



Original article

An evaluation of stress oxidative and serum electrolytes in female hypothyroid patients

Derouiche Samir^{a*}, Djouadi anfal^a,

^aDepartment of Cell and Molecular Biology, Faculty of natural science and life, University of El-oued, El-oued 39000,Algeria.

ARTICLE INFO

Keywords:

hypothyroidism
stress oxidative
electrolyte
sodium
females

ABSTRACT

The thyroid hormones play an important role in many physiological processes. Variations in the levels of thyroid hormones can be one of the main physiological modulators of in vivo cellular oxidative stress. The present study evaluates the effects of hypothyroidism states on stress oxidative in female patients before treatment. 24 cases of overt hypothyroidism were chosen, 24 age matched controls were chosen. Blood samples were collected from them and T3, T4 and TSH levels were measured. Also, MDA, GSH, Sodium, Potassium and Chloride levels in blood was measured. Lipid peroxidation, an index of oxidative stress was significantly elevated ($p < 0.01$) in hypothyroidism patients as compared to control. The results showed a highly significant decrease ($p < 0.01$) in the levels of GSH in all patients with thyroid dysfunction as compared to control. The levels of serum sodium was significantly increased ($p < 0.001$) in cases than controls. Mean serum potassium and chloride levels non-significantly changed in hypothyroid patients when compared to the control subjects. In hypothyroidism patients, there was a significant negative correlation ($r = 0.962$; $P < 0.05$) between the levels of reduced glutathione with concomitant increase in MDA levels. No changes in TSH were observed. There was a no significant correlation between serum MDA values and serum electrolytes levels. The results of this study reveal the importance of monitoring the levels of those stress oxidative parameters and serum electrolytes levels in thyroid dysfunction patients before therapy, especially when the disease is more severe.

© Copyright 2010 BioMedSciDirect Publications IJBMR - ISSN: 0976:6685. All rights reserved.

1. Introduction

The thyroid hormones play an important role in many physiological processes, such as differentiation, growth, development, and the physiology of all cells. One of the most studied effects of the thyroid hormone is the control of the basal metabolic rate (1). Thyroid disease in its various forms is common, affecting some 5% of the population. Hypothyroidism, or under activity of thyroid gland, results from either reduced secretion of thyroxine and triiodothyronine that may be correlated with amplified secretion of Pituitary TSH (2). Oxidants or free radicals are atoms or molecules that are capable of having an independent existence that contain one or more unpaired electrons. These unpaired electrons are highly reactive species that may damage the cells. Antioxidants are the antidote for these free radicals as they quench them and transform them into less reactive forms (3).

It is well known that oxidative stress (OS), defined as an imbalance between radicals and antioxidant defense, is implicated as a pathophysiological mechanism of different diseases and is a topic of growing interest (4). Variations in the levels of thyroid hormones can be one of the main physiological modulators of in vivo cellular oxidative stress due to their known effects on mitochondrial respiration. In particular, it has been suggested that the increases in reactive oxygen species induced by a deficiency of thyroid hormones can lead to an oxidative stress conditions in the liver and in the heart and some skeletal muscles with a consequent lipid peroxidative response (5). The primary role of electrolytes lies in the maintenance of body ionic and water balance. Thus the requirements for strong ions that have characteristic effects on body fluids homeostasis, cannot be considered individually because it is the overall balance that is important (6). In recent years research has focused on outcomes of patients with electrolyte disorders, mainly hypo- and hypernatraemia, which were found to be associated with increased mortality (7). Sodium and potassium are important components of the enzyme Na⁺-K⁺ ATPase, which is an enzyme present on the cell membrane that helps in the transport of water and nutrients across the cell membrane (8). Thyroid hormones regulate the activity of

* Corresponding Author : **Derouiche Samir**
Department of Cell and Molecular Biology,
Faculty of natural science and life,
University of El-oued, El-oued 39000,Algeria.

sodium potassium pumps in most of the tissues(9). In many standard textbooks and reviews different electrolyte disorders were associated with thyroid dysfunction (10). With this background the present study was undertaken to assess the stress oxidative and the alterations in the levels of serum electrolytes in, hypothyroid patients and euthyroid subjects. Hence the present study was done only in female thyroid patients and controls.

2. Subject and Methods

Ethical approval (Appendix) was sought and approved by the Ethical Committee of the Department of Cell and Molecular Biology, Faculty of natural science and life, University of Eloued. We studied patients with newly diagnosed and treated hypothyroidism (24 females), mean aged 40.83 ± 4.98 years were joined in this study. A total of 24 females' healthy volunteers (mean aged 38.83 ± 5.45 years) served as controls with normal serum TSH.

2.1. Inclusion Criteria

Patients who had clinical diagnosis and laboratory findings of hypothyroidism disease for more than three months evidenced

2.2. Exclusion Criteria

To eliminate the factors which might affect free radical antioxidant activity, we excluded all diabetics and other chronic diseases subjects from patient groups and healthy controls.

2.3. Laboratory Investigations

Fasting blood samples were collected and placed into containing tubes. After centrifugation at $3000 \times g$ for 5 min the serum were removed and retained for assay of the level of glucose, MDA, GSH and all the electrolytes, respectively. Serum samples were stored at -20°C until analysis. Serum concentration of total triiodothyronine (T3), total thyroxin (T4) and TSH were measured by mini-VIDIS assay using kit supplied by Biomerieux Marcy-l'Etoile/ France. Serum Electrolyte levels (Na^+ , k^+ & Cl^-) were determined by Electrolyte Analyzer (Easylyte PLUS Na/K/Cl de Medica). The thiobarbituric acid method of Buege and Aust(11) was used to measure MDA, which reacts with thiobarbituric acid to yield a pink color. Absorbances were determined at 532 nm. The reduced glutathione (GSH) was measured spectrophotometrically in serum, by the method of Akerboom and Sies(12), using 5,5dithiobis(2-nitrobenzoic acid). Absorbances were determined at 412 nm.

2.4. Statistical Methodology

The reported data are the means of measurements and their standard error of mean (SEM) values. The results of cases and controls were compared by student's t test using minitab software (version 13.31).

3. Results:

T3 showed significant reduction in hypothyroidism women compared with control group, as shown in Table 1. A similar trend of significance was noticed in the serum level of T4 in women hypothyroid patients. On the other hand there was a significant increase in TSH value of hypothyroid patients when compared to control group. Table 1 shows that there is no significant difference in the age of hypothyroid patients when compared to control group.

as shown in figure 1, serum MDA shows a highly significant increase in hypothyroid patients groups compared with that of control group. A highly significant decrease in serum glutathione reduced GSH occurs in hypothyroid patients group as compared with control group. Also, figure 2 shows a highly significant increase in the levels of serum sodium occurs in hypothyroid group as compared with control group. Serum potassium and chloride shows a no significant difference in hypothyroid patients compared with that of control subjects.

Table 2 shows the results of correlation between oxidative stress index (represented by MDA level) and concentration of GSH and electrolyte in hypothyroid patients, a high significant correlation was noticed between MDA and GSH ($P < 0.05$) in hyperthyroidism patients. Also, a non-significant correlation ($P > 0.05$) was observed between MDA and TSH and between MDA and serum electrolytes in hypothyroid patients.

Table 1 . Clinical characteristics of hypothyroid patients and control subjects

Group description	Control subjects N=24	Hypothyroid patients N=24
Mean age	38.83 ± 5.45	40.83 ± 4.98
T3 ($\mu\text{mol/L}$)	5.01 ± 0.27	$4.73 \pm 0.17^*$
T4 ($\mu\text{mol/L}$)	13.53 ± 1.24	$9.16 \pm 1.25^*$
TSH (mUI/l)	3.68 ± 0.51	$15.02 \pm 5.05^{***}$

Values are mean \pm SE.

Significant difference with control group: * $p < 0.05$, *** $p < 0.001$

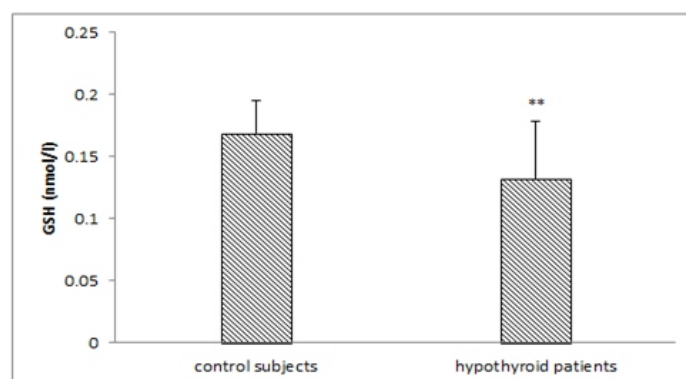
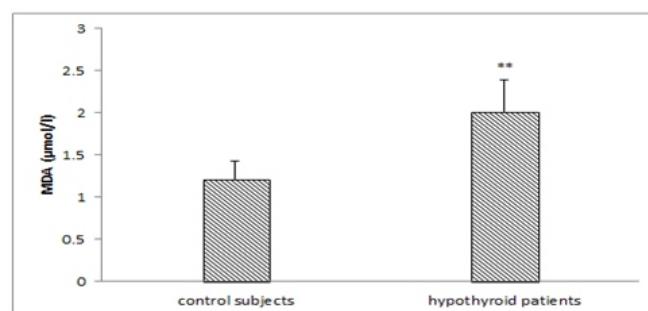


Figure 1. Malondialdehyde (MDA) and reduced Glutathione (GSH) levels in hypothyroid patients and controls subjects. Values are mean \pm SE. Significant difference with control group: * $p < 0.05$, ** $p < 0.01$.

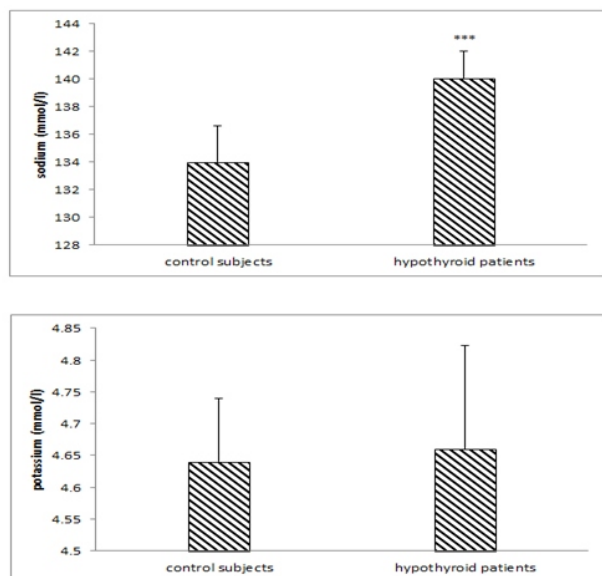


Figure 2. Serum Sodium, Potassium and Chloride level in women hypothyroid patients and controls. Values are mean \pm SE. Significant difference with control group: * $p < 0.05$, *** $p < 0.001$

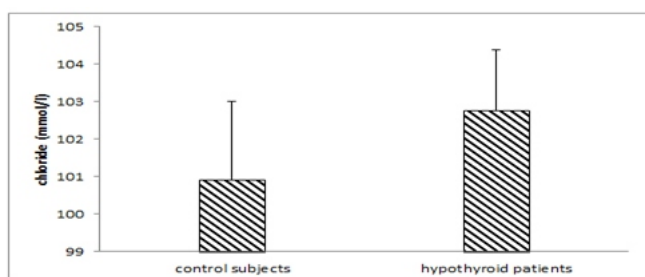


Table 2. Correlation coefficients and the significant levels of different serum chemical components in women patients with hypothyroidism

Component vs. MDA	Hypothyroidism	
	R	P
TSH (mUI/l)	-0.109	0.817
GSH (nmol/l)	-0.962	0.03
Sodium (mmol/l)	0.179	0.671
Potassium (mmol/l)	0.037	0.931
Chloride (mmol/l)	0.306	0.461

4. Discussion

It was the aim of the study to investigate the effects of thyroid function on stress oxidative and serum electrolytes. According to different case reports in the literature someone could expect electrolyte disturbances in any sort of thyroid dysfunction. Hypothyroidism is a very common condition and seen more in women than in men. Earlier statistics also have suggested that hypothyroidism is six times more common in women than in men. The higher prevalence of thyroid disease in women suggests that estrogen might be involved in the pathophysiology of thyroid dysfunction. Estradiol has an antagonistic effect on the hormones T3 and T4. The reason being, estradiol competes with T3 and T4 for binding sites on the receptor proteins(13). Hypothyroidism has been related to some diseases because it causes a hypometabolic state (14). In our results concentration of serum MDA is increased but the GSH concentration is significantly decreased in both hypothyroidism and hyperthyroidism patients as compared to the control group. Impairment in the oxidant/antioxidant equilibrium creates a condition known as oxidative stress(15). There is a complex interaction between antioxidants and oxidants such as reactive oxygen species, which modulates the generation of oxidative stress(16,17). Our findings suggest that hypothyroid patients have more severe oxidative stress than healthy persons. Pathological consequences of hypothyroidism point to a high potential for antioxidant imbalance. Thyroid hormones accelerate cellular reactions and increase oxidative metabolism. By stimulating enzymes that control active transport pumps, demand for cellular oxygen increases, and as ATP production goes up, heat is produced(3). Hypothyroidism causes immunosuppression that may lead to oxidative stress. TSH at a higher concentration may induce secretion of inflammatory cytokines and decrease the antioxidant status(18). Hypothyroidism-associated oxidative stress is the consequence of both increased production of free radicals and reduced capacity of the anti-oxidative defense. Variations in the levels of thyroid hormones can be one of the main physiological modulators of in vivo cellular oxidative stress due to their known effects on mitochondrial respiration(3). However, data on hypothyroidism in humans are conflicting. Baskol et al. showed in a group of 33 patients with primary hypothyroidism elevated MDA and NO levels and low paraoxonase (PON1) activity, while SOD was not different from controls (19). Our hypothyroid patients in the study exhibited significantly elevated levels ($p < 0.001$) of serum sodium and no significant difference of Serum potassium and chloride compared to the controls. Hypernatremia is a common electrolyte problem and is defined as a rise in serum sodium concentration to a value exceeding 145 mmol/L(15). Thyroid hormones are involved in controlling various metabolisms, more importantly lipid metabolism and that of various electrolytes, the hypothyroid patient generally suffers from a slow metabolism resulting in electrolyte disturbances(20). Hypothyroidism is one of the most prevalent endocrine diseases. It can lead to a variety of clinical situations, including congestive heart failure, electrolyte disturbances and coma (21). Yusufi et al demonstrated that in short term hypothyroid rats a large dose of T4 given for four days increased

Na/H exchange in brush border membrane vesicles isolated from the outer cortical zone (proximal convoluted tubule) but not in membrane vesicles prepared from the juxtamedullary cortex (22). Sodium and potassium are important components of the enzyme Na-K ATPase, which is an enzyme on the cell membrane that helps in the transport of water and nutrients across the cell membrane. Thyroid hormones regulate the activity of sodium potassium pumps in most of the tissues (23). Sodium and chloride are interdependent and changes in sodium ions will also be reflected in the chloride ions. It is postulated that hormones which are involved in ECFV (Extracellular Fluid Volume) regulation act on renal sodium transporters may also modulate the renal chloride transporters (24). However, hypothyroidism causes a reversible increase in vasopressin (antidiuretic hormone or ADH) sensitivity of the collecting ducts, thus increasing free water reabsorption. The increased fluid retention, however, is unable to maximally suppress ADH in hypothyroidism (25). As plasma water decreases, increases in plasma sodium concentration and osmolality are sensed by nuclei in the hypothalamus, with a resultant increase in production of ADH by the supraoptic and paraventricular nuclei. ADH acts to increase renal free water reabsorption in the collecting tubule to restore plasma water, resulting in a correction of plasma sodium concentration back toward the normal range (26). Our study is in conformity with the study done by Christoph where we too observed electrolyte changes in hypothyroidism (27). The non-significant variations in potassium and chloride concentrations during the hypothyroid disease and the non-significant correlation with MDA level suggest that neither the dysthyroidism nor stress oxidative had any significant effect on these serum electrolyte levels during the hypothyroid in female patients. The correlation between MDA and GSH in patients with hypothyroidism represents the direct effect of MDA on antioxidant components level. Reduced glutathione functions as a direct free radical scavenger as a co-substrate for glutathione peroxidase (GPx), which explained decreased GSH concentration with increased oxidative stress (28).

5. CONCLUSION

In conclusion, the present study suggests that Hypothyroidism undeniably can be risk factor for increased oxidative stress with enhanced lipid peroxidation and concomitant failure of antioxidant defense mechanism; can eventually lead to many other complications. Also, electrolyte disturbances need to be monitored and treated appropriately to avoid the ill effects resulting from the changes in the serum levels of these cations.

ACKNOWLEDGEMENT

The author thanks the staff of laboratoir of Faculty of natural science and life for providing research facilities to carryout present work

References

- Venditti P, Di Meo S. Thyroid hormone-induced oxidative stress. *Cell. and Mol. Life. Sci.*, 2006; 63(4):414-434.
- Prakash A, Lal AK. Serum Lipids in Hypothyroidism: Our Experience. *Indian J Clin Biochem.* 2006; 21(2): 153-155.
- Bhawna Bhimte B.K, Agrawal V.K, Sharma, Sarika Singh Chauhan. Oxidative stress status in hypothyroid patients. *Biomed. Res.* 2012; 23(2):286-288.
- Kalyanaraman, B. Teaching the basic of redox biology to medical and graduate students: Oxidants, antioxidants and disease mechanisms. *Redox. Biol.* 2013; 1:244-257.
- Yilmaz S, Ozan S, Benzer F, Canatan H. Oxidative damage and antioxidant enzyme activities in experimental hypothyroidism. *Cell. Biochem. Funct.* 2003; 21(4): 325-330.
- AHMAD T, SARWAR M. Dietary electrolyte balance: implications in heat stressed broilers. *World's Poultry Sci.* 2006; 62:638-653.
- Schwarza C, Leichtleb BA, Arampatzis S, Fiedler MG, Zimmermann D, Exadaktylos A K, Lindner D G. Thyroid function and serum electrolytes: does an association really exist? *Swiss Med. Wkly.* 2012; 142: w13669.
- Murgod R, Soans G. Changes in Electrolyte and Lipid profile in Hypothyroidism. *Int. j. life sci. biotechnol. pharmares.*, 2012; 2(3):185-194.
- Beigel F, Edelman IS. The mechanism of the calorogenic effect of thyroid hormone stimulation of Na⁺ + K⁺ activated adenosine triphosphatase activity. *J gen Physiol.* 1971; 57:710.
- Iwasaki Y, Oiso Y, Yamauchi K, Takatsuki K, Kondo K, Hasegawa H. Osmoregulation of plasma vasopressin in myxedema. *J Clin Endocrinol Metab.* 1990; 70(2): 534-539.
- Buege JA, Aust SD. Microsomal lipid peroxidation. In: Fiescher S., Packer L. (Eds.), *Methods in Enzymology*. Academic Press, New-York, 1978; 52:302-310.
- Akerboom TPM, Sies H. Assay of glutathione, glutathione disulfide and glutathione mixed disulfides in biological samples. *Methods enzymol.* 1981; 77:373-382.
- Vasudevan N, Ogawa S, Praff D. Estrogen and thyroid hormone interactions: Physiological stability by molecular specificity. *Physiol. Rev.*; 2002; 82: 923-944.
- Tenorio-Velásquez VM, Barrera D, Franco M, Tapia E, Hernández-Pando R, Medina-Campos ON, Pedraza-Chaverri J. Hypothyroidism attenuates protein tyrosine nitration, oxidative stress and renal damage induced by ischemia and reperfusion: effect unrelated to antioxidant enzymes activities. *BMC Nephrology.* 2005; 7:6-12.
- Derouiche S, Abbas K, Djermoune M, Ben Amara S, Kechrid Z. The effects of copper supplement on zinc status, enzymes of zinc activities and antioxidant status in alloxan induced diabetic rats fed on zinc overdose diet. *International Journal of Nutrition and Metabolism* 2013; 5(5):82-87.
- Samir D, Zine K. Influence of calcium supplements on zinc status, carbohydrate metabolism and the liver activity of detoxifying glutathione enzymatic system in alloxan induced diabetic rats. *Journal of Experimental Biology and Agricultural Sciences*, 2013; 1(6):424-429
- Baynes JW. Role of oxidative stress in development of complications in diabetes. *Diabetes.* 1991; 40:405-412.
- Yilmaz S, Ozan S, Benzer F, Canatan H. Oxidative damage and antioxidant enzyme activities in experimental hypothyroidism. *Cell Biochem. Funct.* 2003; 21(4): 325-30.
- Mancini A, Raimondo S, Segni C D, Persano M, Gadotti G, Silvestrini A, Festa R, Tiano L, Pontecorvi A, Meucci E. Thyroid Hormones and Antioxidant Systems: Focus on Oxidative Stress in Cardiovascular and Pulmonary Diseases. *Int. J. Mol. Sci.* 2013; 14:23893-23909.
- Murgod R, Gladys S. changes in electrolyte and lipid profile in hypothyroidism. *Cell. and Mol. Life. Sci.*, 2012; 2(3): 185-194.
- Kargili A, Turgut FH, Karakurt F, Kasapoglu B, Kanbay M, Akcay A. A forgotten but important risk factor for severe hyponatremia: myxedema coma. *Clinics (Sao-Paulo).* 2010; 65:447-448.
- Yusufi A, Murayama N, Keller Mj, Dousa T. Modulatory effect of thyroid hormones on uptake of phosphate and other solutes across luminal brush border membrane of kidney cortex. *Endocrin.* 1985; 116: 2438-2449,

23. Beigi IF, Edelman IS. The mechanism of the calorogenic effect of thyroid hormone: stimulation of Na⁺ + K⁺ activated adenosinetriphosphatase activity. *J gen Physiol.* 1971; 57:710.
24. Ornellas SD, Grozovsky R, Goldenberg RC, Carvalho DP, Fongi P, Gugginoi WP, Morales M. Thyroid hormone modulates ClC-2 chloride channel gene expression in rat renal proximal tubules. *J. of Endocrin.* 2003; 178:503-511.
25. Gopal B, Anjali M.. Interactions between thyroid disorders and kidney disease. *Indian J Endocrinol Metab.* 2012; 16(2): 204-213.
26. Schrier RW. Body fluid volume regulation in health and disease: A unifying hypothesis. *Ann. Intern. Med.* 1990; 113:155-159.
27. Neela M., Sreenivas N., Shubha J., Sangamesh KK, Manjula R, Mamatha S, Arti Ganiger MB.. study of serum electrolytes in female thyroid patients: a case control study. *J. evid. based med. health.* 2015; 2(8):1023-1028.
- 28- Tripathi U, Deepak N. The plant extracts of *Momordica charantia* and *Trigonella foenum-graecum* have antioxidant and anti-hyperglycemic properties for cardiac tissue during diabetes mellitus. *Oxid. Med. Cell. Longev.* 2009; (5): 290-296.