Are hsCRP Levels and LDL/HDL Ratio Better and Early Markers to Unmask Onset of Dyslipidemia and Inflammation in Asymptomatic Subclinical Hypothyroidism?

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Abstract The implications of subclinical hypothyroidism (SCH) are many amongst which the most important is progression to overt hypothyroidism. Other debatable aspects are its association with cardiovascular risk, neuromuscular and psychiatric dysfunction, increased predisposition to developing metabolic syndrome and an underlying pro-inflammatory state. We aimed to study the lipid profile, lipoprotein(a) [Lp(a)] and hsCRP levels and insulin resistance in a group of patients with SCH in a referral hospital and see if any significant differences exist between them and euthyroids. This is a case–control study where the selection of controls and cases was based on the thyroid profile. Subjects were selected on their visit to clinical biochemistry lab for thyroid function tests. 33 euthyroids were taken as controls (Group I) and 38 patients comprising of subclinical hypothyroids were grouped as cases (Group II). Serum thyroid stimulating hormone (TSH) was in the range of 0.5–5.0 mIU/L for euthyroids and for subclinical hypothyroids the concentration of TSH was more than 5 mIU/L. The concentration of tri-iodothyronine (T_3) and thyroxine (T_4) were in normal reference range in both the groups. Individual lipid profile parameters failed to show a significant p value between cases and controls. The LDL/HDL ratio was highly significant (p value < 0.0001) and hsCRP was also statistically between the two groups

(p value = 0.0054). Lp(a) and insulin resistance did not differ significantly. SCH is a common disorder that frequently progresses to overt hypothyroidism. This study underlines the importance of LDL/HDL ratio rather than measurement of individual lipid profile parameters in bringing to light the dyslipidemic state associated with SCH. Moreover the use of hsCRP to detect an underlying pro-inflammatory state in SCH can also be emphasized.

Keywords Subclinical hypothyroidism · Lipid profile · LDL/HDL ratio · hsCRP

Introduction

Subclinical hypothyroidism (SCH), also known as mild thyroid failure is defined as peripheral thyroid hormones T_3 and T_4 within their reference ranges with the presence of elevated thyroid stimulating hormone (TSH) [1]. There may be few or no associated symptoms suggestive of hypothyroidism. SCH was described in early 1970's after TSH estimation became routine. It is a more common problem than overt hypothyroidism with a prevalence of 3–8 % in the adult population. This prevalence increases with age and is more common in women [2]. Many studies have been conducted worldwide to see if SCH progresses to overt hypothyroidism [3, 4]. The cardiovascular mortality, endothelial dysfunction, underlying inflammation, neuromuscular and psychiatric disturbances, adverse fetal effects in a pregnant subclinical hypothyroid female, association with metabolic syndrome are all debatable aspects as many different studies have given contradictory results [5–16]. SCH is more of a laboratory diagnosis rather than a clinical one [17]. The importance of studying this entity is that it is more common than overt hypothyroidism and there are high chances of its

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progression to hypothyroidism especially if anti-TPO antibodies are positive [4]. Moreover early treatment of SCH may prevent its progression and also reduce morbidity and mortality due to associated pathologies. The aim of the present study was to see if euthyroids and subclinical hypothyroids differed significantly with respect to their lipid profile, Lipoprotein(a) [Lp(a)] and hsCRP levels. Insulin resistance was also compared between the two groups.

Materials and Methods

Thirty-three patients comprised the control group (Group I). These were euthyroids with their TSH levels in the range of 0.5–5.0 mIU/L. The peripheral thyroid hormones, free thyroxine (FT₄) and free tri-iodothyronine (FT₃) were in the normal range. The cases taken were 38 in number and comprised of subclinical hypothyroids (Group II). The TSH levels in this group was more than 5.0 mIU/L and the peripheral thyroid hormones were in the normal range. Thyroid hormones were estimated by the principle of electro-chemiluminescence.

Only freshly diagnosed cases with no history of any prior medication for any pathology pertaining to thyroid were taken. The mean age was 45 ± 11.7 for Group I and 46 ± 10.8 for Group II. Group I had a total of 12 males and 21 females whereas in Group II the number of males and females were 15 and 23 respectively. Age, sex and body mass index (BMI) were statistically matched for both the groups. Patients with history of diabetes mellitus, obesity (BMI > 30 kg/m²), any other acute or chronic illness and previous history of thyroid disorder were excluded from the study. Subjects with a history of drug intake affecting thyroid or lipid profile were excluded from the study. A fasting blood sample was taken and serum separated after centrifugation and stored at -80°C . This was later analysed for lipid profile parameters which included total cholesterol, triglycerides, HDL and LDL. These were done on automated analyser Olympus AU400 by colorimetric method. HDL and LDL were estimated by the direct assay method. Apart from this fasting blood sample was taken in a sodium fluoride-potassium oxalate vial for estimation of sugar and plasma stored after centrifugation at -80°C . Lp(a) was done by ELISA (DRG International Inc., USA). ELISA was done for hsCRP estimation (Diagnostics Biochem Canada Inc.). Insulin levels were measured on Elecsys 2010 (Roche diagnostics) by the principle of electro-chemiluminescence. Insulin resistance was calculated using HOMA-IR.

Statistical Analysis

Statistical analysis was done by SPSS statistical software (SPSS 11.0 for Windows, standard version). The results

were presented as mean $\pm$ standard deviation (SD). Student's *t* test, and Mann–Whitney tests were used for comparison between cases and controls. A *p* value of <0.05 was considered statistically significant.

Results

A total of 33 subjects were taken as controls (Group I) on the basis of their thyroid function tests (TFT). This group had their TFT's within normal reference range i.e. TSH: 0.5–5.0 mIU/L; FT₃: 3.1–6.8 pmol/L; FT₄: 12–22 pmol/L. 38 subjects who were categorised as subclinical hypothyroids (Group II) were taken as cases. Their TSH was more than 5.0 mIU/L. Their peripheral thyroid hormone concentration was in the normal range. Amongst the lipid profile parameters none showed any significant statistical difference between the two groups. Lp(a) also did not differ significantly. No significant difference was noted in insulin resistance values amongst the two groups. Only LDL/HDL ratio and hsCRP showed significant statistical difference between the two groups (*p* value <0.0001 and 0.0054 respectively). The observations made in this study are given below in Tables 1, 2 and 3.

Discussion

SCH is more common than overt hypothyroidism and is being diagnosed more frequently in the recent times [18]. Despite this, the clinical significance of this disorder is still debatable. A controversy still exists regarding routine screening of SCH so as to prevent its progression to overt hypothyroidism [19]. Other debatable aspects about which definitive conclusions are yet to be drawn include the associated dyslipidemic state, cardiovascular risk, neuromuscular and psychiatric dysfunction, underlying proinflammatory state, adverse effects on fetal well being etc.. Moreover there is no consensus on the cut off value of TSH at which treatment should be contemplated [20, 21].

Two large population based studies have provided epidemiological data about SCH. The Wickham survey was conducted in Wickham, County Durham in 1975 with a total of 2,799 subjects who were representative of the Great Britain population in terms of age, gender and social class [22]. 20 years later a follow up was conducted on subjects still alive and following conclusions were made. SCH was defined as TSH of more than 6 mIU/L and it was identified in 7.5 % of females and 2.8 % of males. TSH levels did not vary in males with age but increased markedly in females after 45 years of age. Values of TSH above 2 mIU/L in 1975 increased the probability of developing hypothyroidism, and that was even more likely in the presence of antithyroid antibodies.

Table 1 Table showing values for different parameters in controls (euthyroids)

Group I/controls/euthyroids						
Parameters	N	Mean	SD	Median	Minimum	Maximum
Total cholesterol	33	171.75	37.68	169.00	94.00	255.00
Triglycerides	33	108.15	34.62	113.00	57.00	185.00
LDL	33	104.45	30.71	105.00	45.00	184.00
HDL	33	47.24	10.93	48.00	24.00	67.00
LDL/HDL	33	2.25	0.58	2.23	0.88	3.60
Total cholesterol/HDL	33	3.17	0.67	3.68	1.78	5.00
Lp(a)	33	75.36	6.98	78.00	60.00	82.00
FBS	33	100.63	21.09	99.00	58.00	162.00
Insulin	33	11.32	11.81	8.24	0.97	62.47
Insulin resistance	33	3.08	3.44	1.95	0.23	16.6
hsCRP	33	3464.69	2173.68	3200.00	360.0	7000.00
TSH	33	2.8	1.31	3.37	0.52	4.6
FT ₄	33	16.47	1.73	16.92	13.05	19.03
FT ₃	33	5.04	0.74	5.10	3.30	6.35

Table 2 Table showing values for different parameters in cases (subclinical hypothyroids)

Group II/cases/subclinical hypothyroids						
Parameters	N	Mean	SD	Median	Minimum	Maximum
Total cholesterol	38	180.55	50.32	190.00	74.00	272.00
Triglycerides	38	123.52	61.65	122.50	43.00	311.00
LDL	38	108.71	40.32	107.00	20.00	179.00
HDL	38	45.97	8.52	45.50	35.00	69.00
LDL/HDL	38	6.09	4.05	4.95	1.29	14.58
Total cholesterol/HDL	38	3.96	1.0312	4.13	1.80	6.62
Lp(a)	38	75.50	7.41	78.00	55.00	88.00
FBS	38	108.39	22.31	102.50	77.00	184.00
Insulin	38	10.20	7.01	8.37	0.85	35.30
Insulin resistance	38	2.80	2.38	2.11	0.24	13.36
hsCRP	38	5047.36	2101.59	5400.00	320.00	10000.00
TSH	38	8.248	4.32	6.59	5.10	23.00
FT ₄	38	14.18	1.67	14.10	12.00	17.90
FT ₃	38	4.71	0.569	4.73	3.11	6.2

Table 3 *p* Value of all measured parameters (euthyroids vs. sub-clinical hypothyroids)

Parameters	<i>p</i> Value
Total cholesterol	0.186; <i>t</i> = 1.33
Triglycerides	0.33; <i>t</i> = 0.9
HDL	0.55; <i>t</i> = 0.587
LDL	0.39 <i>z</i> = 0.85
Cholesterol/HDL	0.08 <i>t</i> = 1.77
LDL/HDL	<0.0001 <i>t</i> = 4.97
hsCRP	0.0054 <i>z</i> = 2.77
Insulin resistance	0.7419 <i>z</i> = 0.32

p < 0.05 is significant

Another study, National Health and Nutrition Examination survey III (NHANES III), comprised 16,353 subjects; age ≥ 12 years was conducted amongst the US population [23]. SCH was found in 4.3 % of this population and thyroid peroxidase antibodies (TPOAb) were significantly associated with thyroid failure and were more prevalent in women and the frequency increased with age.

Many studies have also highlighted the fact that serum TSH was the most powerful predictor of the outcome of spontaneous SCH over a period of time. TSH value of more than 4 mIU/L and the presence of thyroid autoantibodies had very high chances of progression to overt hypothyroidism [24–26].

The relationship between SCH and serum lipids remains controversial. In several cross sectional studies, SCH was found to be associated with a variable and somewhat inconsistent increase in total cholesterol, LDL-C, higher levels of oxidised LDL-C and inconsistent changes in serum HDL-C. Moreover this abnormal lipid pattern was observed in individuals with a serum TSH value greater than 10 mIU/L [27–29]. Bakker et al. [30] found a positive correlation between TSH and LDL-C concentrations in euthyroid subjects with insulin resistance. In the Whickham survey, SCH was not related to hyperlipidemia [31]. In the NHANES III, mean cholesterol levels were higher in SCH subjects as compared to euthyroids but no difference was seen in LDL-C or HDL-C. However when adjustments were made for age, sex and lipid lowering drugs, SCH was not related to increased cholesterol levels [32]. In the Rotterdam study, total cholesterol was lower in SCH women than in euthyroid women [33]. Similar data were reported in the Nagasaki study [34]. In the New Mexico Elder Health Survey, there were no differences in total cholesterol, HDL-C, or triglycerides between patients with a serum TSH level below 4.6 mIU/L and those with serum TSH between 4.7 and 10 mIU/L. The levels of LDL-C and HDL-C were higher among women with a serum TSH greater than 10 mIU/L than in euthyroid women, although the difference was not significant [35]. In a large population based study (2,799 adults, 70–79 years), TSH levels were stratified to establish a cut off for the relationship between TSH and serum lipids. A serum TSH level above 5.5 mIU/L was associated with a cholesterol increase of 0.23 mmol/L (10 mg/dL). In a cross sectional study of middle aged patients, Bindels et al. [36] estimated that after correction for age, an increase of 1 mIU/L in serum TSH was associated with a rise in serum cholesterol of 0.09 mmol/L (3.5 mg/dL) in women and 0.16 mmol/L (6.2 mg/dL) in men. They estimated that ~0.5 mmol/L (20 mg/dL) of serum cholesterol could be attributed to SCH. In a study by Bauer et al., it was found that LDL-C was 13 % higher and HDL-C was 12 % higher in elderly women with elevated TSH (TSH > 5.5 mIU/L) versus euthyroid women. The LDL-C/HDL-C ratio was 29 % greater among women with elevated TSH. Women with multiple lipid abnormalities were twice as likely to have increased TSH levels. 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 coronary artery disease (CAD) [37, 38]. However, the possible effects of subtle alterations of thyroid function on lipid profile and atherogenesis remain unclear. There exists a difference of opinion as to whether SCH should be treated or not [39]. The evidence provided by different authors is controversial and concerns different aspects of

this condition. Our study also found no significant difference between the two groups as far as individual lipid profile parameters were concerned.

The likelihood that a cardiovascular event will occur might not be determined solely by atherogenic lipoproteins, but rather by the balance between atherogenic and atheroprotective lipoproteins [40]. Several investigators have shown that the ratio between these particles predicts cardiovascular disease (CVD) risk better than isolated lipoprotein subfractions [41]. Several epidemiological and clinical studies have found that the LDL-C/HDL-C ratio is an excellent monitor for effectiveness of lipid lowering therapies. The LDL-C/HDL-C is a better predictor for risk of heart disease than LDL-C alone. The LDL-C/HDL-C reflects the two way traffic of cholesterol entering and leaving the arterial intima [42]. An ideal ratio of LDL-C/HDL-C at 3.5 has been used as marker of coronary atherosclerosis. The medical community is divided over the use of ratios or measurement of individual lipid parameters so as to predict cardiovascular risk. Our study revealed a significant *p* value of <0.0001 when the LDL/HDL ratio was compared between the two groups despite non-significant statistical association between LDL and HDL values and total cholesterol/HDL ratios in the two groups. This highlights the importance of measurement of all the lipid fractions individually and calculating the ratio of the atherogenic and atheroprotective fractions. This would reflect the actual balance between the two fractions and help in better prediction of a cardiovascular risk. Lp(a) levels also did not vary significantly between subclinical hypothyroids and euthyroids in our study. Studies on the association between Lp(a) and SCH have consistently yielded negative results despite a few of them showing significant association also [43, 44]. In previously reported studies, Lp(a) levels positively correlated with a family history of CAD and diabetes mellitus in euthyroids and SCH subjects. This could point towards genetic predisposition rather than reduced action of thyroid hormones on normal Lp(a) metabolism. Moreover the levels of Lp(a) did not normalise with levothyroxine treatment [45].

C-reactive protein (CRP) is a strong predictor of cardiovascular risk. It is a marker of the underlying pro-inflammatory process of atherosclerosis. Our study showed statistical significance for hsCRP (*p* = 0.0054). Again results have been inconclusive regarding the association between hsCRP and SCH. Three studies have reported high levels of hsCRP in SCH [46–48]. Some studies have also reported that normalization of thyroid state by levothyroxine replacement eventually normalizes hsCRP levels in SCH. In the study by Tuzcu et al., patients with SCH had increased levels of both hsCRP and fasting insulin and there was a positive correlation between hsCRP and fasting insulin levels in SCH patients. However values of insulin resistance given by homeostasis model of assessment—insulin

resistance [$\text{HOMA-IR} = \text{fasting insulin } (\mu\text{IU/mL}) \times \text{fasting glucose mmol/L}/22.5$] were not significantly different between cases and controls. In our study both euthyroids and SCH patients had high values of insulin resistance as against normal expected values of less than 2.63. Euthyroids had a higher insulin resistance of 3.08 as against a value of 2.8 in SCH subjects. This virtually rules out a state of insulin resistance in SCH in our study population.

In the absence of large-scale randomized trials, evidence related to all above discussed parameters remains inconclusive till date in SCH. Our sample size was small but despite that two parameters showed strong statistical significance between euthyroids and SCH. The possible role of hsCRP to bring to light the low grade inflammation possibly associated with SCH needs to be evaluated. Alterations in coagulation profile and homocysteine levels along with changes in levels of hsCRP could make the picture clearer while assessing cardiovascular risk in SCH. Our study also intended to see if increasing TSH levels correlate with a consistent and concomitant increase in total cholesterol, LDL and Lp(a) levels. However, when we categorised the subjects in our study according to increasing levels of TSH and compared them with the lipid status no such observation was made. Such an observation was also made in the study in a group of 100 patients of SCH [49]. This observation therefore fails to support the proposed idea of bringing down the upper limit of TSH levels for normal reference range. Our study highlights the importance of LDL-C/HDL-C in bringing to light the possibly existing dyslipidemia in SCH which would have escaped our notice had only traditional lipid profile parameters been individually measured. This ratio along with hsCRP can highlight a cardiovascular risk in subtle thyroid failure cases and may have the potential to become a part of the screening process to detect and treat those SCH cases with a greater cardiovascular risk.

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