

LIPID PROFILE IN SUBCLINICAL HYPOTHYROIDISM: A TWO CENTERS EXPERIENCE

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ABSTRACT

Background: Subclinical hypothyroidism (SCH) is estimated to affect around 7.5-8.5% of females and 2.8-4.4% of males. One of the features of clinical hypothyroidism is dyslipidemia. There is a great debate about the presence of abnormal lipid profiles in patients with subclinical hypothyroidism (SCH) and whether it is clinically significant or not. Some evidences show reduction in the level of the serum lipid profile after replacement with thyroid hormones. The purpose of this study is to estimate the prevalence of dyslipidemia in patients with subclinical hypothyroidism in Duhok and Erbil cities, Iraq.

Patients and Methods: This is a case-control study that was done on 200 individuals. One hundred patients confirmed with subclinical hypothyroidism were compared with a group of 100 apparently healthy individuals. These two groups were matched for age and sex. The study done in 2 centres; Azadi Teaching Hospital in Duhok and Rizgari Teaching Hospital in Erbil, Kurdistan Region, Iraq from from 1st December 2017 to 1st December 2018.

Results: Dyslipidemia was commoner in patients with subclinical hypothyroidism compared to control group (p value 0.001) compared to the control group (p value 0.766). The total cholesterol and the triglyceride levels were steadily increased in relation to the level of the thyroid stimulating hormone (TSH).

Conclusions: Subclinical hypothyroidism (SCH) is regarded as an atherogenic condition because it increases the cholesterol and the triglyceride levels. Management of subclinical hypothyroidism with thyroid hormones may have a positive impact on the cardiovascular health. It is reasonable to measure the levels of the serum lipids and cardiovascular risk in these patients and to manage them when it is clinically applicable.

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Keywords: Dyslipidemia, Subclinical Hypothyroidism (SCH), Case Control Study.

Thyroid gland abnormalities may be seen at any age. They are more common in adults. Thyroid hormones act in the metabolism in all body systems. Their most clear and well known function is to enhance the body energy production which is caused by acting on the

metabolism of the fat, the carbohydrates and the protein. The fat metabolism is more affected. Thyroid hormones are important to maintain the phospholipids in cell membranes and fatty acids contents of the lipids. Tri-iodothyronine (T3) plays an important function in fat metabolism

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because it regulates the expression of different genes which control fat synthesis and catabolism^{1,2}.

Hypothyroidism is caused by decrease excretion of thyroxin (T4) and T3. Biochemical reduction in T4 and T3 levels will lead to elevation in the serum thyroid stimulating hormone (TSH) level. In clinical hypothyroidism there is high cholesterol levels in the serum and a marked increase in low density lipoprotein (LDL) due to reduction in the catabolism of LDL by decreasing the number of LDL receptors in the hepatocytes. However, debate is present concerning the fat levels in Subclinical hypothyroidism (SCH) and its importance clinically^{3,4}.

Non-symptomatic individuals having elevated thyroid stimulating hormone level with the presence of normal freeT4 levels are called subclinical hypothyroidism. Subclinical hypothyroidism may be changed to overt hypothyroidism in many patients. Patients of SCH are usually non-symptomatic or complain from minimum symptoms. For this reason, SCH is only a diagnosed by investigations⁵.

Clinical thyroid abnormalities may be suspected due to the presence of thyroid enlargement. This condition is common and may be seen in 6-17% of the people^{6,7}. The presence of SCH is commoner in females more than in males and is estimated to be two times more common. All over the world around 7.5-8.5% of women and 2.8-4.4% of men have SCH. The diagnosis depends on the biochemical analysis which is performed using the chemiluminiscence technique. The normal serum TSH level is 0.4 – 4.5 m IU /L. SCH is one of the causes for coronary

artery diseases, fat derangement, and congestive heart failure.

The causes of coronary artery diseases are classified to non-modifiable risk factors such as age, sex, ethnicity, heredity or family history and modifiable risk factors such as hypertension, hyperglycemia, atrial fibrillation, dyslipidemia, abdominal obesity, smoking, lack of exercise, alcohol consumption. Dyslipidemia is among the modifiable cardiovascular risks because it is associated with diastolic dysfunction, abnormal function of the endothelial cells, decreased elasticity of the arteries, coagulation pathways and increase the C-reactive protein (CRP)^{8,9}.

The cause of this fat-level derangements in patients with clinical and subclinical hypothyroidism involves increase in blood cholesterol level which in turn are caused by alterations in the formation, catabolism, mobilization of fat in hepatocytes and adipocytes. Elevated TSH stimulates the hepatocytes to express hydroxyl-methylglutaryl coenzyme-A-reductase, which causes enhancement in cholesterol formation. In patients with hypothyroidism the most prevalent lipid profile derangement is hypercholesterolemia. Elevated level of the very low density lipoprotein (VLDL) and the high density lipoprotein (HDL) is also seen. The triglyceride level is elevated due to an enhancement of the esterification of various types of fatty acids at the hepatocytes¹⁰.

In a new population-based study subclinical hypothyroidism appears to be an independent risk for the development of atherosclerosis of the aorta and ischemic heart diseases. Peri-menopausal women tend to have similar symptoms to

hypothyroidism, so evaluation of thyroid hormones in such group of patients may diagnose subclinical hypothyroidism which may be missed easily^{11, 12}.

Moreover, subclinical hypothyroidism may change to clinical hypothyroidism. The rate of progression is higher with the simultaneous presence of thyroid peroxidase antibodies or increase levels of TSH. Administration of a low dose of thyroid hormones cause a significant reduction in the level of the total cholesterol, non-HDL, LDL, and LDL to HDL values. Recent clinical evidence also shows that treatment with T4 therapy may improve lipid profile in the cases of subclinical hypothyroidism¹³.

MATERIALS AND METHODS

A total number of 200 individuals were included in this study, 100 patients diagnosed with subclinical hypothyroidism with 100 apparently healthy individuals as a control group (matched for age and gender), from 1st December 2017 to 1st December 2018. This study was done in the endocrine clinic at Azadi General Teaching Hospital in Duhok city and Rizgary Teaching Hospital in Erbil city. An informed consent was obtained from patients after explaining the study project. The detailed history was taken and the clinical examination was done for each patient. Each patient was given a special questionnaire to obtain information.

Inclusion and Exclusion Criteria

Inclusion criteria include patients having subclinical hypothyroidism, when TSH is greater than 5.0 m IU/L and the free-T3, the free-T4 are below the reference range which was done two times at six weeks in between each test result. Exclusion criteria

include patients that have factors that alter thyroid function test such as pregnancy, oral contraceptive pills especially that contain only estrogen, steroids, amiodarone, and phenytoin, liver and kidney diseases, positive personal or family history of thyroid abnormalities, smokers, history of a recent surgical intervention and history of acute illness such as critical illness which causes abnormalities in thyroid hormone levels. Also Patients taking medications that lower the lipid levels have been excluded. In older patients, higher TSH (>6) used to diagnose subclinical hypothyroidism, patients more than 65 years of age have been excluded^{14, 15}.

Definition of Dyslipidemia

Dyslipidemia cut-point is based on the AACE guideline, this include; a total cholesterol desirable less than 200 mg/dl, borderline level high between 200- 239, high level greater than 239 mg/dl. HDL cholesterol: dyslipidemic lower than 40 mg/dl in men and lower than 50 mg/dl in women. LDL cholesterol: Optimal lower than 100 mg/dl, near-optimal between 100–129 mg/dl, borderline high between 130-159 mg/dl, high between 160 -189 mg/dl, very high if greater than 189 mg/dl. The triglycerides level: Normal if less than 150 mg/dl, high if between 150-199 mg/dl, Hypertriglyceridemia when the levels are between 200-499 mg/dl, very high if greater than 499 mg/dl¹⁶.

STATISTICAL METHODS

Statistical analyses were done using the Statistical Package for Social Science (SPSS); *p* values less than 0.05 were considered significant.

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RESULTS

The majority of the patients in the study were between 40-50 years (53%) while 26% of the patients were between 50-60 years. Female patients constitute 53 % of the involved participants. The relation between the level of the TSH and the data

taken from the patients showed a significant relation with the dyslipidemia (p value 0.001) and with the HDL (p value 0.002), while no factor had been found to be related to the TSH level in the control group. Other factors and their relation to the TSH are shown in **Tables 1 and 2.**

Table 1: Relation of TSH Level and the Lipid Profile with the Patients Factors in the Patients Group.

	Dependent factor: TSH level for patients group				
	Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	Beta			Lower Bound	Upper Bound
Age	-.046	-.526	.601	-.653	.379
gender	-.061	-.699	.486	-1.002	.480
Dyslipidemia	.769	8.941	.000	3.156	4.959
Total cholesterol	-.046	-.527	.599	-.017	.010
LDL	-.095	-1.075	.285	-.028	.008
TG	-.016	-.201	.841	-.006	.005
HDL	.293	3.201	.002	.031	.133
Comorbidities	-.149	-1.944	.055	-1.858	.020

Abbreviations: LDL: low density lipoprotein, TG: triglycerides, HDL: high density lipoprotein.
The bold number show the predictors

Table 2: Relation of the TSH Level and the Lipid Profile with the Control Group.

	Dependent factor: TSH level for control group				
	Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	Beta			Lower Bound	Upper Bound
Age	-.077	-.697	.488	-.219	.105
Gender	.058	.513	.609	-.343	.581
Dyslipidemia	.059	.299	.766	-.755	1.022
Total cholesterol	-.434	-1.207	.230	-.027	.007
LDL	.305	.854	.395	-.012	.030
TG	.128	.795	.429	-.003	.006
HDL	-.029	-.206	.837	-.027	.022

The relation between the dyslipidemia and the TSH levels is shown in **Figure 1**, the level of the abnormal lipid profile is

significantly high in patients in whom the TSH levels are higher than 5.

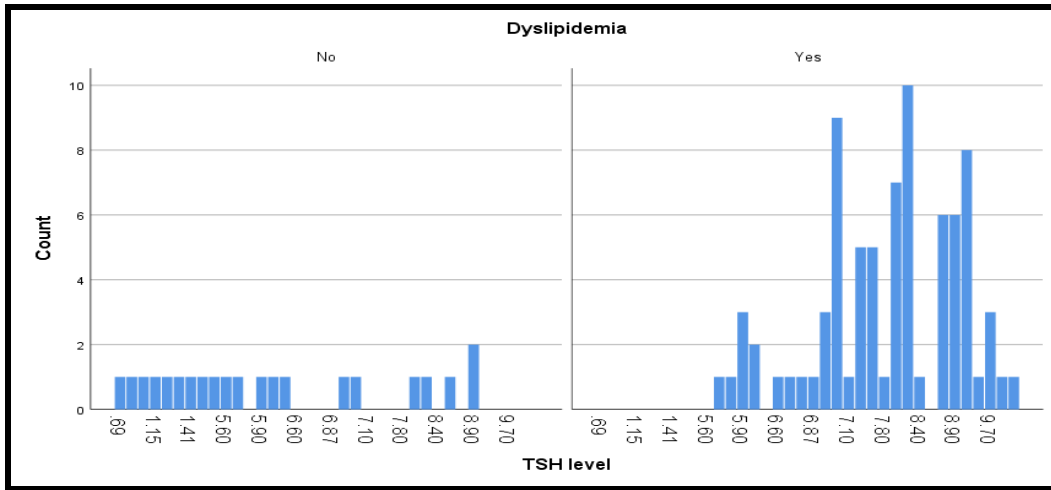


Figure 1: The Relation between the Presence or the Absence of Dyslipidemia and the TSH Level.

The cholesterol and the triglycerides levels tend to be significantly higher in patients

with TSH levels higher than 5, Figures 2 and 3.

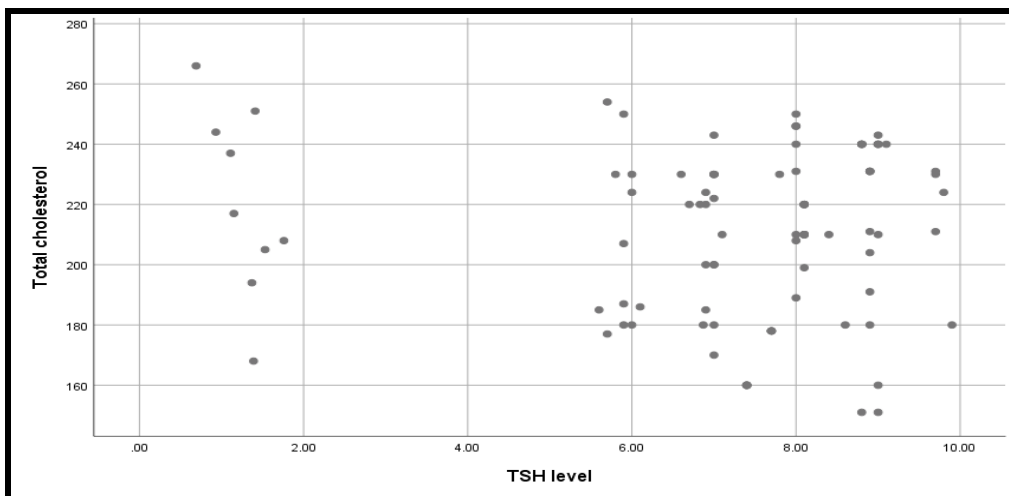


Figure 2: The Relation between the Cholesterol Level and the TSH Level.

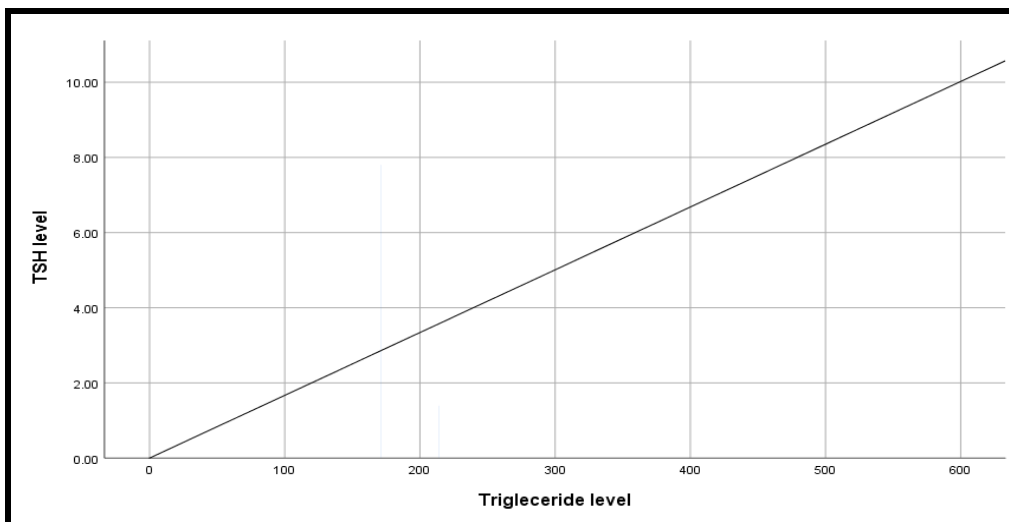


Figure 2: The Relation between the Triglycerides Level and the TSH Level.

DISCUSSION

The presence of SCH increases the risk of development of the clinical hypothyroidism, lipid level derangement, and major cardiac and vascular risk, which include diastolic impairment, coronary artery diseases, cardiac failure and increase in morbidity and death rate. However, SCH may be temporary and improvement may occur with time that is why finding cases, who need management, is a difficult in medical practice¹⁷.

Many authors discovered direct correlation of this abnormality and the development of coronary artery diseases. The presence of abnormal lipid profiles may explain the increased coronary artery events in this population of people because it is direct cause of atherosclerosis. However, numerous articles mention that such relation don't exist¹⁸⁻²¹.

Data from our patients shows a very strong correlation between subclinical hypothyroidism and abnormal lipid profiles as it is found to be commoner in patients with SCH in when compared to the control group (*p* value 0.001 and 0.766) respectively, and this has the same clinical evidence comparing to the findings of numerous other studies worldwide, which also show similar correlation as in our study²².

Further interpretation of dyslipidemic patients; i.e., the cholesterol level and triglycerides level showed a significant increase in their levels when the level of the TSH also get higher. This in accordance to many other studies done in some parts of the globe. LDL level was greater in the patient group when compared to the control group. This relation is found to be statistically not so

significant if its compared to the levels of the HDL which also showed a statistically significant value in the patients group (*p* value of 0.002) but there was no correlation with any of these in the control group. This statistical differences may reflection the pattern of dyslipidemia in the populations of this region and larger population based studies needed to prove or exclude this²³.

Furthermore, evidence emerges that management with thyroid hormones decrease serum lipid levels in patients having SCH which may decrease the morbidities and the mortality from the cardiovascular events, for this reason it is very important to manage patients having SCH and dyslipidemia properly. Even a mild decrease in the cholesterol level of, triglycerides and the LDL may significantly decrease in the cardiac and the vascular morbidity in the future.

Subclinical hypothyroidism is found to be an atherogenic status as it causes dyslipidemia and it enhances the cardiac and the vascular risk. Management of patients having subclinical hypothyroidism with thyroid hormones improves the quality of life and deaths from coronary vascular diseases. It's reasonable to measure the lipid profiles and cardiovascular risk factors in such patients and to manage them with thyroid hormones when it can be applied in clinical practice²⁴.

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پوخته

طهورینه ل شیوی ضهوریین ناظ خوینی دا یا ذیر بینطهیی: طهکولینا لیزانینی یا دوو سهنتهیین جودا

پیشهکی: رهوشین کیم و کوری یا سایروده ردینا ذیر بینطهیی دهیته دانان کو کارتیکنری ل 7,5 تا 8,5 % ذ مییان و 2,8 تا 4,4% ذ نیرهیان دکته نیک ذ سیفتهنن طی کیم و کورییی کیموکاسی و طهورینه ل شیوی ضهوریین ناظ خوینی دایه , ههروهسا طفوطویهکا مهن ههیه سهبارت ظان طهورینا نهری کارتیکنرکا بینطهیی ههیه یان نه. هندهک جار ان نهظ کیمبوونه لئاستی شیوی ضهوری دا دیار دکته نشتی طهورینکرنا هرمونین سایروده ردینا .

نارمانج: نارمانج ذ طی طهکولینی تبطةهشتتا ریذا بهربه لاطبوونا طهورینا شیوی ضهوریین ناف خوینی دا بو وان نهخوشین کو کیم و کوری یا سایروده ردینا ذیر بینطهیی ههیه ل ههردوو باذیرین دهوک و ههولیر ل عیراقی.

ریکین فهکولینی: نهظ طهکولینا رهوش و بهلطهیا لسه 200 کسان هاتیة کرن , ههروهسا دی بهراوردیی دناظبهرا 100 کسین توشبووی ب کیم و کوری یا سایروده ردینا ذیر بینطهیی دطل 100 کسین رهوشا وان یا کلینیکی یا ئاسایی بیت , ههروهسا دی وردهکاری ههیه کرن یا ههردوو طروشان ذ لایی ذی و رهطهزی. نهظ طهکولینه هاتیة کرن ذلایی دوو سهنتهیین جودا ل نهخوشخانا ئازادی یا فیرکرنی لدهوکی و ل نهخوشخانا رزطاری یا فیرکرنی لههولیری , ههریما کوردستانی عیراق . ذ 1 کانینا ئیکي 2017 تا کو 1 کانینا ئیکي 2018.

نهنجام: رهوشین کیموکاسی و طهورینا ل شیوی ضهوریین ناف خینی دا بهلاظتر بوو ل دهف نهخوشین کیم و کوری یا سایروده ردینا ذیر بینطهیی ههیه (ریذا نهطهری 0,000) بهراوردکری دطل طروٹی کونترولکری (ریذا نهطهری 0,766). ریذا کولیسترولی و ضهوریین سیبانه راستهوانه ههطریذهیه دطل ئاستی هرمونین سایروده ردین ل ناظ خوینی دا .

الخلاصة

واجهه الدهون لدى حالات قصور الغدة الدرقية غير السريرية: دراسة خبرة مركزين مختلفين

الخلفية والأهداف: تقدر حالات قصور الغدة الدرقية غير السريرية بأنها تؤثر على حوالي 7.5-8.5% من الإناث و 2.8-4.4% من الذكور. واحدة من سمات قصور الغدة الدرقية غير السريرية هي خلل في واجهة الدهون في الدم ، هناك جدل كبير حول وجود خلل في ملامح الدهون و هل له أهمية سريرية أم لا. تظهر بعض الأدلة انخفاض في مستوى الملف الدهني في الدم بعد الاستعاضة عن هرمونات الغدة الدرقية. الغرض من هذه الدراسة هو تقدير انتشار خلل في ملامح الدهون في الدم لدى المرضى الذين يعانون من قصور الغدة الدرقية الغير السريري في مدينتي دهوك وأربيل ، العراق.

المواضيع و طرق البحث: هذه هي دراسة الحالات والشواهد ، التي اقيمت على 200 شخص. سيتم مقارنة 100 مريض مع قصور الغدة الدرقية الغير السريري مع مجموعة من 100 شخص طبيعى سريريا تتم مطابقة هاتين المجموعتين عن العمر والجنس. الدراسة التي أجريت في مركزين مختلفين و هما مستشفى آزادي التعليمي في دهوك ومستشفى رزكري التعليمي أربيل ، إقليم كردستان ، العراق للفترة من 1 ديسمبر 2017 إلى 1 ديسمبر 2018.

النتائج: كان حالات الخلل في ملامح الدهون في الدم اكثر شيوعا لدى المرضى الذين يعانون من قصور الغدة الدرقية الغير السريرية (القيمة الاحتمالية:0.001) مقارنة مع مجموعة السيطرة(القيمة الاحتمالية:0.766) . مستوى الكوليسترول الكلي ومستويات الدهون الثلاثية يتناسب بشكل طردي مع مستويات هرمون الغدة الدرقية في الدم.

الاستنتاجات: يعتبر قصور الغدة الدرقية الغير سريري سببا لحالات تصلب الشرايين لأنها تزيد من مستوى الكوليسترول ومستويات الدهون الثلاثية. علاج حالات قصور الغدة الدرقية الغير السريري بواسطة هرمونات الغدة الدرقية قد يكون لها تأثير إيجابي على صحة القلب والأوعية الدموية. يجب قياس مستويات الدهون في الدم لتقليل مخاطر القلب والأوعية الدموية لدى هؤلاء المرضى عند ثبوتها سريريًا.