Original article:

Prevalence and association of thyroid disorders with selected risk factors and severity of disease in patients confirmed of Coronary Artery Disease

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Abstract:

Objective: Subclinical hypothyroidism (SCH) has been identified as a risk for atherosclerosis and Coronary Artery Disease (CAD). The aim of this study was to determine the prevalence and association between hypothyroidism or subclinical hypothyroidism (SCH) and lipid parameters, anthropometric data and the severity of coronary artery disease (CAD) in patients awaiting Coronary Artery Bypass Graft Surgery (CABG) from a selected center. *Method:* A cross sectional analytical study was carried out amony patients awaiting CABG in a selected center. Thyroid profile (enzyme immunoassay method), lipoprotein (a) [Lp(a)], C- reactive protein (CRP) (immunoturbidimetric method) were determined and the Gensini score calculated. Lipid parameters and details of current medication were obtained from the medical records and anthropometric data were measured. *Results:* From a total of 102 patients 3% were on treatment for hypothyroidism and 15% had subclinical hypothyroidism. A significantly high (p= 0.04) percentage of SCH patients (75%) were dyslipidemic. There were no significant differences observed in lipid profiles and Lp(a) among SCH and euthyroid patients when the total sample or dyslipidemic sample was considered. However, a significantly high percentage (58%, *p*<0.05) of SCH patients on statins had a higher level of low density lipoprotein cholesterol (LDLc) compared to euthyroid dyslipidemic patients. A significant negative (*p*< 0.05) correlation was observed between thyroid stimulating hormone concentration and high density lipoprotein cholesterol (r= -0.67) in SCH group. No significant differences were observed in anthropometric data, CRP or Gensini score of SCH and euthyroid patients with CAD. *Conclusion:* The prevalence of dyslipidemia among SCH patients with CAD was significantly high. The patients suffering from SCH exhibited higher levels of LDLc compared to euthyroid patients from both the total and dyslipidemic groups. SCH patients under statin treatment displayed a higher LDLc suggesting a strong association between coronary artery disease and thyroid disease.

Keywords: Subclinical hypothyroidism, hypothyroidism, coronary artery disease, lipid profile, anthropometric parameters, Gensini score, CRP

Introduction

Cardiovascular diseases (CVDs) are a leading cause of mortality worldwide and coronary artery disease (CAD) has become one of the most prevalent conditions among South Asians[1]. In Sri Lanka, the proportional mortality due to CAD is 25.7%[2]. Atherosclerosis is the main cause for CAD and many biochemical [elevated homocysteine, fibrinogen, Lp(a), LDLc particle size and CRP] and other risk factors (diabetes, hypertension, obesity, sedentary

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lifestyle, smoking, alcohol, family history of CAD, menopause and advancing age) are recognized as causes for the increased prevalence. Dyslipidemia characterized by elevated serum triglyceride (TG), elevated LDLc and reduced serum high density lipoprotein cholesterol (HDLc) is a hallmark of the disease[3]. The CAD initiates at an early stage in life and continues throughout adulthood[4]. The risk factors for CAD reported among Sri Lankans include, prevalence of hypercholesterolemia (>5.2 mmol/l), high LDLc (>3.4mmol/L), high TG (>1.7mmol/L) and low HDLc (<1.0 mmol/L) being 53.6%, 24.7%, 22.7% and 53.1% respectively[5].

Lipoprotein metabolism as well as some CVD risk factors are significantly affected by thyroid hormones, i.e: metabolism and production of adipokines, insulin sensitivity, oxidative stress and metabolic syndrome[6,7]. Overt hypothyroidism is a well-established factor for atherosclerotic cardiovascular disease. Hypothyroidism increases atherogenic LDLc, induce diastolic hypertension, change coagulability and directly affect smooth muscle cells[8]. Subclinical hypothyroidism, defined as mildly elevated thyroid stimulating hormone (TSH) with low to normal free tri-iodothyronine (fT_3) and free tetra-iodothyronine (fT_4), is also identified to be associated with risk of atherosclerosis and CAD[9]. Significantly increased carotid artery intima thickness was reported with subclinical hypothyroidism compared to normal controls[10]. The prevalence of SCH ranged between 4% - 10% in the general population and was between 7% - 26% in elderly[11,12]. The prevalence of SCH in patients with dyslipidemia ranged between 1.4% - 26%[13]. A population based cross sectional study of elderly women with subclinical hypothyroidism reported an age-adjusted prevalence of aortic atherosclerosis (odds ratio, 1.7 [95% CI, 1.1 to 2.6]) and myocardial infarction (odds ratio, 2.3 [CI, 1.3 to 4.0])[14].

In contrast, some do not report an association between SCH and risk of atherosclerosis[15,16]. Transient or persistent SCH was not associated with risk of CAD, heart failure or cardiovascular mortality in elderly[17,18]. Therefore, consideration of subclinical hypothyroidism as a risk factor for ischemic heart disease is still debatable. However, as no data is available on thyroid functions of CAD patients in Sri Lanka, the aim of the present study was to determine the prevalence of hypothyroidism, SCH and effect of the thyroid function on lipid profiles and severity of CAD of dyslipidemic patients awaiting Coronary Artery Bypass Graft Surgery in a selected center.

Method

Study population: The research was conducted as a cross sectional study during 2013 and 2014. Study sample consisted of 67 males and 35 females awaiting CABG at the Cardiothoracic Unit, Sri Jayewardenepura General Hospital, Thalapathpitiya, Sri Lanka. All consenting patients referred to the centre for CABG were included until the sample size was fulfilled irrespective of other factors.

Sample size: The required sample size with an estimated prevalence of 30% CVD[19], at 95% significance level and 10% margin of error was 81. A study sample of 102 was enrolled.

Thyroid profile assay: Pre-operative blood samples (12 – 14 hour fasted) were collected. Serum was separated (3500 rpm, 5–10 min) and TSH, fT_3 and fT_4 were measured by enzyme immunoassay completion method by Mini-Vidas analyzer (Biomerieux, France).

Lipoprotein(a) assay: Lp(a) content was measured by an immunoturbidimetric method (Thermo Scientific, Finland) with pre-operative blood samples. The absorbance of the immune-complex, produced from Lp(a) and anti-serum was measured at 340 nm by Konelab 20XT (Thermo Scientific, Finland).

CRP assay: CRP was measured using turbidimetric immunoassay (Biolabo, France) using Konelab 20XT (Thermo Scientific, Finland) on pre-operative blood samples. The absorbance at 340 nm was measured against the absorbance of standard.

Lipid profile and data from data records: Data on total cholesterol (TC), LDLc, HDLc, TG were collected from each patient's data records and TC: HDLc ratio calculated.The lipid profile was analysedat the enrolment of patients for surgery. Information related to dyslipidemia and hypothyroidism was also gathered from data records of respective patients.

Anthropometric parameters: Weight and height were measured by weighing scale (Health scale, China) and stadiometer respectively. Waist, hip and midarm circumference were measured using non-stretchable tape. Body mass index (BMI) and the waist to hip ratio were calculated.

Gensini score: The Gensini score system[20] was used to evaluate the severity of CAD from coronary angiography. The data of coronary angiography were gathered from the medical records of patients. The Gensini score was computed by assigning a severity score according to the degree of luminal narrowing and geographical importance of each coronary stenosis.

Ethics approval and consent to participate: The study was approved by Ethics Review Committees of Faculty of Medical Sciences, University of Sri Jayewardenepura (635/12) and Sri Jayewardenepura General Hospital, Thalapathpitiya, Sri Lanka. Written informed consent was obtained after explaining the purpose of the study to each volunteer prior to commencement of the study.

Statistical Analysis: All statistical analyses were carried out using SPSS version 16.0 (2007, SPSS for Windows, SPSS Inc., Chicago, IL, USA) package. The results were expressed as mean ±1 standard deviation and the *p* value of less than 0.05 considered significant. Non-parametric significances were analysed by Mann-Whitney U test. Correlations were analysed by Spearman test.

Results

The average ages of male and female patients were 56.9 ±10 and 57.8 ±7 respectively. From the total sample 15% (n=15) of individuals were SCH and not previously diagnosed. The age distribution of SCH patients was 39 to 63 years. Distribution of SCH was significantly (p=0.04) high among males (17.9%) compared to females (11.4%). The 3% of patients diagnosed as hypothyroid were on treatment with L-thyroxin.

From the study sample 87.3% (n=89) of individuals had a history of dyslipidemia and were on statins treatment (majority under the treatment of 20 mg or 40 mg (60%) of atorvastatin). When considering the dyslipidemic (n=89) patients 13.5% of them were SCH.

Table 1 shows the values of thyroid profile (TSH3, fT3, fT4), lipid profile (TC, LDLc, HDLc, TG, TC: HDLc ratio), Lp(a), CRP, BMI, waist circumference, waist to hip ratio, mid arm circumference and Gensini score of euthyroid and SCH individuals of the total sample and dyslipidemic individuals. The average values for fT3 and LDLc levels of hypothyroid patients were 3.5±0.8 nmol/L and 121±43 mg/dL respectively. Hypothyroid individuals (n=3) were excluded in the analyses.

Apart from the TSH concentration no significant differences were observed in thyroid profiles, lipid profiles, Lp(a), CRP, BMI, waist circumference, waist to hip ratio, mid arm circumference and Gensini score among SCH and euthyroid patients when total sample or dyslipidemic sample was considered.

However, when considering the LDLc concentrations of SCH or euthyroid dyslipidemic patients under statins, 30% of patients had higher levels above normal reference value of <100 mg/dL [3]. There was a significant association (p= 0.04) between SCH and desirable level of LDLc (< 100 mg/dL) concentration of dyslipidemic patients on statins. Majority of SCH patients (58%; 7/12) had LDLc concentrations above 100 mg/dL. Dyslipidemic SCH patients were on atorvastatin of 20 mg (80%) and 40 mg (20%). Among euthyroid patients with CAD, only 26% (20 out of 75) had LDLc> 100mg/dL. A non-significant (*p*> 0.05) positive correlation was observed between TSH and TC: HDL (r=0.5), and a significant negative correlation between TSH with HDL (r= 0.67) in SCH group.

Discussion

The present study intended to study the prevalence of SCH and its association with risk of atherosclerosis in a cohort of individuals with confirmed CAD as data are not available for Sri Lankans and to observe parallels with reported data for South Asian and other populations. In the present study SCH was considered as TSH> 5 mIU/L as it is the upper limit of the reference range[21].

Among the dyslipidemic individuals, 13.5% were found to be SCH based on diagnosis criteria[9]. Similarly an Indian study revealed the prevalence of SCH among dyslipidemics as 14.7%[22]. When all SCH patients in this study were considered the prevalence of dyslipidemia among them was 80% (12 of 15). The prevalence of dyslipidemia and subclinical hypothyroidism in the United States was 53%[23] and 4.3%[24] respectively and the dyslipidemic with SCH were 83% and the study concluded that SCH was associated with high prevalence of dyslipidemia and CAD[9]. Present prevalence data on dislipidemic with SCH compares well with observations of above studies.

L-thyroxin replacement therapy on lipid based cardiovascular risk in SCH has shown that the changes of lipid profile due to mild elevation of TSH have been rendered with the treatment[25]. According to an Indian study low HDLc, high serum TC and LDLc were found in patients with TSH above 10 mIU/L who were not on statins[22]. In a study conducted among both groups of individuals with arterial fibrillation (symptomatic and asymptomatic) when combined SCH have been revealed that increased level of TC, LDL, TG, atherogenicity and decreased level of HDL compared to control group[26]. In contrast, Mahajan et al (2018) has reported a normal homeostatic and metabolic function in both SCH and overt hypothyroid patients compared to control group[27]. However in the present study such

Table 01 Thyroid profile, lipid profile, Lp(a) and other parameters of total, SCH and euthyroid individuals

Measurements	Total sample (n=102)	Total sample (n =99*)		p value	Dyslipidemic group (n=87*)		p value	Reference ranges
		SCH (n =15)	Euthyroid (n=84)		SCH (n =12)	Euthyroid (n=75)		
TSH3 (μUI/mL)	3.2 ± 3.9	7.9 ± 6.3 (range:4.5 – 27.1)	2.0 ±1.0	0.003	8.7 ± 7.0 (range:5 –27.1)	1.9 ± 0.9	0.000	0.4-4.5 [a]
FT3 (nmol/L)	3.9 ± 1.1	4.3 ± 1.0	3.8 ± 1.1	0.13	4.1 ± 1.0	3.9 ± 1.1	0.5	3.5-7.8 [a]
FT4 (pmol/L)	15.2 ± 3.4	14.9 ± 1.4	15.3 ± 3.4	0.19	14.8 ± 0.8	15.1 ± 3.3	0.5	9.0-25 [a]
Lp(a) (mg/dL)	50 ± 38	48.0 ± 38.0	50.2 ± 3.9	0.72	38.0 ± 21.3	52.3 ± 4.0	0.2	< 30 [b]
TC (mg/dL)	150 ± 36	152.1 ± 40.5	150.0 ± 35.3	0.70	158.7 ± 35.9	151.2 ± 36.6	0.3	< 200[c]
LDLc (mg/dL)	92 ± 36	91.9 ± 35.1	89.5 ± 29.4	0.5	92.5 ± 35	91.0 ± 30.0	0.5	< 100[c]
HDLc (mg/dL)	34 ± 9	38 ± 9.2	33.1 ± 9.5	0.13	38.0 ± 10.0	33.7 ± 9.6	0.2	< 40[c]
TG (mg/dL)	133 ± 60	118.5 ± 28.3	134.5 ± 63.7	0.08	122.0 ± 30.6	135.1 ± 62.4	0.4	< 150[c]
TC : HDLc	4.6 ± 1.2	4.1 ± 1.1	4.6 ± 1.2	0.47	4.3 ± 1.2	4.6 ± 1.2	0.7	< 5[c]
CRP (mg/L)	7 ± 8	6.3 ± 5.9	6.9 ± 8.6	0.70	7.2 ± 6.4	7.4 ± 9.1	0.9	< 6[a]
BMI (kg/m^2)	24.8±3.8	25.1 ± 4.3	24.9 ± 3.6	0.89	25.5 ± 4.2	25.1 ± 3.7	0.8	
Waist circum:	94.5 ±9.2	92.7 ± 11.7	95.0 ± 8.9	0.48	94. ± 11.2	95.3 ± 8.6	0.6	
Waist: hip ratio	1.0 ±0.06	0.9 ± 0.08	1.01 ± 0.06	0.53	1.0 ± 0.09	1.0 ± 0.05	0.98	
Mid arm circum: (cm)	27.5 ±3.1	27.2 ± 3.8	27.5 ± 2.9	0.91	27.7 ± 4.0	27.7 ± 2.9	0.8	< 24
Gensini score	48 ± 26	49 ± 26	47.7 ± 25.0	0.57	46.3 ± 27.8	47.8 ± 24.6	0.9	-

[a]Manual of standard operation procedure, sample collection and reference range for clinical chemistry, World Health Organization, Ministry of Health and the Department of Biochemistry, Medical Research Institute, Sri Lanka, [b]Reference range as per lipoprotein(a) kit, [c]Third Report of the National Cholesterol Education Programme (Adult Treatment Panel III), 2002.

* Hypothyroid patients were excluded in the analyses.

differences in lipid profile of euthyroid and SCH patients were not observed. This may be due to all dyslipidemic patients being on statins treatment or due to the small sample size. The percentage of the SCH individuals who had LDLc concentration >100 mg/dL was significantly (*p*=0.04) high compared to dyslipidemic euthyroid patients. This reflects clearly the ineffectiveness of statins treatment without treating SCH and susceptibility of SCH individuals to develop dyslipidemia. Further, in such patients continuous monitoring of LDLc is important in preventing further complications. It is essential that such patients are made aware of the importance of compliance with continuous monitoring of the lipid profile and the necessity to change the drug dose accordingly.

Serum TSH had positively correlated with TC and LDLc whereas fT3 and fT4 negatively correlated with TC and LDLc in SCH individuals[28]. However, serum TSH of SCH individuals of present study had significant negative correlation with HDLc and a non-significant positive correlation with TC: HDL ratio. This suggests that contribution to increasing HDLc is a factor to be considered among the SCH patients in Sri Lanka.

CRP is a predictor of risk of MI, stroke or peripheral vascular disease in asymptomatic individuals of CHD[29,30,31]. In the present study there was no any significance different observed among total and dyslipidemiceuthyroid between SCH patients. Though CRP is reported as elevated in patients with familial hypercholesterolemia[32], correlations of CRP with any of the lipid parameter or Lp(a) was not observed in this study. Analysis with high sensitivity CRP may overcome the lack of correlations.

When considering the anthropometric parameters

no significant differences were observed among total and dyslipidemic euthyroid and SCH patients. A retrospective study conducted among apparently healthy individuals also reported no significant differences of BMI and waist circumferences among euthyroid and SCH individuals[33]. The study had analyzed the incidence of CAD (presence of plaques), obstructive CAD (stenosis $\geq$ 50% -calculated by Coronary Computed Tomography angiography) and coronary artery calcium score of SCH and euthyroid patients. The SCH group had significantly high value for coronary artery calcium score compared to the euthyroid group. The incidence of CAD and coronary artery calcium score >100 were also significantly high among SCH male compared to euthyroid male. However, the obstructive CAD was not significantly different[33]. In the present study all of the individuals were CAD and Gensini score was not significantly different between SCH and euthyroid individuals. Another retrospective study with the patients of acute coronary syndrome who underwent angiography had revealed SCH group had greater incidence of multi vessel disease (18 vs. 12, p = 0.1904). The study concluded SCH is not an independent risk factor for early occurrence of CAD and is not associated with severity and angiographic pattern of CAD[34]. Another study also concluded that CAD events or CAD mortality were not associated with thyrotropin levels within the reference ranges[35]. SCH individuals had also exhibited increased concentration of Lp(a)[36]. Elevated Lp(a) concentration in hypothyroid patients had normalized on L-thyroxin replacement therapy[37] and some studies reported no effect on treatment with L-thyroxin on Lp(a)[38]. In the present study Lp(a) concentration was not significantly different between euthyroid and SCH individuals. Thus compared to lipid parameters, elevated Lp(a) singles out as an independent risk factor[39].

Conclusions

According to these observations we can conclude that the prevalence of subclinical hypothyroidism among CAD patients was 15%. The patients suffering from SCH exhibited higher levels of LDLc compared to euthyroid patients from both the total and dyslipidemic groups. SCH patients under statin treatment displayed higher LDLc suggesting a strong association between coronary arterial disease and thyroid disease.

Screening of CAD patients for SCH and treatment may be beneficial in achieving target level of LDLc with statins treatment. Thus individuals identified as subclinical hypothyroid or hypothyroid should be made aware of their susceptibility to develop CAD if other modifiable and non-modifiable risk factors are prevalent as the above conditions afflict a certain percent of the population.

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