

# Dyslipidemia in Subclinical Hypothyroidism: A Case-Control Study

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## Abstract

Subclinical hypothyroidism (SCH) affects 7.5-8.5% of women and 2.8-4.4% of men. Overt hypothyroidism is characterized by dyslipidemia, however controversy persists regarding the lipids level in SCH and its clinical significance. Recent evidence shows that T4 replacement therapy may improve lipid profile. The aim of this study is to assess the prevalence of dyslipidemia in SCH, this first study to assess dyslipidemia among patients with SCH in Duhok, Iraq is a case-control study, comparing 60 patients diagnosed with subclinical hypothyroidism to 60 healthy individuals (matched for age and gender). The study conducted at the endocrine clinic at Azadi Teaching Hospital in Duhok Governorate, Kurdistan Region, Iraq from 1<sup>st</sup> June 2016 to 1<sup>st</sup> June 2017. Dyslipidemia was much more prevalent in patients with SCH compared to control group ( $p < 0.001$ ). In further analysis of dyslipidemia total cholesterol and triglyceride levels were statistically higher among cases in comparison to controls ( $p < 0.001$ ) for both. LDL level was higher among cases in comparison to controls but did not reach statistical significance ( $p = 0.087$ ). While there was significant difference regarding HDL level among female gender cases and controls ( $p = 0.003$ ), there was no significant difference regarding difference in HDL level among male gender cases and controls ( $p = 0.653$ ). SCH is considered atherogenic condition as it increases dyslipidemia and it increases overall cardiovascular risk. It's important to assess lipid profile and CVS risk in these patients and to treat with levothyroxine when it's clinically applicable

**Keywords:** Dyslipidemia, Subclinical hypothyroidism (SCH), Case control study.

## Introduction

Thyroid disorders may occur at any stage of life. They are more commonly encountered in the mid age and adulthood. Thyroid hormones influence nearly all major metabolic pathways. Their most obvious and well-known action is the increase in basal energy expenditure obtained by acting on protein, carbohydrate and lipid metabolism. The lipid metabolism is more influenced by the thyroid hormone [1]. Thyroid hormones are of vital importance in maintaining the initial level of phospholipids in cell membranes and fatty acids composition of the lipids [2]. Tri-iodothyronine (T3) plays a critical role in lipid metabolism by regulating genes involved in lipogenesis and lipolysis [3, 4].

Hypothyroidism results from reduced secretion of both thyroxine (T4) and T3. Biochemically decrease in T4 and T3 concentrations leads to increased serum thyroid stimulating hormone (TSH) level [5,6]. Overt hypothyroidism is characterized by hypercholesterolemia and a marked increase in LDL because of a decreased fractional clearance of LDL by a reduced number of LDL receptors in the liver. However controversy persists regarding the lipid levels in subclinical hypothyroidism (SCH) and its clinical significance [1,7].

Asymptomatic patients with raised TSH and normal FT4 concentration are known as subclinical hypothyroid. SCH is mild thyroid disorder if left untreated leads to overt hypothyroidism in many cases. Patients of SCH are mostly asymptomatic or have minimal symptoms. Thus, SCH is solely a laboratory diagnosis [5]. Although clinical diagnosis of thyroid dysfunction is suspected by the presence of a small goiter [8]. It is a common condition affecting 6-17% of the general population [9].

The incidence of SCH is more common in women than men, almost twice [10]. Worldwide prevalence of SCH is found to be 7.5-8.5% in women and 2.8-4.4% in men [11]. The diagnosis is based upon biochemical testing which is done by chemiluminescence technique. The normal TSH range is 0.4 – 4.5 mIU/L TSH [5].

Subclinical hypothyroidism is a risk factor for increased incidence of coronary events, increased rates of congestive heart failure and lipid abnormalities. Dyslipidemia is one of many modifiable and non-modifiable cardiovascular risk factors like diastolic hypertension, impaired endothelial function, increased arterial stiffness, and coagulation parameters and elevated C-reactive protein levels are associated with subclinical hypothyroidism [11].

The Pathophysiology lies behind the lipid alterations of overt and SCH includes elevations in serum total cholesterol due to changes in the synthesis, metabolism, and mobilization of lipids in liver and adipose tissue. High TSH level induces the hepatic expression of hydroxy methyl glutaryl coenzyme A reductase, which results in increased cholesterol synthesis [12]. In hypothyroid patients the most frequent lipid abnormality is

hypercholesterolemia. Elevation of very low density lipoproteins (VLDL) and high density lipoproteins (HDL) have also been reported. Plasma triglycerides are increased because of an enhanced esterification of fatty acids at hepatic level [1].

In recent population based surveys SCH emerged as an independent risk factor for aortic atherosclerosis and myocardial infarction [13, 14]. Many of the perimenopausal symptoms are similar to symptoms of hypothyroidism, so evaluation of thyroid profile in these patients might show the presence of SCH which can be masked by perimenopausal symptoms[15].

Moreover, SCH may progress to overt hypothyroidism. The rate of progression is higher with the concomitant presence of thyroperoxidase antibodies or higher levels of TSH [16]. After treatment with small doses of levothyroxine there was a significant decrease of total cholesterol, non-HDL-C, LDL-C, and LDL-C to HDL-C values [17]. Recent evidence also shows that T4 replacement therapy may improve lipid profile in the cases of SCH[18].

## Patients And Methods

The population of this case control study consisted of a total 120 individuals, 60 patients diagnosed with SCH, while 60 healthy individuals in control group (matched for age and gender), from 1<sup>st</sup> June 2016 to 1<sup>st</sup> June 2017, who come for follow up in the endocrine clinic at Azadi General Teaching Hospital. The informed consent was taken from every patient after full explanation of the study; this all was performed under medical ethics. The detailed history of all such patients was taken and complete physical and relevant clinical examination was performed. A specially-designed questionnaire was used to obtain information from participants.

The study included patients who fulfill criteria of SCH, when TSH is more than 5.0 mIU/L and free T3, free T4 are at the lower end of the reference range repeated twice at least 6 weeks apart. While exclusion criteria include any factors altering TFT[19] which include; pregnancy, drugs like estrogen-containing oral contraceptives, amiodarone, phenytoin and steroids, liver and renal disorders, previous Thyroid disorders or family history of thyroid diseases, smoking, history of recent surgery [20] and history of acute illness as critical illness is often associated with alterations in thyroid hormone concentrations in patients with no previous history of thyroid disease[21, 22]. Patients on lipid lowering agents were not included. Those patients who are older in age, higher TSH (>6) used to define SCH, while patients older than 65 years excluded from study.

Dyslipidemia cut points based on AACE guidelines [23] which includes; total cholesterol desirable < 200 mg/dl, Borderline high 200- 239, High > 239 mg/dl. High density lipoprotein -cholesterol: dyslipidemic Low < 40 mg/dl in males, <50 mg/dl in females. Low density lipoprotein -cholesterol: Optimal < 100 mg/dl, near optimal 100–129 mg/dL, Borderline high 130-159 mg/dl, High 160 -189 mg/dl, very high > 189 mg/dl. Triglyceride: Normal < 150 mg/d, High 150-199 mg/dl, Hypertriglyceridemic 200-499 mg/dl, very high > 499 mg/dl.

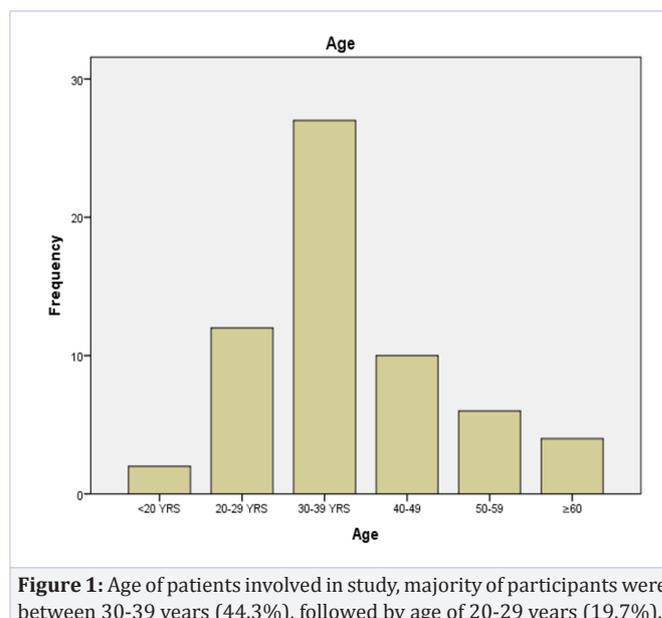
All data were analyzed using the Statistical Package for Social Science (SPSS); Spearman's correlation test was used for comparison of IGF1 levels before and after treatment, while paired student t-test was used to assess differences in GH between the groups. P values less than 0.05 were considered significant. All data were analyzed using the Statistical Package for Social Science (SPSS); Significance of association between various risk factors was assessed using Chi-square test. Level of statistical significance was set at < 0.05.

## Results

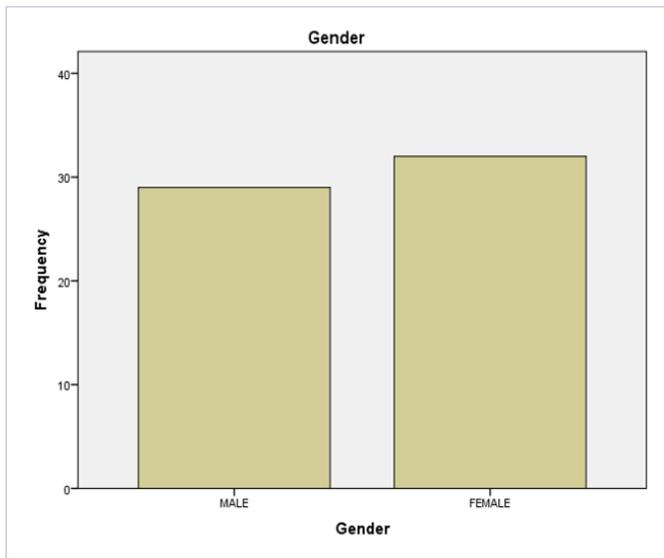
The median age of patients at presentation was 47.3 (SD of 9.9), with majority of patients between 30-39 years as shown in Figure 1. Male constitutes 32 (52.5%), female constitutes 29 (47.5%) as shown in Figure 2. majority of patients have no co morbidities (97%), while 3% of cases have associated DM as shown in Figure 3.

Prevalence of dyslipidemia as general was higher among subclinical hypothyroidism cases (TSH>5) in comparison to control group (TSH≤5) (p<0.001), dyslipidemia was increased as level of TSH increased as shown in Figures 3, 4 and 5. In further analysis of dyslipidemia total cholesterol level was statistically higher among cases in comparison to controls (p<0.001) as shown in Figure 6. LDL level was higher among cases in comparison to controls, however it didn't reach statistical significance (p=0.087) as shown in Figure 7. Triglyceride level was also statistically higher among cases in comparison to controls (p<0.001) as shown in Figure 8: Prevalence of high triglyceride level among cases (TSH>5) and Controls (TSH≤5) (p<0.001).

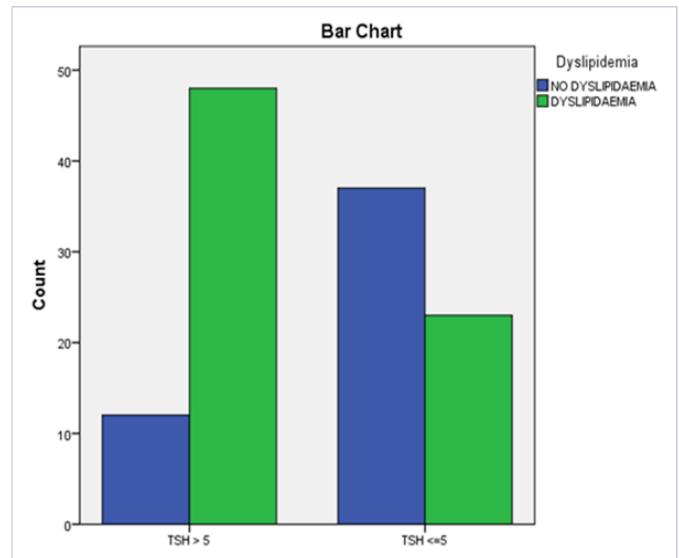
Regarding HDL there was gender difference, as there was no significant difference regarding difference in HDL level among male gender cases and controls (p=0.653), as shown in Figure 9, while there was significant difference regarding HDL level among female gender cases and controls (p= 0.003), as shown in Figure 10.



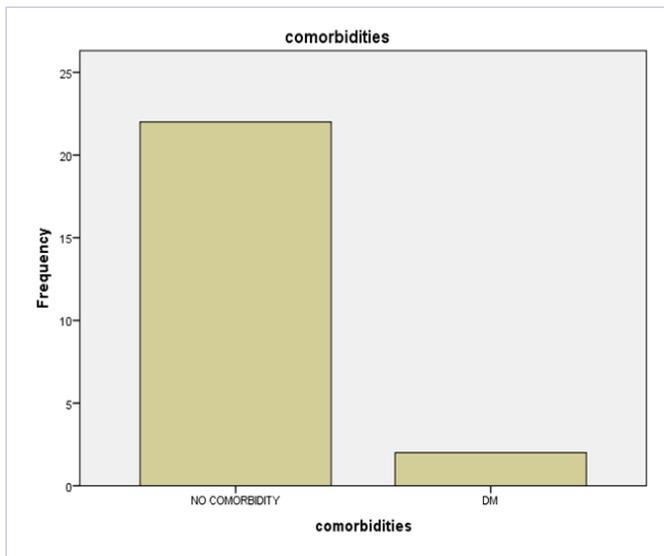
**Figure 1:** Age of patients involved in study, majority of participants were between 30-39 years (44.3%), followed by age of 20-29 years (19.7%).



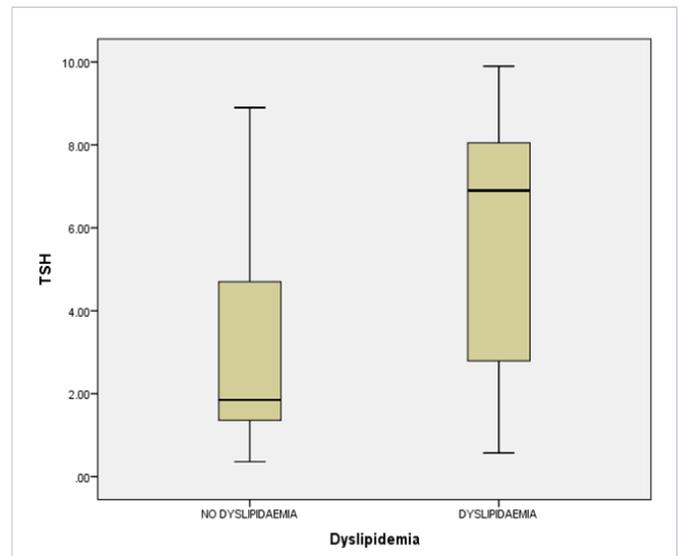
**Figure 2:** Gender of patients involved in study, male constitutes 32 (52.5%), female constitutes 29 (47.5%).



**Figure 4:** Prevalence of Dyslipidemia among cases (TSH>5) and Controls (TSH≤5) (p<0.001).



**Figure 3:** Co morbidities associated with subclinical hypothyroidism, majority of patients have no co morbidities (97%), while 3% of cases have associated DM.



**Figure 5:** Dyslipidemia prevalence according to TSH level, the prevalence of dyslipidemia increased as level of TSH increased.

## Discussion

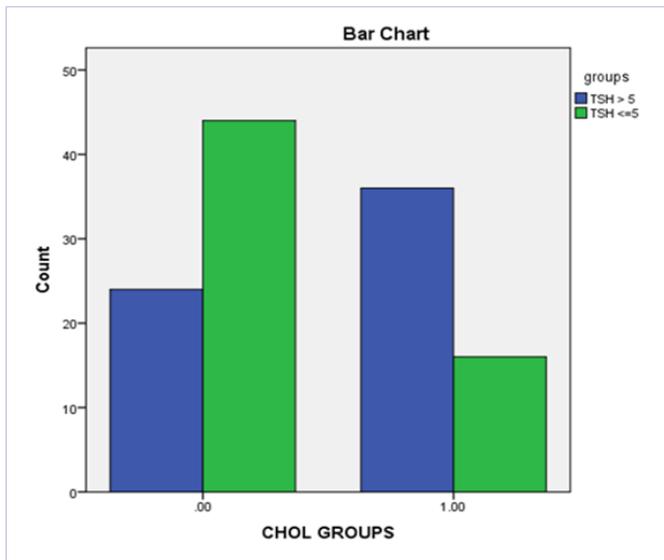
Consequences of SCH include risk of progression to overt hypothyroidism, dyslipidemia, and adverse effects on cardiovascular system, which include diastolic dysfunction, ischemic heart disease (IHD), heart failure and the overall increase in mortality. SCH can be transient and full recovery occurs subsequently [24-27], therefore, careful patient selection is crucial, and treatment is a real challenge in clinical practice.

There are many studies which found positive relation between SCH and IHD[28-35], the presence of dyslipidemia may be one of explanations of higher incidence of IHD in this group of patients, as it is well known that dyslipidemia predispose to atherosclerosis. However there are many studies which did not

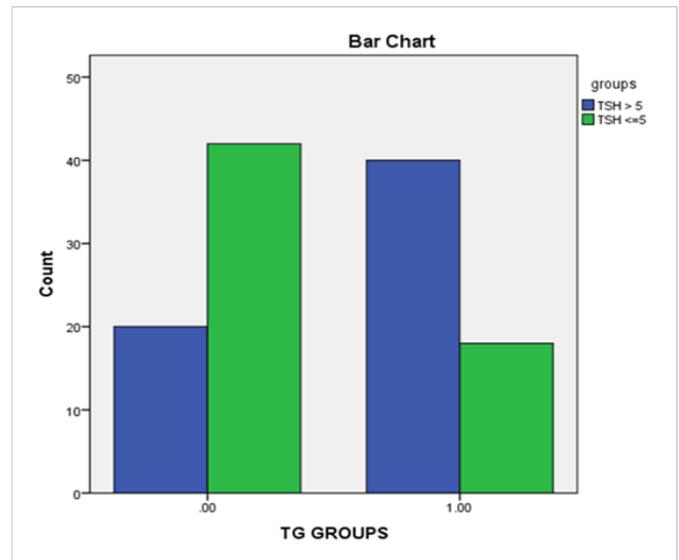
find a positive correlation between SCH and dyslipidemia[16, 36, 37].

Our study shows a strong association between SCH and dyslipidemia as dyslipidemia was much more prevalent in patients with SCH in comparison to control group and this was in accordance with results of many other studies, which also find the same[38-43].

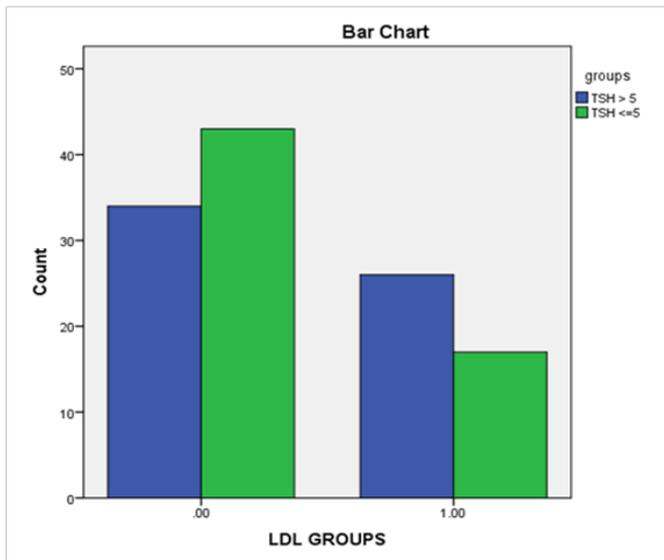
In further analysis of dyslipidemia total cholesterol and triglyceride levels were statistically higher among cases in comparison to controls for both, this in accordance to many other studies[44]. LDL level was higher among cases in comparison to controls; however it did not reach statistical significance. While there was significant difference regarding HDL level among female gender cases and controls, there was no significant



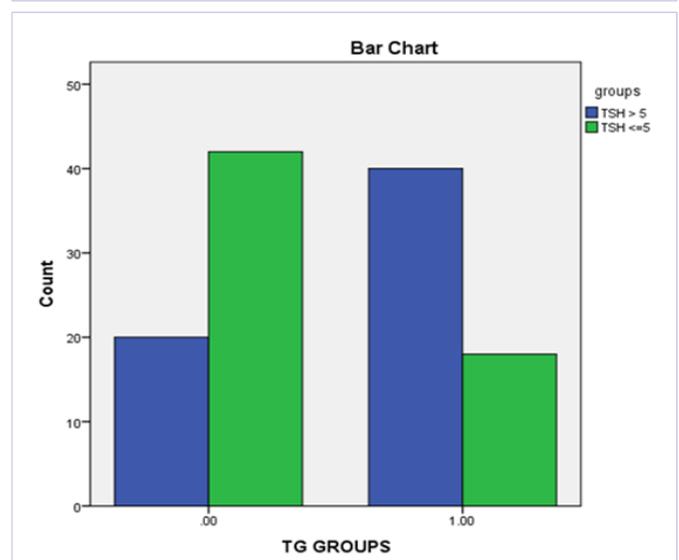
**Figure 6:** Prevalence of high total cholesterol level among cases (TSH>5) and Controls (TSH≤5) (p<0.001).



**Figure 8:** Prevalence of high triglyceride level among cases (TSH>5) and Controls (TSH≤5) (p<0.001).



**Figure 7:** Prevalence of high LDL level among cases (TSH>5) and Controls (TSH≤5) (p = 0.087).



**Figure 9:** Prevalence of high HDL level among male gender cases (TSH>5) and Controls (TSH≤5) (p = 0.653).

difference regarding difference in HDL level among male gender cases and controls, this may be reflection on the difference in pattern of dyslipidemia in Iraqi populations.

Furthermore there is emerging evidence that treatment with thyroxin lowers serum lipid in SCH that is why it is important to treat cases of SCH with dyslipidemia. Even small reductions in levels of total cholesterol, triglyceride, and LDL result in significant reduction in cardiovascular morbidity[45, 46].

## Conclusion

In conclusion, SCH is considered atherogenic condition as it increases dyslipidemia and it increases overall cardiovascular risk. Treatment of SCH with levothyroxine improves quality of life, dyslipidemia, and overall cardiovascular risk. It is reasonable to assess lipid profile and CVS risk in these patients and to treat

with levothyroxine when it's clinically applicable.

## Acknowledgements

### Compliance with Ethical Standards

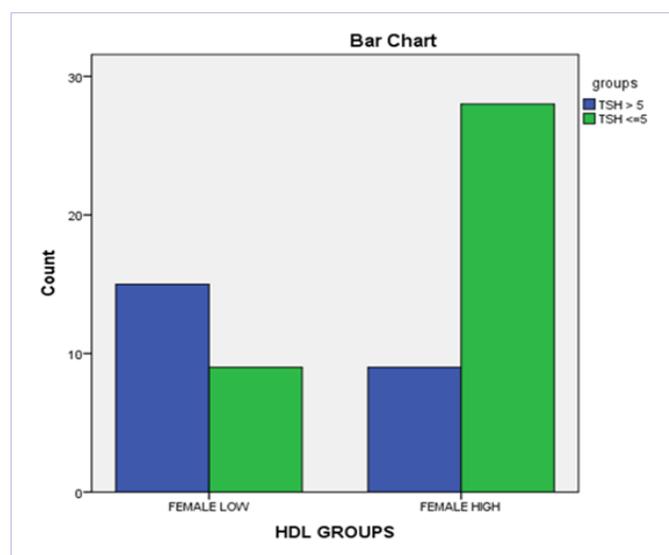
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### Disclosure

The authors declare that they have no conflict of interest.

### Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.



**Figure 10:** Prevalence of high HDL level among female gender cases (TSH>5) and Controls (TSH≤5) ( $p = 0.003$ ).

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