

# Activation of Cardiac TNF- $\alpha$ in Altered Thyroid State-Induced Cardiometabolic Disorder

Ayodeji Folorunsho Ajayi<sup>1</sup>, Roland Eghoghosoa Akhigbe<sup>1,2\*</sup>, Lydia Oluwatoyin Ajayi<sup>3</sup>

<sup>1</sup>Department of Physiology, College of Health Sciences, Ladoke Akintola University of Technology, Ogbomoso, Oyo State, NIGERIA.

<sup>2</sup>State Specialist Hospital, Osogbo, Osun State, NIGERIA.

<sup>3</sup>Department of Biochemistry, Faculty of Basic Medical Sciences, College of Health Sciences, Ladoke Akintola University of Technology, Ogbomoso, Oyo State, NIGERIA.

## ABSTRACT

**Background:** It is a known fact that altered thyroid state is associated with cardiometabolic disturbances. Raised TNF- $\alpha$  and lipid peroxidation have also been reported to be involved in the pathogenesis of cardiometabolic disorders. **Aim:** The present study evaluates the effect of dysthyroidism on cardiac TNF- $\alpha$  and lipid peroxidation, and whether the effect is estradiol-dependent. **Methods:** Male white New Zealand rabbits were randomized into three groups; control, carbimazole-induced hypothyroidism, and levothyroxine-induced hyperthyroidism. **Results:** Dysthyroidism led to altered glucose metabolism and dyslipidaemia with elevated LDL, TNF- $\alpha$ , and MDA. There was also decreased HDL, GSH, catalase, and 17 $\beta$ -estradiol. Serum electrolytes and hemorheological variables were not significantly affected. **Conclusion:** These findings demonstrate that dysthyroidism-induced cardiometabolic disturbance is associated with elevated cardiac TNF- $\alpha$  and oxidative stress via an estradiol-dependent mechanism.

**Key words:** Dysthyroidism, Lipid Peroxidation, TNF- $\alpha$ , Oxidative Stress, Cardiometabolic Disorder.

**Correspondence**  
**Dr. Roland Eghoghosoa Akhigbe**

Department of Physiology,  
College of Health Sciences,  
Ladoke Akintola University of  
Technology,  
Ogbomoso, Oyo State,  
NIGERIA;  
State Specialist Hospital,  
Osogbo, Osun State, Nigeria,  
NIGERIA.

**Ph.no:** +234 803-5924989

**E-mail address:** akhigberoland@gmail.com

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## INTRODUCTION

Thyroid hormones are catabolic hormones which are known to play essential roles in various metabolic processes. Altered thyroid states have been reported to be associated with metabolic disorders as well as cardiovascular diseases.<sup>1,2</sup> Hypothyroidism has been reported to impair cardiac contractility, decreased cardiac output, increased vascular resistance, reduced chronotropy, cardiac atrophy, and cardiac failure.<sup>3-5</sup> The effect of hypothyroidism on cardiac function is linked with attendant dyslipidaemia and atherosclerosis.<sup>6-11</sup> On the other hand, hyperthyroidism-induced cardiovascular dysfunction is due to the hyper metabolic state and accelerated free radical production in the mitochondria with resultant changes in the antioxidant defense system caused by high levels of thyroid hormones.<sup>12,13</sup>

Even within the normal range of thyroid-stimulating hormone (TSH), total cholesterol, triglycerides and LDL increase while HDL reduces with increasing level of TSH.<sup>14</sup> Thyroid hormones stimulate the first step of cholesterol synthesis by inducing 3-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) reductase. Triiodothyronine (T3) controls LDL receptor gene activation by the direct binding of T3 to specific thyroid hormone responsive elements (TRES).<sup>15</sup> T3 also controls sterol regulatory element-binding protein-2 (SREBP-2), thus regulating LDL receptor's gene expression.<sup>16</sup> Faure *et al.* also reported that T3 protects LDL from oxidation.<sup>17</sup> Thyroid hormones has been documented to affect HDL metabolism by enhancing cholesteryl ester transfer protein (CETP) activity which is involved in the conversion of cholesteryl esters from HDL2 to the very low density lipoproteins (VLDL) and TGs to the opposite direction.<sup>18</sup> Thyroid hormones have also been shown to induce lipoprotein lipase which catabolizes the TG-rich lipoproteins, and the hepatic lipase (HL).<sup>19,20</sup> They also up-regulate apolipoprotein AV (ApoAV), which plays a major role in TG regulation.<sup>21</sup>

Besides the effect of thyroid hormones on plasma lipids, their effects on other metabolic parameters which are associated with cardiovascular diseases include their influence on adipocyte metabolism and the pro-

duction of adipokines.<sup>22-24</sup> Lipid peroxidation is also affected by thyroid function with studies however showing controversial outcomes.<sup>17-25</sup>

This study thus determines the effect of dysthyroidism on lipid profile, cardiac TNF- $\alpha$  and lipid peroxidation, and whether the effect is estradiol-dependent.

## MATERIALS AND METHODS

### Experimental animals

Male white New Zealand (*Oryctolagus cuniculus huxley*) rabbits of comparable weights were used for the study. Experimental animals were obtained from the Animal Holdings of the Department of Physiology, Ladoke Akintola University of Technology, Nigeria. They were fed with standard rabbit chow and water *ad libitum*. Animals were handled under standard laboratory conditions of a 12:12 hour light/dark cycle in a temperature and humidity controlled room (temperature: 28 °C–31 °C, humidity of 45%–50%).<sup>26,27</sup>

### Treatment

Rabbits were randomly allocated to one of the three experimental groups of 10 animals each. Hypothyroidism was induced by administration of 5 mg/250 g body weight of carbimazole, while hyperthyroidism was induced by administration of 5  $\mu$ g/100 g body weight of levothyroxine. Treatment lasted for 35 days. Doses of carbimazole and levothyroxine were based on previous studies.<sup>28,29</sup> Animal maintenance and handling was performed according to the NIH Guide for the Care and Use of Laboratory Animals (NIH publication No 86-23, revised 1985 and 1991) and the UK requirements for ethics of animal experimentation (Animals Scientific Procedures, Act 1986).

### Biochemical assays

At the end of the 35-day experiment, blood samples were collected via cardiac puncture, serum was obtained, and biochemical parameters were assayed. Fasting plasma levels of total cholesterol (TC), triglyceride (TG), and HDL-cholesterol (HDL-C) were assayed by standard enzymatic

method coupled with spectrophotometry using assay kit (Randox Lab Ltd., UK). LDL-cholesterol (LDL-C) was calculated using Friedewald's formula.<sup>27-30</sup> Plasma glucose and 17 $\beta$ -estradiol were also determined using standard laboratory kit (Randox Lab Ltd., UK).<sup>31,32</sup>

Lipid peroxidation index, malondialdehyde (MDA), reduced glutathione (GSH) and catalase were evaluated as previously documented.<sup>33,34</sup>

### TNF- $\alpha$ immunoassay

This assay employs the quantitative sandwich enzyme immunoassay technique. An antibody specific for TNF- $\alpha$  was pre-coated into a microplate. All reagents and working standards were prepared and 100 $\mu$ L of dilution buffer was added to the blank wells. 100 $\mu$ L of standard and samples were added per well and covered with the plate sealer. This was incubated for 2 hours on a microplate shaker at room temperature. Each well is aspirated and washed four times. Washing is done by filling each well with 1x wash buffer (300 $\mu$ L) using a squirt bottle. After the last washing, any remaining wash buffer is removed by aspirating or decanting. The plate is then inverted and blotted against a clean paper towel. 100 $\mu$ L of detection antibody working solution was then added to each well and covered with the plate sealer. This was incubated for another 2 hours on a microplate shaker at room temperature. The aspiration/wash procedure was repeated. 100 $\mu$ L of Avidin-HRP conjugate working solution was now added to each well and incubated for 1 hour on a microplate shaker at room temperature. It was protected from light. The aspiration/wash procedure was again repeated. 100 $\mu$ L of Substrate solution was added to each well, incubated for 4 minutes at room temperature and protected from light. 100 $\mu$ L of stop solution was added to each well, which caused the colour in the wells to change from blue to yellow. The optical density of each well was determined using the micro-plate reader set to 450nm wavelength.

A standard line is constructed by plotting the mean absorbance for each standard on the y-axis against the concentration on the x-axis and a best line of fit is drawn through the points on the graph. Using the best line of fit, the TNF- $\alpha$  concentration of the heart tissue is deduced.

### Statistical analysis

Statistical analysis was performed using SPSS. Results were reported as mean  $\pm$  standard error of mean (S.E.M.). One way analysis of variance (ANOVA) was used to analyze for the significance of differences between means followed by post hoc Duncan's multiple range test. Statistical significance was assigned at a *p*-value of less than 0.05.

## RESULTS

### Effect of dysthyroidism on plasma glucose and lipids

Plasma glucose level was altered by dysthyroidism; it was reduced in hyperthyroid rats but raised in hypothyroid rabbits, although the rise observed in the hypothyroid rabbits was marginal. Cholesterol and triglyceride were significantly higher in hypothyroidism and lower in hyperthyroidism respectively. HDL-cholesterol was significantly lowered by dysthyroidism. The reduction observed was more in hyperthyroid rabbits. LDL-cholesterol was significantly elevated by dysthyroidism (Figure 1).

### Effect of dysthyroidism on hemorheological parameters and serum electrolytes

Although, dysthyroidism led to elevation of hemorheological parameters, this was marginal (Figure 2). Serum electrolytes, indices of renal function, were also not significantly altered (Figure 3).

### Effect of dysthyroidism on cardiac TNF- $\alpha$

Cardiac TNF- $\alpha$  was significantly raised in dysthyroid rabbits. Hyperthyroidism led to 46.4% rise, while hypothyroidism caused 78.4% rise (Figure 4).

### Effect of dysthyroidism on indices of lipid peroxidation

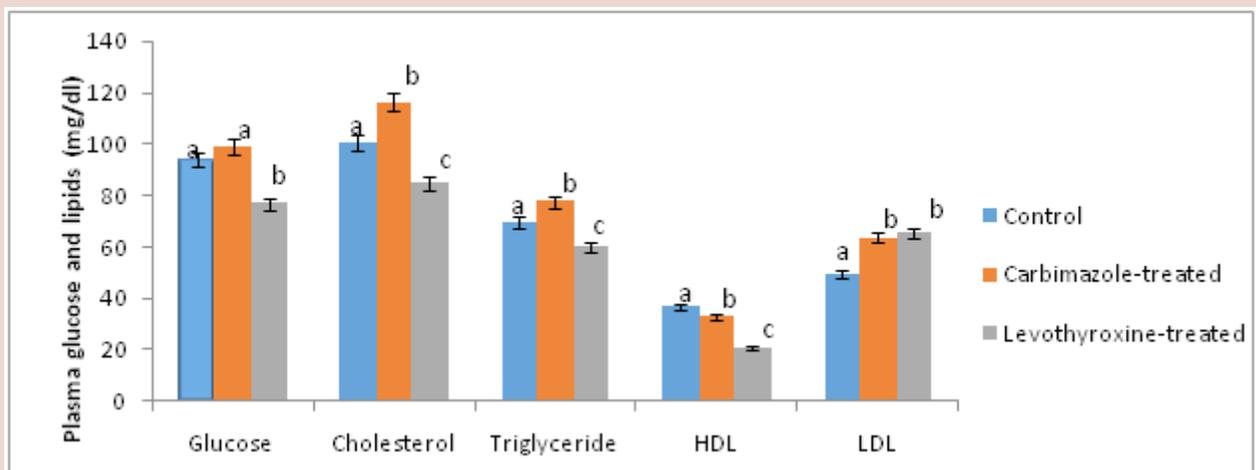
Dysthyroidism led to significant rise in cardiac and renal MDA. The rise was observed to be more in hypothyroid rabbits. Cardiac catalase and renal catalase activities were significantly reduced in dysthyroidism. Serum MDA was significantly elevated in dysthyroidism when compared to the control. Serum catalase activity was significantly reduced in dysthyroidism. This was more in hyperthyroid rabbits. Cardiac GSH, renal GSH and serum GSH activities were comparable in all groups (Figure 5).

### Effect of dysthyroidism on 17 $\beta$ -estradiol

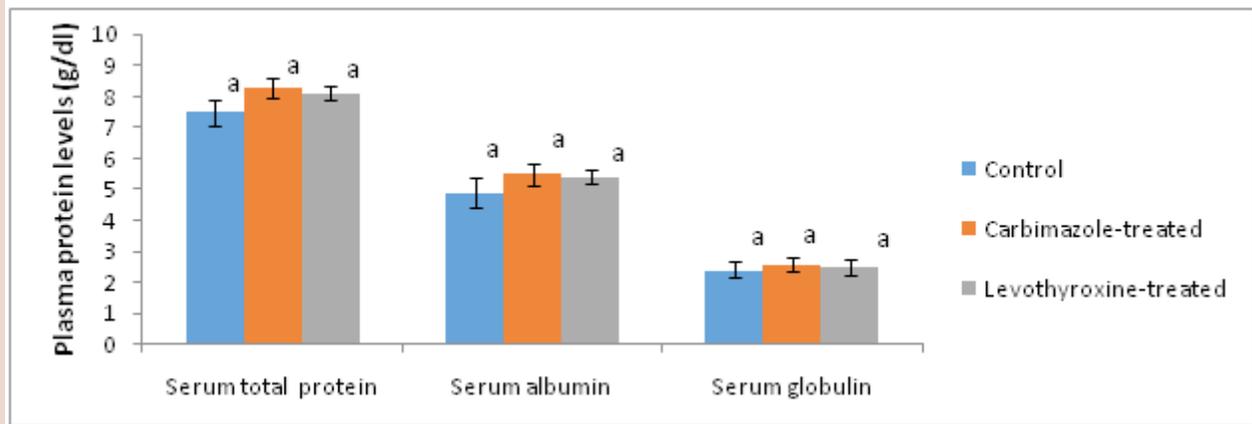
Figure 6 illustrate the circulating level of plasma 17 $\beta$ -estradiol. It was observed that 17 $\beta$ -estradiol level was reduced by about 11% in hypothyroid rabbits and 9% in hyperthyroid rabbits (Figure 6).

## DISCUSSION

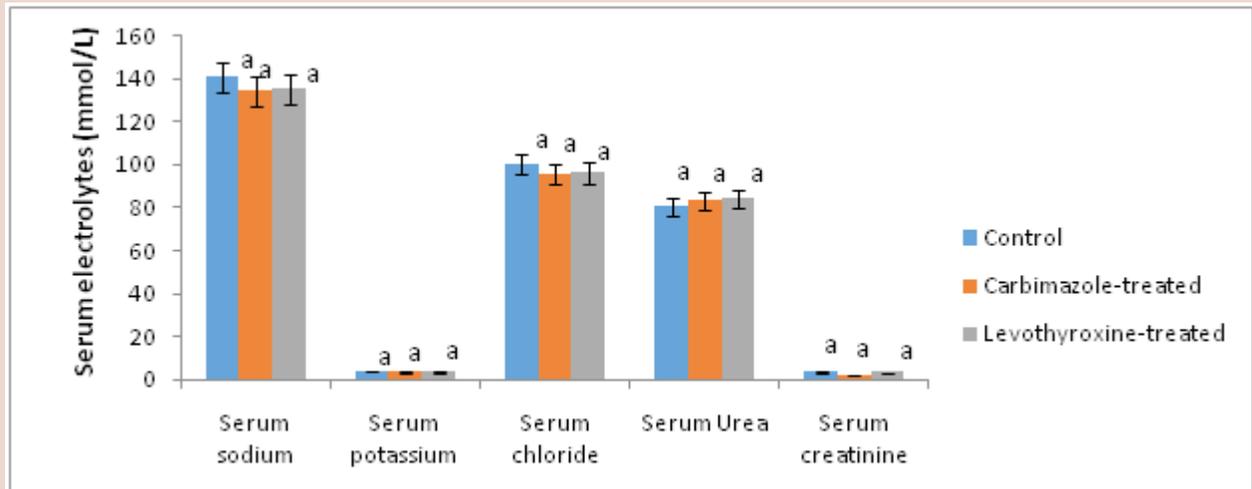
The key novel finding of the present study is the activation of cardiac TNF- $\alpha$  in dysthyroidism and its association with oxidative stress and estradiol. In addition, we confirmed the observation that altered thyroid state led to dyslipidaemia. According to our knowledge, this is the



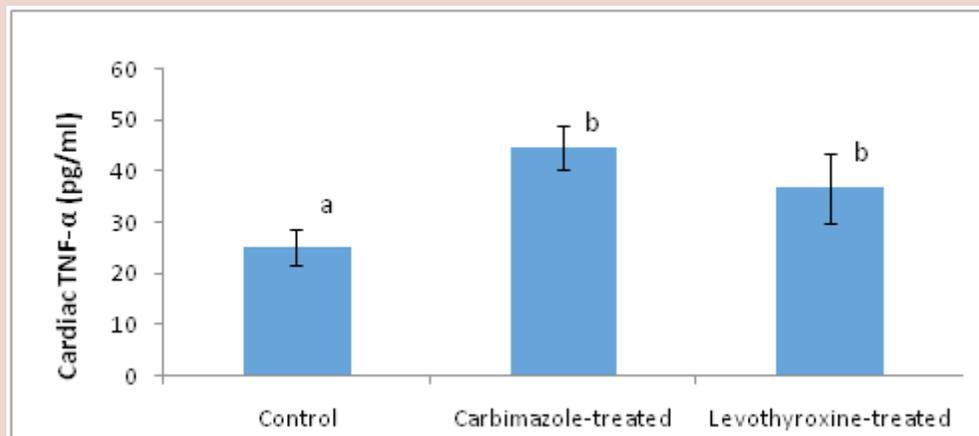
**Figure 1:** Effect of dysthyroidism on plasma levels of glucose and lipids Bars carrying different letters on the same parameter are statistically different at *P*<0.05



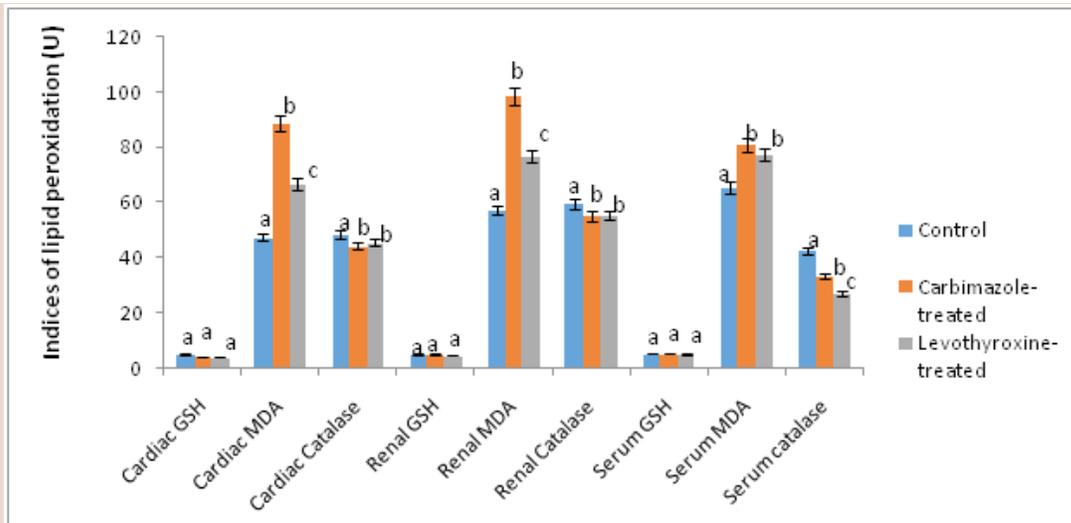
**Figure 2:** Effect of dysthyroidism on plasma proteins Bars carrying different letters on the same parameter are statistically different at  $P < 0.05$



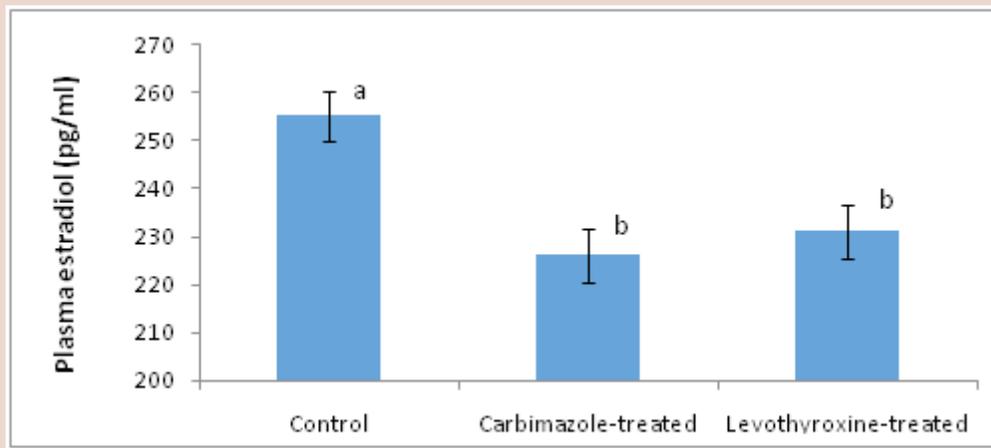
**Figure 3:** Effect of dysthyroidism on renal function Bars carrying different letters on the same parameter are statistically different at  $P < 0.05$



**Figure 4:** Effect of dysthyroidism on cardiac TNF- $\alpha$  Bars carrying different letters are statistically different at  $P < 0.05$



**Figure 5:** Effect of dysthyroidism on lipid peroxidation indices Bars carrying different letters are statistically different at  $P < 0.05$



**Figure 6:** Effect of dysthyroidism on plasma estradiol Bars carrying different letters are statistically different at  $P < 0.05$

first study to report the association in dysthyroidism between oxidative stress, inflammatory molecule and estradiol. Recognizing the public health challenges associated with altered thyroid state, the findings of our study may provide essential information about the complex associations between hormonal milieu and inflammatory mechanisms.

Glucose and lipid metabolisms are very sensitive to altered thyroid states; hence optimal levels of thyroid hormones are important for glucose and lipid metabolism. Although, plasma glucose level was similar in the control and hypothyroid animals, it was significantly reduced in hyperthyroid state. Hypothyroidism also led to increase in cholesterol and triglyceride levels while these lipids were observed to be reduced in hyperthyroid state. Alteration of thyroid state led to significant rise in LDL-cholesterol and decline in HDL-cholesterol. These findings are in tandem with previous studies that also reported dyslipidaemia in a similar trend in association with altered thyroid state.<sup>35,36,37</sup> These changes are due to the regulatory effect of thyroid hormones on lipoprotein metabolism. Thyroid hormone stimulates hepatic de novo cholesterol synthesis by inducing the 3-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA)

reductase that catalyzes the conversion of HMG-CoA to mevalonate.<sup>38</sup> This causes a rise in intracellular cholesterol concentration in hyperthyroidism and a decline in hypothyroidism. Thyroid hormone also stimulates CETP and LPL.<sup>19,20</sup> Dyslipidaemia seen in altered thyroid state has been reported to predispose to atherosclerotic coronary artery disease (CAD).<sup>39,40</sup> High LDL-cholesterol and low HDL-cholesterol is a factor in the aetiopathogenesis of atherosclerosis. It reduces endothelial synthesis or bioavailability of nitric oxide which is a potent vasodilator.<sup>27</sup> However, high HDL-cholesterol enhanced endothelial function by augmenting nitric oxide biosynthesis and bioavailability, and suppressing formation of free radicals, thereby preventing the deleterious effect of LDL-cholesterol in vasculature.<sup>27-41</sup>

There are accumulating data to support the role of plasma proteins, especially albumin, as hemorheological factors that play essential role in the development of cardio metabolic disorders.<sup>27</sup> They have been shown to modulate blood and plasma viscosity.<sup>42</sup> Our present results revealed that dysthyroidism is associated with rise in plasma proteins; however, the changes observed in these hemorheological factors were marginal.

Similarly, no significant change was observed in the renal function of dysthyroid rabbits.

Tumour necrosis factor-alpha (TNF- $\alpha$ ) is a 157 amino acid cytokine and is produced in response to inflammatory or infectious stimuli by macrophages, lymphocytes, neutrophils and structural cells like fibroblasts and smooth muscle cells.<sup>43</sup> Due to the large population of macrophages, the liver and spleen remain major sources of TNF- $\alpha$ ,<sup>44</sup> although the myocardium also synthesizes TNF- $\alpha$  (45) in response to endotoxin, pressure or volume overload, ischaemia/reperfusion and oxidative stimulus through nuclear factor kappa B (NF $\kappa$ B) mediated mechanism.<sup>46,47</sup> The present study revealed that dysthyroidism led to a rise in cardiac TNF- $\alpha$ . Though this seems to be the first study that documents the effect of dysthyroidism on cardiac TNF- $\alpha$ , this observation is in complete agreement with previous studies that documented a rise in serum TNF- $\alpha$  in hyperthyroidism and hypothyroidism. The higher cardiac TNF- $\alpha$  observed in dysthyroidism may account for cardiometabolic disturbances seen in patients with altered thyroid states. TNF- $\alpha$  has been reported to cause apoptosis of myocardial cells via mechanisms of cell death.<sup>48,49,50</sup> The VEST trial documented that TNF- $\alpha$  is directly related to the New York Heart Association (NYHA) functional stage of patients with HF and that the highest levels of TNF- $\alpha$  were associated with a worse prognosis.<sup>51</sup> This was reported to be due to negative inotropic action and a disturbance of beta-adrenergic receptor sensitivity caused by TNF- $\alpha$  via the inducible nitric oxide synthase (iNOs) system.<sup>51</sup> Increased TNF- $\alpha$  level is associated with a disturbance of left atrial function and an advanced degree of left ventricular diastolic and systolic dysfunction.<sup>52</sup> Although a low level of TNF- $\alpha$  may confer a short-term cardio protection,<sup>53,54</sup> a prolonged exposure and high level of TNF- $\alpha$  have deleterious effects on the heart.<sup>55</sup>

Several mechanisms might explain the connection between dysthyroidism and cardiometabolic disorder. In the present study, although altered thyroid states did not affect GSH, they led to a higher level of lipid peroxidation index, MDA, and a significant decline in catalase activities in the serum, heart and kidneys. This also seems to be the first study to report the association between dysthyroidism-induced cardiometabolic disorders with cardiac redox status. Our observations were in consonance with the results of Torun *et al.*<sup>56</sup> and Akinci *et al.*<sup>57</sup> that documented a similar trend in the serum levels of MDA and catalase. Oxidative stress, which is characterized by an imbalance between free radicals and antioxidants in favour of radicals, participates in the pathogenesis of many diseases and their complications.<sup>58,59</sup> The levels of ROS are controlled by antioxidant enzymes, such as superoxide dismutase (SOD), glutathione peroxidase (GSH-Px).<sup>27-29,60</sup> Malondialdehyde (MDA) is a useful index for lipid peroxidation and thus used as an indicator for oxidative damage in cells and tissues.<sup>59</sup> The altered redox state seen in dysthyroidism possibly accounts for the activation of cardiac TNF- $\alpha$  with resultant cardio metabolic disorder.

Also, it is worthy of note that the present study also observed a decline in the circulating level of 17 $\beta$ -estradiol. This is another key finding of the present study. It is a known fact that estradiol is cardio protective. A decline in estradiol thus has a deleterious effect on the cardiac function. 17 $\beta$ -estradiol has been reported to have lipid-lowering effect by inhibiting cholesterol accumulation, influencing hepatic lipid metabolism, elevating the circulatory levels of HDL and preventing LDL-oxidation.<sup>61</sup> The cardioprotective effect of 17 $\beta$ -estradiol has also been related to its anti-atherogenic effect on monocyte chemo-attractant protein 1 (MCP-1), a chemokine expressed in atherosclerotic lesions.<sup>62,63,64</sup> 17 $\beta$ -estradiol inhibits monocyte chemo-attractant protein 1 (MCP-1) by lowering the production of TNF- $\alpha$ .<sup>65</sup> The decline in 17 $\beta$ -estradiol circulatory level observed in dysthyroidism in the study also accounts for the associated dyslipidaemia and elevated cardiac TNF- $\alpha$ .

Conclusively, this study expands on the documentation of previous studies that reported dyslipidaemia and elevated levels of serum TNF- $\alpha$  in altered thyroid states by demonstrating increased lipid peroxidation, and reduced antioxidants and estradiol levels in relation to activation of cardiac TNF- $\alpha$  in dysthyroidism. These new data provide an approach to understanding the pathogenesis of cardio metabolic disorders associated with altered thyroid states, with possible prognostic implications.

## CONFLICT OF INTEREST

All authors declared no conflict of interest.

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