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Subclinical hypothyroidism in India: an imperative risk for coronary artery disease (CAD)

Abstract

The study is planned to detect the prevalence of sub clinical hypothyroidism in healthy urban population of India and to assess the risk of CAD in them. After informed consent, age related 678 consecutively seen normal individuals of mid to high socio economic status were enrolled for the study. Battery of investigations included fasting and postprandial (pp) state plasma glucose, serum lipid profile (Cholesterol, HDL, LDL and Triglycerides) and thyroid markers (fT3, fT4 and TSH). The tests were done on Beckman CX5 auto analyzer except thyroid profile which was analyzed on Roche Elecsys 2010 analyzer. Body mass index (BMI) was calculated. To rule out reversible cardiac ischaemia in these individuals, they were subjected to Tread Mill Test. Out of total population, 87% individuals were euthyroids having normal serum TSH (group I) and 13% of population had subclinical hypothyroidism (Group II) with moderate rise in serum TSH levels(group II, $p<0.001$). Male to female sex ratio in group I was 4:1 as compared to 3:2 in group II. S cholesterol and triglyceride levels were moderately high but comparable in both the groups. The serum HDL and LDL levels were also comparable in both these groups ($p<0.61$ & 0.63 respectively). No significant difference was found in BMI. Individuals with pp plasma glucose of more than 140mg/dL or prior history of high blood glucose (fasting>126 and pp>140mg/dL) were labeled as diabetics. No statistical difference was found in its prevalence in both these groups ($p<0.26$). Patients who showed positive TMT were labeled as CAD positive. The number of CAD positive individuals in group II was more ($p<0.001$) therefore it is concluded that a large number (13%) of random urban population of India is affected by subclinical hypothyroidism. Hyperlipidemia and positive TMT may put them at a risk of CAD.

Keywords: subclinical, hypothyroidism, urban, population, hyperlipidemia

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Abbreviations: CAD, coronary artery disease; PP, post prandial; TSH, thyroid stimulating hormone; BMI, body mass index; HDL, high density lipoprotein; LDL, low density lipoprotein; SCH, sub clinical hypothyroidism; CH, coronary heart disease; TMT, tread mill test

Introduction

Accurate diagnosis and treatment of subclinical hypothyroidism (SCH) is challenging in clinical practice because normal limits of TSH differs in various studies.[1] Subclinical Hypothyroidism (SCH) is defined as mild elevation in serum TSH levels with normal fT3 and fT4 concentration. The prevalence of this disease is 4-10% in the general population of United States. Up to 20% women older than 60 years of age are affected with subclinical hypothyroidism in their study.[2,3] It is also known that the SCH is more prevalent in elderly age group (over 50 years) because TSH increases with age.[4] The disease is more common in women than in men. Franklyn has shown its prevalence in women (7.5%) than in men where occurrence was only 2.8% of total population.[5] The importance of sub marginal elevation of TSH values is not known however elevated levels are associated with abnormalities of lipid metabolism (increased total cholesterol and low density lipoprotein cholesterol) that can lead to coronary artery disease and depression.[6,7] It is also associated with endothelial dysfunction,[8] aortic atherosclerosis and myocardial infarction.[9] A search of database of Medline and Embase by Rodondi et al.[10] has suggested that subclinical hypothyroidism is associated with an increased risk of coronary heart disease.[10] According to them, subclinical hypothyroidism is associated with an increased risk of CHD events and CHD mortality in those with higher TSH levels, particularly with TSH of 10μIU/L or greater. This report has shown the implication of SCH as a risk factor for CAD. The study was compiled from the data of 11 prospective cohorts in the United States, Europe, Australia, Brazil, and Japan.[10] There is paucity of similar information from developing countries like India. Therefore this study was planned to assess the prevalence of subclinical hypothyroidism in healthy urban population of India belonging to mid to high socioeconomic strata and the risk of coronary artery disease in affected individuals.

Materials and methods

After informed consent, age related 678 consecutively seen asymptomatic normal individuals were included in the study. They belonged to mid to high socioeconomic strata. The test population was comprised of 77% males (n=526) and 23% females (n=152). Detailed data from their clinical, biochemical and cardiac examination was collected. Biochemical investigations included fasting and Post Prandial (PP) plasma glucose, S total cholesterol, HDL, LDL cholesterol and serum triglycerides. These tests were processed on Beckman CX5CE auto analyzer. Serum fT3, fT4 and TSH were analyzed on Roche 2010 electrochemiluminiscence analyzer. Test population was divided into 2 groups depending on their serum TSH levels. Group I is consisted of euthyroid individuals with normal S TSH and group II had subclinical hypothyroid patients. Serum TSH was high in these patients. The incidence of hypertension and diabetes in these individuals was compared. The patients recently diagnosed

with high post prandial glucose (>140mg/dl) or previous history of diabetes were labeled as diabetics. Individuals detected recently with high blood pressure (over 80/120mm) or the treated cases of high BP were categorized as hypertensive. Body mass index (BMI) was calculated using the weight and height data and was expressed as Kg/m^2. TMT was performed in all cases to detect reversible ischemia in these individuals.

Statistical analysis

Statistical analysis was done using student's t test and Pearson chi square test. P value less than 0.05 was taken as significant.

Results and discussion

After detailed inquest, out of 678 subjects, eighty eight individuals (Group II, 13%) had serum TSH levels in the range of 4.27-13.05µIU/mL (8.66±4.39, p<0.001) with normal fT4 levels. Remaining 590 individuals (87%) had normal serum TSH (Group I) with normal fT4. A significant difference is found in fT4 values of individuals from both these groups (p<0.01). Male-female sex ratio in group I was 4:1 (p<0.958) whereas in group II, it was 3:2 (p<0.85) (Table 1). Subjects from both the groups had increased levels of triglycerides (168.2 vs. 158.3mg/dL, p<0.33), therefore no direct correlation was established between high serum triglycerides and increased TSH levels. No statistical difference was found in BMI of individuals of both the groups (p<0.069) (Table 2). No significant correlation of subclinical hypothyroidism was found with diabetes and hypertension (p<0.26 and <0.69). However, there was a direct correlation between coronary artery disease (TMT positive cases) and subclinical hypothyroidism. Numbers of positive cases were more in group II when compared to group I (12.8% 4 Vs 2.8%, p<0.001). This may be due to cardiotoxic effects of increased thyrotropin levels in group II. No history of bradycardia was found in any of these individuals (Table 3).

Table 1 Demographic details of sample population

Demographic details	Overall population (n = 678)		Group I euthyroid (n= 590)		Group II hypothyroid (n =88)	
Sex	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
No. of Patients	526	152	473	117	53	35
Percentage (%)	77	23	80	20	60	40
M:F Sex Ratio				4:1		3:2
Age (yrs) (Mean ± SD)	48.6±11.8	48.8±10.35	47.8±11.1	47.7±10.7	49.4±12.5	49.9±10.0
p VALUE S		NS		<0.95		<0.85

Table 2 Serum biochemistry of sample population

Serum biochemistry	Group I (Euthyroid) (n=590)	Group II (Hypothyroid) (n=88)	Biological reference interval	P value
Fasting Plasma Glucose(mg/dL)	108.1±35.85	100.2±20.2	76-110	< 0.003
Postprandial Plasma Glucose(mg/dL)	117.1±56.4	111.89±49	< 140	< 0.412
Cholesterol(mg/dL)	193.8±38.6	200±43.24	<200	<0.259
HdL Cholesterol(mg/dL)	41.7±9.49	42.08±9.57	<40	<0.61
LdL Cholesterol(mg/dL)	127.02±32.8	128.95±36.67	<130	<0.63
Triglyceride(mg/dL)	157.52±87.6	168.14±101.32	<150	<0.33
Body Mass Index(BMI) (Kg/m^2)	26.5±3.86	27.34±3.95	23-25	<0.069
fT3(pmol/L)	4.5±0.85	4.45±1.02	2.8-7.1	<0.61
fT4(pmol/L)	15.6±2.47	13.99±2.87	12-22	**<0.00**
TSH (µIU/mL)	2.18±0.93	8.66±4.39	0.27-4.2	**<0.000**

Table 3 Clinical details of sample population

Clinical condition	Group I (Euthyroid) (n=590)			Group II (Hypothyroid) (n=88)			p value
	Negative (n)	Positive (n)	% Frequency of disease	Negative (n)	Positive (n)	% Frequency of disease	
Diabetes	473	117	19.80%	75	13	14.70%	<0.26
Hypertension	434	156	26.40%	63	25	28.00%	<0.69
Bradycardia	None	--	--	None	--	--	--
Coronary artery disease	573	17	2. 80 %	78	10	12. 80 %	<0.004

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This is the first report from Indian subcontinent showing prevalence of subclinical hypothyroidism in large number of individuals (13%) belonging to middle income group from the northern India. Their serum TSH concentration was significantly high when compared to euthyroids ($p<0.000$) .The fT4 concentration in these subjects was within normal range but significantly lower than the control population ($p<0.00$).

The affected individuals were asymptomatic and unaware of the fact that this condition may lead to frank hypothyroidism if not treated early. The cause can be attributed to Iodine deficiency. The deficiency is largely found in northern part of India.[11] A similar study of higher incidence of SCH (19.7%) has been reported by Kvetny et al.[8] in Danish population, possibly due to the presence of iodine deficiency in the region of Jutland where this study was conducted.[8] However, the cutoff for S TSH was different in Danish population and Indian population. The criteria for defining subclinical hypothyroidism in Danish population was over 3µU/mL with normal fT3 and fT4 concentration whereas in our sample population the subclinical hypothyroidism was characterized as S TSH>4.2µU/mL and normal fT3 and fT4 concentration. Therefore the individuals having TSH in between 3-4.2µU/mL were labeled as normal in our population whereas it was SCH in Danish population. This can also be due to racial differences between the two populations. In the general population of United States the prevalence of the disease was only 4-10%.[2,3] It is important to note that subclinical hypothyroidism is only laboratory evaluation based diagnosis with no clinical signs or symptoms. It is defined as an elevation in serum thyroid stimulating hormone (TSH) above the reference range with normal fT3 and fT4 concentrations. This represents the earliest stage of thyroid dysfunction. Although the condition represents the early stage of thyroid dysfunction, the benefits of detecting and treating subclinical disease are not yet clearly established.[12] It is shown that SCH is more prevalent in females. A large study demonstrated a prevalence of elevated TSH in 16% of men and 21% of females over the age of 74 years.[3] In our sample population, there was more number of females in hypothyroid group (Group II, 40%) as compared to euthyroid group (20%). The Whickham survey has also shown a high risk of overt hypothyroidism in women having high serum thyrotropin levels.[13] In our test population we found more number of CAD cases in group II than in group I. This can be attributed to high serum triglyceride levels in them. It is interesting to note that the eating habits of north Indians involve consumption of lot of fried stuff, which may raise their triglyceride levels significantly. The association of cardiovascular disease with subclinical hypothyroidism has been described by many investigators. Kvetny et al.[8] have shown higher frequency of cardio vascular disease in young hypothyroid males with age below 50 years.[8] They also describe high triglyceride levels as one of the reason for this. Hypothyroidism is also known to exert effect on hepatic triglycerides assembly and secretion.[14]

Conclusion

Our study demonstrates that approximately 13% of random urban population of India belonging to mid to high socioeconomic strata carries subclinical hypothyroidism. The subjects with subclinical hypothyroidism have elevated serum levels of LDL cholesterol and Triglycerides, which might account for the increased risk of CAD in them. The high risk of developing overt hypothyroidism in them, if remain untreated. Screening of the general population to trace these subjects and treat the subclinical hypothyroidism would be a new approach to reduce the risk of CAD in them. Studies to investigate the molecular basis of this syndrome are warranted.

Consent

The individuals visited our center for primary health check up screening and lab test was the part of their paid package. The study is based on the compilation and analysis of data retrospectively obtained from the lab tests done. Therefore the written consent could not be obtained from them.

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None.

Conflict of interest

There is no conflict of interest with that could be perceived as prejudicing the impartiality of the research reported.

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