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Changes of Certain Metabolic and Cardiovascular Markers Fructosamine, H-FABP and Lipoprotein (a) in Patients with Hypothyroidism

Ahmed Naseer Kaftan¹, Farah H. Naser², Muslim A. Enaya²**ABSTRACT**

Background: Disorders of thyroid gland are common in general population, and it's the most common affecting the endocrine system after diabetes mellitus. Thyroid function regulates a wide range of metabolic parameters, as well as affects some cardiovascular disease risk factors. Fructosamine is produced by a reaction between albumin (protein) and glucose; it is used to monitor patients with diabetes for short-term glycemic changes. H-FABP is present in the cytoplasm of cardiac myocytes, and delivers fatty acids into these cells. It has been shown to increase in myocardial injury. Lipoprotein LP(a) is consist of a special apolipoprotein called apoprotein (a), and it's recognized as a cardiovascular disease independent risk factor. **Objective:** To study whether certain metabolic and cardiovascular markers (fructosamine, H-FABP and lipoprotein (a) are changed in hypothyroid patients. **Methods:** The current study included 280 overt hypothyroid, 272 with subclinical hypothyroidism compared with 270 healthy individuals of matched age and gender. For all subjects serum (TSH, T4, T3, FBS, HbA1c, fructosamine, triglycerides, cholesterol, lipoprotein (a), and Heart-type Fatty Acid-Binding Protein (H-FABP)) was measured. **Results:** Serum fructosamine level significantly elevated (p value <0.05) in patient with hypothyroidism when compared with control group, and no significant change between subclinical and control groups. There is no significant change in serum H-FABP between study subjects. There is significant increase in lipoprotein (a) in patient with hypothyroidism and those with subclinical group when compared with control group. **Conclusion:** Serum fructosamine and level is significantly changed in patients with overt hypothyroidism when compared with euthyroid subjects. Also, we conclude that hypothyroidism increase risk of cardiovascular diseases by changing non-traditional marker such as lipoprotein (a), and no effect on H-FABP concentration.

Keywords: fructosamine, H-FABP, lipoprotein (a), hypothyroidism.

1. BACKGROUND

Thyroid disorders are one of the common and chronic medical conditions, Thyroid disorders can be classified according to the severity of clinical findings, the presence or absence of thyroid auto-antibodies, serum levels of thyroid hormones, or the physiological or biochemical changes in the target tissues (1). Hypothyroidism can manifested in overt or subclinical forms, subclinical thyroid disorders are more common than overt diseases; they can be asymptomatic and, therefore, undiagnosed and untreated, leading to significant adverse complications (2). The data of global prevalence of thyroid disorders demonstrate significant variations due to variable definitions of the disorders especially the subclinical thyroid disorder and also due to variant study populations and variant study design. In previous studies, prevalence of overt hypothyroidism or its subclinical form range between 2-4% and 4-20%, respectively, both being significantly higher in women aged more than 60 years (3). There is a certain relationship between thyroid dysfunction and cardiovascular diseases and type two diabetes mellitus probably through insulin resistance, changes in lipids, lipoproteins metabolism and inflammatory pathways (4, 5). Glycated proteins for example: Glycated hemoglobin, serum fructosamine can be used as glycaemic markers to set the level of glycation, Glycated hemoglobin (HbA1c) which is one of the long-term measures of

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glycation (2-3 months), now used as the cornerstone of diagnosing diabetes mellitus and also assessing glycemic control (6). Fructosamine is a generic name specified to a structure called (plasma protein ketoamines). In blood, fructosamine is mainly Glycated albumin, as albumin is the most abundant protein in plasma. It is also called Glycated serum proteins or Glycated albumin It is produced by a non enzymatic spontaneous reaction between an amino group of a protein with a carbonyl group of a glucose molecule, and is used to monitor glycemic control over a shorter time from two to three weeks to assess management of diabetes mellitus (7). Lipoprotein(a) (LP(a)) is a special type of LDL, containing a protein called apolipoprotein(a) (also known as apo(a), several genetic and epidemiological studies have reported relation between higher plasma concentrations and atherosclerotic diseases (8). H-FABP is a small cytoplasmic protein is involved in active fatty acid metabolism, it released from injured myocardium following ischemic episodes (9). H-FABP is released within 1-2 hours after chest pain onset, peaked after 5-10 hours and remains elevated up to 24-36 hours; it's used clinically as early sensitive biomarker for detection of myocardial injury (10).

2. OBJECTIVE

To study whether certain metabolic and cardiovascular markers (fructosamine, H-FABP and lipoprotein (a), are changed in hypothyroid patients.

3. MATERIAL AND METHODS

The current study included 280 overt hypothyroid, 272 with subclinical hypothyroidism attending the Endocrinology and diabetes center, Najaf , Iraq from (June–December 2019), compared with 270 healthy individuals of matched age (30-55) and gender.

The study individuals were divided to three groups:

I: included apparently healthy control (euthyroid) individuals (n = 270). By clinical examinations without signs and symptoms or previous history of thyroid disorders.

II: included patients with the clinically established hypothyroidism (n = 280).

III: included subjects with subclinical hypothyroidism (n =272).

The diagnoses of hypothyroidism were established, depending on the history, clinical examination and thyroid hormones levels: TSH >4.2 μ IU/ml, T4 <59 nmol/L, T3 <1.0 nmol/L). Subclinical hypothyroidism is defined as TSH >4.2 μ IU/ml, T4: 59-135 nmol/L. Patients taking Statins, pregnant women and those with malignancy, diabetes were excluded. Written informed consent was obtained from each study subject. The study was approved by the Ethical committee of Kufa University. Five ml samples of blood were collected by venipuncture under aseptic technique and were analyzed for the following biochemical parameters.

Total T3, total T4, and TSH by Electro Chemiluminescence immune assay method using Cobas Roche e411 auto analyzer (Roche Diagnostics GmbH, Mannheim,

Germany). Serum fasting glucose by endpoint method: enzymatic glucose oxidase horseradish peroxidase using chemistry auto analyzer Randox Daytona plus (Randox Laboratories Ltd., Crumlin, UK).

EDTA blood for HbA1c testing by latex enhanced immunoturbidimetric method using chemistry auto analyzer Randox Daytona plus.

Serum cholesterol by enzymatic cholesterol oxidase method using chemistry auto analyzer Randox Daytona plus.

Serum fasting triglycerides by enzymatic glycerol kinase method using chemistry auto analyzer Randox Daytona plus.

Serum fructosamine was measured by the Nitro blue Tetrazolium reduction method using auto analyzer Randox Daytona plus.

Serum H-FABP by Immunoturbidimetric method using chemistry auto analyzer Randox Daytona plus.

Serum lipoprotein (a) by Immunoturbidimetric method using chemistry auto analyzer Randox Daytona plus.

Statistical analysis

Statistical analyses have carried out by the using IBM SPSS statistics software (version 25; IBM, New York, USA). Data expressed as mean \pm SD, analyzed by ANOVA test with post hoc analysis. The association of independent variables among groups has been evaluated with the use of univariate and multivariate logistic regressions. The odds ratio (OR) with 95% confidence interval (95% CI) has been estimated. Spearman's correlation analysis has been applied to determine the variable correlations. P values of less than 0.05 were considered statistically significant

4. RESULTS

Table 1 show background characteristics of study subjects including gender, age and BMI. There is no significant difference between in gender, age and BMI between study subjects. Table 2 show comparison of thyroid function tests (TSH, T4, and T3) among study subjects, it demonstrate significant differences in serum TSH, T4, T3 and serum TSH only between hypothyroid and subclinical hypothyroid group respectively when compared with the control euthyroid group. Table 3 show comparison of glycemic parameters (FBS, HbA1c, fructosamine) among euthyroid hypothyroid and subclinical hypothyroid groups, there is no significant change in serum FBS and HbA1c between study subjects, serum fructosamine level where significantly elevated (p value <0.05) in patient with hypothyroidism when compared with control group, and no significant change between subclinical and control groups. Table 4 show comparison of lipid and cardiovascular parameters (triglycerides, total cholesterol, H-FABP and lipoprotein (a) among euthyroid hypothyroid and subclinical hypothyroid groups. There is significant increase in total cholesterol and triglycerides and lipoprotein(a) in hypothyroidism group and sub clinical hypothyroid group respectively when compared with control group (p value <0.05), and no significant change in H-FABP between study subjects. Table 5 show Univariate and Multivariate logistic re-

Parameter	Control (Euthyroid)	Subclinical hypothyroid	P value*	Hypothyroidism	P value*
Male, Female	(140,130)	(151,121)		(158,122)	
	N = 270	N = 272		N = 280	
Age	42.9±7.2	43.1±6.9	0.7	42.6±7.1	0.6
BMI	21.6±1.8	21.6±1.7	0.8	21.6±1.8	

Table 1. Background characteristics of study subjects. Data expressed as mean ± SD. * p value when compared with euthyroid group, P value <0.05 is considered statistically significant

Parameter	Control (Euthyroid)	Subclinical hypothyroid	P value*	Hypothyroidism	C
	n = 270	n = 272		n = 280	
TSH (µIU/mL)	2.2±1.1	16.6±4.7	<0.01	55.9±13.5	<0.01
Total T4 (nmol/L)	98.0 ±24.4	97.0 ±22.2	0.5	44.2±9.2	
Total T3 (nmol/L)	2.3 ±0.8	2.2±0.7	0.5	1.2±0.3	

Table 2. Mean comparison of thyroid function tests among study subjects. Data expressed as mean ± SD, * p value when compared with euthyroid group, P value <0.05 is considered statistically significant

Parameter	Control (Euthyroid)	Subclinical hypothyroid	P value*	Hypothyroidism	P value*
	n = 270	n = 272		n = 280	
FBS (mmol/L)	4.6±0.4	4.7±0.5	0.08	4.7±0.5	0.07
HbA1c (mmol/mol)	36.7±2.8	37.0±2.8	0.1	37.1±2.7	0.1
Fructosamine (pmol/L)	241.2±24.0	245.1±20.0	0.1	311.2±29.2	< 0.1

Table 3. Mean comparison of glycemic parameters (FBS, HbA1c, fructosamine) among euthyroid, hypothyroid and subclinical hypothyroid groups. Data expressed as mean ± SD. * p value when compared with euthyroid group. P value <0.05 is considered statistically significant

gression analysis of the study subjects, fructosamine show significant effect (OR: 1.03. % CI 95 (1.02-1.03) (P value <0.05) in both univariate and multivariate analysis by considering age, gender BMI, FBS and HbA1c as covariates, while H-FABP and lipoprotein (a) were significant only in univariate model. Table 6 show correlation of serum fructosamine, H-FABP and lipoprotein (a) with other study variables. There is significant (p<0.05) correlation fructosamine and lipoprotein(a) with TSH, T4, T3, cholesterol and triglycerides respectively, also these significant (p<0.05) correlation between fructosamine and lipoprotein (a). Regarding H-FABP these is significant (p<0.05) correlation with age, cholesterol and triglycerides.

5. DISCUSSION

Determining the effect of thyroid gland on metabolic and cardiovascular pathways could direct the clinically related definition of thyroid function and show important targets for controlling related morbidity. Previous studies demonstrate the changes of fructosamine, H-FABP and lipoprotein (a) in hypothyroid patients in

different populations. However the current study is the first one that shows this relation in Arab population's especially Iraqi one as there is a differences in genetic and environmental factors. The current study demonstrated that fructosamine level was significantly elevated (p value <0.05) in patients with hypothyroidism when compared with control (euthyroid) group, These findings are in agreement with previous studies by Lloyd (11), Larsen *et al* (12) , Kim *et al* (13), Sharma *et al* (14), Soni *et al* (15), and Chowdhry (16). Till now there is no explanation of how these changes in serum fructosamine concentration occur in patient with thyroid disease, however it was proposed that these findings could be due to change in plasma proteins turnover (17, 18). Other study confirms that fructosamine level affected by abnormal protein turnover as in patients with hypothyroidism, where turnover of protein is decreased). The half life of fructosamine level then will increase when there is reduction in protein turnover, so fructosamine is useful to measure the peripheral metabolic effect in those with thyroid diseases (19). Furthermore, it was found in our study that there is significant correlation between serum TSH and serum fructosamine and this finding also reported by Koga (20). The explanations for the abnormally high fructosamine levels in normoglycemic hypothyroid patients are:

Prolongation of half life of fructosamine due to decrease metabolism which prolong half life of plasma proteins.

Changes in homeostasis of glucose with decreased absorption and also decreased utilization is associated with increase insulin levels and insulin resistance may cause minor increase in the concentrations of glucose thus participate in serum proteins glycation.

Increase glycation of proteins due to increase in oxidative stress.

Parameter	Control (Euthyroid)	Subclinical hypothyroid	P value*	Hypothyroidism	P value*
	n= 270	n= 272		n=280	
Total cholesterol (mmol/L)	3.8±0.7	5.0±0.5	<0.01	7.5±0.7	<0.01
Triglycerides (mmol/L)	1.3±0.1	2.4±0.3	<0.01	3.9 ±0.9	<0.01
H-FABP (ng/mL)	3.0±1.4	3.2±1.4	0.08	3.2±1.3	0.08
Lipoprotein (a) (mg/dL)	44.8±17.3	65.3±8.6	<0.01	74.7±8.5	<0.01

Table 4. Mean comparison of lipid and cardiovascular parameters (triglycerides, total cholesterol, H-FABP and lipoprotein (a) among euthyroid hypothyroid and subclinical hypothyroid group. Data expressed as mean ± SD. * p value when compared with euthyroid group. P value <0.05 is considered statistically significant

Inflammation of low grade will be caused by the formation of free radical and its complications. Increased immunoglobulin's because of inflammation and increase rates of glycation of immunoglobulin's.

Glycated proteins accumulation in tissues will resist minor proteolysis and become other free radicals source (21, 22).

In the current study, we studied if serum H-FABP level is changed in patients with hypothyroidism. Previous studies have reported that hypothyroidism accelerates cardiovascular risk (23). H-FABP is a specific and sensitive marker for myocytes injury, thyroid disorders may has an effect on muscular tissue as other studies reported (24), so we suppose that H-FABP may increase in hypothyroid patients, and this finding have been reported by Gunes F. *et al.*(25). Our study reported that there is no significant increase in serum H-FABP in patients with hypothyroidism and this finding also has been reported by Tatal E. *et al.* (26). Our finding could be explained by that most of patients participated in this study have normal BMI and most of them are premenopausal females and these could affect the severity of cardiovascular risk also the different durations of hypothyroidism among patients may lead to insignificant H-FABP levels. Many studies demonstrated that thyroid disorders, including overt and subclinical hypothyroidism significantly change the lipid profile and increase cardiovascular risk, because thyroid hormones involved in lipid metabolism, synthesis and mobilization (27). LP(a) is a LDL-C type fraction, it has been reported as to have an atherogenic and thrombogenic effect, LP(a) may be affected by thyroid function because it is known that LP(a) would go during its metabolic process through the LDL-C receptor in which thyroid hormones affect the expression of the gene of this receptor (28). Our study reported that serum cholesterol and fasting triglycerides was significantly elevated (p value <0.05) in hypothyroid and subclinical hypothyroid groups when compared with control (euthyroid) group. In this study serum lipoprotein(a) was found be significantly elevated (p value <0.05) in hypothyroid and subclinical hypothyroid groups when compared with control (euthyroid) group. This finding has been reported by De Bruin T. *et al.*, Engler H, Becerra A.*et al.* (29-31). While other studies reported no significant change in lipoprotein (a) in patient with hypothyroidism (32), these conflicting finding could be due that lipoprotein (a) affected by genetic polymorphism and its concentration vary greatly among population and also the metabolism of it is not well understood (33-36).

6. CONCLUSION

It was concluded from this study that serum fructosamine level is significantly changed in patients with overt hypothyroidism when compared with euthyroid subjects. So fructosamine could be considered as a diagnostic criterion in thyroid disorders. Also we conclude that hypothyroidism increase risk of cardiovascular diseases by changing non-traditional marker such as lipoprotein (a), and no effect on H-FABP concentration.

Statement of Ethics: All methods done in this research including human participants were in accordance

Variable	Univariable logistic regression		Multivariable logistic regression	
	OR (95%CI)	P value	OR (95%CI)	P value
Fructosamine	1.03(1.02-1.03)	< 0.01	1.03(1.02-1.03)	<0.01
H-FABP	1.1(1.0-1.2)	0.04	0.9(0.9-1.0)	0.8
Lipoprotein (a)	1.5(1.3-1.8)	<0.01	1.0(0.9-1.0)	0.6

Table 5. Univariable and Multivariable logistic regression analysis of the study subjects. OR: Odds ratio, CI: confidence interval. P value < 0.05 is considered statistically significant. Age, gender, BMI, FBS and HbA1c are considered as covariates

Parameter	Fructosamine		H-FABP		Lipoprotein (a)	
	r	P value	r	P value	r	P value
Age	-0.07	0.8	0.07	0.03	0.007	0.8
BMI	0.06	0.8	-0.009	0.7	-0.01	0.7
TSH	0.7	<0.01	0.06	0.06	0.6	<0.01
T4	-0.6	<0.01	0.01	0.6	-0.6	<0.01
T3	-0.4	<0.01	-0.01	0.6	-0.4	<0.01
FBS	0.06	0.09	-0.04	0.2	0.07	0.02
HbA1c	0.01	0.6	0.03	0.2	0.03	0.3
Cholesterol	0.6	<0.01	0.08	0.01	0.5	<0.01
Triglycerides	0.6	<0.01	0.07	0.03	0.6	<0.01
Fructosamine			0.01	0.6	0.4	<0.01
H-FABP	0.01	0.6			0.01	0.7
Lipoprotein (a)	0.4	<0.01	0.01	0.7		

Table 6. Correlation of serum fructosamine, H-FABP and lipoprotein (a) with other study variables. P value <0.05 is considered statistically significant. r: correlation coefficient

with the ethical standards of Kufa Ethical Committee and with the 1964 Helsinki Declaration and its later amendments or related ethical standards. Informed consent was taken from all individual participants involved in this research.

- **Author’s Contribution:** The corresponding author Ahmed Kaftan involved in ethical approval and participant consent, sample collection, supply and measurement of parameters and statistics. The co-author Farah Hassoon involved in participant weight measurement, theoretical part, plagiarism and printing.
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