Available Online through
www.ijpbs.com

IJPBS |Volume 2| Issue 2 |APRIL-JUNE |2012|128-134

Assessment of the Cardiovascular Risk in Subclinical Hypothyroidism

Anand Pyati[*1], Sudharani Dhuttargi[2], Nagaraj[1], Debasmita Das[3]*

[1] *Department of Biochemistry, BLDEU's Shri B M Patil Medical College, Bijapur, Karnataka.*
[2] *Al-Badar Dental College, Gulbarga, Karnataka, India.*
[3] *BLDEU's Shri B M Patil Medical College, Bijapur, Karnataka, India.*
*Corresponding Author Email: anandpyati999@gmail.com

BIOLOGICAL SCIENCES
RECEIVED ON 05-05-2012

RESEARCH ARTICLE
ACCEPTED ON 27-05-2012

ABSTRACT

Background: *The decision about whether to screen patients for subclinical hypothyroidism (SCH) is clouded by inconsistent evidence of association of dyslipidemia and other risk factors of cardiovascular disease with SCH and also any benefit from early treatment.* ***Objective:*** *To determine whether the known risk factors of cardiovascular disease such as hypertension, increase in fasting blood glucose and lipid abnormalities are more significant in patients with subclinical hypothyroidism when compared with those in euthyroid individuals and to find out any correlation between the TSH levels and lipid profile parameters in subclinical hypothyroidism subjects.* ***Methods:*** *A total of 60 subjects comprising 30 subclinical hypothyroidism patients and 30 age & sex matched healthy controls were included in the study. In all the subjects BMI, blood pressure, fasting blood glucose and lipid profile tests were analyzed by standard methods.* ***Results:*** *We found that, serum mean levels of diastolic blood pressure, total cholesterol, triglycerides were significantly higher in SCH patients than in controls and were statistically significant ($p < 0.05$). The percentage of subjects having higher BMI, hypertension, elevated TC, LDL, TG, and decreased HDL was higher in SCH patients than in controls. Among the SCH patients, TSH levels were positively correlated with that of total cholesterol and triglycerides.* ***Conclusion:*** *There were higher prevalence rates for hypertension, elevated triglycerides, an undesirable lipid profiles in SCH patients in our study which seem to increase the cardiovascular risk and weigh in favour of treatment of patients with subclinical hypothyroidism.*

KEYWORDS: *Subclinical hypothyroidism, Dyslipidemia, Hypertension, Cardiovascular risk, Euthyroid*

INTRODUCTION

Subclinical hypothyroidism (SCH) is defined as a serum TSH concentration above the statistically defined upper limit of the reference range when serum free T4 (FT4) concentration is within its reference range[1].

Subclinical hypothyroidism or mild thyroid failure is a common problem, with a prevalence of 3% to 8% in the population without known thyroid disease. The prevalence increases with age and is higher in women. After the sixth decade of life, the prevalence in men approaches that of women, with a combined prevalence of 10%[2].

Subclinical thyroid disease is, by its very nature, a laboratory diagnosis. Patients with subclinical disease have few or no definitive clinical signs or symptoms of thyroid dysfunction[1]. Before diagnosis of SCH, other causes of an elevated TSH level, such as recovery from nonthyroidal illness, assay variability, presence of heterophile antibodies interfering with the TSH assay, and certain cases of central hypothyroidism with biologically inactive TSH and thyroid hormone resistance, should be excluded. However, the most common cause of elevated TSH is autoimmune thyroid disease. Previous radioiodine therapy, thyroid surgery, and external radiation therapy can also result in mild thyroid failure. Transient SCH may occur after episodes of postpartum, silent, and granulomatous thyroiditis[3].

The clinical importance of and therapy for mild elevation of serum TSH (<10 mIU/L)[1] and the exact upper limit of normal for the serum TSH level remain subjects of debate[4]. When the TSH level is above 10 mIU/L, levothyroxine therapy is

generally agreed to be appropriate[5]. However, management of patients with a serum TSH level of less than 10 mIU/L is controversial. Some authors argue for routine and some for selective therapy[6].

Despite some conflicting results, many studies found that subjects with subclinical hypothyroidism have higher total cholesterol and low density lipoprotein cholesterol levels than euthyroid subjects. Few studies have showed that subjects with subclinical hypothyroidism have increased C-reactive protein values. Subclinical hypothyroidism has been associated with increased risk for atherosclerosis. However, data on coronary heart disease (CHD) in subjects with subclinical hypothyroidism are conflicting[7].

Small percentage of these patients advance to overt hypothyroidism each year, Lipid abnormalities are reported to be more common in patients with overt hypothyroidism and are thought to contribute to the disproportionate increase in cardiovascular risk in these persons. Controversy continues over whether elderly individuals should be screened for subclinical hypothyroidism. The decision about whether to screen patients for this disorder is clouded by inconsistent evidence of association of dyslipidemia and other risk factors of cardiovascular disease with SCH and also any benefit from early treatment. A few trials have found that persons with subclinical hypothyroidism who are given L-thyroxine experience some improvements in their energy level and feelings of well-being[8].

Cardiovascular diseases (CVDs) are the most common cause of mortality, primarily affecting older adults. Heart disease causes nearly 700 000 deaths annually in the United States. Although established risk factors explain most cardiac risks, significant attention has been focused on alternative biochemical markers to assist in identifying those at risk of a clinical cardiac event. Previous studies have suggested that abnormal levels of thyroid stimulating hormone (TSH) may represent a novel cardiac risk factor[9].

If one can prove clearly that a SCH is definitely associated with lipid abnormalities, then one can go for general screening and treatment of patients with SCH with levothyroxine and thereby preventing the overt hypothyroidism and thereby the cardiovascular complications at a very early stage.

There are few population-based studies that have compared lipid levels in patients who have subclinical hypothyroidism with lipid levels in euthyroid persons. So the purpose of this study is to determine whether the known risk factors for the CAD such as hypertension, increase in fasting blood glucose and lipid abnormalities are more significant in patients with subclinical hypothyroidism when compared with those in euthyroid individuals.

MATERIALS AND METHODS

A cross sectional study of Assessment of cardiovascular risk in subclinical hypothyroidism subjects was carried out from April 2011 to December 2011. We selected 30 subclinical hypothyroidism cases aged ≥ 40 years from among the patients referred by the physicians to the clinical biochemistry department, BLDEA Hospital and Research Centre, Bijapur, Karnataka, (attached to teaching institute, Shri B M Patil Medical College, Bijapur.) and 30 age and sex matched healthy euthyroid controls from the general population according to the inclusion and exclusion criteria mentioned below. This study was approved by the Ethical and Research Committee of BLDEU's Shri B M Patil Medical College, Bijapur and all the subjects gave an informed consent before undergoing further investigations.

Inclusion criteria: subclinical hypothyroidism cases having TSH in the range of 4.50 to 14.99 mU/L and a T4 value greater than 4.5 µg/dL. The euthyroid controls having normal TSH values.

Exclusion criteria: Obese (BMI ≥ 30 kg/m^2) subjects, smokers, those with known hypothyroidism, previous radioactive iodine therapy, thyroidectomy, external radiation, consumption of drugs known to cause SCH, primary or secondary dyslipidemia, diabetes mellitus, renal and hepatic failure, or other systemic diseases were excluded from the study.

The subjects' BMI was determined from height and weight. BMI (Kg/m^2) = Weight/(Height)^2.

Measurements of blood pressure were taken with a mercury sphygmomanometer. In order to record the blood pressure, subjects were seated quietly for at least 5 minutes in a chair (rather than on an exam table) with their backs supported and their arms bared and supported at heart level. Two or more readings, separated by 2 minutes were then averaged. In cases, where the first two readings differed by more than 5 mm Hg, an additional reading was obtained and averaged with the previous reading. For hypertension WHO classification was used according to which subjects having a blood pressure of ≥140/90 mmHg is labelled as hypertensive.

Venous blood samples were drawn at 8 AM following a 12 hours fast, in a plain bulb from the subjects, with all the aseptic precautions. Blood samples were centrifuged within 30 minutes at 3000 rpm for 5 min. and serum was separated. Serum samples were stored at -20° C until assayed.

Serum T_3, T_4 and TSH levels were measured by ELISA method[10,11,12,13,14,15] using immunoassay analyzer. Serum fasting glucose was estimated by Glucose oxidase - peroxidase (GOD – POD) method[16], Serum total cholesterol (TC) and triglycerides (TG) were determined by enzymatic colorimetric assay[17] (CHOD-PAP method using Statfax-2000 semiautoanalyzer). High-density lipoprotein cholesterol (HDL-C) was determined enzymatically in the supernatant after dextran–magnesium-induced precipitation of other lipoproteins. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula[18].

STATISTICAL SIGNIFICANCE

Descriptive data is presented as mean ± SD and range values. Statistical analysis was carried out using a paired Student's t-test for all variables. The Pearson's correlation coefficient is used to evaluate the degree of association between two variables. For all the tests, p-value of 0.05 or less was considered for statistical significance.

RESULTS

The present study includes 30 subclinical hypothyroidism patients and 30 age and sex matched healthy controls.

Table – 1: Demographics of the sample population

Characteristic	Subclinical hypothyroidism (SCH) (n = 30)	Euthyroid controls (EC)(n = 30)
Sex		
Male	06	06
Female	24	24
Age		
40 – 45 yrs	5	6
46 – 50 yrs	8	8
51 – 55 yrs	10	12
56 – 60 yrs	07	04

Table 1 shows age and sex wise distribution of cases and controls studied. The study included 30 cases of subclinical hypothyroidism with a mean age of 51.3 ± 5.6 years, and 30 healthy controls with a mean age of 50.4 ± 5.3 years. Subclinical hypothyroidism and euthyroid control subjects were well matched with respect to age and sex.

It is evident from the table that the subclinical hypothyroidism is more common in women among the age group of 51 – 55 years.

TABLE – 2: Comparison of clinical and biochemical parameters between subclinical hypothyoidism subjects and healthy euthyroid controls

Variable	SCH Patients (Mean±SD)	Euthyroid controls (Mean±SD)	P value	Statistical significance
Age (yrs)	51.3 ± 5.6	50.4 ± 5.3	-	-
BMI (kg/m^2)	27.6 ± 4.8	25.9 ± 5.0	0.18	NS
SBP (mm Hg)	131.1 ± 15.2	125.6 ± 16.3	0.18	NS
DBP (mm Hg)	86.8 ± 11.4	79.4 ± 9.8	0.008	HS
TSH (mIU/L)	8.42 ± 2.1	3.37 ± 0.61	0.000	HS
T3 (ng/dL)	146.6 ± 20.0	145.2 ± 18.7	0.78	NS
T4 (µg/dL)	7.64 ± 1.45	7.97 ± 1.94	0.45	S
FBG (mg/dL)	96.3 ± 21.2	94.6 ± 15.9	0.72	NS
TC (mg/dL)	213 ± 53.7	184.5 ± 43.3	0.025	HS
TG (mg/dL)	115.5 ± 40.7	95.3 ± 23.9	0.02	S
LDL (mg/dL)	122.5 ± 34.5	112.3 ± 22.4	0.17	NS
HDL (mg/dL)	38.3 ± 8.4	41.5 ± 6.8	0.11	NS

P value ≤ 0.05 is considered as statistically significant

BMI = Body mass index; SBP = Systolic blood pressure; DBP = Diastolic blood pressure; TSH = Thyroid stimulating hormone; T3 = Tri-iodothyronine; T4 = Tetra-iodothyronine; FBG = Fasting blood glucose; TC = Total cholesterol; TG = Triglycerides; LDL-C = Low density lipoprotein; HDL-C = High density lipoprotein; S = Statistically significant; HS = Highly significant.

Table 2 shows clinical and biochemical characteristics of the study subjects. Serum mean levels of diastolic blood pressure (86.8 ± 11.4), total cholesterol (213 ± 53.7), triglycerides (115.5 ± 40.7) were significantly higher in SCH patients than in controls (79.4 ± 9.8, 184.5 ± 43.3, 95.3 ± 23.9 respectively) and were statistically significant ($p < 0.05$). Serum mean levels of BMI (27.6 ± 4.8), Systolic blood pressure (131.1 ± 15.2), fasting glucose (96.3 ± 21.2), HDL – C (38.3 ± 8.4), LDL – C (122.5 ± 34.5) were not significantly different from the values in controls (25.9 ± 5.0, 125.6 ± 16.3, 94.6 ± 15.9, 41.5 ± 6.8, 112.3 ± 22.4 respectively).

Table – 3: Risk factors for cardiovascular disease in SCH patients

Variable	SCH Patients (%)	Euthyroid controls (%)
BMI (> 27.5 kg/ m^2)	46.7	33.4
SBP (≥ 140 mm Hg)	30	16.7
DBP (≥ 90 mm Hg)	50	10
FBS (≥ 110 mg/dL)	20	20
TC (> 200 mg/dL)	43.4	16.7
TG (> 150 mg/dL)	16.7	3.4
LDL (> 130 mg/dL)	30	16.7
HDL (< 30 mg/dL)	20	0

The percentages of patients and controls with increased BMI, blood pressure, abnormal lipid profiles are given in table 3. The percentage of subjects having higher BMI (>27.5 kg/m^2), hypertension (>140/90 mm Hg), elevated TC (>200 mg/dL), LDL (130> mg/dL), TG (150> mg/dL), and decreased HDL (<30 mg/dL) was higher in SCH patients than in controls.

Among the SCH patients, TSH levels were positively correlated with that of diastolic blood pressure (r = 0.0492) total cholesterol (r = 0.3267) and triglycerides (r = 0.5464). (r = Spearman rank correlation coefficient).

DISCUSSION

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 hormone replacement therapy on serum lipids and on the risk for cardiovascular disease[19, 20]. However, the possible effects of subtle alterations of thyroid function as in SCH on lipid profile and atherogenesis remain unclear[21]. There is, in fact, doubt as to whether SCH should be treated because the evidence in terms of dyslipidemia, hypertension or glucose intolerance provided by different authors is controversial. However, there is increasing evidence that SH is associated with dyslipidemia and hypertension in the elderly which can be a potential risk factor for the development of CVD in the near future[22].

In the present study we demonstrated that, SCH subjects have statistically significant higher mean levels of serum total cholesterol, TG and thus representing a more atherogenic lipid profile when compared with the age and sex matched euthyroid controls. In a substantial number of studies, TC and LDLc are seem to be elevated in SCH compared to controls. However there are studies which do not confirm these findings.

Overt hypothyroidism patients in their fifth or sixth decades of life have significantly higher diastolic blood pressure than in age-matched controls[23], whereas the association between subclinical hypothyroidism and hypertension is controversial[24]. In this study, we found that approximately 50% of SCH patients had diastolic hypertension compared with 10% in euthyroid controls, this difference is statistically significant. Also the percentage of subjects having systolic hypertension was slightly higher in SCH patients (30%), than in controls (16.7%), and the difference is not statistically significant. Several studies have reported impaired left ventricular diastolic and systolic myocardial functions in subclinical hypothyroidism[25] which were reverted to normal during levothyroxine replacement therapy[26]. Exposure of aortic endothelial and vascular smooth muscle cells to triiodothyronine (T3) resulted in cellular relaxation. Two binding sites specific for T3 were identified. When cells were exposed to T3, no effect on phosphorylation or nitric oxide production were observed, suggesting that T3 acted directly on the vascular smooth muscle cells to cause vascular relaxation[27].

Previous study results revealed conflicting data on serum lipid concentrations in subclinical hypothyroidism. Total cholesterol and HDL-C were elevated in several studies, but were not different from those in controls in most other studies. Lower serum HDL-C levels were reported in few studies and were not different from euthyroid controls in most other studies[28]. In our study we found that the percentage of patients with atherogenic lipid profiles (elevated total cholesterol/HDL-C and LDL-C/HDL-C) was higher in SCH patients than in controls.

There is a growing body of evidence indicating that elevated triglyceride levels are an independent risk factor for cardiovascular disease[29]. Hypertriglyceridemic patients often develop a lipoprotein profile characterized by elevated triglycerides and LDL-C and low HDL-C[30]. It is estimated that the aggregated risk associated with triglycerides greater than 220 mg/dL and a total cholesterol/HDL-C ratio greater than 5.0 to be 25% of the cardiovascular events[31].

A meta-analysis of 17 population-based studies of triglyceride levels and cardiovascular disease identified a 76% increase in cardiovascular disease risk with a 1 mmol/L (89 mg/dL) increase in triglyceride levels[32]. Our findings are in agreement with previous studies demonstrating that approximately 16.7% of patients with subclinical hypothyroidism had hypertriglyceridemia when compared to 3.4% in control subjects.

The findings of this study must be interpreted within the limitations of the study design. Our assumption that the subclinical hypothyroid group is homogeneous might ignore the possibility that a subgroup of these persons might be at greater risk for hyperlipidemia. In addition, because of the cross-sectional nature of this analysis, it is difficult to ascribe causality to any associations we have found. Because we do not know whether thyroid test abnormalities

preceded elevations in triglyceride levels, it cannot be definitely stated that one leads to the other. Further evaluation of this relationship with longitudinal data would be necessary to support a causal link.

CONCLUSION

The high prevalence rates for hypertension, elevated triglycerides and an undesirable lipid profiles in SCH patients, found in our study may increase the risk of accelerated atherosclerosis and premature coronary artery disease and seem to weigh in favour of treatment of patients with subclinical hypothyroidism.

REFERENCES

1. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, et al. Subclinical Thyroid Disease Scientific Review and Guidelines for Diagnosis and Management. JAMA, January 14, 2004—Vol 291, No. 2, 228-238.
2. Hollowell JG, Staehling NW, Flanders WD, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab. 2002;87(2):489-499.
3. Cooper DS. Subclinical hypothyroidism. N Engl J Med. 2001;345(4): 260-265.
4. Surks MI, Hollowell JG. Age-specific distribution of serum thyrotropin and antithyroid antibodies in the US population: implications for the prevalence of subclinical hypothyroidism. J Clin Endocrinol Metab. 2007 Dec;92(12):4575-4582. Epub 2007 Oct 2.
5. Gharib H, Tuttle RM, Baskin HJ, Fish LH, Singer PA, McDermott MT. Subclinical thyroid dysfunction: a joint statement on management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and the Endocrine Society. Thyroid. 2005;15(1):24-28.
6. Chu JW, Crapo LM. The treatment of subclinical hypothyroidism is seldom necessary. J Clin Endocrinol Metab. 2001;86(10):4591-4599.
7. Rodondi N, Newman AB, Vittinghoff E, Rekeneire ND, Satterfield S, Harris TB, et al. Subclinical Hypothyroidism and the Risk of Heart Failure, Other Cardiovascular Events, and Death. Arch Intern Med. 2005;165:2460-2466.
8. Hueston WJ and Pearson WS. Subclinical Hypothyroidism and the Risk of Hypercholesterolemia. Ann Fam Med 2004; 2:351-355.
9. Cappola AR, Fried L P, Arnold AM, Danese MD, Kuller LH, Burke GL, et al. Thyroid Status, Cardiovascular Risk, and Mortality in Older Adults. JAMA. 2006;295:1033-1041
10. Soos M, Siddle K. Immunol methods. 1982;51;57-68.
11. Wada HG, Danisch RJ, Baxter SR. Clin Chem. 1982;28:1862-66
12. Walker, W H O, Introduction: an approach to immunoassay. Clin Chem. 1977;23;384.
13. Kerkegaard C, Friis T, Siersback-Nielsen K, Acta Endocrinol. 1974;77;71.
14. Wistom GB. Enzyme immunoassay. Clin Chem. 22:1243;1976.
15. Schuurs AH, Van Weeman BK. Review. Enzyme-immuneassay. Clin. Chem. Acta. 81;1:1977.
16. Burtis CA, Ashwood ER. Teitz Textbook of Clinical Chemistry, 2nd ed. W.B.Saunders company; 1994: 961-2.
17. Nader R, Warnick GR. Lipids, lipoproteins, apolipoproteins and other cardiovascular risk factors. In : Burtis CA, Ashwood ER and Bruns DA, eds. Tietz text book of clinical chemistry and molecular diagnostics, 4th edn. New Delhi : Elsevier Co., 2006; 916-52.
18. Rifai N, Iannotti E, DeAngelis K, Law T. Analytical and clinical performance of a homogeneous enzymatic LDL –cholesterol assay compared with the ultracentrifugation-dextran sulfate-Mg^{2+} method. Clinical Chemistry. 1998; 44(6): 1242-50.
19. Tunbridge WMG, Evered DC, Hall R, Appleton D, Brewis M, Clark F et al. Lipid profiles and cardiovascular disease in the Wickham areas with particular reference to thyroid failure. Clinical Endocrinology. 1977; 7: 495–508.
20. Pucci E, Chiovato L & Pinchera A. Thyroid and lipid metabolism. International Journal of Obesity 2000; 24 (Suppl 2): S109–S112.
21. Kahaly GJ. Cardiovascular and atherogenic aspects of subclinical hypothyroidism. Thyroid 2000 10 665–679.
22. Cooper DS. Subclinical thyroid disease: a clinician's perspective. Annals of Internal Medicine 1998 129 135–138.
23. Saito I, Saruta T 1994 Hypertension in thyroid disorders. Endocrinol Metab Clin North Am 23:379–386.
24. Canaris GJ, Manowitz NR, Major G, Ridgway C 2000 The Colorado thyroid disease prevalence study. Ann Intern Med. 160:526–534.
25. Forfar JC, Wathen CG, Todd WT, Bell GM, Hannan WJ, MuirAL, Toft AD 1985 Left ventricular performance in subclinical hypothyroidism. Q J Med 224:857–865.
26. Biondi B, Fazio S, Palmieri EA, Carella C, Panza N, Cittadini A, Bone F, Lombardi G, Sacca L 1999 Left ventricular diastolic dysfunction in patients with subclinical hypothyroidism. J Clin Endocrinol Metab 84:2064–2067.
27. Ojamaa K, Klemperer JD, Klein I 1996 Acute effects of thyroid hormone on vascular smooth muscle. Thyroid. 6:505–512.
28. Kung AWC, Pang RWC, Janus ED 1995 Elevated serum lipoprotein (a) in subclinical hypothyroidism. Clin Endocrinol. 63:445–449.
29. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on

Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) 2001 JAMA 285: 2486–2497.

30. Brewer HB 1999 Hypertriglyceridemia: Changes in the plasma lipoproteins associated with an increased risk of cardiovascular disease. Am J Cardiol 83:3F–12F.
31. Assmann G, Schutt H, Von Eckardstein A 1996 Hypertriglyceridemia and elevated lipoprotein (a) are risk factors for major coronary events in middle aged men. Am J Cardiol 77:1179–1184.
32. Austin MA 1999 Epidemiology of hypertriglyceridemia and cardiovascular disease. Am J Cardiol 83:13F–16F.

***Corresponding Author:**
Dr. ANAND PYATI*[1]
Department of Biochemistry,
BLDEU's Shri B M Patil Medical College,
Bijapur, Karnataka.
e-mail: *anandpyati999@gmail.com*