration, the final body weight of rats in both hyper- and hypothyroid groups was significantly lower compared with euthyroid rats. Our result corroborated with previous studies [28,29]. It was also observed that the hypothyroid rats significantly gained body weight compared with initial body weight; however the weight gain was lower compared with euthyroid rats. This is in agreement with the study of Khalawi et al. [23]; Barakat and El-Masry [29]. The mechanism responsible for the increase in body weight in hypothyroid rats could be due to a reduction in the basal metabolic rate which the rats undergo following the administration of PTU [30]. In hyperthyroid group, there was an increase in final body weight compared with initial body weight. This contrasted with the findings of Ai et al. [31] and Yi et al. [32] who reported a decrease in final body weight of hyperthyroid rats. This may be as a result of the differences in the doses of L-thyroxine used in the induction of hyperthyroidism in rats. While Ai et al. [31] and Yi et al. [32] used 1 mg/kg and 20 mg/100 g of L-thyroxine respectively, the current study used 0.1 µg/g body weight.

The significant decrease in serum antioxidant vitamins A, C, and E observed in both hypo- and hyperthyroid rats compared with control corroborated with previous researchers [27,33]. The possible mechanism underlying the decreased serum antioxidant vitamins A, C, and E following the administration of PTU and L-thyroxine could be due to increased generation of ROS leading to oxidative stress in the experimental hypo-and hyperthyroid rats.

Vitamin A is a potent antioxidant and acts as a scavenger of free radicals either independently or as a part of large antioxidant system. Clinical and experimental studies showed enhanced generation of free radicals in hyperthyroidism.

Hyperthyroidism is known to be a hyper metabolic state that is accompanied by an increase in the total consumption of oxygen, leading to the formation of reactive oxygen species and other free radicals, or the occurrence of oxidative stress (8). Hence the antioxidant system including vitamin A was overwhelmed due to oxidative stress induced by experimental induced hyperthyroidism in rats [34,35].

Vitamin E was reported to be an important factor in quenching free radicals and increasing the capability of the immune system [36]. In this study, serum vitamin E decrease in experimental hypothyroid and hyperthyroid rats. This may be explained by the excessive production of ROS and presumably due to its use in preventing free radical damage that seems more extensive in thyroid dysfunction in rats [33].

It has also been shown by other researchers that ROS inhibit the activity of an enzyme responsible for the conversion of T_4 to the active hormone T_3 and that sufficient vitamin E levels may mitigate that effect [37]. Vitamin E, as powerful antioxidant, might have indirectly caused the destruction of hydrogen peroxide (H_2O_2), the required oxidizing agent for iodide oxidation, thus leading to a decrease in thyroid hormone biosynthesis [27]. This finding is consistent with the previous researches that highlighted the importance of the effects of Vitamin E in oxidative stress and as a component of the antioxidant defence system [38].

Vitamin C (ascorbic acid) is regarded as the major aqueous phase antioxidant which is capable of "scavenging" reactive oxygen species by reducing free radicals to more stable species [27]. The current study demonstrated a decreased serum vitamin C in hypothyroid and hyperthyroid rats compared with control. The result in the present study, corroborated with earlier studies [39,40] who independently reported lower levels of vitamin C and increase oxidative stress in hyperthyroidism.

In the current study there was a significant negative correlation between tT_3 and vitamin A, also between vitamin E and tT_4. The significant negative correlation established between tT_3 and vitamin A may probably be due to an important role played by thyroid hormones in oxidative metabolism. This has been suggested by some researchers that increase in tT_3 may be accompanied by increase generation of ROS and hence a decrease in serum antioxidant vitamin A [33]. The significant negative correlation also established between serum vitamin E and tT_4 is an indication that increase in tT_4 was accompanied by increased generation of free radicals [41], which overwhelm the antioxidant capacity including vitamin E which explains its decreased serum level in rats with induced-thyroid dysfunction.

Vitamin E is a major lipid soluble antioxidant that converts the peroxyl radical to much less reactive hydroperoxides, thereby inhibiting the propagation step in lipid peroxidation [27].

In this study there was no significant correlation between thyroid hormones and vitamin C in hypothyroid and hyperthyroid rats. Also there was no significant relation between serum thyroid hormones and antioxidants vitamins in hypothyroidism.

5. CONCLUSION AND RECOMMENDA-TION

The current study established the role of oxidative stress in hypothyroidism and hyperthyroidism and underscores the role of antioxidant vitamins A, C and E in delaying the consequence of hypothyroidism and hyperthyroidism or otherwise.

6. LIMITATION OF THE STUDY

A major limitation in this work is the small sample size as well as the time constraint for the conduct of the research. If time permitted, the second phase of the study would have continued to assess the effect antioxidant vitamins A, C and E supplementation on the Wister rats with induced thyroid dysfunction.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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