CORRELATION OF OVERT HYPOTHYROIDISM AND CERTAIN CARDIOVASCULAR DISEASE RISK FACTORS [+]

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Abstract:

Some thyroid dysfunctions like overt hypothyroidism, abnormality might be including fat metabolism which resulted in unusual lipid profile leading to increased risk of cardiovascular diseases. Hence, this study was conducted to identify the correlation between overt hypothyroidism and lipid profile. Markers of lipid profile were investigated in association with the age and gender of hypothyroid group. The results elucidate a frequency of high level subjects of 75%, 41.7%, 75% and 41.7% in hypothyroid patients compared to 30.3%, 24.2%, 37.9% and 25.8% in euthyroid controls for cholesterol, triglyceride, LDL, and VLDL respectively. The differences were significant with cholesterol and LDL only. The differences in the mean concentration for all lipid markers between the hypothyroid and euthyroid groups were significantly higher on behalf the hypothyroid group. The results with males were almost similar to those of female and with no significant difference. For most of the lipid markers there were a higher frequency and mean concentration between the young (18-45 years) and old (46-67years) age groups on behalf of the old age group but without any significance. These results may conclude the presence of positive correlation between overt hypothyroidism and cardiovascular diseases by means of the significant elevation in the serum lipids among patients group in comparison with healthy control group.

علاقة قصور الدرقية الظاهري ببعض عوامل الخطورة لامراض القلب والاوعية الدموية

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المستخلص :

في بعض اختلالات الغدة الدرقية مثل امراض قصور الدرقية الظاهرة, يكون التاثير على الاستقلاب الطبيعي ممتدا الى استقلاب الدهون والذي قد ينتج عنه نمط غير طبيعي في قيم الدهون المصلية مما يزيد خطورة الاصابة بامراض الجهاز القلبي الوعائي. وعيه فان هذه الدراسة قد اجريت لتحديد العلاقة التبادلية ما بين مستوى هرمونات الدرقية ومستوى الدهون المصلية في المرضى المصابون بقصور الدرقية الظاهري مع محاولة تحديد قوة ذلك الارتباط من خلال حدة التغيرالمتبادل الذي يصيب هذه المستويات ومدى تأثرها بعمر وجنس المريض. اظهرت النتائج ارتفاعا في قيم الكولسترول, الدهون الثلاثية, البروتينات الدهنية قليلة الكثافة, والبروتينات الدهنية ذات الكثافة القليلة جدا في 58.3-75% من المرضى الاناث مقارنة مع 24.2-37.9% في مجموعة الاناث الاصحاء. بالنسبة للذكور فقد كان الارتفاع في قيم الدهون المصلية انفة الذكر يتراوح ما بين 40-70% من افراد مجموعة المرضى مقارنة ب 22.2-

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30.6% من افراد مجموعة السيطرة. هذه الفروقات في كلا الجنسين كانت معنوية عندما جرى تحليلها احصائيا (*P<0.05*). اما بالنسبة لتاثير العمر على مستويات الدهون المصلية فقد لوحظ ارتفاعا طفيفا في تلك المستويات في الاعمار المتقدمة (46–80سنة) عند مقارنتها بالاعمار الاصغر سنا (18–45 سنة) ولكن بدون فارق احصائي معنوي (P>0.05). من هذه النتائج نستنتج ان المصابين بقصور الدرقية الظاهري هم اكثر عرضة للاصابة بامراض الجهاز القلبي الوعائي مثل ارتفاع ضغط الدم, تصلب الشرايين, امراض القلب الاحتشائية وغيرها من الاصحاء الذين لا يعانون من اختلال وظيفي في عمل الغدة الدرقية.

Introduction :

Thyroid dysfunction is relatively a common disease which affects people, irrespective of their age and gender. Hypothyroidism is a clinical syndrome which is caused due to the deficiency of thyroid hormones, resulting in a generalized slowing down of the metabolic process. The incidence of hypothyroidism varies, depending on geographical and the environmental factors such as dietary iodide, goitrogen intake, the genetic characteristic of the population and the age distribution of the population. Clinical hypothyroidism occurs in 1.5-2% of women and 0.2% of men [1]. Hypothyroidism affects the cardiovascular, pulmonary, renal, neuromuscular, nervous and reproductive systems and its signs and symptoms are reversible on treatment with levothyroxine (T4).

A majority of the cardiovascular signs and symptoms are associated with a derangement in the lipid metabolism [2]. Thyroid hormones stimulate the utilization of the lipid substrates, owing to an increased mobilization of the triglycerides which are stored in the adipose tissue [3]. Hypothyroidism is associated with dyslipidaemia, thus contributing to the development of atherosclerosis. In hypothyroidism patients, there is a negative effect on the lipoprotein profile [low high-density lipoprotein-cholesterol (HDL-C) and high total cholesterol (TC) and low-density lipoprotein-cholesterol (LDL-C)] and may translate into a sizable cardiovascular risk if left untreated [4]. Indeed, even within the normal range of thyroid-stimulating hormone (TSH) values, a linear increase in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TGs) and a linear decrease in high-density lipoprotein cholesterol (HDL-C) levels has been observed with increasing TSH [5].

Lipid abnormalities are reported to be more common in patients with overt hypothyroidism and are thought to contribute to the disproportionate increase in cardiovascular risk [6]. The above abnormalities of lipid metabolism associated with overt hypothyroidism predispose to the development of atherosclerotic coronary artery disease (CAD) [7]. Moreover, hypothyroidism can adversely affect other CVD risk factors, further contributing to increasing CAD risk. Decreased thyroid function not only increases the number of LDL particles, but also promotes LDL oxidability [8]. Furthermore, hypothyroidism increases plasma homocysteine levels [9], which can be attributed to the hypothyroidism-induced decline of kidney function [10]. In addition, thyroid failure is strongly associated with arterial hypertension (especially diastolic) *via* sympathetic and adrenal activation [11], and increased vascular stiffness [12]. Subjects with overt hypothyroidism also exhibit impaired endothelial function [13], increased uric acid [14] and phosphate levels [15], all of which are associated with increased CVD risk [16].

The first aim of this study was to identify the relationship between the thyroid profile and the total cholesterol and the low density lipoprotein (LDL) levels among overt hypothyroid subjects. The second aim was to elucidate any correlation between the severity of hypothyroidism and levels of the measured markers of lipid profile. Finally, this study was

aimed to find out the effect of gender and age on the correlation between hypothyroidism and lipid profile.

Materials and methods :

Subject: This project was conducted in Baghdad Education Hospital of Baghdad Medical City for the period from September–October/ 2012. Sixty eight patients with hypothyroidism were enrolled in this study of which 48 females and 20 males with an age range from 18–67 years. One hundred and two healthy individuals were also included in this study of which sixty six females and thirty six males with a similar age range. All patients and healthy controls enrolled in this study were volunteers who were notified about the objectives of this study and had write their consents before donated their blood samples.

Samples and tests: Venous blood samples were drawn after 12 hours of overnight fasting. Serum was separated and divided into two parts. The first part was analyzed by VIDAS automated quantitative enzyme-immunoassay to determine the free tri-iodothyronine (fT3), free thyroxin (fT4) and thyroid stimulating hormone (TSH). The second part of the serum was estimated on chemistry analyzer by using the Biolabo kit for total cholesterol, triglycerides and Randox kit for LDL cholesterol (calculated using Friedewald's formula) and VLDL. The lipid concentration was considered to be altered when the total cholesterol was ≥ 200 mg/dl, the triglycerides were ≥ 160 mg/dl, LDL cholesterol was ≥ 100 mg/dl and VLDL >32 mg/dl.

Guide for lipid markers value: For lipid profile, the normal, borderline and high values for cholesterol, triglycerides, LDL and VLDL are shown in Table 1.

Table (1): Guide for lipid markers value [17]

Marker	Value		
	Normal	**Borderline**	**High**
Cholesterol (mgs/dl)	<200	Upto 239	>240
Triglyceride (mgs/dl)	<160	------	>180
LDL	<100	100-160	>160
VLDL	<38	----	>38

Guide for hormonal markers values: For TSH, T3 and T4 hormones, Table 2 illustrates the normal and abnormal values.

Table (2): Guide for the investigated hormonal markers value in the current study [18]

Marker	Value				
	Normal	**Mild-moderate high**	**Sever High**	**Mild-moderate low**	**Sever low**
TSH (µlu/ml)	0.25-5.0	>5.0-20.0	>20.0	<0.25-0.09	<0.09
T3 (Pmol/l)	4.0-8.3	>8.3-12.00	>12.00	<4.0-2.50	<2.50
T4 (Pmol/l)	9.0-20.0	>20.0-25.0	>25.0	<9.0-6.5	<6.5

Statistical analysis: Statistical analysis was done using SPSS version 10 computer software (Statistical package for social sciences). Pearson's Chi-Square was used to extract the P value which was considered significant when P value was <0.05 and non significant when P value was > 0.05.

Results and discussion :

Table 3 shows the correlation between hypothyroidism and lipid profile values according to age in female hypothyroid patients. The mean concentration of cholesterol (Ch) for all female hypothyroid patients was 266.2 mg/dl. The majority of cases (75%) were with high cholesterol level compared to those with low cholesterol level (25%) with a significant (*p<0.05*) difference, however no significant differences were found in the frequency of high cholesterol level and the mean concentration level between the two age groups (*p>0.05*). A very similar profile to the cholesterol profile was found with low density lipoprotein (LDL). For triglyceride (TG), the mean concentration among hypothyroid female patients was 170.9 mg/dl but with no significant difference in the frequency between patients with normal or high TG level. The same was true when the frequency of normal and high TG level as well as the mean concentration between the two age groups were compared. A very similar profile to the triglyceride profile was noticed with very low density lipoprotein (VLDL).

Table (3): The correlation between hypothyroidism and lipid profile values according to age in females hypothyroid patients

Hypothyroidism female cases (n) = 48 (100%)							
Lipid profile	Value	Age group (years): n (%)					
		18-45 n=26 (54.2%)		46-67 n=22 (45.8%)		Total n=48 (100%)	
		№ (mean)	%	№ (mean)	%	№ (mean)	%
Ch.*	Normal	8 (162)	30.8	4 (170)	18.2	12 (164.7)	25
	High	18 (282)	69.2	18 (318)	81.8	36 (300.0)	75
	Total	26 (245.1)	100	22 (291)	100	48 (266.2)	100
TG.*	Normal	16 (119)	61.5	12 (129)	54.5	28 (123.3)	58.3
	High	10 (223)	38.5	10 (252)	45.5	20 (237.5)	41.7
	Total	26 ((159)	100	22 (184.9)	100	48 (170.9)	100
LDL	Normal	8 (86)	30.8	4 (92)	18.2	12 (88.0)	25
	High	18 (220)	69.2	18 (233)	81.8	36 (226.5)	75
	Total	26 (178.8)	100	22 (194.8)	100	48 (191.9)	100
VLDL	Normal	16 (23)	61.5	12 (26)	54.5	28 (24.3)	58.3
	High	10 (45)	38.5	10 (50.2)	45.5	20 (47.5)	41.7
	Total	26 (31.5)	100	22 (36.9)	100	48 (34)	100

***Ch= Cholesterol, TG= Triglyceride.**

Table 4 illustrates the lipid profile in euthyroid healthy females. For all lipid markers, the frequency of subjects with normal level was higher than those with high level (72.3%, 77.3%, 68.2%, and 77.3% in 18-45 years age group and 68.2%, 75%, 61.4%, and 73.3% in 46-67 years age group for cholestrol, TG, LDL and VLDL respectively). This was true for total

subjects of the group where the total frequency of the high level lipid markers were 69.7%, 75.8%, 62.1% and 74.2% for cholesterol, TG, LDL and VLDL respectively. All the above results were with a significant difference ($p<0.05$). Concerning the mean concentrations, they were 186.7, 136.2, 105.8 and 26.7 mg/dl for cholestrol, TG, LDL, AND VLDL respectively.

Table (4): The correlation between euthyroidism and lipid profile values according to age in female healthy controls

Euthyroid female controls (n) = 66 (100%)							
Lipid profile	Value	Age group (years) n (%)					
		18-45 n=22 (33.3%)		46-67 n=44 (66.7%)		Total n=66 (100%)	
		№ (mean)	%	№ (mean)	%	№ mean)	%
Ch.	Normal	16 (145)	72.3	30 (160)	68.2	46 (154.8)	69.7
	High	6 (236)	27.3	14 (270)	31.8	20 (260)	30.3
	Total	22 (169.8)	100	44 (195)	100	66 (186.7)	100
TG	Normal	17 (107)	77.3	33 (124)	75	50 (118.2)	75.8
	High	5 (180)	22.7	11 (198)	25	16 (192.4)	24.2
	Total	22 (123.6)	100	44 (142.5)	100	66 (136.2)	100
LDL	Normal	14 (78)	68.2	27 (84)	61.4	41 (83.8)	62.1
	High	8 (127)	31.8	17 (151)	38.6	25 (142)	37.9
	Total	22 (95.8)	100	44 (109.9)	100	66 (105.8)	100
VLDL	Normal	17 (21.4)	77.3	32 (23)	73.3	49 (22.4)	74.2
	High	5 (36)	22.7	12 (40.6)	27.3	17 (39.2)	25.8
	Total	22 (24.7)	100	44 (27.8)	100	66 (26.7)	100

***Ch= Cholesterol, TG= Triglyceride.**

In comparison of the lipid profile between the hypothyroid group and euthyroid group in females, it was clear that all lipid markers were higher in the hypothyroid group than the euthyroid group with significant differences for the cholesterol and LDL (Tables 3, 4 and 7). Furthermore, the frequency of the subjects with high level of all lipid markers was higher than those with normal level in the hypothyroid group whereas the opposite was true in the euthyroid group with almost significant differences for all lipid markers (Tables 3, 4 and 7).
Table 5 shows that all lipid profiles for the cholesterol, triglycerides, LDL and VLDL in male hypothyroid patients were similar to their corresponding markers in female hypothyroid patients in their frequency and mean concentrations. Table 6 illustrates the correlation between a group of healthy males with euthyroidism and the lipid profile according to their ages. For all lipid markers, the frequency and the mean concentration profiles were similar to their corresponding that were noticed with healthy females.

Table (5): The correlation between hypothyroidism and lipid profile values according to age in males hypothyroid patients.

Total hypothyroidism male cases (n) = 20 (100%)							
Lipid profile	Value	Age group (years): n (%)					
		18-45 n=6 (30%)		46-67 n=14 (70%)		Total 20 (100%)	
		№ (mean)	%	№ (mean)	%	№ (mean)	%
Ch.	Normal	2 (160)	33.3	4(165)	28.6	6 (163.3)	30
	High	4(279)	66.7	10 (299)	71.4	14 (293.2)	70
	Total	6 (239.3)	100	14 (260.7)	100	20 (254.2)	100
TG	Normal	4 (112)	66.7	8 (123)	57.1	12 (119.3)	60
	High	2 (220)	33.3	6 (230)	42.9	8 (227.5)	40
	Total	6 (148)	100	14 (168.90	100	20 (162.6)	100
LDL	Normal	2 (85)	33.3	4 (93)	16.7	6 (90.3)	30
	High	4 (204)	66.7	10 (228)	83.3	14 (221.1)	70
	Total	6 (164.3)	100	14 (189.4)	100	20 (181.9)	100
VLDL	Normal	4 (22)	66.7	8 (24)	57.1	12 (23.3)	60
	High	2(44)	33.3	6 (46)	42.9	8 (45.5)	40
	Total	6 (29.3)	100	14 (33.4)	100	20 (32.2)	100

***Ch= Cholesterol, TG= Triglyceride.**

Table (6): The correlation between Euthyroidism and lipid profile values according to age in male healthy controls

Euthyroid male controls (n) = 36 (100%)							
Lipid profile	Value	Age group (years) n (%)					
		18-45 n=15 (33.3%)		46-67 n=21 (66.7%)		Total n=36 (100%)	
		№ (mean)	%	№ (mean)	%	№ (mean)	%
Ch.	Normal	11 (138)	73.3	15 (145)	71.4	26 (142)	72.2
	High	4 (234)	26.7	6 (248)	28.6	10 (242.4)	27.8
	Total	15 (172.5)	100	21 (174.4)	100	36 (169.9)	100
TG	Normal	12 (105)	80	16 (122)	76.2	28 (114.7)	77.8
	High	3 (175)	20	5 (187)	23.8	8 (182.5)	22.2
	Total	15 (119)	100	21 (193.2)	100	36 (129.8)	100
LDL	Normal	11 (77.3)	73.3	14 (74)	66.7	25 (75.5)	69.4
	High	4 (139)	26.7	7 (147)	33.3	11 (144)	30.6
	Total	15 (93.8)	100	21 (98.3)	100	36 (96.4)	100
VLDL	Normal	12 (21)	80	16 (24.5)	76.2	28 (23)	77.8
	High	3(35.6)	20	5 (37.5)	23.8	8 (36.8)	22.2
	Total	15 (23.9)	100	21 (27.6)	100	36 (26.1)	100

In comparison of the lipid profile between the hypothyroid group and euthyroid group in males, and as it was with females, all lipid markers were higher in the hypothyroid group than the euthyroid group with significant differences for the cholesterol and LDL (Tables 5, 6 and 7). Furthermore, the frequency of the subjects with high level of all lipid markers was higher (as that with females) than those with normal level in the hypothyroid group whereas the opposite was reported in the euthyroid group with almost significant differences for all lipid markers (Tables 3, 4 and 7). The differences in the mean concentration of all lipid markers and the frequency of high and normal level for all lipid markers were similar in female and male subjects in hypothyroid and euthyroid groups.
Table 7 summarized the statistical analysis for all results of the study.

Table (7): Statistical analysis for all results

Crosstab	Pearson's Chi-Square (P value)	Crosstab	Pearson's Chi-Square (P value)
Case X Gender	0.530 (NS)*	Gender X LDL	0.467 (NS)
Case X Age	0.312 (NS)	Gender X VLDL	1.000 (NS)
Case X Cholesterol	0.000 (HS)**	Age X Gender	1.000 (NS)
Case X TG	0.005 (HS)	Age X Case	0.312 (NS)
Case X LDL	0.000 (HS)	Age X Cholesterol	1.000 (NS)
Case X VLDL	0.132 (NS)	Age X TG	0.706 (NS)
Gender X Age	1.000 (NS)	Age X LDL	0.724 (NS)
Gender X Cholesterol	0.584 (NS)	Age X VLDL	0.566 (NS)
Gender X TG	0.555 (NS)		

***NS= Not significant, **HS= Highly significant**

The changes in lipid profile components noticed in the present study are common abnormalities of lipoprotein metabolism associated with hypothyroidism. The elevation in Cholesterol, TG, LDL and VLDL in hypothyroidism is accounted for by the effect of thyroid hormone on lipoprotein-lipase activity [19] and the expression of the LDL receptor [20]. In the current study, cholesterol, triglycerides and LDL levels were significantly high in hypothyroid patients when compared with the controls. In hypothyroidism, the coronary lipid risk factors seem to be associated with lipid peroxidation indicating the presence of oxidative stress in hypothyroid patients and its association with atherogenic dyslipidemia [21]. Thyroid hormones have profound effects on the cardiovascular system [22]. By affecting the metabolism of lipids, hypothyroidism accelerates the process of atherogenesis and elevates cardiovascular risk. Although LDL is widely accepted as the major atherogenic lipoprotein, TG-rich lipoproteins such as chylomicron remnants, whose clearance is reduced in hypothyroidism [23] and very LDL remnants still play an important role in atherogenesis. These remnants are taken up by macrophages in the arterial walls to produce foam cells and thus may be a risk factor for atherosclerosis [24]. There is a positive association between serum TSH levels and total cholesterol (TC) and LDL levels. In hypothyroidism, there is usually an elevated level of TSH hormone which consequently increasing the serum level of TG and LDL [13] as it was noticed in the present work. Thyroid hormones increase adipose tissue lipolysis as measured by high free fatty acids or glycerol release [25]. The total content of saturated fatty acids (FA) in serum was found to be high and the total content of unsaturated FA was low in hypothyroid patients [26]. From the above facts, the high body weight and high atherogenic lipids in hypothyroidism can be explained indirectly as a subsequence of the reduction of thyroid hormones. The hypercholesterolemia is an important factor of atherosclerosis. High-density lipoprotein are particles with numerous athero-

protective functions, including facilitation of reverse cholesterol transport, improvement of endothelial function, protection of LDL from oxidation, limitation of hemostasis and retardation of inflammatory activity related to the vascular wall [27].

This study found no significant differences in the lipid profile between females and males. A higher lipid values was documented among older patients (46-67 years) than younger patients (18-45 years), however statistically this was non-significant. The association between high lipid profile (mainly in cholesterol, TG and LDL) and hypothyroidism was highly significant which conclude that overt hypothyroidism may predispose for cardiovascular diseases including hypertension, atherosclerosis, ischemic heart disease and others and reducing the level of these lipid values by medications is as important as treating the hypothyroidism itself.

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