

# Dyslipidemia among Patients with Subclinical Hypothyroidism: A Case Control Study

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## ABSTRACT

**Background:** Thyroid disorders usually associated with lipid abnormalities. Sub clinical hypothyroidism is defined as condition, in which thyroid stimulating hormone concentration is elevated when serum thyroid hormones T3 and T4 are at normal levels.

**Aim:** To find out whether sub-clinical hypothyroidism associated with lipid alteration, and the validity of signs and symptoms according to Zulewski scoring system in diagnosing patients with subclinical hypothyroidism

**Materials and Methods:** Case - control study included 50 newly diagnosed cases of subclinical hypothyroidism patients who fulfill the criteria for the study was included and 100 euthyroid subject proved by biochemical tests who considered to be control group and evaluated by clinical (Zulewski scoring system of hypothyroidism), biochemical parameter including thyroid function test TFTs and lipid profile.

**Results:** Majority of cases were females within the age interval 15-45 years .There was possible association between age group 15-45 years and sub-clinical hypothyroidism although, this association was not significant, females were more presented in both cases and controls with male to female ratio 1:5.25 and 1:2.2 for cases and controls respectively, the mean ages of the females and males cases were 39.46±4.64 and 47.11±6.73 years. Feeling cold and increase weight were the most frequent complains (60% & 52%) respectively. According to Zulewski scoring system this test was proved to has sensitivity and specificity of 64%, 85% respectively, the positive predictive value was 68%, negative predictive value 82.5% and the likelihood ratio was 10.42. Cases with sub-clinical hypothyroidism have an elevated lipid profile for total cholesterol level (P=0.05) and low density lipoprotein and so higher atherogenic index (mean 5.25±1.04),(P=0.000).

**Conclusion:** Atherogenic lipid abnormalities were observed in adult subjects with SCH and Zulewski scoring system can be used in diagnosing subclinical hypothyroidism as it showed high sensitivity and specificity.

**Key words:** thyroid, hypothyroid, sub-clinical hypothyroid, thyroid stimulating hormone, thyroxin, lipid disorder.

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## INTRODUCTION

Hypothyroidism is one of the most frequent endocrine disorders affecting 4.6% of the adult population. 90% of the cases represent subclinical hypothyroidism<sup>(1)</sup>. Sub-Clinical Hypothyroidism (SCH) can be best defined as a high serum thyroid stimulating hormone (TSH) and normal serum total/free thyroxine (T4), triiodothyronine (T3) concentrations associated with few or no symptoms/signs of hypothyroidism. It is referred to as a state of mild thyroid failure and is essentially a laboratory diagnosis<sup>(2,3)</sup>. Laboratory range a TSH value above 10 mU/l is regarded as indication for treatment<sup>(4)</sup>. For values between 4 and 10 mU/l an individualized pragmatic treatment approach based on the presence of clinical signs of hypothyroidism may be justified<sup>(5)</sup>. Some patients however should be treated regardless of their clinical symptoms including women in childbearing age who want to become pregnant<sup>(6)</sup>. Patients with goiter, and patients with history of Graves' disease<sup>(8)</sup>. Subjects with such thyroid disorder do not show particularly symptom of overt hypothyroidism and the patient specifically do not show a clinical picture representing thyroid hormone deficiency and it usually diagnosed on the thyroid function test in the medical diagnostic laboratories<sup>(9)</sup>.

The prevalence SCH has been estimated to be from 1.4% to 8%<sup>(10)</sup>. Subclinical hypothyroidism is more prevalent than most people realize; again, because it is asymptomatic. In recent studies performed across the United States, it is estimated that (on average) roughly 4% of all men and 8% of all women men are sub clinically hypothyroid .However,

these averages rise with age, and it has been estimated that 8% of men over 60 and 15% of women over the age of 60 are sub clinically hypothyroid. In Europe, SCH is more prevalent in areas of iodine sufficiency. Thyroid disorder can be correlated with other metabolic abnormalities among all are dyslipidemia, cardiovascular, liver diseases and anemia<sup>(4)</sup>.

The American Academy of Family Physicians and the American Association of Clinical Endocrinologists recommend periodic assessment of thyroid function in older women.

The American Thyroid Association advocates for more frequent earlier screening, recommending measurement of TSH beginning at age 35 and every 5 years thereafter<sup>(11,12)</sup>. Once diagnosed ,treatment of SCH is recommended by endocrine groups to limit potential risk , given that harm from appropriate therapy is unlikely<sup>(13,14)</sup>. There is consensus on the need to treat subclinical hypothyroidism of any magnitude in pregnant women and women who are contemplating pregnancy, to decrease the risk of pregnancy complications and impaired cognitive development of the offspring<sup>(15)</sup>.

It is universally accepted that overt hypothyroidism associated with elevation of serum lipid profile and total cholesterol. Particularly low density lipoprotein cholesterol <sup>(16)</sup>. The reason why SCH also should be a matter for further investigation, it is due to dyslipidemia which is associated with this type of thyroid disorder with nearly the same pattern of dyslipidemia, but still there are a lot of controversy arguments about whether sub-clinical hypothyroidism constantly and universally associated with lipid disorder<sup>(17)</sup>.

The aim of the present study was to report the trends of different lipids concentration in cases with SCH state and control group, for both sexes and all ages in addition to profile the symptomatology of SCH using Zulewski scoring system and its validity in diagnosing Subclinicalhypothyroidism.

## MATERIALS AND METHODS

After administrative agreement of Nineveh directorate of health , a case control study was conducted in Nuclear &Oncology hospital center & in Ibn –Sina Teaching Hospital in Mosul City over 3 months period from 30<sup>th</sup> June 2011 to 30<sup>th</sup> September 2011.It was carried on a sample of 50 newly diagnosed cases of SCH [Normal free T3 (2.5-3.9 pg/ml) & free T4 (0.61-1.12 ng/dl), TSH more than4.1 IU/ml (cases) and (100) Euthyroid persons who were proved with biochemical tests (controls). Written consent was obtained from each person before participation a special questionnaire which prepared and designed to this study was completed to all cases and control subject participated in this study. A clinical scoring system defined by Zulewski et al. in 1997 <sup>(18)</sup> consists of (12) symptoms and signs of hypothyroidism was used to evaluate the clinical characteristics of the study population.

**Table 1: Zulewski symptoms and signs of hypothyroidism <sup>(18)</sup>**

Symptoms	Present	Absent
Diminished sweating	1	0
Hoarseness	1	0
Paresthesia	1	0
Dry skin	1	0
Constipation	1	0
Impairment of hearing	1	0
Weight increase	1	0
Physical signs	Present	Absent
Slow movement	1	0
Delayed ankle reflex	1	0
Coarse skin	1	0
Per orbital puffiness	1	0
cold skin	1	0
sum of all symptoms and signs present	12	0

The value of total score is given as the sum of the present symptoms and signs.Hence , euthyroid is indicated by a score of (0-2) points , SCH (3-5) and overt hypothyroidism (>5) points . Patients included in the study will be evaluated with clinical (Zulewski scoring system of hypothyroidism ) ,biochemical parameter including thyroid function test TFTs (Total triiodothyronin (TT3 )Total thyroxin (TT4) and Thyroid stimulating hormone(TSH) and serum lipid profile (after at leaser 14 hour fasting) (total cholesterol (TC), low density lipoprotein (LDL-C) ,high density lipoprotein (HDL-C) ,and triglyceride (TG).

All patients who were already on thyroxin, or using drugs which causing dyslipidemia (beta blockers, steroids) or

hypolipidemic drugs and even patients who are not willing to give an informed consent were excluded from the present study .

Odds ratio (OR) was used to determine the presence of association between the event of interest and risk factors; in addition X<sup>2</sup> test and z- test for two means were used to determine the statistical significant .P- value of <0.05 were considered significant in the analysis of the present study<sup>(19)</sup> Validity and reliability of Zulewski score system were calculated too.

## RESULTS

Table 2 shows a possible association between age group 15-45 years and SCH (OR=1.49.), although, this association is not significant (95%CI=0.7537-3.2955). The mean ages of the female and male cases were 39.46±4.64 and 47.11±6.73 years respectively while the mean ages of females and males controls were 42.03±6.64 and 40.74±6.82 years respectively.

Females were found to be predominating in both cases and control with male to female ratio of 1:5.25 and 1:2.2 for cases and controls respectively. The same table shows significant association between SCH and sex (OR =2.36) (95%CI=0.9914 - 5.6118, P=0-05).

**Table 2: Age and sex distribution of the study population:**

Age (years)	Cases		Controls		Total		OR	95% C I	P-value*
	No.	%	No.	%	No.	%			
15-45	3	72%	62	62%	98	66.5%	1.49	0.7537 -	NS
	6								
45-65	1	28%	38	38%	52	33.5%			
	4							3.2955	
<b>Total</b>	5	100%	100	100%	150	100%			
	0								
<b>Sex</b>									
<b>Females</b>	42	84%	69	69%	111	80.67%	2.3	0.9914	0.05
<b>Males</b>	8	16%	31	31%	39	19.33%	6	-	
<b>Total</b>	50	100%	100	100%	150	100%		5.6118	

\*Chi-square test was used.

Based on Zulewski scoring system of hypothyroidism Table 3 depicts that cold skin was the most frequently observed sign which is found in 60 % of the cases followed by Increase weight in 52%, constipation in 46% , slow movement in 26% and parasthesis in 24% of the cases.

**Table 3: Frequency of hypothyroid symptoms and signs based on Zuelwsky scoring system**

Sign & symptoms	No.	%
Cold skin	30	60%
Increase weight	26	52%
Constipation	23	46%
Slow movement	13	26%
Parasthesis	12	24%
Dry skin	10	20%
Delay ankle reflex	8	16%
Hoarsness	6	12%
Deminish sweating	4	8%
Course skin	3	6%
Limitation of hearing	2	4%
Periorbital odema	0	0%

Table 4 shows distributions of cases according to Zulewski score and biochemical test results. The sensitivity and specificity of Zulewski score in diagnosing SCH found to be 64% and 85% respectively. Positive and negative predictive values were 68% and 82.5% respectively and likelihood ratio was 10.42

**Table 4: Distributions of cases according to Zulewski score and biochemical test**

		Biochemical test		Total
		SCH	EU	
Zulewskiscore	Positive	32	15	47
	Negative	18	85	103
Total		50	100	150

Table 5 demonstrates the mean values of biochemical test of TFTs and lipid profile  $\pm 2$  SD for both cases and controls. TSH value was significantly higher in cases ( $P=0.000$ ). It is also showed that the mean values of lipid profile (total cholesterol and low density lipoproteins) of the cases were significantly higher, the same is true for the atherogenic index, ( $P= 0.000$ ) each

**Table 5: Mean values of TFT, lipid profile and atherogenic index**

Parameter		Cases Mean $\pm 2SD$	Controls Mean $\pm 2SD$	P-value*
TFT	T3 (ng/dl)	2.01 $\pm$ 0.63	1.84 $\pm$ 0.52	NS
	T4 (ng/dl)	106.98 $\pm$ 34.13	99.04 $\pm$ 21.14	NS
	TSH (IU/ml)	8.31 $\pm$ 2.59	2.79 $\pm$ 1.81	0.000
Lipid profile	TC (mg/dl)	204.98 $\pm$ 35.35	175.83 $\pm$ 32.56	0.000
	TG(mg/dl)	163.7 $\pm$ 28.123	110.1 $\pm$ 24.52	NS
	HDL(mg/dl)	39.4 $\pm$ 6.05	40.79 $\pm$ 7.7	NS
	LDL(mg/dl)	132.64 $\pm$ 32.57	114.15 $\pm$ 29.37	0.000
	VLDL(mg/dl)	32.38 $\pm$ 19.75	25.89 $\pm$ 18.74	0.05
Atherogenic index		5.25 $\pm$ 1.04	4.32 $\pm$ 0.75	0.000

\*z-test for two means was used.

Comparing SCH cases and controls in relation to the presence or absence of dyslipidemia, (Table 6). Being a cases with SCH have extra odds of having dyslipidemia about two and a half times with a very high significant association ( $OR=2.6, 95\%CI, P=0.009$ ).

**Table 6: Distributions of cases according to Zulewski score and presence or absence of dyslipidemia**

dyslipidemia	Subclinical hypothyroidism		Total	OR	95% CI	P-value*
	Cases	Controls				
Present	32	40	76	2.6	1.32-5.38	0.009
Absent	18	60	74			
Total	50	100	150			

\*Chi-square test was used.

## DISCUSSION

Subclinical hypothyroidism is a common condition characterized by supranormal thyroid-stimulating hormone TSH levels, suggesting a mild impairment of a thyroid hormone effect at the tissue level; despite free thyroxine i.e. FT4 levels in the normal range.<sup>(3)</sup> In the present study SCH is more common in the age group of 15-45 years which constitute 72% of cases comparing to the age group 45-65 years old (28%), and 84% of the cases were females and 16% were males, this result is consistent with the results obtained by study done in Mosul city by AL- Shahiry (20). It is also consistent with the result obtained by Ebadi and Afshar<sup>(21)</sup>.

The nature and degree of dyslipidemia in overt hypothyroidism has been demonstrated in many studies and there is no doubt about the beneficial effects of thyroid substitution on serum lipids and on the risk for CAD, However, the possible effects of subtle alterations of thyroid function on lipid profile and atherogenesis remain controversy<sup>(22)</sup>. The present study found that cases with SCH comparing with euthyroid control subjects have higher lipid profile. These results were consistent with the results obtained from a case control study conducted in Greece in 2001 by Efstathiadou and pearson<sup>(23)</sup>. It is also consistent with a cross sectional study done in coastal Andhra Pradesh India in 2011 by Shekhar1 et al.<sup>(24)</sup>, and in USA<sup>(25)</sup> It is also agree with the results of cross sectional study done in South Carolina America in 2004 by Huesten. et al.<sup>(26)</sup>, But Rotterdam study report that total cholesterol was not elevated in SCH<sup>(27)</sup>. and also in Saudia Arabia<sup>(28)</sup>.

Zulewski et al. (18) designed a symptom rating score based on the Billewicz index to evaluate symptoms and signs in the new thyroid function-testing era. Fourteen symptoms and signs of hypothyroidism, were evaluated in 332 subjects 50 with overt hypothyroidism, 93 with SCH and 189 euthyroid controls based on TSH assays. Using this score, 62% of overtly hypothyroid patients were correctly diagnosed as compared to 42% with the Billewicz index<sup>(29)</sup>. Similarly, 24% of SCH patients were classed as overtly hypothyroid (Billewicz index 6%). This score showed correlation with free thyroid hormone levels but not with TSH in overtly hypothyroid patients. In SCH patients, there was positive correlation with free thyroxine and TSH levels. This score is currently useful in helping to evaluate overt hypothyroidism clinically but is less helpful in the context of SCH. It also carries the inconvenience of a trained clinician asking patients about 12 symptoms and examining them for five signs<sup>(29)</sup>. In this study Zulewski scoring system was used in patients with SCH. Patients with SCH either have no apparent or few of clinical features of overt hypothyroidism<sup>(15)</sup>.

This study showed that 60 % of the patients presented with cold skin and 52% with increase weight , constipation was found in 46%, parasthesis in 24%, dry skin in 20% , course skin in 6% and periorbital edema was not found. These result is somewhat differ from that obtained from a study done by AL-Shahiry<sup>(20)</sup>, where it revealed that parasthesis was at the top of list (59%) followed by puffiness in 51%, increased weight in 17% and coarse skin was not found. These variations may be due to in part to the difference in the sample size.

In the present study Zulewski test has a sensitivity of 64%, specificity (85%) , positive predictive value (PPV) (86%) , negative predictive value (NPV) (82%) and the likely hood ratio was equal to 10.42 which means that a positive test result is ten times likely to occur in a patient with SCH than in control euthyroid subject<sup>(29)</sup>. These results are almost consistent with other studies (taking into consideration that in the present study the sensitivity, specificity, PPV and the NPV of the whole Zulewski score was calculated not for each single sign or symptom). AL- Shahiry<sup>(20)</sup>; showed that the sensitivity was 12.6%-68.5% for coarse skin and parasthesis ; respectively . Also it is consistent with the high rang of sensitivity which is reported by Zulewski et al. in 1997<sup>(18)</sup> who reported 22%-77% for hearing impairment and ankle reflex relaxation time respectively , and in contrary to the result of Canaries et al. <sup>(25)</sup>who found a range of sensitivity 2.9-28.3% for deeper voice and drier skin respectively. This difference may be due to the difference in the sample size.

On the other hand , high value of specificity of Zulewski scoring in the present study was reported in different studies as Zulewski et al. <sup>(18)</sup> their range of specificity was 42.5%-98.7% for pulse rate and slow movement respectively and AL-Shahiry<sup>(20)</sup> (56.3-100%) for parasthesis and coarse skin respectively. While Canaries et al. <sup>(30)</sup> showed a range of specificity of 74.7%-97.6% for drier skin and deeper voice respectively.

The same thing applied to the high value of PPV and NPV in the present study which are almost consistent with the result of Zulewski et al., 1997<sup>(18)</sup> (50.2- 96.5%) for PPV for pulse rate and slow movement respectively and 70% NPV (excluding cold intolerance and bradycardia).

## CONCLUSIONS

Atherogenic lipid abnormalities were observed in adult subjects with SCH, Majority of cases are female within the age interval 15-45 .Zulewski scoring system can be in diagnosing subclinical hypothyroidism as it showed high sensitivity and specificity.

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