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Original Research Article

Prevalence of subclinical hypothyroidism in children and adolescents of northern Andhra Pradesh population and its association with hyperlipidemia

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ABSTRACT

Background: The thyroid dysfunction particularly, subclinical hypothyroidism (SCH) is quite a common clinical condition in paediatric population but there is limited data available regarding its prevalence in children and adolescents in our population. The present study was aimed to know the prevalence of thyroid dysfunction particularly SCH in children and adolescents of northern Andhra Pradesh population and its association with hyperlipidemia.
Methods: A retrospective study of 600 subjects (Children=272, Adolescents=328) between 6-19 years of age were included and the following parameters were examined: age, sex, total triiodothyronine (tT3), total tetraiodothyronine (tT4), thyroid stimulating hormone (TSH), total cholesterol, triglycerides (TGL), LDL and HDL cholesterol. The subjects were divided into group I and group II on the basis of age (in years), subjects between 6- ≤12 years age were grouped as group I and 12-≤19 years were as group II.
Results: Out of 272 children and 328 adolescents studied, the prevalence of thyroid dysfunction was found to be 9.9% and 10.4 % respectively. The prevalence of subclinical hypothyroidism in children was 7.7% where as 4.9% in adolescents. In both the groups, females were predominantly affected with thyroid dysfunction as compared to males. Significantly elevated serum levels of total cholesterol, TSH and TGL were observed in SCH subjects when compared to euthyroid subjects ($p<0.05$). Statistically significant lower levels of HDL cholesterol were found in SCH as compared to euthyroids ($p<0.05$). However, no difference was noticed in the levels of total T3, total T4 and LDL cholesterol between SCH and euthyroids.
Conclusions: The prevalence of thyroid dysfunction was found to be 10.2% in study population. SCH was observed in 7.7 % and 4.9% respectively in children and adolescent groups. Subclinical hypothyroidism (SCH) was the most predominant thyroid dysfunction found in our studied population with a prevalence of 6.2% (both children and adolescents). Correction of thyroid dysfunction particularly SCH in early childhood is highly essential to prevent the impairment of psychomotor and cognitive development.

Keywords: Euthyroid, Hyperlipidaemia, HDL, Overt hypothyroidism, Total cholesterol, Subclinical hypothyroidism

INTRODUCTION

Thyroid hormones play an invaluable role in maintenance of growth, metabolism and mental development in infants and children. The prevalence of thyroid dysfunction depends not only on gender, age, ethnic and geographical background and but most importantly on iodine intake. Thyroid disorders are still prevalent in many parts of India despite successful implementation of National Iodine Deficiency Diseases Control Program (NIDDCP).[1]

Recently, Marwaha et al., conducted a large nationwide survey on the thyroid status after salt iodization in India and found that the prevalence of subclinical hypothyroidism (SCH) and overt hypothyroidism (OH) was 6.1% and 0.4% respectively.[2] The most common presenting symptom of hypothyroidism in children is declining height velocity that results in short stature. It is insidious in onset, and it may be present for several years before other symptoms develop.[3] Thus, any child with declining height velocity should be evaluated for hypothyroidism. SCH is a biochemical condition characterized by serum levels of thyroid stimulating hormone (TSH) above the statistically defined upper limit of reference range in the presence of normal concentration of total T_4 or free T_4, and without clinical features of hypothyroidism.[4] SCH is mostly detected accidentally as most of the patients manifest few or no significant signs of thyroid dysfunction. However, goiter, poor school performance, weight gain, increased cholesterol levels, impaired growth velocity, excessive sleepiness, impaired psychomotor and cognitive development are the most frequently found abnormalities in paediatric population.[5] The most common causative factor for SCH is chronic autoimmune thyroiditis characterized by high titers of thyroid peroxidase antibodies, thyroglobulin antibodies and rarely TSH receptor blocking antibodies.[6] However, mutations in several proteins involved in TSH action including TSH receptor gene and mutations of dual oxidase 2 (DUOX2), phosphodiesterase 8B and thyroidperoxidase have also been demonstrated as causes of TSH elevation.[7-10]

Although some clinicians consider SCH as a benign normal variation and thyroid hormone can be supplemented to lower the TSH levels and the exact cause of TSH elevation is unknown. But recent studies show higher mortality rates in young hypothyroid adults due to coronary heart disease and high TSH levels signify the importance of SCH and proving that SCH is not harmless.[11] However, studies exploring the thyroid dysfunction in children and adolescents in our population are few with differing conclusions. Hence, the present retrospective study was taken with an aim to know the prevalence of thyroid dysfunction particularly SCH in children and adolescents of northern Andhra Pradesh population and its association with hyperlipidemia.

METHODS

In this retrospective study, the subjects who have visited Paediatric and General Medicine outpatient departments of Anil Neerukonda Hospital for different medical problems from Mar 2016 to June 2017 between 6-19 years of age were included (n=600) (Children=272, Adolescents=328), whose thyroid profile and lipid profile were analyzed.

The subjects aged between 6-12 years (children) were named as group I and 12-19 years (adolescents) were as group II. The medical diseases or drugs that affect thyroid dysfunction were excluded from the study. Since the analysis of both group I and group II was based on the preexisting data available with hospital information system, informed consent was not taken from the subjects. The study was approved by the Ethics Committee of Anil Neerukonda Hospital. Thyroid dysfunction (hypothyroidism, subclinical hypothyroidism, hyperthyroidism and subclinical hyperthyroidism) was defined as per the standard cut offs of T_3, T_4 and TSH in different age groups of manufacturer's manuals. The following cuts off values were considered to diagnose the thyroid dysfunction as mentioned in manufacturer's manual.

Table 1: Values to diagnose thyroid function.

For	Total T3 (ng/mL)	Total T4 (µg/dL)	TSH (µIU/mL)
6-10 years	0.8-2.4	6.3-13.2	0.25-5
11-15 years	0.8-2.15	5.5-11.8	0.25-5
16-20 years	0.8-2.15	4.2-11.8	0.25-5

Finally, an attempt was made to know the association of studied biochemical parameters with SCH and euthyroid subjects. The difference in the concentrations of biochemical parameters between both the groups was evaluated by student's t test, one-way analysis of variance and the p-value of <0.05 was considered to be significant.

RESULTS

Table 2: Anthropometric and baseline biochemical characteristics of study population.

Parameter	Group I (children age 6-≤12 years) (n=272)	Group II (adolescents 12-≤19 years) (n=328)
Age (in years)	8.64±1.75	14.3±2.53
Gender Males (n=250) Females (n=350)	 122 (44.9%) 150 (55.1%)	 128 (39%) 200 (61%)
Total cholesterol (mg/dl)	146±14.5	145±13.9
Triglycerides(TGL) (mg/dl)	60.4±11.2	56±11.2
HDL cholesterol (mg/dl)	38.1±3.15	37.3±1.7
LDL cholesterol (mg/dl)	115±26.6	119±27.9
Total T_3 (ng/ml)	1.36±0.30	1.34±0.23
Total T_4 (µg/dl)	7.81±1.12	7.81±0.99
Thyroid stimulating hormone (TSH) (µiu/ml)	2.82±1.72	2.51±1.55

In the present study, 272 children (male: female=122:150) and 328 adolescents (male: female=128:200) with a mean age (in years) of 8.64±1.75 and 14.3±2.53 respectively were evaluated. The base line characteristics such as age, gender, thyroid profile and lipid profile are depicted in Table 2.

Table 3: Distribution of thyroid dysfunction in children and adolescents of study population.

Thyroid function	Group I (children, n=272) (%)	Group II (adolescents, n=328) (%)
Euthyroid	245 (90.1)	294 (89.6)
Overt hypothyroidism (OH)	5 (1.8%	15 (4.6)
Subclinical hypothyroidism (SCH)	21 (7.7)	16 (4.9)
Overt hyperthyroidism	1 (0.4)	3 (0.9)

The mean ±SD of serum total cholesterol (mg/dL), triglycerides (TGL) (mg/dL), high density lipoproteins (HDL) (mg/dL) and low-density lipoproteins (LDL) cholesterol of group I and group II were 146±14.5, 145±13.9, 60.4±11.2, 56±11.2, 38.1±3.15, 37.3±1.7 and 115±26.6, 119±27.9 respectively. Similarly, mean ±SD of serum total triiodothyronine (tT3) (ng/mL), total tetraiodothyronine (tT4) (µg/dL) and TSH (µIU/mL) of group I and group II were 1.36±0.30, 1.34±0.23; 7.81±1.12, 7.81±0.99 and 2.82±1.72, 2.51±1.55 respectively (Table 3). The distribution of thyroid dysfunction in both children and adolescent groups has been given in Table 3 and Figure 1. Out of 272 children studied in group I, 245 (90.1%) were found to be euthyroid, 27 (9.9%) were found to be having thyroid dysfunction.

Similarly, in adolescents, the thyroid dysfunction was found to be in 34 cases (10.4%). In both the groups, SCH was found to be having more number of subjects as compared to other types of dysfunction. Among 272 subjects of group I, 21 (7.7%) subjects were affected with SCH whereas 16 (4.9%) were affected in adolescents (Table 3).

Table 4: Classification of thyroid dysfunction according to age and gender in study population.

Thyroid function	Group I (n=272)		Group II (n=328)	
	Males (n=122) (%)	Females (n=150) (%)	Males (n=128) (%)	Females (n=200) (%)
Euthyroid	113 (92.6)	132 (88)	116 (90.6)	178 (89)
Overt hypothyroidism	2 (1.6)	3 (2)	6 (4.7)	9 (4.5)
Subclinical hypothyroidism	7 (5.7)	14 (9.3)	5 (3.9)	11 (5.5)
Overt hyperthyroidism	0	1 (0.7%)	1 (0.8%)	2 (1%)

Table 5: Differences in biochemical parameters in euthyroid and subclinical hypothyroidism of study population.

Biochemical parameter	Euthyroid (n=539)	Subclinical hypothyroidism (n=37)	P-value
Total t3 (ng/ml)	1.35±0.23	1.32±0.52	0.49
Total t4 (µg/dl)	7.86±0.91	7.63±0.70	0.13
TSH (µIU/ml)	2.19±0.48	7.56±1.51	<0.001*
Total cholesterol (mg/dl)	142±10.6	176±5.8	<0.001*
TGL (mg/dl)	54.9±6.19	87.7±6.12	<0.001*
HDL (mg/dl)	38.1±2.26	34±1.14	<0.001*
LDL (mg/dl)	116±27.8	118±28.2	0.67

Note: p-value <0.05* significant

Out of 122 males studied in group I, the thyroid dysfunction found to be having 9 cases where as in adolescents it was found to be in 12 cases out of 128 subjects studied. In a similar manner, out of 150 female children, 18 were found to be suffering from thyroid dysfunction. However, in group II, thyroid dysfunction has been noticed in 12 males and 22 female subjects which is little higher as compared to group I. In both the groups, female subjects were observed to be predominant over the males (Table 4). Finally, an attempt was made to know the differences in biochemical parameters of euthyroid and SCH subjects and the data has been given in Table 5. The mean ±SD of tT3, tT4 and TSH of euthyroid and SCH subjects were 1.35±0.23, 1.32±0.52; 7.86±0.91, 7.63±0.70; and 2.19±0.48, 7.56±1.51 respectively. Significantly elevated levels of TSH were observed in SCH subjects as compared to euthyroid subjects ($p<0.05$). However, no significant difference was noticed in the levels of tT3 and tT4 between euthyroid and SCH subjects. Similarly, the mean ±SD of total cholesterol (mg/dL), TGL (mg/dL), HDL and LDL cholesterol (mg/dL) of euthyroid and SCH subjects were 142±10.6, 176±5.8; 54.9±6.19, 87.7±6.12, 38.1±2.26,

34±1.14 and 116±27.8, 118±28.2 respectively. Statistically significant higher levels of total cholesterol, TGL and lower levels of HDL cholesterol were noticed in SCH subjects as compared to euthyroid group ($p<0.05$, $p<0.05$ and $p<0.05$ respectively) whereas no significant difference was observed in the serum levels of LDL cholesterol between both the groups.

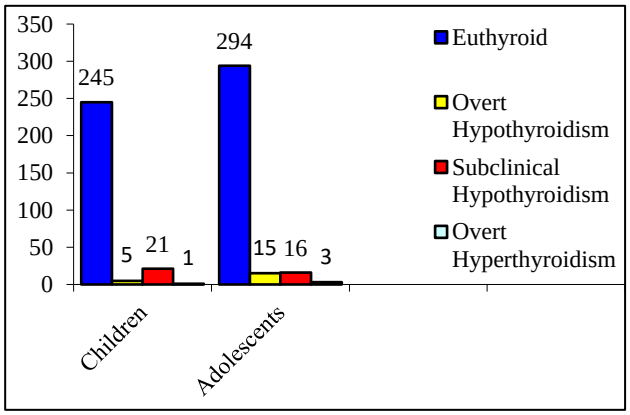

Figure 1: Comparative distribution of thyroid function in children and adolescents of study population.

DISCUSSION

It is a well-known fact that thyroid hormone is essential for the growth and maturation of many target tissues, including the brain and skeleton. As a result, altered thyroid gland function in infancy and childhood affect not only in the metabolic consequences of thyroid dysfunction as in adult patients, but also in unique effects on the growth and /or maturation of thyroid hormone-dependent tissues. It has been observed from various studies that about 42 million people in India suffer from thyroid disease.[12]

In this retrospective study, out of 600 subjects of both children and adolescents studied, the thyroid dysfunction was found to be 10.2 %. Our results were in accordance with the previous study where the prevalence was 9.18%.[13] In a population based study from India, it has been observed that 12% of children aged 5-16 years were found to have thyroid dysfunction in which TSH levels above the reference range.[14] However, the prevalence of thyroid dysfunction in children and adolescents is lesser than adult population where the prevalence was found 19.6%.[15]

The prevalence of thyroid dysfunction was found to be higher in female population (12%) as compared to males (7.4%) in children and adolescent's groups (12 % vs 7.4% and 10% vs 9.4% respectively). Similar results were also explained by Lakshminarayana et al., where the females have higher prevalence in both children and adolescent groups.[13] The higher prevalence of thyroid dysfunction in young females can be attributed to the difference in sex hormones and pubertal growth pattern.

Congenital hypothyroidism is more frequent in newborns with Down syndrome (DS) than in the healthy children population.[16] It has been suggested that some patients with SCH have functional, clinical, or biochemical reflections of hypothyroidism that are more common than age-matched controls.[17] The most commonly observed abnormalities in the pediatric population include weight gain, increased cholesterol levels, impaired growth velocity, anemia, sleepiness, weakness, and impaired psychomotor and cognitive development.[5] It was observed that SCH has been associated with hypercholesterolemia, atherosclerosis and ultimately coronary heart disease mostly in those with a TSH concentration of 10 mIU/L or more.[18] In the present study, the SCH was the most prevalent thyroid abnormality found in the study population of children and adolescents (6.2%). Our results were in consistent with the earlier studies carried out by Marwaha et al., and Lakshminarayana et al., where the incidence was 6.1% and 4.1% respectively.[2,13] Among the children group, the prevalence was 7.7% where as 4.9% in adolescent group. In both the groups, female subjects have the higher prevalence of thyroid dysfunction, SCH. Similar trend was also observed in earlier studies.[2,13]

According to research data, the natural course of SCH in adults seem to progress to overt hypothyroidism in proportions ranging from 1 up to 20%.[19] However, most recent longitudinal studies show that at about 1/3 of patients with SCH has normalization of TSH in due course of time whereas most of the rest have persistent mild TSH elevation, in which causes of SCH will be considered. In a recent prospective study, it has been observed that out of 92 children between 5-15 years of age with "idiopathic" SCH, 38 patients had normal TSH levels (none in the first 6 months, 16 between 6 and 12 months and 22 between 12 and 24 months).[20] The most common cause of acquired OH in both children and adults is autoimmune or Hashimoto's thyroiditis (AIT).[21] In India, a very few prospective studies were conducted to evaluate the natural progression of SCH to overt hypothyroidism in pediatric age group. In a cohort study of SCH, autoimmune thyroiditis (AIT) and goiter were followed and found that the development of hypothyroidism was 12.5%. Similarly, in another prospective study by Lazar et al., followed SCH children for 5 years and found that 73.6% of them normalized TSH.[22] On the contrary, none of the SCH children has developed overt hypothyroidism in another study.[23]

Total cholesterol and LDL levels are increased in overt hypothyroidism despite the decreased thyroid function is accompanied by reduced activity of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG-Co A reductase). This may be due to decreased LDL-receptors activity that results in decreased catabolism of LDL and IDL.[24] In the present study, overt hypothyroidism was found to be in 20 subjects, 5 (1.8%) and 15 (4.1%) in children and adolescents respectively. In both the groups, females were more prone for this type of dysfunction. Our results

were in accordance with the earlier study where the prevalence was identified as 3.05%.25 On the contrary, a lesser prevalence of 0.4% was also claimed in another study.[2] However, the prevalence of overt hypothyroidism was higher in adolescent group than children group, (4.6% versus 1.8%).

Out of 600 subjects studied (children and adolescents), the prevalence of hyperthyroidism was found to be in 5 subjects (0.7%). Among children group, only 1 subject (0.4%) was affected with overt hyperthyroidism where as in adolescents 3 (0.9%) were affected. The prevalence of hyperthyroidism is known to increase during childhood and reaches its peak during adolescent age and also is more common in females than males.[25]

It is well known that thyroid dysfunction adversely affects the lipid metabolism. Cumulative evidence shows that both overt hypothyroidism and SCH can result in hyperlipidemia that may lead to increased risk of cardiovascular disease.[26] Increased cholesterol synthesis and absorption, decreased hepatic lipase and lipoprotein lipase activities and defect in the receptor mediated catabolism of LDL cholesterol are the reasons for the elevated LDL cholesterol level in hypothyroidism. The elevation in LDL cholesterol levels may be accompanied by increased formation of oxidized LDL cholesterol which in turn causes enhanced risk of atherosclerosis.[27]

A significant association was observed by some authors between SCH and a higher risk of hypertension and dyslipidemia.[28] Patients with TSH concentration ≥10 mIU/L are at a greater risk of developing coronary heart disease, heart failure with low ejection fraction as compared to population with normal thyroid function.[29] However, the relationship between SCH and dyslipidemia is still controversial.

In the present study, significantly higher levels of cholesterol, TGL and lower levels of HDL cholesterol were found in SCH subjects when compared to euthyroid subjects. However, no significant variation of LDL levels was found between SCH and euthyroid groups. At a younger age, it was noticed that SCH has more severe pathophysiological effects resulting in vascular disease, endothelial dysfunction or a direct effect on myocardium.[30] Our results were in association with Lai et al., where the higher levels of TGL and Lower HDL levels were observed.[31] Similarly, Iqbal et al., also claimed similar results in SCH patients after performing a follow-up study in males, whereas increased cholesterol, LDL cholesterol and apo B levels in females.[32] On the contrary, total cholesterol levels were not found to be elevated in Rottedam study.[30]

Earlier and recent studies also show that T_4 replacement therapy may improve lipid profile and LDL to HDL cholesterol ratio in the cases of subclinical hypothyroidism with Hashimoto thyroiditis.[32] In another study, a significant reduction in the concentrations of total cholesterol, non-HDL and apo-B was found, but without significant changes in the serum concentrations of LDL, HDL cholesterol, TGL, apolipoprotein A-I, and Lp(a) after levo-thyroxine replacement.[33] The reduction in total cholesterol levels were inversely correlated with an increase in free T_4 levels, but not correlated with changes in TSH levels.[34]

CONCLUSION

The prevalence of thyroid dysfunction was found to be 10.2% in study population. SCH was observed in 7.7 % and 4.9% respectively in children and adolescent groups. Subclinical hypothyroidism (SCH) was the most predominant thyroid dysfunction found in our studied population with a prevalence of 6.2% (both children and adolescents). Correction of thyroid dysfunction particularly SCH in early childhood is highly essential to prevent the impairment of psychomotor and cognitive development. There is a need for large prospective studies designed to conclude whether thyroid abnormalities (and particularly SCH) are associated with CVD.

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