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SERUM AND GASTRIC TISSUE ELECTROLYTE LEVELS IN CARBIMAZOLE-TREATED AND LEVOTHYROXINE-TREATED MALE NEW ZEALAND WHITE RABBITS

Ajayi Ayodeji Folorunsho[1]*, Akhigbe Roland Eghoghosoa[1], Ajayi Lydia Oluwatoyin[2], Adeleye Gbenga Sunday[3] and Adebayo-Gege Grace Iyabo[4]

[1]Department of Physiology, Faculty of Basic Medical Sciences, Ladoke Akintola University of Technology, P.M.B. 4000, Ogbomoso, Nigeria.

[2]Department of Biochemistry, Faculty of Sciences, Adeleke University, P.M.B. 250 Ede, Nigeria.

[3]Department of Physiology, Ekiti State University, P.M.B. 5363 Ado Ekiti, Nigeria.

[4]Departmet of Physiology, Faculty of Basic Medical Sciences, Bingham University, P.M.B. 005 KM 26, Abuja-Keffi Road, Auta-Baleef, Nigeria.

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***Corresponding Author**
Ajayi Ayodeji Folorunsho
Department of Physiology, Faculty of Basic Medical Sciences, Ladoke Akintola University of Technology, P.M.B. 4000, Ogbomoso, Nigeria.

ABSTRACT

Thyroid and gastrointestinal tract functions are connected in both health and disease conditions. Thyroid hormones regulate metabolic function; therefore its disorders are associated with electrolyte imbalance. This study provides scientific information on gastric tissue electrolyte level, and its relationship with serum electrolyte level in altered thyroid state. It also documents the effect of dysthyroidism on adherent gastric mucus content, a gastro protective factor, and gastric architecture. Fifteen healthy male New Zealand White Rabbit of comparable weight were randomly allocated into three (3) groups (n=5), Control, Carbimazole-treated (5mg/250g bw) and Levothyroxine-treated (5µg/100g bw) groups. Treatments were given orally for 35 days. Thyroid function test, body weight change, serum and stomach tissue electrolyte, adherent gastric mucus content, oxidative stress parameters and histology of the stomach were assessed at the end of the treatments. There was a significant rise in gastric levels of chloride and bicarbonate in hyperthyroidism. These electrolytes significantly declined in hypothyroidism. However, gastric sodium level significantly declined in hyperthyroidism. Adherent gastric mucus content significantly

increased in hyperthyroidism, but reduced in hypothyroidism. Dysthyroidism led to significant rise in MDA and depletion of catalase and GSH. Hypothyroidism also led to loss of parietal cells and marked gastric ulceration. It was concluded that the alteration in the gastric levels of electrolytes explains the gastric dysfunction seen in altered thyroid state. This is associated with lipid peroxidation.

KEYWORDS: Oxidative stress, antioxidant, dysthyroidism, gastric ulcer, parietal cell, electrolytes.

INTRODUCTION

A relationship between thyroid function and electrolyte disorder in patients with severe altered thyroid state only have been proposed.[1] Electrolytes such as sodium, potassium, chloride and bicarbonate are important component of the body homeostasis and necessary for the normal functioning of body cells.[2] They are important in acid-base balance in the body tissues and gastric tissue, hence essential for gastric acid secretion.[3] Bicarbonate ion is an important component of the barrier that protects the stomach from assaults,[4] which means that a balanced electrolyte level is essential for the maintenance of the integrity of the gastric mucosa.

Thyroid hormones are regulators of body haemodynamic, thermoregulation, and metabolism.[5] Hypothyroidism results in low potassium level and this could result in oedema.[6] Hypokalaemia, hypomagnesaemia and hypercalcaemia have been reported in patients with thyrotoxicosis.[7,8] Thyroid hormones also regulate the activity of sodium-potassium pumps in most of the tissues.[5] Sodium and potassium are important components of the enzyme Na-K ATPase, which is important in the transport of water and nutrients across the cell membrane. Besides, altered thyroid states may have effects on the secretion of mucus in the epithelial lining of the stomach,[9] which shows the importance of the relationship between the thyroid and the gastrointestinal tract protection and the need to further elucidate this in relationship to electrolyte balance in the gastric mucosa. There is a dearth of information on the changes in serum and gastric tissue electrolyte levels in altered thyroid states. This study aimed at providing information on gastric tissue electrolyte levels in thyroid dysfunction, and the relationship between serum and stomach tissue electrolyte level in altered thyroid state. The effect of the possible electrolyte alteration on adherent gastric mucus content was also evaluated. The role of oxidant and antioxidants were assessed.

MATERIALS AND METHODS

Experimental Animals

Fifteen healthy male New Zealand White Rabbit weighing between (1500 – 1800g) were obtained from the Teaching and Research Farm, Faculty of Agricultural Science, Ladoke Akintola University, Ogbomoso, Nigeria. They were randomly allocated into three (3) groups n=5, Control (Euthyroid), Carbimazole -treated (hypothyroid) and Levothyroxine-treated (hyperthyroid) groups. The rabbits were kept in wire meshed cages, standard laboratory pelletized feed and water was given *ad libitun* and they were acclimatized for two weeks at a room temperature of 37^0C before the commencement of the experiment in the Animal house of the Department of Physiology, Ladoke Akintola University of Technology, Ogbomoso, Oyo state, Nigeria.

Experimental Design

The control animals were administered 1 ml of distilled water each, The Carbimazole-treated rabbits were given Carbimazole at a dose of 5mg/250g bw of each animal, while, the Levothyroxine- treated rabbits (Levothyroxine) were given Levothyroxine at a dose of 5µg/100g bw of each animal. All treatments were given orally for 35 days as previously described by Ajayi *et al*.[10] Animals were sacrificed at the end of the experiment, and the thyroid function test, body weight change, serum and stomach tissue electrolyte, adherent gastric mucus content, oxidative stress parameters and histology of the stomach were assessed. The rabbits were given humane care throughout the experiment, while, the study was carried out according to the institution guidelines and the Helsinki declarations on the use of animals for research purpose was followed.[11]

Determination of Body Weight

The weights of the animals in grams were measured with weighing balance before the commencement of the experiment and at the end of the experiment to determine the weight changes of the animals. The percentage change in body weight of the rabbits was determined as a ratio of weight change to the initial weight multiplied by 100.

Preparation of serum and tissue homogenate

The rabbits were sacrificed by cervical dislocation, after which blood samples were drawn with needle and syringe from the apexes of the heart into a plain bottle. Then the stomachs were harvested. The blood samples were centrifuged at 3000 revolutions per minute for 15 minutes to obtain the serum. The removed stomach samples were rinsed in 1.15% KCl, dried

and weighed, before cutting into pieces and homogenized in an equal volume of chilled 10mM Tris/HCl buffer of pH 7.4 and 0.25M sucrose solution.

Determination of serum and tissue electrolyte

Serum and Tissue electrolyte levels were determined using automated chemistry analyzer ROCHE module Cobas 6000 (C0401 and C0601) and ROCHE kits.[12]

Determination of adherent gastric mucus content

Adherent gastric mucus content was assay using the method of Come *et al*.[13] as described by Oluwole and Saka.[14]

Determination of Malondialdehyde (MDA) and antioxidant enzymes in stomach tissue homogenate

The principle of Varshney and kale[15] was used to determine the lipid peroxidation concentration which was based on the reaction of malondialdehyde (MDA) with thiobarbituric acid (TBA) forming an MDA-TBARS adjunct which absorbed at 532 nm. Reduced glutathione (GSH) level in the stomachtissue homogenatewas determined by the method described by Ellman[16] which was modified by Hissin and Hilf.[17] Catalase enzyme activity was measured by method described by Aebi.[18]

Histological study

The histological study of the stomach was performed using method previously described.[19,20] A part of stomach tissue was fixed in 10% formalin solution, after this fixation was carried out; the procedure for paraffin embedding of the tissue was done. Section was then cut at thickness of 5 microns and stained with haematoxyline and Eosin (H&E). Then slide were examined under light microscope to view morphological changes.

Statistical Analysis

Data obtained were expressed as Mean ± Standard deviation. They were analyzed using one-way analysis of variance complemented with unpaired t-test. The Turkey's Multiple Comparison Test was used as post hoc test, $P < 0.05$ vales were considered significant.

RESULTS

Thyroid Hormones Level Following Administration of Carbimazole and Levothyroxine

Table 1 below shows the serum concentrations of triiodothyronine (T3), thyroxine (T4) and thyroid stimulating hormone at the end of the treatment (TSH), T3 and T4 concentrations

were significantly ($p<0.05$) higher in Levothyroxine-treated group compared to the control, while their concentrations were significantly ($p<0.05$) lower in the Carbimazole-treated group compared to the control, but the concentration of TSH was significantly ($p<0.05$) lower in Levothyroxine -treated group and higher in Carbimazole-treated group compared to the control.

Table 1: Thyroid Hormones Level Following Administration of Carbimazole and Levothyroxine (MEAN±S.E.M).

Thyroid variable	Control	Carbimazole-treated	Levothyroxin-treated
T3 (µg/dl)	1.18±0.06*	0.31±0.09**	6.62±0.16 ***
T4 (ng/dl))	10.68±0.11*	9.11±0.13**	13.60±0.24***
TSH (ng/dl)	1.38±0.05*	1.92±0.03**	1.02±0.01***

*Significant difference at P<0.05 between carbimazole and levothyroxine treatments compared with control.

**Significant difference at P<0.05 between carbimazole treatment compared with control.

***Significant difference at P<0.05 between levothyroxine treatment compared with control.

Percentage weight Change following administration of carbimazole and Levothyroxine in male rabbits

Fig. 1 below shows a decreased percentage weight change in Carbimazole-treated group compared to the control and marked decreased percentage weight change in Levothyroxine-treated group compared to the control and carbimazole treatment at the end of the experimental period.

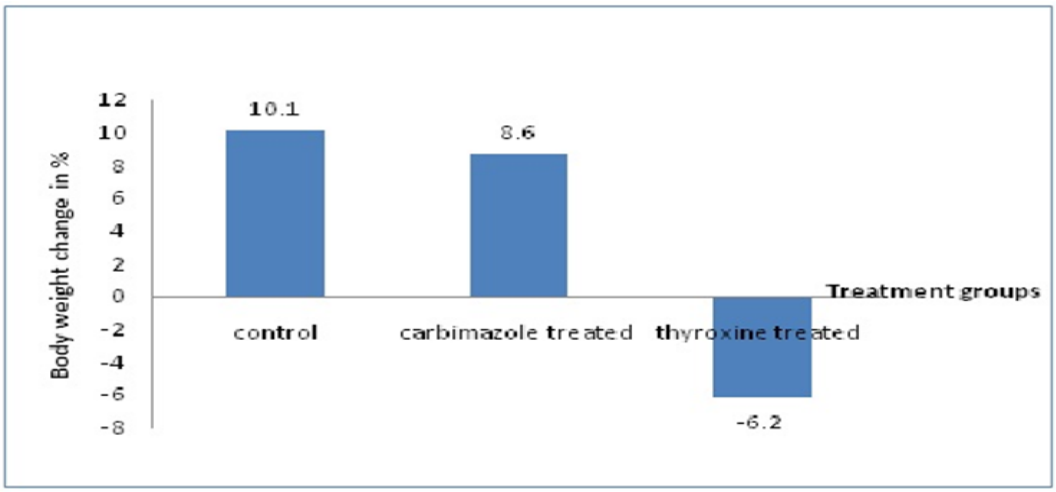

Figure 1: Percentage Body Weight Change following Administration of Levothyroxine and Carbimazole in Male Newzealand White Rabbits.

Effect of administration of Carbimazole and Levothyroxine on serum and stomach tissue electrolyte levels

Fig. 2 below shows that though there were changes in serum levels of sodium, potassium and chloride, these were only marginal. However, serum bicarbonate was significantly raised in hyperthyroidism and declined in hypothyroidism. Similarly, gastric level of potassium was similar in hyperthyroidism and hypothyroidism. Gastric sodium was reduced in hyperthyroidism. Gastric bicarbonate ion concentration was significantly higher in levothyroxine-induced hyperthyroidism compared to the control, while gastric bicarbonate ion concentration in carbimazole-induced hypothyroidism was significantly lower compared to the control. The same pattern was observed in the gastric concentration of chloride ion.

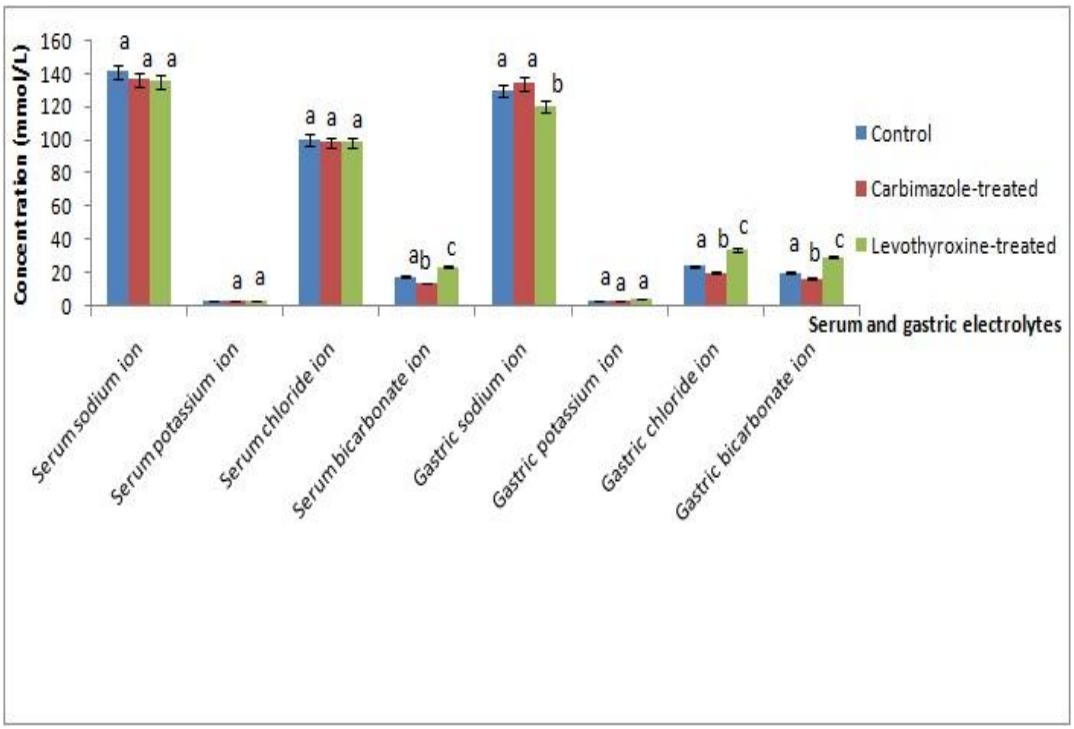

Figure 2: Effect of altered thyroid state on serum and gastric electrolytes.

Bars carrying different letters on the same parameter are statistically different at $P<0.05$.

Effect of administration of carbimazole and Levothyroxine on adherent gastric mucus content

Table 2 showed that adherent gastric mucus content was higher in Levothyroxine-treated rabbits compared to the control, but lower in Carbimazole-treated rabbits compared to the control.

Table 2: Effect of administration of carbimazole and Levothyroxine on adherent gastric mucus content (MEAN±S.E.M).

Treatments	Adherent gastric mucus content (mg/g)
Control	0.40±0.02*
Carbimazole treatment	0.29±0.02**
Levothyroxine treatment	1.05±0.02 ***

*Significant difference at P<0.05 between carbimazole and levothyroxine treatments compared with control.

**Significant difference at P<0.05 between carbimazole treatment compared with control.

***Significant difference at P<0.05 between levothyroxine treatment compared with control.

Effects of Administration of Carbimazole and Levothyroxine on Stomach Tissue Antioxidants Level in Rabbits

In Table 3 below, there was significant (p<0.05) differences between MDA in control, carbimazole and levothyroxine-treated rabbits. With carbimazole-treated rabbit having the highest, followed by the levothyroxine treatment and the least was recorded in the control. But, for catalase and GSH the reverse was the case, control rabbits have the highest followed by thyroxine treatment and the least was recorded in the carbimazole treatment.

Table 3: Effects of administration of carbimazole and levothyroxine on stomach tissue MDA and antioxidants level in male rabbits (MEAN±S.E.M).

Markers	Control group	Carbimazole-treated	Levothyroxine-treated
MDA (nmol/g)	48.04±0.41*	86.20±1.70**	74.28±2.35***
CAT (µmol/min)	68.10±4.94*	46.88±11.64**	54.52±6.09***
GSH (µmol/g)	6.60±0.42*	2.19±0.51**	3.92±0.92***

*Significant difference at P<0.05 between carbimazole and levothyroxine treatments compared with control.

**Significant difference at P<0.05 between carbimazole treatment compared with control.

***Significant difference at P<0.05 between levothyroxine treatment compared with control.

Histological study of the stomach following the administration of carbimazole and levothyroxine

Fig. 3 below shows the photomicrography of histological slide of the control rabbit showing a normal hiso-architecture of the stomach with intact parietal cells and *muscularis mucosa,*

while the carbimazole-treated rabbits have laceration and ulceration on the *muscularis mucosa* with atrophy parietal cells, but the levothyroxine-treated rabbit showed numerous parietal cells and zymogenic cells with intact shape and size, but there are mild ulceration of *muscularis mucosa*.

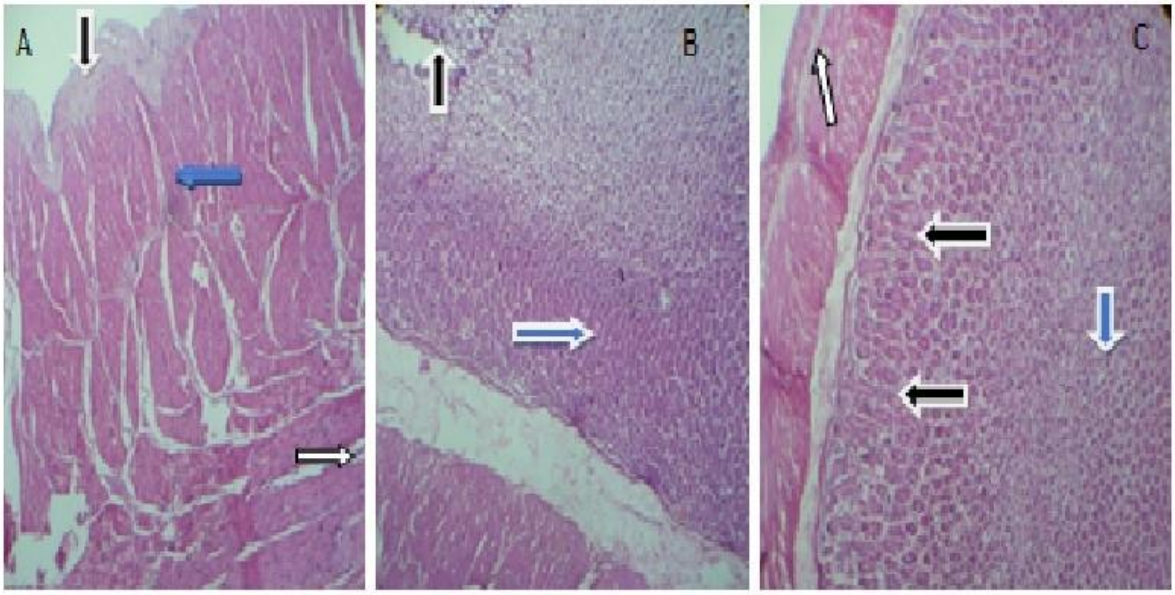

Figure 3: Photomicrograph cross sections of the stomach of control (A), carbimazole-treated (B) and levothyroxine-treated (C) rabbits at H&E 100 X.

A. The section present normal hiso-architecture of the stomach with intact parietal cells and *muscularis mucosa*.

Legend

Black Arrow: Surface Epithelium

Blue Arrow: Neck of Glands

White Arrow: Parietal Cells in the fundus of the stomach

B. The section showed laceration and ulceration on the *muscularis mucosa* as indicated by black arrow as well as atrophy parietal cells.

Legend

Black Arrow: Laceration of Muscularis mucosa

Blue Arrow: Atrophy Parietal cells

C. The section showed numerous parietal cells and zymogenic cells with intact shape and size, with mild ulceration of *muscularis mucosa*.

Legend

Black Arrow: Parietal Cells

Blue Arrow: Zymogenic or Chief Cells

White Arrow: Mild ulceration of muscularis mucosa

DISCUSSION

Carbimazole is a drug of choice in the treatment of hyperthyroidism, after the absorption it is converted to methimazole the active form that prevents the coupling of thyroid peroxidase and iodination of thyroxine residue on thyroglobulin, which eventually results into the reduced production ofT_3 and T_4,[21] while Levothyroxine used in this study is a synthetic form of thyroxine employed in the treatment of hypothyroidism; it is converted to its active metabolite, L-triiodothyronine (T_3), T_3 and T_4 bind to thyroid receptor in the cell nucleus and this results into increase metabolic activities by the control of DNA transcription and protein synthesis as a result of increased T_3 and T_4, in circulation.[22]

Treatment of rabbits with carbimazole and levothyroxine in this study resulted into hypothyroid and hyperthyroid state respectively, as shown by the reduced T_3 and T_4 with increase TSH levels seen in carbimazole-treatment compared to the control, while increased T_3 and T_4 with reduced TSH levels were seen in levothyroxine-treatment compared to the control. These results are consistent with our previous observations reported.[23,10,24] The decrease in T_3 and T_4 with corresponding increase in TSH levels obtained after carbimazole treatment, with the increase in T_3 and T_4 with corresponding decrease in TSH levels as a result of thyroxine treatment are due to the control of the hypothalamic-pituitary-thyroid-axis negative feedback mechanism.[25]

Treatment of rabbit with carbimazole resulted in mild reduction in percentage weight gained compared to the control. A similar reduction in weight gain was recorded in propylthiouracil-induced hypothyroidism and neonatal hypothyroidism,[26] which suggests that normal level of thyroxine is required for normal growth and optimal conversion of nutrients. Treatment of rabbits with Levothyroxine resulted in significant loss of weight; reports have it that increase in thyroid hormone level increases metabolic rate which leads to weight loss.[27,28]

Thyroid hormones are important in the regulation of electrolytes level in the body.[5] Serum levels of sodium, potassium and chloride were comparable across the control, hypothyroid and hyperthyroid animals. This is in agreement with our previous findings that documented marginal changes in serum electrolyte levels in altered thyroid state.[1,24] However, this is not in agreement with some documentations that reported elevated levels of serum sodium and potassium ions in both hypothyroid and hyperthyroid patients with cardiovascular diseases.[29,31] Sodium and potassium ions are essential component of Na-KATPase. This enzyme is present on the cell membrane and important for the transport of water and nutrients across cell membrane and the thyroid hormone regulate the functions of sodium-potassium pump in most of the tissues of the body such as kidney and cardiac tissues.[32,5] However, it is novel that this study observed a significant rise in gastric levels of bicarbonate and chloride ions in levothyroxine-induced hyperthyroidism, and a significant fall in carbimazole-induced hypothyroidism.

Chloride ion is required for the production of gastric hydrochloric acid from the parietal cell in the gastric gland of the stomach.[33] Also bicarbonate ion is an important component of the barrier that protects the stomach from assaults,[4] which means that Thyroid hormones affect both gastric acid secretion and gastro protection and proper monitoring of chloride and bicarbonate levels in thyroid disorder maybe necessary even for the maintenance of gastric mucosa integrity during treatment.

Adherent gastric mucus content was higher in Levothyroxine-treated rabbits compared to the control, but lower in Carbimazole-treated rabbits compared to the control in this study, which is in consonant with previous report.[14] This results confirm the concept that thyroid hormone is important in gastric mucosal growth, differentiation and physiology of its barrier.[34] The high mucus content recorded in levothyroxine-treated rabbit could be one of the mechanism of action responsible for the accelerated gastric ulcer healing recorded in levothyroxine-treated rats by Adeniyi *et al*.,[35] therefore, altered thyroid states may have effects on secretion of mucus in the epithelial lining of the stomach.[9]

Oxidative stress in the stomach was observed in both carbimazole and levothyroxine treatments compared to the control, but the concentration of MDA in carbimazole treatment was higher than that of levothyroxine, also the antoxidant enzymes (Catalase and GSH) were lower in carbimazole and levothyroxine treatments compared to the control, but antioxidant enzymes activities in levothyroxine treatment was higher than that of carbimzole treatment.

Similar results were obtained for cardiac tissue,[24] although thyroid hormones induce oxidative stress, and this may lead to leaky gut and reduced motility in hypothyroidism,[36] however in hyperthyroidism, thyroid hormone-activated mitochondrial mechanisms may provide defense against excessive gastric tissue damage.[37] This was confirmed by the numerous parietal cells and zymogenic cells with intact shape and size, with mild ulceration of *muscularis mucosa* seen in levothyroxine-treated rabbits, as against the laceration and ulceration on the *muscularis mucosa* as well as atrophy parietal cells seen in carbimazole-treated rabbits.

CONCLUSION

The present study revealed that gastric dysfunction observed in dysthyroidism is associated with alteration in gastric electrolyte levels and adherent gastric mucus content. These changes are lipid peroxidation-dependent. Since electrolyte level is important in acid-base balance and gastro-protection, the alteration in gastric tissue electrolytes accounts for gastric ulceration seen in altered thyroid state, particularly hypothyroid state. Monitoring of electrolyte levels may be important in the management of thyroid dysfunction.

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