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# Evaluation of MDA and serum minerals in patients with overt and subclinical hypothyroidism

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Abstract---Hypothyroidism is a common disorder of the thyroid gland in which the gland cannot compete with the body requirement of the thyroid hormones, trijodothyronine (T3) and thyroxine (T4). Hypothyroidism is classified into overt (OH) and subclinical (SbH), in which the first comprises the cases that have elevated levels of thyroid- stimulating hormone (TSH) and reduced levels of T4 while the second comprises the cases with elevated TSH but normal T4 levels. The goal of the present study is to investigate the level of malondialdehyde (MDA) and some minerals (calcium, magnesium, and phosphorus) in patients with SbH and OH. For this purpose, 80 patients from Al-Yarmook Teaching Hospital were enrolled in the study half of them were diagnosed with OH and the other half were diagnosed with SbH. The study has been controlled with 40 healthy people of comparable age and all of the three groups were contained 50% males and females. The anthropometric examination of subjects has revealed that the body mass index (BMI) and waist to hip ratio (WHpR) were significantly (p<0.05) altered among control, OH, and SbH subjects. The level of MDA was significantly increased in hypothyroidism patients. The OH subject has shown the highest level of MDA, the SbH subjects have shown significantly (p<0.05) lower level compared to OH patients and significantly (p<0.05) higher level compared to control. The levels of Mg and P were significantly (p<0.05)increased in OH subjects compared to SbH and control, while SbH subjects have shown non-significant (p>0.05) levels compared to control. On the contrary, serum Ca level was significantly (p<0.05) reduced in OH subjects compared to SbH and control, while the SbH and control have shown non-significant value (p>0.05). Also, MDA has

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shown to be correlated significantly (P<0.05) with WHpR in OH patients. The Receiver Operating Characteristic (ROC) analysis has indicated the usefulness of using MDA in the prognosis of OH and SbH with excellent sensitivity. In conclusion, the increase of MDA as a consequence of lipid peroxidation could involve the final conversion of subclinical hypothyroidism to the overt kind.

*Keywords*---Hypothyroidism, MDA, calcium, magnesium, phosphorus, oxidative stress.

### 1. Introduction

Hypothyroidism is a common disorder of the thyroid gland (ThG) [1]. It is a chronic pathological condition characterized by the inability of ThG to produce sufficient amount of the thyroid hormones, triiodothyronine (T3) and thyroxine (T4) [2]. Essentially, ThG is stimulated by the interior pituitary hormone, thyroid stimulating hormone (TSH) [3, 4]. Upon this stimulation, ThG releases T4 and T3 to the circulation in ratio of 10:1 approximately [5]. Thyroid hormones trigger multiple cells in the body, transmitting an important primary signal to enable cells for performing important metabolic processes [6].

Hypothyroidism affects approximately 2% of adult females. Primarv hypothyroidism, which makes up for around 95 percent of all cases and is most common in females over 60 years of age, is nearly ten times less common in males than in females [7]. Generally, hypothyroidism arises either from insufficient iodine intake [8] or from immunological reasons (Hashimoto's disease) [9]. Overt hypothyroidism (OH) is a term used to describe a clinical situation in which the ThG produces very low concentration of T4 under the stimulation with high concentration of TSH [10]. Subclinical hypothyroidism (SbH) is the other clinical situation of primary hypothyroidism, in which the ThG produces sufficient amounts of T4 but under the stimulation with elevated concentrations of TSH [11].

In biological systems, the free radicals and reactive oxygen species (ROS) have direct link to the metabolic processes [12]. Therein, any dysregulation in the metabolic processes may result in elevated levels of ROS [13-16]. One of the most cellular macromolecules which is being affected by the increased levels of ROS are the lipids, especially the unsaturated fatty acids [17, 18]. So, ROS results in lipid peroxidation which subsequently leads to cells apoptosis and necrosis [19]. Malondialdehyde (MDA) is one of the final products in lipid peroxidation process and is frequently used as biomarker for indicating oxidative stress [20, 21].

Minerals play significant roles in many biofunctions of living systems [22]. From the most important minerals that present in the human body in relatively high concentrations are calcium (Ca), magnesium (Mg), and phosphorus (P) [23]. Altered serum levels of these minerals have been linked to many disorders in humans [24-26]. The main goal of this study is to investigate the relationship between oxidative stress and the progression of primary hypothyroidism by measuring MDA level in OH and SbH patients. The possibility of using MDA in the prognosis of hypothyroidism, and its correlation with Ca, Mg and P were further goals in this work.

### 2. Experimental

#### 2.1. Subjects and samples collection

The study has included 80 patients with primary hypothyroidism disease collected from Al-Yarmook Teaching Hospital (Baghdad, Iraq). According to their diagnosis, patients were divided into two groups, OH and SbH, each group was contained 40 subjects with age range 20-59 year. Additionally, 40 healthy people (with age range 20-59 year) were volunteered as control for the study. Subjects were collected based on standard criteria in which the age, and gender distribution was comparable between subjects among the three groups. Each subject was followed a weight, height and hip measurement for the calculation of body mass index (BMI) and waist to hip ration (WHpR). Blood samples were collected then, and centrifuged (1500xg for 10 min) to separate the serum. The serum samples were stored at -20 °C until analyses. The subjects were collected during September 2021 to December 2021.

### 2.2. Methods

The serum of each sample was analyzed for TSH, T3, T4, MDA, Ca, Mg, and P. Thyroid function parameters were analyzed by using cobas e411 (Roche, Germany). The evaluation of MDA in serum was performed by using the spectrophotometric method of Benge and Aust [27]. Commercial kits (Linear, Spain) were used for the determination of serum Ca, Mg and P.

#### 2.3. Statistical analyses

The Statistical Process for Social Sciences (SPSS) version 26 software and Excel 2016 were used to examine the data. The data is presented as a mean and standard deviation (SD). The three groups' means were compared using analysis of variance (ANOVA), proceeded by a post-hoc Tukey's test for mean differences between the two groups. The association between MDA and the other factors in OH and SbH patients was tested using Pearson's correlation coefficient (r). The area under the curve (AUC) and cut-off values were applied to examine the sensitivity of MDA as a diagnostic marker using the receiver operating characteristic (ROC) test. For percentages comparisons, the Chi-square test was used.

## 3. Results

#### 3.1. Subjects characteristics

The demographic presentation of the subjects is shown in Table 1. The age was non-significantly (p>0.05) different among control (37.85±8.67 year), SbH (38.73±11.03 year) and OH subjects (38.13±11.67 year). Also, BMI was observed to be significantly higher (p<0.05) in OH (27.85±2.72 kg/m<sup>2</sup>) and SbH subjects (25.73±2.67 kg/m<sup>2</sup>) compared to control (23.02±2.12 kg/m<sup>2</sup>). The BMI was also

significantly higher (p<0.05) in OH compared to SbH subjects. The value of WHpR was also significantly higher (p<0.05) in SbH (0.82±0.09) and SbH subjects (0.87±0.06) compared to control (0.78±0.06). Tukey's test was indicated a further significant higher value (p<0.05) of WHpR in favor of OH subjects compared to SbH subjects.

### 3.2. Clinical parameters

The results of thyroid function parameters are listed in Table 2. The level of TSH was significantly elevated (p < 0.05) in OH ( $15.98 \pm 5.04 \text{mIU/L}$ ) and SbH (14.1±3.06mIU/L) compared to control (2.37±0.76mIU/L). According to Tukey's test, OH subjects have shown significantly higher levels (p < 0.05) of TSH compared to SbH subjects. The level of T3 was significantly lower (p<0.05) in OH patients  $(0.98 \pm 0.34 \text{ nmol/L})$ compared to SbH (1.25±0.36nmol/L) and control  $(1.33\pm0.31$  nmol/L). The differences of T3 were non-significant (p>0.05) between SbH and control. The level of T4 was significantly lower (p < 0.05) in OH patients  $(2.64 \pm 1.12 \mu g/dL)$ compared to SbH  $(7.61 \pm 1.61 \mu g/dL)$ and control  $(7.38\pm1.18\mu g/dL)$ . The differences of T4 were non-significant (p>0.05) between SbH and control.

The level of MDA (Table 2) was significantly (p<0.05) elevated in OH (2.81±0.61µmol/L) and SbH (2.40±0.43µmol/L) patients compared to control (0.85±0.10µmol/L). According to Tukey's test, OH subjects have shown significantly higher levels (p<0.05) of MDA compared to SbH subjects.

Serum Ca level (Table 2) was significantly reduced (p<0.05) in OH (9.0±0.49 mg/dL) compared to SbH (9.22±0.32 mg/dL) and control (9.30±0.30 mg/dL). Furthermore, Mg level was significantly higher (p<0.05) in OH (2.68±0.61 mg/dL) compared to SbH (2.23±0.37 mg/dL) and control (2.05±0.12 mg/dL). Also, P level was increased significantly (p<0.05) in OH (5.26±1.75 mg/dL) compared to SbH (3.69±0.37 mg/dL) and control (3.48±0.38 mg/dL). According to Tukey's test, the differences of Ca, Mg and P were non-significant (P>0.05) between SbH subjects and control.

#### 3.3. Correlation

Pearson's correlation coefficient (r) values of MDA with the other variables in OH and SbH patients are shown in Table 3. The only significant correlation was observed between MDA and WHpR in OH patients (r=0.343, p= 0.030), as shown in Figure 1.



Fig. 1. The correlation between MDA and WHpR in the serum of OHT patients.



Fig. 2. ROC curve of MDA. A) For OH subjects; B) For SbH subjects.

#### 3.4. ROC curve

The ROC curve has shown the usefulness of MDA in the prognosis of OH and SbH. In OH disorder, MDA has shown to be excellent sensitive marker (AUC=1.0, p<0.0001) with cut-off value 1.43µmol/L (sensitivity= 100% and specificity= 100%). In SbH disorder, MDA has shown to be excellent sensitive marker (AUC=1.0, P<0.0001) with cut-off value 1.415µmol/L (sensitivity= 100% and specificity= 100%), Figure 2.

Parameter		Control, N=40 Mean±SD	OH, N=40 Mean±SD	SbH, N=40 Mean±SD	<i>p</i> -value
Age (year)		$37.85\pm8.67^{a}$	38.13±11.67ª	38.73±11.03ª	0.931
BMI (kg/m2)		$23.02 \pm 2.12^{a}$	$27.85 \pm 2.72^{b}$	25.73±2.67°	0.0001*
Waist circumference (cm)		80.98±5.36ª	$99.90 \pm 8.72^{b}$	94.28±9.61°	0.0001*
WHpR		$0.78\pm0.06^{a}$	$0.87 \pm 0.06^{b}$	0.82±0.09°	0.0001*
Gender	Male%	50%	50%	50%	0.999
	Female%	50%	50%	50%	

Table 1 Characteristic of the study subjects

Same letters indicate non-significant differences (p>0.05), while different letters indicate significant differences (p<0.05) according to the post-Hoc Tukey's test. \* Significant at p<0.05 according to ANOVA test.

Table 2: The levels of biochemical parameters in patients and control

Parameter	Control, N=40 Mean±SD	OH, N=40 Mean±SD	SbH, N=40 Mean±SD	<i>p</i> -value
TSH (mIU/L)	$2.37\pm0.76^{a}$	$15.98 \pm 5.04^{b}$	14.1±3.06 <sup>c</sup>	0.0001*
T3 (nmol/L)	1.33±0.31ª	$0.98\pm0.34^{b}$	$1.25\pm0.36^{a}$	0.0001*
T4 (μg/dL)	$7.38 \pm 1.18^{a}$	$2.64 \pm 1.12^{b}$	7.61±1.61ª	0.0001*
MDA (µmol/L)	$0.85\pm0.10^{a}$	$2.81\pm0.61^{b}$	2.40±0.43°	0.0001*
Ca (mg/dL)	$9.30\pm0.30^{a}$	$9.0\pm0.49^{b}$	$9.22\pm0.32^{a}$	0.001*
Mg (mg/dL)	$2.05\pm0.12^{a}$	$2.68\pm0.61^{b}$	$2.23\pm0.37^{a}$	0.0001*
P (mg/dL)	$3.48\pm0.38^{a}$	$5.26 \pm 1.75^{b}$	$3.69 \pm 0.37^{a}$	0.0001*

Same letters indicate non-significant differences (p>0.05), while different letters indicate significant differences (p<0.05) according to the post-Hoc Tukey's test. \* Significant at p<0.05 according to ANOVA test.

Table 3 Correlation between MDA and other variables in OH and SbH patients

Doromotor	OH, N=40		SbH, N=40	SbH, N=40	
Farameter	r	p	r	p	
Age (year)	-0.014	0.933	-0.091	0.576	
BMI (kg/m2)	0.189	0.243	-0.042	0.796	
WHpR	0.343*	0.030	0.052	0.752	
TSH (mIU/L)	-0.156	0.336	0.220	0.172	
T3 (nmol/L)	0.194	0.231	0.020	0.900	
T4 ( $\mu g/dL$ )	0.113	0.487	-0.217	0.178	
Ca (mg/dL)	0.060	0.714	0.038	0.817	
Mg (mg/dL)	-0.119	0.465	0.087	0.594	
P(mg/dL)	-0.228	0.157	-0.280	0.081	

#### 4. Discussion

Hypothyroidism results in many clinical signs related to the low rates of metabolism [6]. It has been documented that primary hypothyroidism can be divided into OH and SbH based on the clinical presentation of the patients. In this study, patients were said to have SbH when the level of T4 was higher than  $5\mu g/dL$  and TSH level was higher than 5 mIU/L. The OH was determined when the level of T4 was lower than  $5\mu g/dL$  and TSH level was higher than  $5\mu g/dL$  and TSH level of T3 was discarded from this differentiation criteria as the major thyroid hormone in the circulation is T4, and is followed deiodination process within target cells that converts T4 to the active form (T3). This was in agreement with other studies [28, 29].

The anthropometric results (Table 1) indicated that both OH and SbH patients were overweight. In fact, it is an expected result which essentially arises as a consequence of thyroid hormone action. In addition, T3 is responsible of inducing lipolysis in target cells and thus any decrease of T3 level would lead to the accumulation of the body fats [30], and thus, the energy intake and expenditure balance would be shifted and then weight is gradually increased [31, 32]. Additionally, it has been suggested that OH causes weight gain by raising mucin deposition in the skin and other tissues, as well as water and salt retention [33]. Furthermore, clinical data suggests that even minor thyroid malfunction, such as subclinical hypothyroidism, is associated with considerable weight fluctuations [34], yet it remains unclear.

The level of MDA was significantly elevated in both OH and SbH patients (Table 2). Torun et al. [35] have reported elevated MDA levels in OH and SbH patients, the authors have attributed the increase of oxidative stress status in SbH to the alteration in lipid metabolism. Also, other studies have indicated elevated lipid peroxidation in hypothyroidism [36-38]. The main mechanism by which oxidative stress is increased in hypothyroidism is not fully understood. Since the production of ROS can be affected by the metabolic condition directly through the mitochondrial respiratory chain [39], then it is safe to presume that hypothyroidism leads to oxidative stress through mitochondrial dysfunction. Several studies have reported a mitochondrial dysfunction in OH [40-42] and SbH [43, 44]. Another way to increase oxidative stress in hypothyroidism patients could be a failing in the antioxidant defense system. Several studies have reported a reduction in certain antioxidants [45-47], which support this presumption. Furthermore, MDA was correlated positively with WHpR (Figure 1) in OH patients which introduce other influencer (overweight) that increases oxidative stress. Overweight increases oxidative stress by enhancing the production of ROS and reducing antioxidants [48-50].

The results have indicated that OH patients suffers from a decrease of serum Ca level with an increase in Mg and P levels. Similar results were reported by Sridevi et al. [51] and Şim Şek et al. [52]. The authors have linked the alteration of these minerals directly to the ThG. The hormone T4 controls calcium levels in the blood by releasing calcium into the extracellular space. Less T4 in the circulation, and hence less T4 entrance into the cells, results in reduced extracellular calcium

release in hypothyroidism [53]. The results of Mg and P were contradicted with Baltaci et al. [54] who reported that Mg and P do not alter in hypothyroidism.

# **5. Conclusions**

Based on the results of the study, the significant elevation of MDA in OH and SbH indicate systemic oxidative stress. The MDA was shown an excellent sensitivity in the prognosis of both OH and SbH. Moreover, the significant graduate increase of MDA from healthy people to SbH patients reaching the OH patients may consider as straight pathway explaining the conversion of SbH to OH with time. Further investigations are required to clarify this topic.

# **6.** Conflicts of interest

There are no conflicts to declare.

# 7. Acknowledgments

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