STUDY OF CLINICAL AND BIOCHEMICAL PROFILE OF SUBCLINICAL HYPOTHYROIDISM IN CHILDREN

Dissertation submitted for

M.D., DEGREE EXAMINATION

BRANCH VII PEDIATRIC MEDICINE

THE TAMIL NADU DR.M.G.R MEDICAL UNIVERSITY

CHENNAI

INSTITUTE OF CHILD HEALTH AND HOSPITAL FOR CHILDREN
MADRAS MEDICAL COLLEGE
CHENNAI

APRIL 2017

CERTIFICATE

This is to certify that the dissertation titled **STUDY OF CLINICAL AND BIOCHEMICAL PROFILE OF SUBCLINICAL HYPOTHYROIDISM IN CHILDREN** submitted by **DR.POORNACHAND.V** to the Faculty of Pediatrics, **THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY, CHENNAI** in partial fulfillment of the requirements for the award of **M.D., DEGREE (PEDIATRICS)** is a bonafide research work carried out by him under our direct supervision and guidance.

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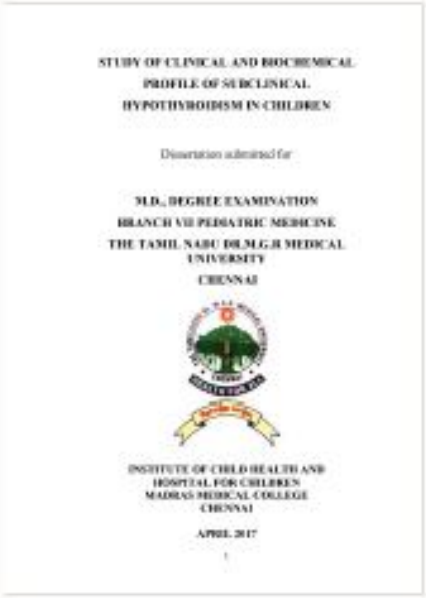

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ABBREVATIONS

Ad-SOS	–	Amplitude dependent Speed of Sound.
AIT	–	Autoimmune Thyroiditis.
ATP	–	Adenosine Tri-Phosphate.
BA	-	Bone Age.
BMD	–	Bone Mineral Density.
BMI	–	Body Mass Index.
BTT	–	Bone Transmission Time.
CA	–	Chronological Age.
DBP	–	Diastolic Blood Pressure.
DIT	–	Diiodotyronine.
DXA	–	Dual energy X-ray Densitometry.
FSH	–	Follicle Stimulating Hormone.
HCG	–	Human Chorionic Gonadotropin.
HDL	–	High Density Lipoprotein.
IVRT	–	Isovolumic Relaxation Time.
IVS	–	Interventricular Septum.
LH	–	Leutenizing Hormone.
LVIDd	–	Left Ventricular Internal Diameter diastole.
LVIDs	–	Left Ventricular Internal Diameter systole.
LVPW	–	Left Ventricular Posterior Wall Thickness.
MIT	–	Monoiodotyrosine.
NIS	–	Sodium (Na^+) Iodide Symporter.
PCT	–	Precontraction Time.

QUS – Quantitative Ultrasound.

RT3 – Reverse Triiodotyrosine.

RXR – Retinoid X Receptor.

SCH – Subclinical Hypothyroidism.

T3 – Triiodothyronine.

T4 – Thyroxine.

TBG – Thyroid Binding Globulin.

TDE – Tissue Doppler Echo.

TG – Thyro Globulin.

TPO – Thyroid Peroxidase.

TRE – Thyroid Response Element.

TRH – Thyrotropin Releasing Hormone.

TSH – Thyroid Stimulating Hormone.

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INTRODUCTION

Thyroid hormones Thyroxine (T4) and Triiodothyronine (T3) exert important effects on growth and development including early effect on central nervous system development, regulation of body temperature, and influence on various metabolic pathways. Disorders of thyroid gland are common forms of childhood endocrinal disorders encountered in day to day clinical practice.

DEVELOPMENT[1]

"Thyroid is the first endocrine organ to develop by 5^{th} week of gestation". It originates from two structures - neural crest and primitive pharynx.

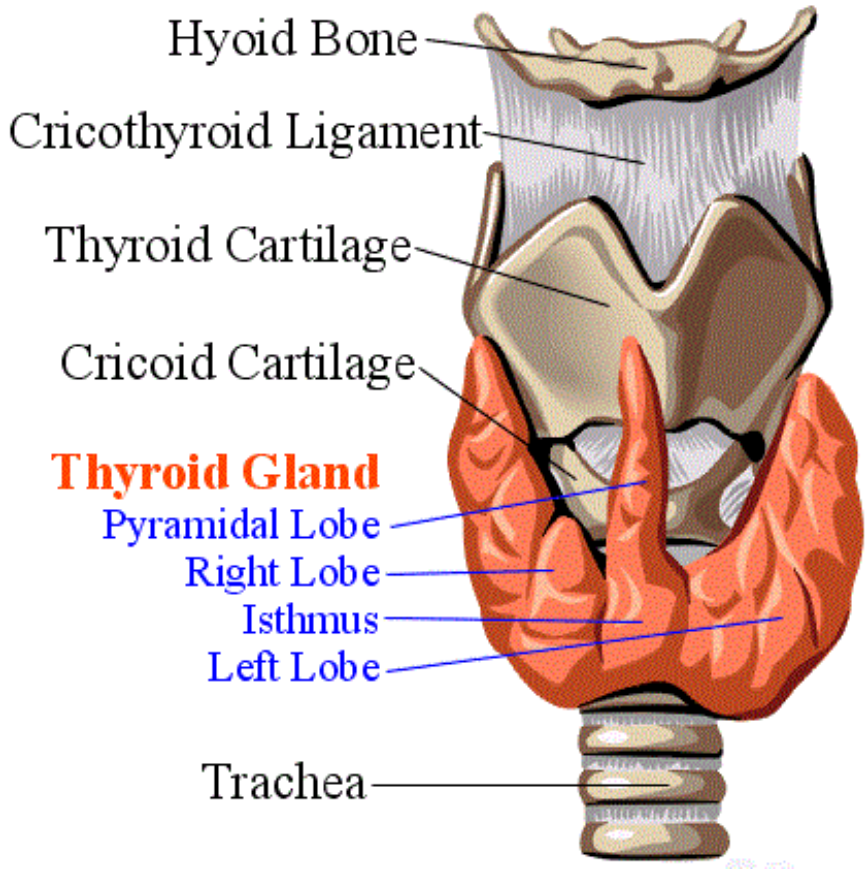
Proliferation of endodermal epithelial cells on the median surface of developing floor of the pharynx forms thyroid gland.

ANATOMY[2]

Thyroid gland is the largest endocrine organ. It is situated in front of the larynx between cricoid cartilage and sternum. The gland is bi-lobed (right and left lobes), connected by narrow bridge of tissue called Thyroid Isthmus. Sometimes pyramidal lobe arises from Isthmus.

Thyroid gland is highly vascular, the blood supply is derived from Superior and Inferior Thyroid Arteries (originating from external carotid artery) and an inconstant artery called Thyroidea ima. Venous blood drains into venous plexus present in the fibrous capsule. Thyroid has also got rich a

lymphatic supply. Superior portion and Isthmus of the gland drains into Internal Jugular lymph nodes, inferior portion of the gland drains into pre and paratracheal group of lymph nodes.



HISTOLOGY[3]

Thyroid gland contains two functionally and morphologically distinct endocrine systems.

The gland is covered by fibrous capsule. It is divided into lobules by fibrous septa extending from the capsule. Each lobule is made up of aggregation of follicles. Each follicle contains follicular cells or Thyrocytes, these are single layer of cuboidal epithelial cells. Thyrocytes rests on a basement membrane.

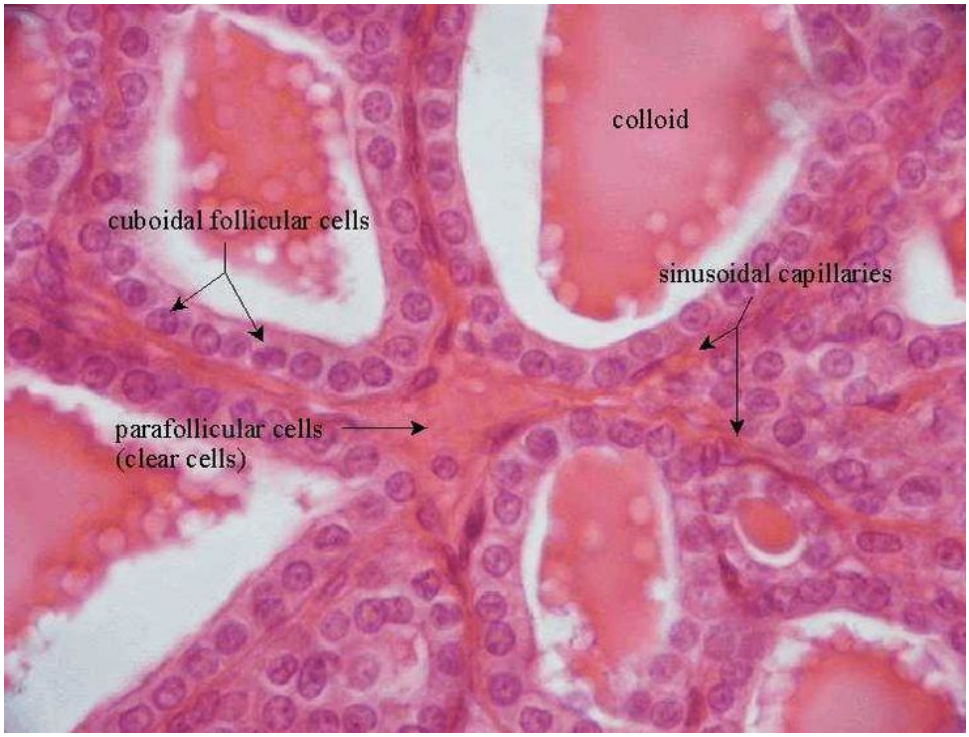
Centre of each follicle has a cavity which is filled with homogenous material known as colloid. Colloid contains thyroglobulin; a large protein with numerous residues of iodinated thyroid hormones including biologically active T3 and T4. Thyroid hormones are stored in thyroglobulin.

Thyroid gland also contain C-cells (or Parafollicular cells), these cells are scattered between follicular cells and basement membrane, and in the interval between follicles.

C-cells secrete the hormone Calcitonin.

Connective tissue stroma surrounding the follicles contains dense capillary plexus, lymphatic capillaries and sympathetic nerves.

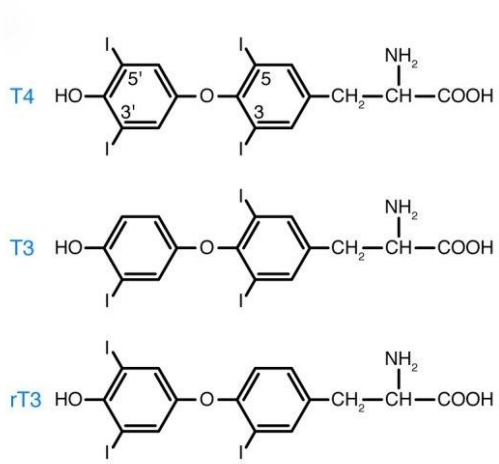
HISTOLOGY OF THYROID GLAND



FORMATION AND SECRETION OF THYROID HORMONE[4]

CHEMISTRY

Primary hormones synthesized by thyroid gland are Thyroxine (T4) and Triiodothyronine (T3). Both hormones are amino acids which contains iodine. T3 is generated peripherally at the site of action by de-iodination. Biological activity of T3 is greater than T4. Small amount of reverse triiodothyronine (RT3) is also present in thyroid venous blood and RT3 is biologically inactive.



IODINE HOMEOSTASIS

Iodine is an essential mineral for thyroid hormone synthesis. Absorption of dietary iodine takes place in intestine and it enters into circulation. 20% of absorbed iodine enters thyroid gland and utilized for thyroid hormone synthesis, remaining 80% is excreted in urine. Iodine deficiency and Iodine excess both inhibits thyroid function.

IODINE TRANSPORT

The basolateral membrane of thyrocytes contains Na^+ - I^- symporter (NIS) which transports two Na^+ and one I^- into the thyrocytes against an electrochemical gradient for I^-. Energy for this secondary active transport is provided by $Na^+ – K^+$ ATPase which transports Na^+ out of thyroid cells.

Iodine exits the thyrocytes across apical membrane and enters the colloid. This step is mediated by Cl^- / I^- exchanger known as 'Pendrin'.

THYROID HORMONE SYNTHESIS

Thyrocytes synthesizes thyroglobulin; it is secreted into colloid by process of exocytosis. Iodide undergoes a process known as organification at the interface between thyrocyte and colloid.

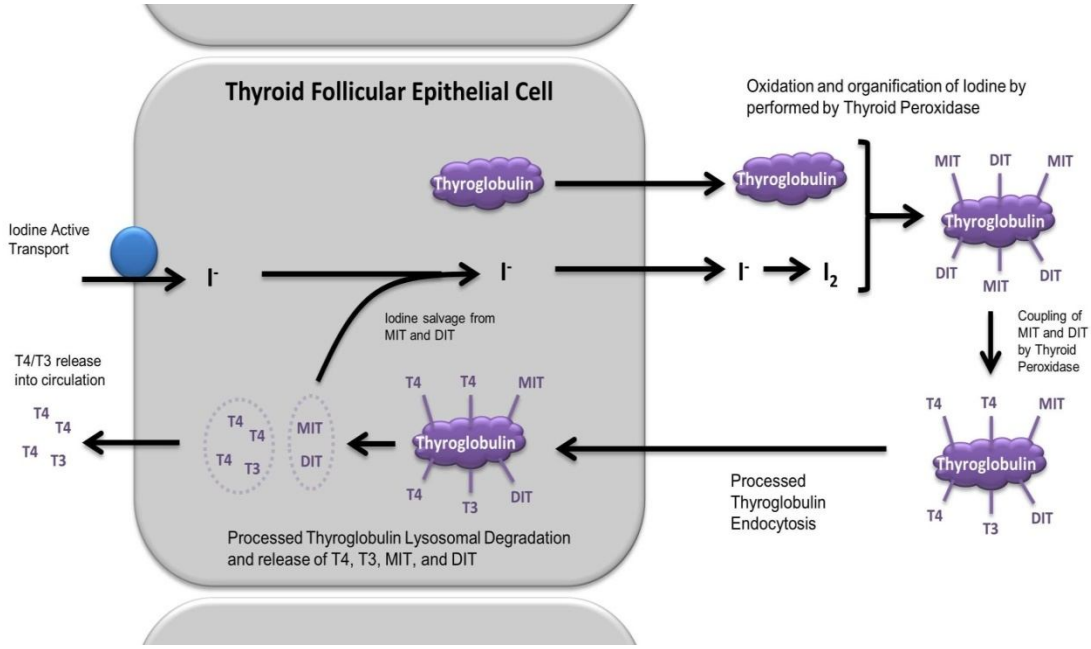
Thyroid peroxidase (TPO) found in the apical membrane of thyrocytes mediates the oxidation reaction of Iodide with the secreted thyroglobulin. Here Iodide is embedded into carbon 3 position of tyrosine residues of thyroglobulin molecules.

First product of thyroid peroxidase is Monoiodotyrosine (MIT). MIT undergoes iodination and forms Diiodotyrosine (DIT). Two DIT molecules undergo a process of oxidative condensation to form T4. Oxidative Condensation of MIT with DIT forms T3. This coupling reaction is mediated by thyroid peroxidase.

Reverse T3 is formed by condensation of DIT and MIT.

Thyroid hormones remain as a part of thyroglobulin and are stored in colloid. Secretion of thyroid hormone occurs when there is a need by the process of endocytosis of colloid followed by lysosomal degradation. However both MIT and DIT are not secreted.

Iodotyrosine de-iodinase is responsible for de-iodination of iodinated tyrosine. This step is necessary to recycle, recover iodine and bound tyrosine for further hormone synthesis.



THYROID HORMONE TRANSPORT

Thyroid hormones are relatively lipophilic. This maintains equilibrium between free form and larger pool of thyroid hormones which are bound to proteins both in plasma and tissues. Free forms of thyroid hormones which are

secreted into circulation are physiologically active. These free hormones maintain negative feedback mechanism for pituitary secretion of Thyroid stimulating hormone (TSH). Protein binding maintains large pool of hormones which can be mobilized as and when required.

Plasma proteins which bind thyroid hormone includes albumin, prealbumin called Transthyretin and a globulin well-known as Thyroxine binding globulin (TBG). Albumin has the largest capacity to bind T4, while TBG has the least.

Half-life of T3 is shorter than half-life of T4, and action on tissue is much more rapid owing to its lesser binding capacity with plasma protein.

Total T4 and T3 levels can be measured by Radio immune assay. Direct assays also measures free forms of the hormone. Estimating the free form is clinically relevant as these are active forms and variation in binding protein due to both congenital and acquired causes can affect the levels of total thyroid hormone.

THYROID HORMONE METABOLISM

Thyroid hormones are mainly metabolized by process of de-iodination mediated by de-iodinases. This process takes place in liver, kidney and many other tissues.

De-iodinases are also responsible for local supply of T3.

Three forms of de-iodinases act on thyroid hormones- D1, D2 & D3.

D1 and D2 contribute to formation of T3, and D3 acts as a main source of RT3 in blood and tissues. These de-iodinases contain rare amino acid Selenium in place of Sulfur.

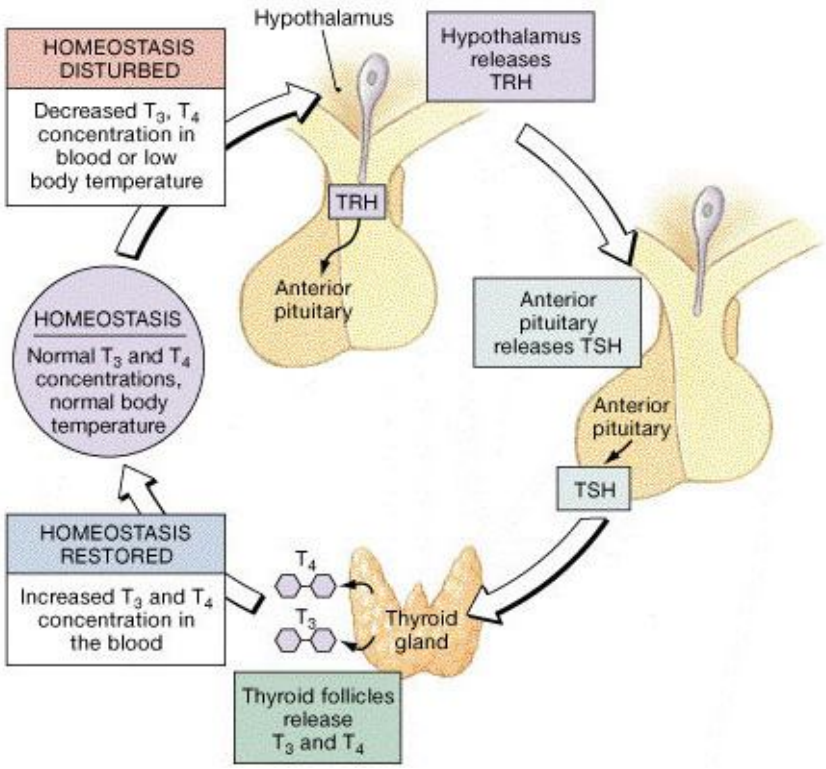
T4 and T3 get conjugated in liver and form sulfates and glucouronides. It is then secreted into bile, part of which is reabsorbed and undergoes entero-hepatic circulation, remaining part is excreted in stools.

REGULATION OF THYROID SECRETION-FEEDBACK MECHANISM

Variation in circulatory level of pituitary TSH regulates thyroid function. TSH secretion is in turn under the control of hypothalamic Thyrotropin releasing hormone (TRH).

When Thyroxine is low, it stimulates production of TRH. TRH acts on anterior pituitary gland and releases TSH which acts on thyroid gland to increase the secretion of T3 and T4.

Free T3 and T4 by negative feedback mechanism inhibits TSH secretion.



TSH – CHEMISTRY AND METABOLISM

TSH is a glycoprotein containing 211 amino acids. It consists of α and β subunits. Gene for α subunit is located on chromosome 6 and for β subunit is located on chromosome 1. TSH α-subunit is identical to α-subunit of LH, FSH and α-HCG, and β-subunit of TSH confers functional stability.

TSH receptor is typical 6 protein coupled seven transmembrane receptor.

Excessive TSH causes hyperplasia of thyroid gland and results in formation of goiter.

TSH is degraded mainly in kidney and to lesser extent in liver.

EFFECTS OF THYROID HORMONES

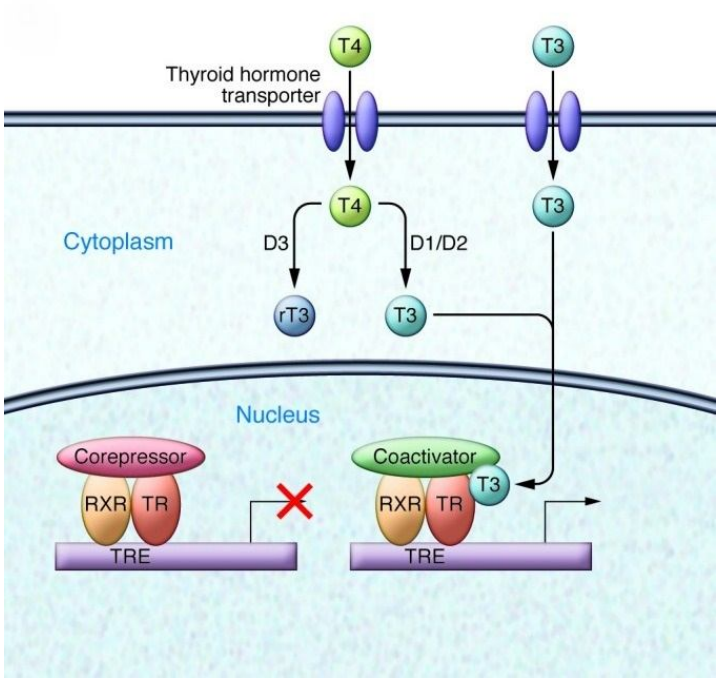
Thyroid hormones affect growth and development, regulates lipid metabolism and increases intestinal absorption of carbohydrates. The comprehensive effects of thyroid hormone take place as a result of stimulation of O_2 consumption.

MECHANISM OF ACTION[38]

Thyroid hormones are lipophilic. It enters the cell and binds to the nuclear receptors. Thyroid hormone receptor belongs to the super family of hormone sensitive nuclear transcription factors. The hormone – receptor complex exerts its effect by binding to DNA via zinc finger motifs.

The thyroid hormone-receptor complex forms a heterodimer with retinoid X receptor (RXR) at specific thyroid hormone response elements (TRE) on the DNA. There by it augments or in some cases reduces the expression of various genes which are involved in regulation of cell function.

T3 is lightly bound to plasma protein than T4; it binds to thyroid hormone receptor more avidly. Hence T3 acts more rapidly and is 3-5 times more potent than T4.



EFFECTS OF THYROID HORMONE

1. CELLULAR METABOLIC ACTIVITY

Thyroid hormone increases the metabolic activities of most of the tissues in the body. It can increase BMR up to 60-100% above the normal. Both rate of protein synthesis and rate of protein catabolism are increased.

Thyroid hormones increases number and activity of mitochondria, resulting in increased generation of ATP.

Thyroid hormone also increases Na^+-K^+ ATPase activity; this process utilizes energy and generates heat – one of the mechanisms for increased BMR.

Thyroid hormone makes the membrane leaky to Na^+ ion. It results in activation of sodium pump and increases heat production.

Increased metabolic rate leads to

- Increased need for Vitamins and Vitamin deficiency syndromes may be precipitated.
- Increased Nitrogen excretion. In the absence of adequate food intake breakdown of endogenous proteins and fat takes place resulting in weight loss.

Accumulation of carotene in blood stream due to impaired hepatic conversion of carotene to vitamin A is responsible for yellow tint of skin in hypothyroidism

2. EFFECT ON CARDIOVASCULAR SYSTEM

a) Increases blood flow and Cardiac output.

Increased metabolic activity in tissues causes increased utilization of oxygen than during normal period. This process releases higher amount of metabolic end products causing vasodilatation and increased blood flow. Cutaneous blood flow is increased in order to dissipate excess amount of heat generated. As a result cardiac output increases to 60% or more above the normal in presence of excess thyroid hormones. And in very severe hypothyroidism cardiac output falls to a value of 50% or less.

b) Increases heart rate.

Thyroid hormones have direct stimulant effect on excitability of cardiac myocytes which increases the heart rate. Increase in heart rate is more when compared to increase in cardiac output under the influence of thyroid hormones. Heart rate can be considered as a sensitive physical sign which helps to determine whether patient has increased or diminished thyroid function.

c) Increased heart strength.

In presence of slight excess of thyroid hormone, strength of heart increases due to increased enzyme activity. However marked increase reduces heart muscle strength due to excessive protein catabolism.

d) Effect on Blood pressure.

Systolic BP is elevated to 10-15 mm Hg and Diastolic pressure falls to a considerable level. Mean arterial pressure usually remains normal. Pulse pressure often increases.

3. EFFECT ON RESPIRATORY SYSTEM

Increased rate of metabolism increases o_2 utilization and increases co_2 production. This activates mechanisms which increases rate and depth of respiration.

4. EFFECT ON GASTROINTESTINAL TRACT

Thyroid hormone increases appetite and food intake.

Increases rate of secretion of digestive juices.

Increases GI motility.

Hyperthyroidism often causes diarrhea and hypothyroidism can lead to constipation.

5. EFFECT ON NERVOUS SYSTEM

“Thyroid hormones have significant effect on brain development mainly cerebral cortex, basal ganglia and cochlea”. It increases rapidity of cerebration.

Thyroid hormone also influences reflexes; reaction of stretch reflex is shortened in hyperthyroidism and prolonged in hypothyroidism.

Deficiency of thyroid hormones during early developmental period can cause mental retardation, deafness and rigidity.

6. EFFECT ON GROWTH

"Process of normal growth and maturation occurs under the influence of thyroid hormones". Thyroid hormones also potentiate the effect of growth hormone on tissues. Absence of thyroid hormone decreases growth hormone secretion. Hence hypothyroid children will have delay in appearance of ossification center and bone growth is delayed.

7. EFFECT ON CARBOHYDRATE METABOLISM

"Thyroid hormones increases rate of intestinal absorption of carbohydrates, increases glucose uptake by the cells, enhances glycolysis and gluconeogenesis and increases Insulin secretion". All the effects results from increase in cellular metabolic enzymes.

8. EFFECT ON LIPID METABOLISM

"Thyroid hormone enhances rapid mobilization of lipids from fat". It reduces plasma Cholesterol, Triglycerides and Phospholipids by increasing cholesterol secretion into bile and consequent loss in feces.

NORMAL TSH LEVEL

Secretion of TSH occurs in a pulsatile manner and it shows diurnal variation.

Radioimmunoassay, Chemiluminescence or Electrochemiluminescence methods are third generation TSH assays which are used by most of the commercial kits for assessing TSH concentration. The reference range for these assays provided in the kit by various manufacturers differs and TSH level above the laboratory reference values are considered as abnormal by most pediatric practitioners. Hence normogram for TSH in Indian children was put forward by Marwaha et al from their population studies in India. In this study which involved children aged 5-16 years, the mean value and 97^{th} percentile value for TSH through radioimmunoassay method were 3.17mIU/L and 7.5mIU/L each. Authors described a reference range of 1.33-5.01mIU/L as normal values for Indian children.

SUBCLINICAL HYPOTHYROIDISM (SCH)

Subclinical hypothyroidism can be defined as a "serum thyroid-stimulating hormone (TSH) concentration above statistically defined upper limit of normal range and serum free thyroxine within reference range".[5] Prevalence of SCH in adults ranges from 4 to10%.[6] Prevalence in pediatric population is estimated to be less than 10 %.[7] "Persistently elevated TSH over a period of time is one of the best indicator to assess true prevalence of SCH in pediatric population".

Most of the patients with SCH have no signs or symptoms, on the other hand a few patients have typical symptoms suggestive of hypothyroidism and number of other symptoms such as weight gain, cold intolerance, constipation, neck swelling which are similar in frequency and similarity to age matched euthyroid controls.[8]

In adult population subclinical thyroid disease is associated with marginally increased risk of progression to overt thyroid disease,[42] abnormal lipid levels,[40] increased risk for atherosclerosis[41] resulting in increased cardiovascular morbidity and mortality.[39] No controlled studies are available in pediatric population evaluating the outcomes in SCH children treated with L-thyroxine versus those children who received placebo.

Children differ from adults in the causes, the natural history of the thyroid dysfunction, as well as consequences of the disorder. We cannot extrapolate available adult data to children. There are very few available pediatric randomized controlled trial data regarding treatment of subclinical hypothyroidism.

DIFFERENTIAL DIAGNOSIS OF TSH ELEVATION AFTER INFANCY[9]

REVERSIBLE CAUSES

- Autoimmune thyroiditis.
- During recovery from acute illness.
- During recovery from sub-acute thyroiditis.
- Anti-thyroid drugs.
- Simple obesity.
- Deficiency of cortisol.
- Error in laboratorial estimation.

IRREVERSIBLE CAUSES

- Autoimmune thyroiditis.
- Developmental anomalies such as Thyroid dysgenesis.
- Subtotal / hemithyroidectomy.
- Radiotherapy of neck region.
- Reidel's thyroiditis.

ETIOLOGY OF SUBCLINICAL HYPOTHYROIDISM[10]

Causes of subclinical hypothyroidism can be classified into two distinct subgroups.

1. Transient SCH.
2. Persistent SCH.

TRANSIENT SCH

1. Random Variation in TSH levels.[11]

TSH level fluctuates physiologically in apparently healthy person during different hours of the day as well as over time. Fasting TSH during early morning hours and late morning levels were compared in a study which involved 100 patients. It was found that in 97 subjects TSH concentration decayed by a mean value of 26%. For example If TSH >5mIU/l is defined as abnormal, an individual can have a TSH of 6mIU/L at one point of time and 4.0mIU/L on another.

2. Non-Thyroidal Illness.

Active illness or recurrent acute illness can cause a transient decrease in production of thyroid hormone. Similarly transient rise in TSH occurs normally during recovery phase to restore normal levels of Free T4 and TSH in a short span of time.

3. Mild Auto Immune Thyroiditis (AIT) Which undergoes Recovery.[17]

Pediatric AIT may undergo spontaneous remission as the disease does not inevitably destroy the gland. This allows thyroid gland to recover and results in normalization of TSH level. It can occur even in cases where enlargement of thyroid gland persists.

PERSISTENT SCH

1. "Normal TSH range is the range in which 95% of values in healthy people fall". Hence TSH level at or slightly higher than the upper limit of normal expanse can be seen in 2.5% of individuals.

2. Children who are born small for Gestational Age.

In the Argentina study by Keselman et al[12] involving 53 children born SGA with mean age of 5.6 ± 3.2 years showed magnified TSH response for Thyrotropin releasing hormone (TRH) when compared to control population. Mean T4 levels was identical in both groups but the group with magnified TRH response showed higher mean TSH value of 6.2 (4.2-14.6) when compared to normal TRH response group with mean TSH of 3.2 (1.6-7). The authors postulate that intrauterine growth retardation children may have abnormal set point for TSH due to abnormal TSH regulatory circuit without alteration in thyroid function.

3. Mild Abnormalities in Thyroid development.

In a study by D Leonardi et al[13] children having mild elevation in TSH which was detected during newborn screening were followed up. 8 of 19 children who had elevated TSH showed unilobar thyroid hypoplasia or hemi-agenesis of thyroid gland.

4. Mild Stable Autoimmune Thyroiditis.

Autoimmune thyroiditis over a period of time either resolves or it can result in thyroid failure. Variant of AIT can be present in which gland's ability to produce thyroid hormone is minimally impaired and it can maintain stable levels of thyroid hormones over an extended time period.

5. Obesity.

Exact mechanism behind elevation of TSH in obesity has not been clearly explained. SCH can be seen more often than overt hypothyroidism in obese children. Several reports are available where obesity is associated with high TSH.

In a study by S Chikunguwo et al[14] of 86 patients who underwent weight reduction surgery, 10.5% patients showed abnormal thyroid test undeviating from SCH and showed a strong interrelationship between BMI and TSH.

6. TSH- Receptor (TSH – R) mutation.

As a result of mutation, TSH receptor will have a reduced ability to bind TSH or it is not activated by TSH. Hence TSH concentration of 2-4 times the normal amount is required to activate TSH-Receptors to the optimum.

Studies have shown that few children diagnosed with SCH will have defined mutation involving TSH – receptor (TSH-R) gene. In the Japan study by S Narumi et al[15] which involved 102 children showed 3 children having "mutation in each of two TSH-R genes" and 3 children having "single mutation in TSH-R gene". In a recent report[16] of 39 children having non autoimmune SCH, 11 of 39 or 28% had TSH-R mutation.

NATURAL HISTORY OF SCH

Subclinical hypothyroidism in children is a remitting process. Over a period of time elevation in TSH levels returns to normal level or it may remain mildly elevated. In children having persistent TSH elevation, a stable equilibrium exists which allows normal thyroid hormone production; thus these children can be considered as normal variants. According to studies number of cases which progress to overt hypothyroidism is very small. Hence immediate treatment may not be essential.

In the report by Moore[17] on 18 children with mild to significant TSH elevation, normal levels of T4, positive anti-thyroid antibodies, and some cases with a goiter, 11 children were observed without treatment and 7 received treatment. TSH regularized in 7, and in 10 children it remained mild to moderately elevated with normal levels of T4 and one patient had low T4 and elevated TSH. This study shows that AIT can prevail for years without progressing to overt hypothyroidism. Thyroid function may recover over time in patients with moderate TSH elevation.

However studies in adults with idiopathic SCH or autoimmune SCH show that progression to overt hypothyroidism is common. Initial presentation with goiter, elevation in anti-TG antibodies, progressive increase in anti-TPO antibodies and TSH values may indicate progression towards overt hypothyroidism.

CONSEQUENCES OF UNTREATED SCH IN ADULTS

- Cardiac dysfunction, atherosclerotic disease, cardiovascular mortality.
- Abnormal lipid parameters; Elevated total and Low-density lipoprotein cholesterol.
- Systemic symptoms of hypothyroidism.
- Neuropsychiatric symptoms.
- Progression to overt hypothyroidism with symptoms.

REVIEW OF LITERATURE

Marwaha et al[18] did a community based study among 24685 school-age children. The study sample represented four geographical zones of India. Children from 36 schools across 13 different states were enrolled. Main aim of the study was to obtain a normative data for thyroid functions in Indian children. These Subjects underwent evaluation for serum FT3, FT4, TSH, anti-TPO antibodies and thyroid ultrasound. Authors defined a reference population where children did not had personal or family history of thyroid disease, use of thyroid medications, goiter, abnormalities on ultrasound (hypo echogenicity or nodularity) or positive anti-thyroid antibodies.

Among these 24,685 children who underwent clinical evaluation, 8665 children were selected for the study. 5343 subjects formed the reference population. From the study, the mean, median, 3rd and 97th percentiles of FT3, FT4 and TSH were obtained.

Mean	3.17mIU/L
97^{th} percentile	7.5mIU/L
Range	1.33-5.01mIU/L

"Through the study authors defined a range of 1.33-5.01mIU/L as the normal TSH value for Indian children".

Martin Surks et al[5] reviewed total of 195 scientific articles on SCH which were published between the year 1995 and 2002 from various databases. Through the study authors defined Subclinical hypothyroidism as "a serum TSH concentration above the statistically defined upper limit of the reference range with serum free T4 (FT4) concentration within its reference range".

Cerbone et al[19] in their cross sectional case controlled study analyzed growth in children having subclinical hypothyroidism. 36 children in the age group 9.7±0.6 years (range of 4-18 years) with persistent SCH were enrolled for the study. 36 age and sex matched controls were selected. Clinical and biochemical parameters such as height, weight, BMI, bone age (BA) / chronological age (CA) ratio, thyroid function test were evaluated in these children at the beginning and during follow up longitudinally for 3.3±0.3 (range of 2-9.3) years.

Height (-0.8±0.2 SD), BMI (-0.1±0.2 SD), Bone age / Chronological age ratio (0.92±0.6 SD) in SCH group were normal at the beginning and no parameters showed worsening with respect to height (-0.7±0.2 SD), weight (-0.1±0.2 SD) and BA/CA (0.97-0.03) during follow up. Authors concluded that "SCH in children will not have significant alteration in growth, bone maturation and BMI without any therapeutic intervention".

Grandone et al[20] selected a population of 938 obese children and adolescents. Baseline anthropometric measurements, metabolic and hormonal values were estimated in children with higher TSH levels. These children were followed up and parameters were repeated after 6 months of weight loss intervention.

The main aim of the study was to

1. Ascertain the distribution of elevation in TSH level among young obese Italian population.
2. To determine metabolic and cardiovascular risk factors associated with very high levels of TSH in obese children.
3. To verify reversal of TSH elevation after weight loss.

120 patients (12.8%) were diagnosed to have hyperthyrotropinemia (TSH $\geq$4mIU/L).

64 patients underwent weight reduction intervention and 23 showed significant decrease in TSH and FT3. A positive relationship was established between TSH and BMI Z-scores with p value of 0.0045, and between FT3 and BMI Z-scores with p value of 0.0035. No association was made between TSH and lipid levels.

Authors concluded that

1. Moderate TSH elevation can be frequently seen in obese children.

2. Increased TSH is not associated with metabolic risk factors.
3. Hyperthyrotropinemia will be reversed after weight loss intervention.

Harikumar et al[21] conducted a study to find out the association between body mass index (BMI) and TSH level in euthyroid children and subclinical hypothyroid obese children. TSH level among obese children was compared with TSH level of overweight children.

Cohort of 50 children and adolescents in the age group 2-18 year were recruited. Patients were divided into two groups.

First group: 20 overweight children (BMI between 85^{th} to 95^{th}centile).

Second group: 30 obese children (BMI > 95^{th}centile).

Authors observed that 4 overweight children and 9 obese children had TSH in the range between 4.5-10mIU/L with normal T3, T4 concentration. The mean TSH in first group (3.22 ± 3.1mIU/L) was comparable with mean TSH of second group (3.63 ± 2.2mIU/L, p=0.3491). No association was noted between TSH and BMI ('r' value of 0.0014 and p value of 0.9924). The authors concluded that "the degree of obesity will not have significant impact on serum TSH".

Shalitin et al[22] conducted the study among 207 obese children and adolescents in age group of 5-18 years to institute the prevalence of elevated thyroid-stimulating hormone (TSH) and to analyze the relationship between

changes in TSH levels and other metabolic and hormonal parameters before and after these children underwent weight reduction intervention. Study group was evaluated with “anthropometric measurements, biochemical, metabolic and hormonal parameters before and following weight reduction intervention”.

Initial Free T4 levels were within normal limits in all cases. Among 207 subjects 46 (22.2%) had TSH elevation (> or =4.0mIU/l). Significant elevation in triglycerides was seen in participants with elevated TSH than participants with normal thyroid function ($p = 0.011$). Significant correlation was found between baseline TSH with triglyceride levels ($r = 0.261$, $p < 0.001$), and no correlation with age and anthropometric variables. 142 participants underwent weight reduction intervention and 27 (19 %) had hyperthyrotropinemia. Authors could not derive significant association between changes in TSH level with changes in body mass index-standard deviation score.

Results showed a significant association between the final TSH level and triglyceride concentration (‘r’ value of 0.167 and p value 0.045), and also between the decrease in TSH concentration and decrease in waist circumference (‘r’ value of 0.291, and p value of 0.013). Hence they concluded that “hyperthyrotropinemia and normal free T4 levels appear to be frequently found in obese children”. Since there exists a significant interrelationship between hyperthyrotropinemia with waist circumference and higher triglyceride they raise the question of the obligation to treat the elevated TSH levels in children with obesity.

Di Mase et al[23] in the cross sectional prospective trial evaluated the possible effect of untreated SCH on bone health. 25 children and adolescents in the age group 9.8 ± 3.5 years with untreated idiopathic SCH were enrolled in the study. From the time of diagnosis these children were followed up for 3.3 ± 0.3 years. 25 age and sex matched healthy children were randomly selected as controls. DXA was done to evaluate lumbar spine bone mineral density (BMD) and QUS at proximal phalanges of the non-dominant hand to assess bone quality. It was measured as "amplitude-dependent speed of sound (Ad-SoS) and bone transmission time (BTT)".

Results:

	Patients	**Controls**
"BMD Z-scores"	−0.4 ±1.36	−0.2±1.2
"Ad-SOS Z scores"	0.01±1.0	0.1±1.2
"BTT Z-scores"	−0.03±0.8	0.04±1.1

All values both in patients and in controls were within the normal range, no statistical significance was observed between the two groups.

Authors came to a conclusion that neither the duration of SCH nor TSH levels had significant influence on bone health despite long duration of idiopathic SCH.

Chen et al[24] conducted a cross sectional study of 880 subjects comprising 541 females and 339 males without overt thyroid illness. Mean age of presentation was 11.15±2.34 years. 124 children were diagnosed to have

SCH. The study was carried out to discover the interrelationship between blood pressure and thyroid function.

Investigation was done based on a stratified random cluster sampling method which comprised of questionnaire and measurements of parameters such as blood pressure, height, and body weight. Thyroid function test was done on fasting blood sample.

Authors observed a significant positive relationship between Serum TSH and FT3 with both systolic and diastolic blood pressure Z-scores with p value of 0.05. No correlation was established between FT4 and SBP-Z or DBP-Z with $p > 0.05$. Subclinical hypothyroidism subjects had significantly higher SBP-Z and DBP-Z scores when compared to euthyroid subjects with p value of 0.05. Significantly increased values of both SBP-Z and DBP-Z with TSH levels were observed in boys with p value of <0.05, however, such observations were not made in girls. “Study findings supported the hypothesis that elevated TSH and FT3 concentrations will increase the blood pressure in children without overt thyroid disease”.

Ittermann et al[25] in their study involving 12353 subjects, studied the relationship between serum TSH level and blood pressure. Study subjects were divided into two groups. First group comprising 3-10 year old children (n=6435) and second group comprising 11-17 years old adolescents (n=5918).

Systolic and Diastolic blood pressure were measured twice after 5 minutes of rest. Hypertension was defined by increase in SBP and DBP using age, gender and height specific reference.

In both group 1 and group 2, results suggested a significant association between serum TSH and hypertension with p value of 0.045 and < 0.001 respectively. Positive association between high serum TSH with systolic and diastolic blood pressure was observed.

Authors concluded that "a positive correlation exists between serum TSH and Hypertension in children and adolescents. Hence Subclinical hypothyroidism is associated with increased risk of hypertension".

Radetti et al[26] did a study and evaluated 160 children with Hashimoto's thyroiditis, which included 43 males and 117 females. Mean age of study group was 9.10±3.6 years. The study population was divided into two groups.

Group 1: Patients with normal levels of TSH (n=105).

Group 2: Patients with slightly elevated TSH concentration (n=55).

Initial assessment was done and these children were observed regularly for at least 5 years to see whether they remained to be euthyroid or if their TSH levels did not rise two fold above the upper limit of normal.

Baseline anthropometric parameters, thyroid function tests and serum concentration of anti-thyroid antibodies were similar in the both the groups.

During follow up authors observed that 16 patients became euthyroid, 39 children remained to be SCH. Of these 39 SCH children 16 had TSH value of one to two folds above the upper limit of normal. 23 children had TSH more than two folds above upper limit of normal.

The data of the patients who became euthyroid was compared with the data of patients whose thyroid function deteriorated, and it revealed significantly elevated thyroglobulin antibody concentration and thyroid volume at initial presentation in the latter group.

Authors concluded that "presence of goiter and elevated anti-TG antibodies at presentation, along with progressive increase in both Anti-TPO antibodies and TSH, may predict future development of hypothyroidism".

Zois et al[27] in their study followed 29 children and adolescents in 12-18 years age group with AIT for 5 years to trace the advancement of the disease.

At the time of diagnosis 25 children (86%) were positive for thyroid peroxidase auto antibodies (TPO-Abs), and all children became positive during follow-up. 17 children (59%) were positive for Thyroglobulin auto antibodies (TG-Abs) at diagnosis and 3 more children (69%) became positive during follow up. Both antibodies were raised at the termination of the observation period ($p < 0.005$). 7 children (24%) already had subclinical hypothyroidism, and during follow up it persisted and 4 more new children developed subclinical hypothyroidism. TG-Abs were positive in 5 (45%) of these children. Thyrotropin (TSH) was also increased at the end of the study. Entire

study group had TSH value more than 2.5mIU/L but no one advanced to have overt hypothyroidism.

Authors concluded that, both antibody types increased in frequency and level over period of time. “TPO-Abs is the predominant marker of autoimmunity, and elevated TPO Abs can be considered as a predictive factor for impending thyroid failure in children with AIT”.

Gopalakrishnan et al[28] studied 98 subjects in the age group of 8-18 years who had autoimmune thyroiditis and diffuse goiter. 3 groups were formed based on thyroid function status. Euthyroidism as group1, SCH as group 2, and hypothyroidism as group 3.

At initial presentation, around 25% (n=24) were euthyroid, around 33% (n=32) had subclinical hypothyroidism and the remaining 42% (n=42) had hypothyroidism. Patients were observed for a minimum duration of 2 years. Euthyroid and SCH subjects were monitored with thyroid function test every 6 months. At the end of observation period 3 subjects in euthyroid group and 4 subjects with subclinical hypothyroidism developed overt hypothyroidism.

Authors concluded that “Subjects with goitrous autoimmune thyroiditis need periodic monitoring of thyroid function. Development of thyroid dysfunction is insidious and may not be accompanied by symptoms and clinical signs”.

Cerbone et al[29] in their cross sectional and controlled study investigated the clinical and biochemical cardiovascular risk factors in children with idiopathic mild SCH. In adults SCH is known to be associated with higher risk of coronary heart disease.

49 children aged 8.5±0.5 years and 49 age, height and sex matched controls were selected for the study. At the entry both the groups underwent clinical and biochemical assessment for cardiovascular risk. These children were followed up for 2 years.

Assessment index for Systolic and diastolic blood pressure, body mass index (BMI), waist to height ratio, lipid profile, homocysteine, high-sensitivity serum C-reactive protein, fibrinogen, adiponectin, and insulin were measured.

Authors found that "Waist/height ratio ($p<0.0001$), atherogenic index ($p=0.001$), triglycerides/High-density lipoprotein-cholesterol ratio ($p=0.01$), and homocysteine levels ($p=0.002$) were significantly higher and high-density lipoprotein was significantly lower (0.003) in SCH subjects when compared with controls". Other clinical and biochemical cardiovascular risk factors did not show significant difference.

Authors concluded that **"**mild idiopathic SCH may be associated with subtle pro-atherogenic abnormalities; these changes may not represent early stage of atherogenesis".

Vitale G et al[30] investigated the cardiac effects of SCH by assessing left ventricular myocardial regional function.

20 women with SCH and 20 age matched controls were enrolled into the study. Both the group underwent standard Doppler Echocardiogram and Pulsed Tissue Doppler (TD).

Standard Doppler in SCH patients showed an increase in left ventricular pre ejection period, pre ejection period/LV ejection time ratio and isovolumetric relaxation time (IVRT).

"In SCH patients TD analysis showed prolonged myocardial precontraction time (PCT(m)), PCT(m)/myocardial contraction time ratio, and myocardial relaxation time (RT(m)) at the level of both posterior septum and mitral annulus".

A positive correlation was found between TSH and IVRT, RT(m) and PCT(m)/myocardial contraction time ratio.

Study indicates that "lack of thyroid hormone is associated with poor LV contractility and relaxation".

Gönül catli et al[31] in their study to search for evidence suggesting treatment for childhood SCH evaluated left ventricular function using M-mode Echocardiogram and Tissue Doppler Echo (TDE).

31 children with SCH and 32 euthyroid age and sex matched controls were recruited into the study. Left ventricular function was assessed using

M-mode echo at the baseline and 6 months after attaining euthyroid state. Pretreatment parameters were compared with controls and post treatment parameters.

Parameters of left ventricular morphology such as Intra Ventricular Septal (IVS) thickness and Left Ventricular mass Index were slightly increased in SCH children when compared with control group ($p<0.05$).

In TDE children with SCH had significant change in Left Ventricular Systolic function (lower isovolumic contraction time) and Left Ventricular Diastolic function (lower Em, higher E/Em ratio and longer isovolumic contraction time) when compared to controls ($p<0.05$). Significant augmentation in systolic and diastolic parameters was observed 6 months after attaining euthyroidism (p value <0.05).

This study shows "SCH is associated with subclinical alteration of LV function and L-thyroxine treatment improves LV systolic and diastolic function".

However improvement of LV function may be associated with natural course of disease or physiological linear growth in children.

Wasniewska et al[32] in their study prospectively evaluated the course of SCH in children and adolescents in whom all etiological causes and risk factors for SCH had been excluded.

92 patients with mean age of 8.1±3.0 years having idiopathic SCH were recruited into the study. Children were followed up for 2 years. General clinical status, thyroid function test and serum concentration of anti-thyroid antibodies were evaluated at entry and during follow up at6, 12 and 24 months.

Reports showed that during the study mean TSH followed a progressive decreasing trend while Free T4 levels remained unchanged. In 38 patients (41.3%) TSH level returned to normal, while in 54 (58.7%) remaining children it remained in SCH range.

None of them developed overt hypothyroidism.

Authors concluded that "SCH Children showed a progressive decrease in TSH values, as majority of patients (88%) became euthyroid or maintained their TSH and no association exists between change in TSH with Either FT4 values or clinical status".

Moore et al[17] studied 18 patients aged 5-19 years with autoimmune thyroiditis and elevated serum TSH. These children were followed up for a mean duration of 5.8 years. 11 of them had never received treatment, 7 patients were followed up after treatment discontinuation. TSH, FT4 and thyroid gland size as well as signs and symptoms of hypothyroidism were monitored during the observation period.

At the end of observation period, TSH normalized in 7 children, 10 children continued to have elevated TSH with normal FT4 concentration.

Author came to a conclusion that “SCH may be benign and a remitting process. Regular follow up is necessary rather than treating them empirically”.

In the study by **Jaruratanasirikul et al**[33] 46 subjects with Hashimoto's thyroiditis were recruited. These subjects were followed up for 5.9±0.3 years. Three groups were formed based on thyroid function.

Group 1 comprising of 28 euthyroid subjects.

Group 2 comprising of 8 SCH subjects.

Group 3 comprising of 10 hypothyroid subjects.

At the end of observation period it was found that out of 8 patients with SCH, 4 became euthyroid. Other 4 patients developed overt hypothyroidism. It was also observed that all patients in both euthyroid and hypothyroid groups had normal growth and attained puberty normally.

Authors concluded that “without medication goiter size remained the same. Baseline Clinical or biochemical markers will not predict who will become euthyroid or hypothyroid”.

Lazar et al[34] in their study analyzed database of 121052 children in the age 0.5-16 years. These children were followed up for 5 years. The principal objective of the study was to understand the natural history of initial abnormal TSH. Patients who had overt hypothyroidism or hyperthyroidism on initial testing were excluded from the study.

They reported that 3% had SCH during first TSH estimation. During 5 year follow-up TSH values normalized in varying proportions depending upon degree of initial TSH levels. In the second TSH determination, around 74% of SCH subjects normalized their TSH. Around 25% of subjects remained to be SCH. Around 2% had increased TSH above 10mIU/L with normal FT4 levels. 0.03% of subjects developed overt hypothyroidism.

Among those subjects with TSH > 10mI/L, in 40 % TSH normalized, in 33% TSH reduced to SCH range; around 25% maintained TSH >10mIU/L and 0.2 % became overt hypothyroidism.

Authors concluded that “the predictive factors for a sustained highly elevated TSH were initial TSH > 7.5mIU/liter ($p = 0.014$) and female gender ($p = 0.047$)”. Age was not found to be a significant predictive factor.

STUDY JUSTIFICATION

- SCH in adults is known to be associated with increased risk for progression to overt thyroid disease, lipid disorders, increased risk of atherosclerosis and mortality and morbidity due to cardiovascular disease.
- Many studies in adults are available establishing the evidence associating these morbidities with SCH.
- Studies on these aspects in children particularly Indian children are lacking.
- Controversy also exists in treating SCH with Thyroxine.
- We conducted the study to evaluate the clinical status and co-morbidities associated with SCH in children attending endocrinology department in Institute of Child Health and Hospital for Children.

OBJECTIVES

The main objective of the study is to

1. Analyze signs and symptoms presented by children diagnosed with SCH.
2. To study clinical and biochemical profile of these children with SCH in the age group2-12 years.

- Anthropometry.
- Systolic and Diastolic blood pressure.
- Heart rate.
- Presence of goiter.
- Fasting lipid profile.
- Autoimmune anti-thyroid antibodies.
- Ultra sonogram neck.
- Bone age estimation from X-ray.
- Echocardiogram to assess Left ventricular dimensions and LV systolic function.

MATERIALS AND METHODS

STUDY DESIGN

- Descriptive study.

STUDY SETTING

- Endocrinology OPD of Institute of Child Health and Hospital for Children.

STUDY PERIOD

- October 2015 to August 2016.

TIMELINE

DATA COLLECTION - October 2015 to August 2016

DATA ANALYSIS AND MANUSCRIPT PREPARATION - August 2015

SUBMISSION OF REPORT – September 2015

STUDY POPULATION

Children attending endocrinology OPD, biochemically confirmed to have Subclinical hypothyroidism who meets the inclusion criteria.

SAMPLE SIZE

62 Patients.

INCLUSION CRITERIA

- Children 2- 12 year of age.
- Biochemically confirmed subclinical hypothyroidism.

EXCLUSION CRITERIA

- Known case of congenital heart disease.
- Obese children.

CASE DEFINITION

"Children with normal free T4 level and slightly elevated TSH concentration (5-10mIU/L)" in the age group 2-12 years.

ETHICAL CONSIDERATIONS

Ethical clearance was obtained from the Institutional Review Board. Informed written consent was obtained from the parents of the study subjects. Strict confidentiality of data was maintained throughout the study.

STUDY MANOEUVRE

1. Children satisfying inclusion criteria were recruited into the study.
2. Informed written consent was obtained from the parents of study subjects.
3. The baseline demographic characteristics and clinical characteristics were obtained from all the children at the time of registration at endocrine clinic after detailed history taking and clinical examination.
4. Age was calculated in years from date of birth.
5. History of autoimmune disease in the family was enquired.
6. History of thyroid disease in family was specifically asked.
7. Principal complaint for which the child has sought medical help was recorded.
8. Height was measured by making the child stand bare-footed and the heel, buttocks, shoulders and occiput touching the wall and looking straight ahead. Measurements were read directly after lowering the cursor or placing horizontally held wooden board to touch the top of the head. Accuracy to the nearest 0.1 cm. Z-score was calculated by using WHO charts for children below 5 years and IAP chart above 5 years.
9. Weight was measured with subjects wearing light cloths and no shoes using calibrated electronic scale. Accuracy to the nearest 100 grams. Z-score was calculated by using WHO charts for children below 5 years and IAP chart above 5 years.

10. BMI was calculated from standardized formula.

$$\frac{\text{Weight in kg}}{(\text{Height in meter})^2}$$

Z-score was calculated using WHO charts for children below 5 years and IAP chart above 5 years

11. Heart rate was counted for one full minute in sitting position.

Normal heart rate by age.[35]

Approximate age range	**Heart rate**
Newborn	100-160/min
0-5months	90-150/min
6-12months	80-140/min
1-3years	80-130/min
3-5years	80-120/min
6-10years	70-110/min
11-14years	60-105/min

12. BP was measured thrice at an interval of 1 minute using appropriate sized cuff in the right upper limb in sitting position after 5 minutes of rest. Sphygmomanometer was held at the level of heart. Mean value of second and third measurements was taken.

Z-score was calculated for systolic and diastolic BP measurements separately. Data such as height, weight and age were taken into consideration while calculating the Z-score.

13. Neck examination was made standing behind the patient, neck placed in a semi flexed position to note the presence of goiter.

14. Thyroid function tests:

Thyroid function test was performed on early morning venous blood sample after 12 hours of fasting. TSH and free T4 levels were measured using enzyme immunoassay method.

Normal values:

Parameters	Normal values
TSH	0.3-5.0mIU/L
Free T4	0.78-2.1mIU/L
Free T3	0.89-2.62mIU/L

15. Auto immune antibodies :

Autoimmune Anti-thyroid antibodies levels namely anti Thyroid Peroxidase (anti-TPO) antibodies also known as anti-Microsomal antibodies and anti-Thyroglobulin (anti-TG) antibodies were measured using electrochemiluminescence assay.

Normal values:

Parameters	**Normal values**
Anti-TPO antibodies	0-5.61IU/ml
Anti-TG antibodies	0-4.1IU/ml

16. Serum lipid profile:

Early morning fasting venous blood sample was collected for lipid profile analysis. Serum concentrations of Total cholesterol, HDL, Triglycerides were measured.

Cholesterol and Lipid distribution in children (50^{th} percentile values).[36]

Lipid/Lipoprotein	Male		Female	
	5-9 years	10-14 years	5-9 years	10-14 years
Total cholesterol (mg/dl)	153	161	164	159
Triglycerides (mg/dl)	48	58	57	68
High-density lipoprotein (mg/dl)	55	55	52	52

17. X ray bone age :

    X-ray bone age was obtained based on appearance of ossification centers.

18. Ultrasonogram neck was done in children with Goiter and positive autoimmune antibodies to look for changes in the gland echogenicity.

19. Two dimensional guided M-mode echocardiogram :

    M-mode Echocardiogram was performed by cardiologist for assessing left ventricular dimension and left ventricular systolic function.

“M-mode measurements of LV internal dimension in diastole (LVIDd) and systole (LVIDs), end diastolic posterior wall (PW) and interventricular septum (IVS) thickness were obtained”.

Z-scores were calculated for left ventricular left ventricular dimensions based on height and weight of the individual.

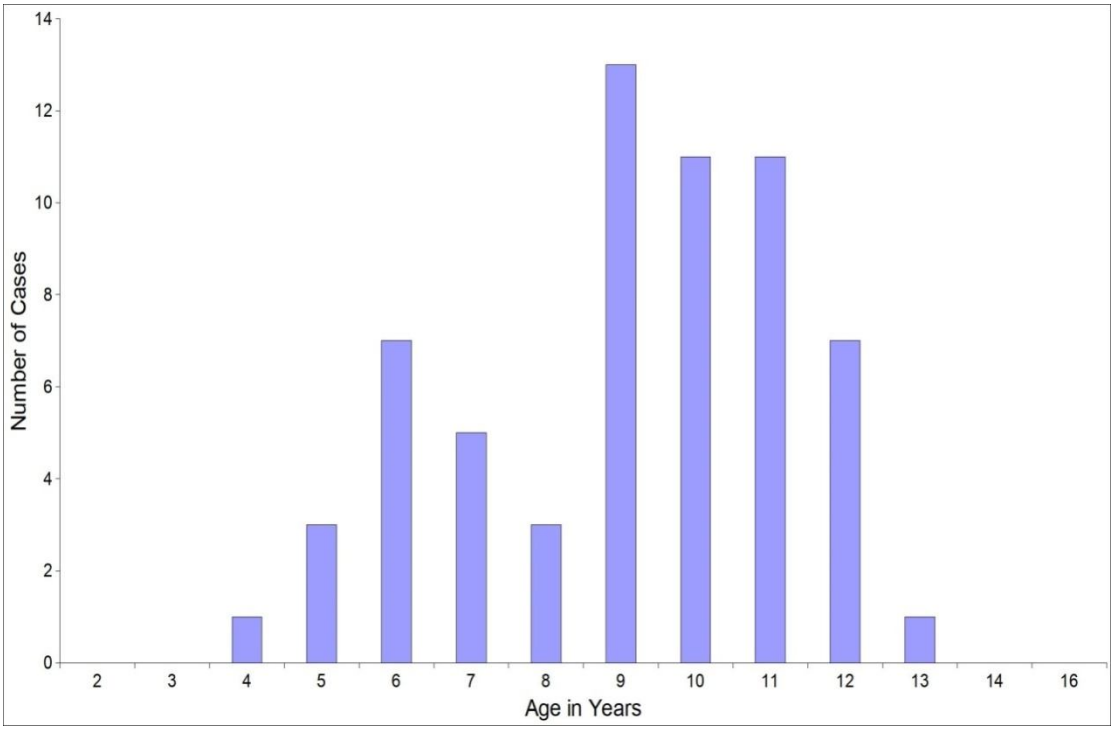
LV systolic function was assessed based on fractional shortening and wall thickening.

Mean value of FS is 36%, with 95% prediction limits of 28% to 44%. Normal mean ejection fraction is 66% with ranges of 56% to 78%.[37]

OBSERVATIONS

AGE DISTRIBUTION

CHART 1



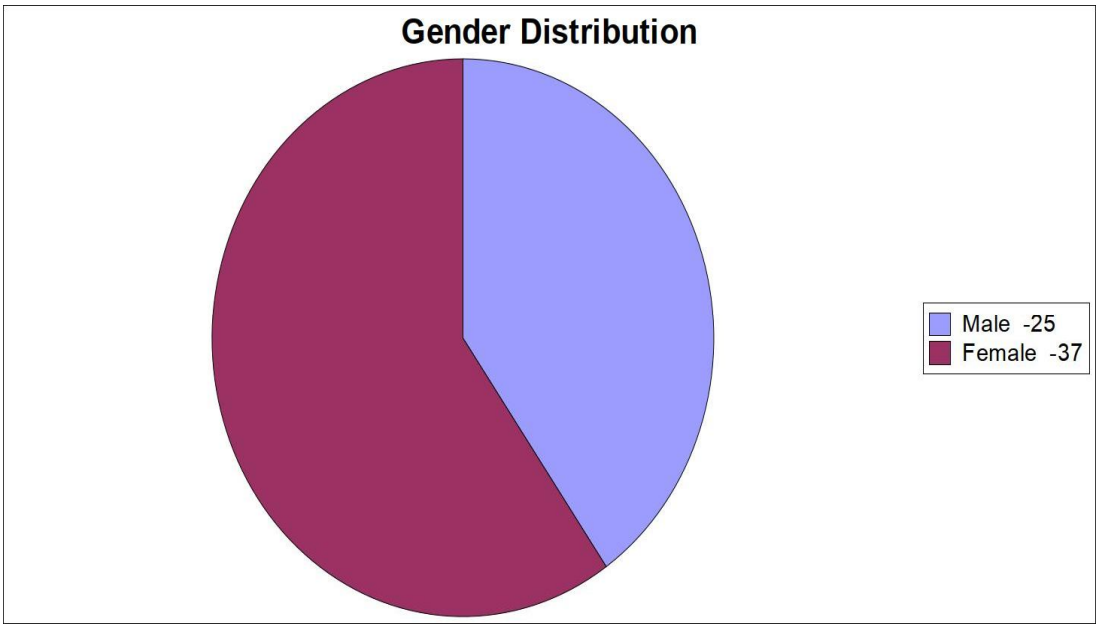
Our study population consisted of children with SCH between the age group 2-12 years.

Average age of presentation was 8.42 years.

Lowest age of presentation was 3.5 years. Highest age was noted to be 12 years.

GENDER

CHART-2

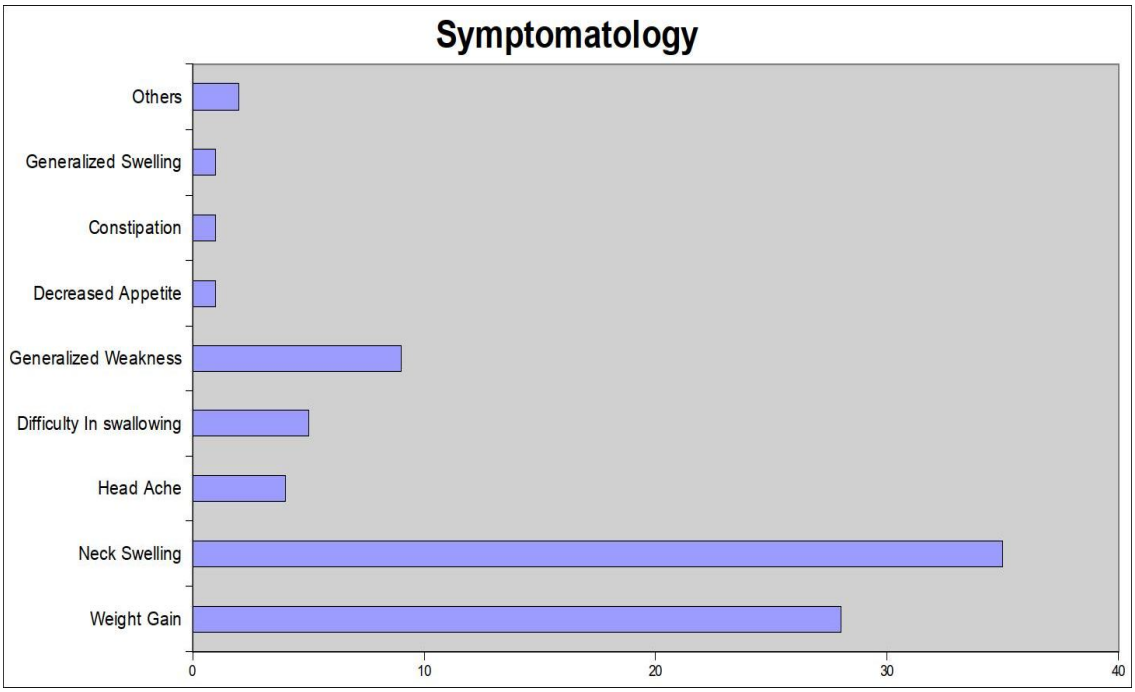


In the study subjects 59.7% were female, and 40.3% were male. There is as a definitive female predominance.

Female: Male ratio in our study was 1.48:1.

SYMPTOMS

CHART-3



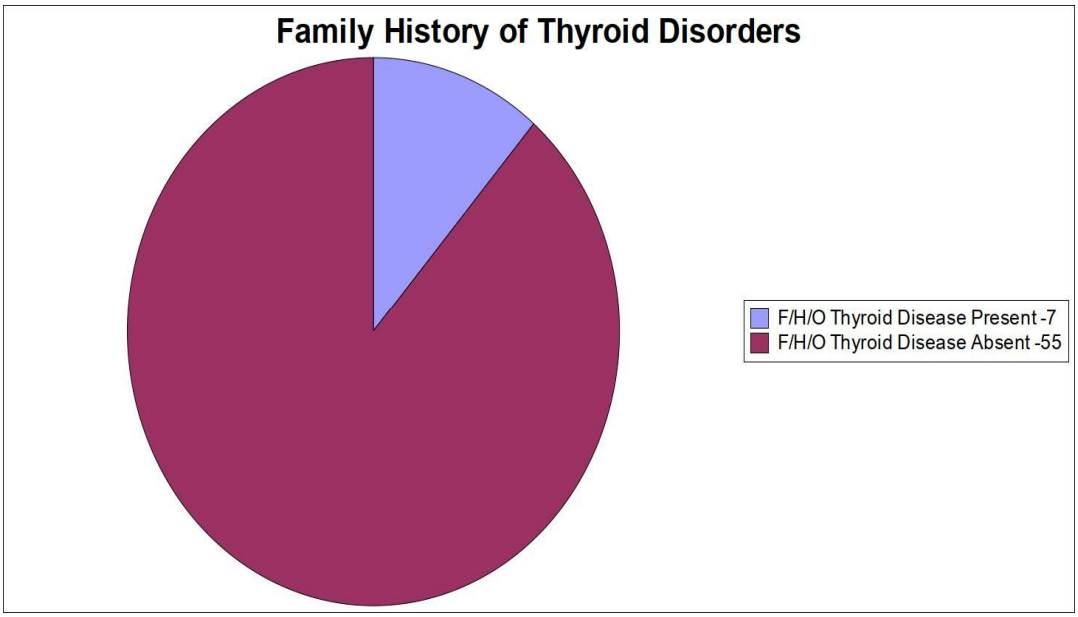
When symptomatology was analyzed we found that 35 patients presented with complaints of neck swelling, 28 with excessive weight gain, 9 subjects had generalized weakness, 5 subjects with difficulty in swallowing. Symptoms such as decreased appetite, head ache, constipation and generalized swelling were mainly associated with above mentioned complaints.

Generalized weakness was the major associated symptom which was seen in 8 individuals. Followed by difficulty in swallowing and head ache.

Some of the non-specific complaints were also registered by the subjects such as vomiting and upper respiratory tract symptoms cough and rhinorrhea.

FAMILY HISTORY

CHART-4

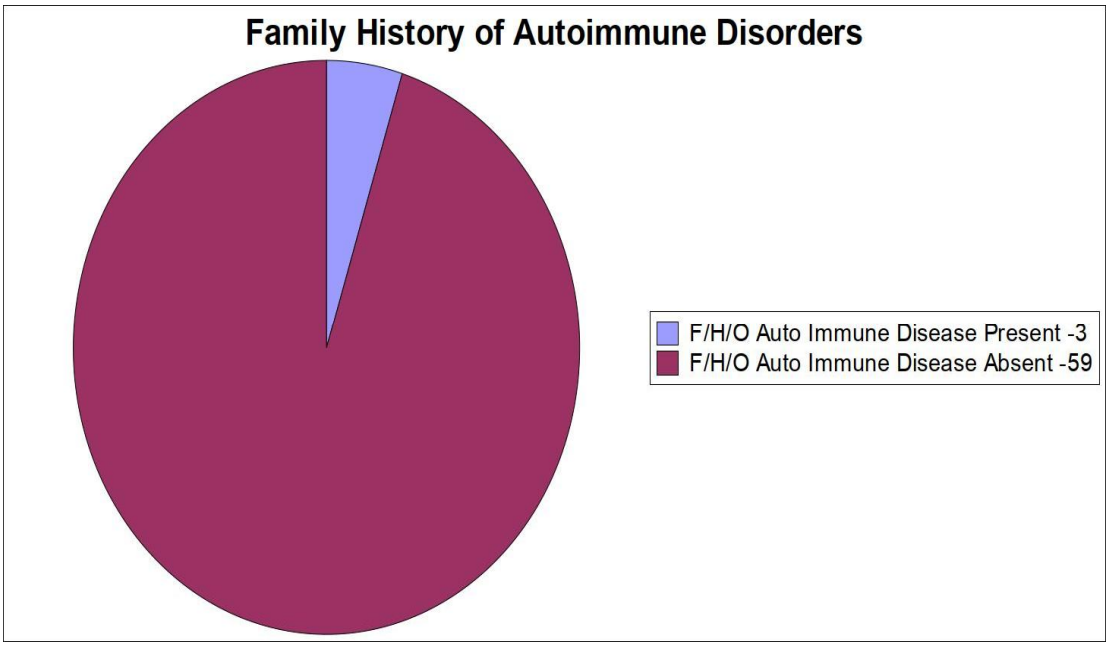


History of thyroid disease in family was enquired and 7 children (11.29%) had a positive family history of thyroid disease.

Only female children had the positive family history of thyroid disease.

AUTOIMMUNE THYROIDITIS

CHART-5

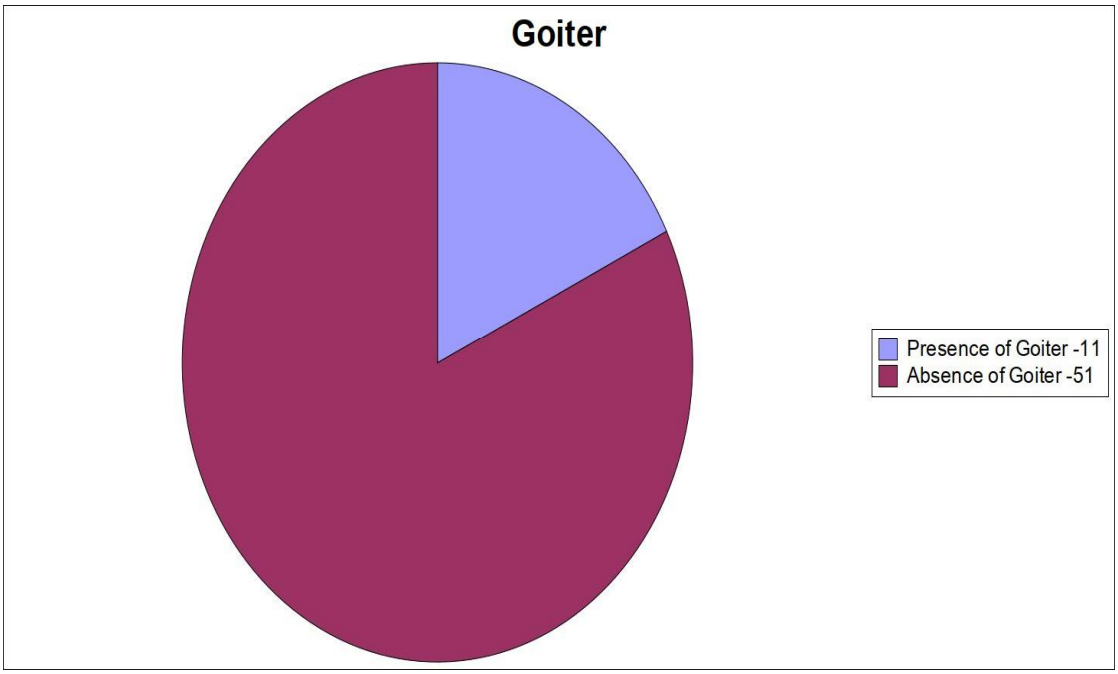


Family history of autoimmune thyroiditis was enquired. There were 3 female children with family history of autoimmune disease in the study population. It constitutes to 4.83%.

Two children had history of both thyroid disease and autoimmune disease in the family.

GOITER

CHART-6



Above pie diagram shows goiter was found in 11 subjects (17.74%).

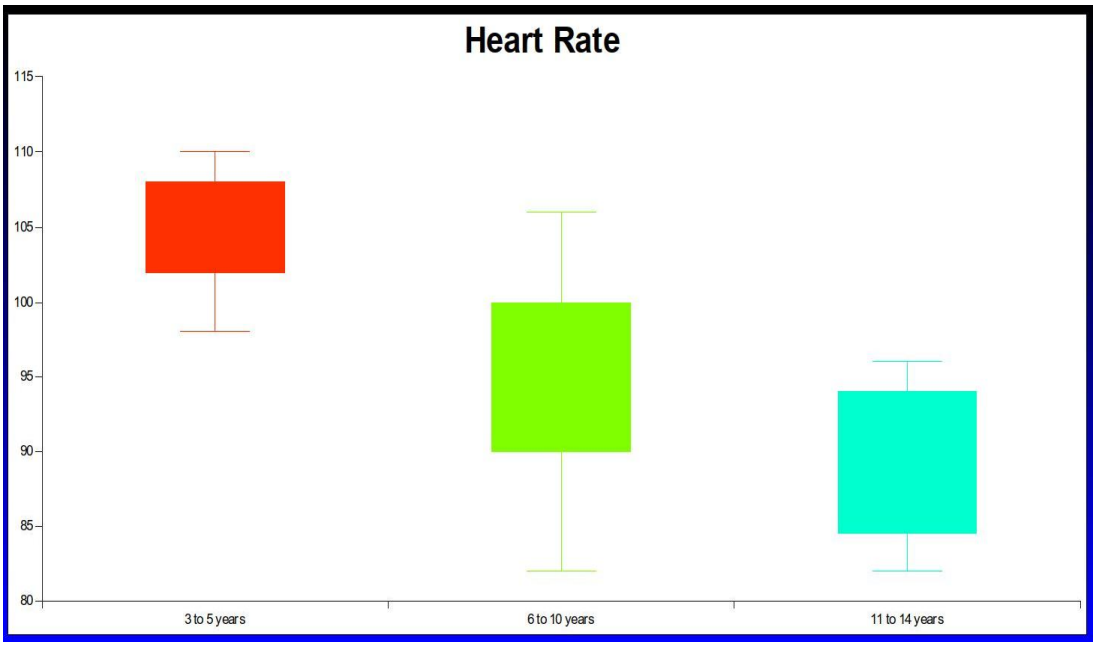
10 children (90.9%) were female and only 1 (9.1%) male.

Goiter:

Sex	Frequency	Percentage
Female	10	90.9%
Male	1	9.1%
Total	11	100%

HEART RATE DISTRIBUTION

CHART-7



All children were divided into three groups based on age as 3-5 years, 6-10 years and 11-14 years.

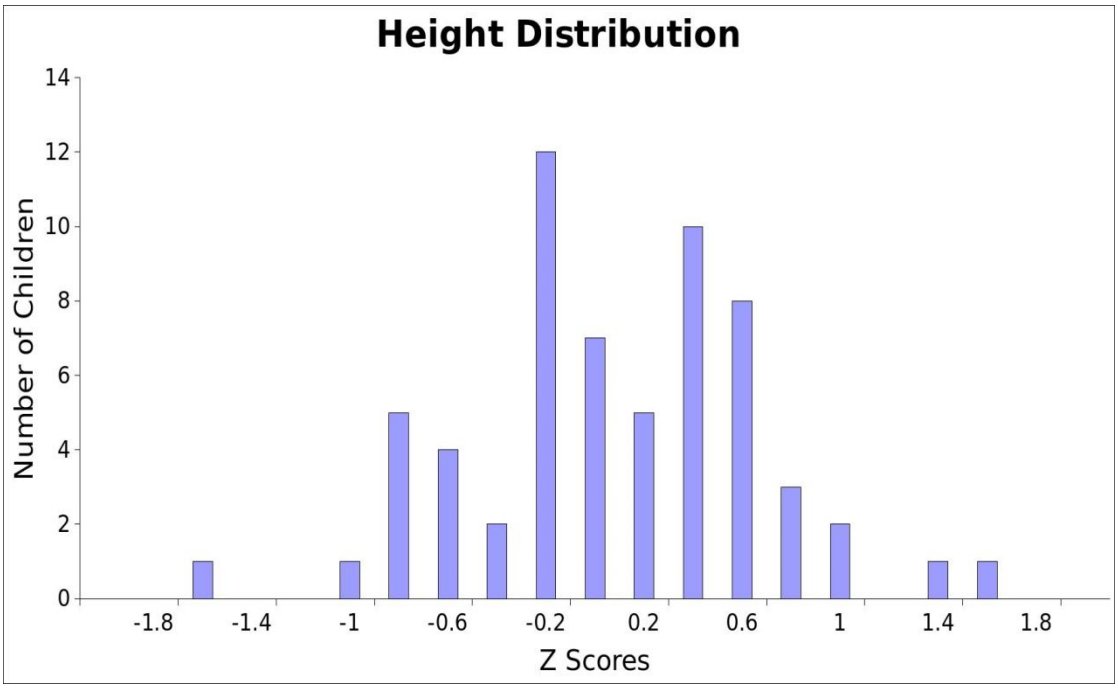
Distribution of heart rate was plotted according to these age groups.

TABLE: NORMAL HEART RATE

Age group	Heart rate	
	Minimum	Maximum
3-5 years	98	110
6-10 years	82	106
11-14 years	82	96

HEIGHT

CHART-8



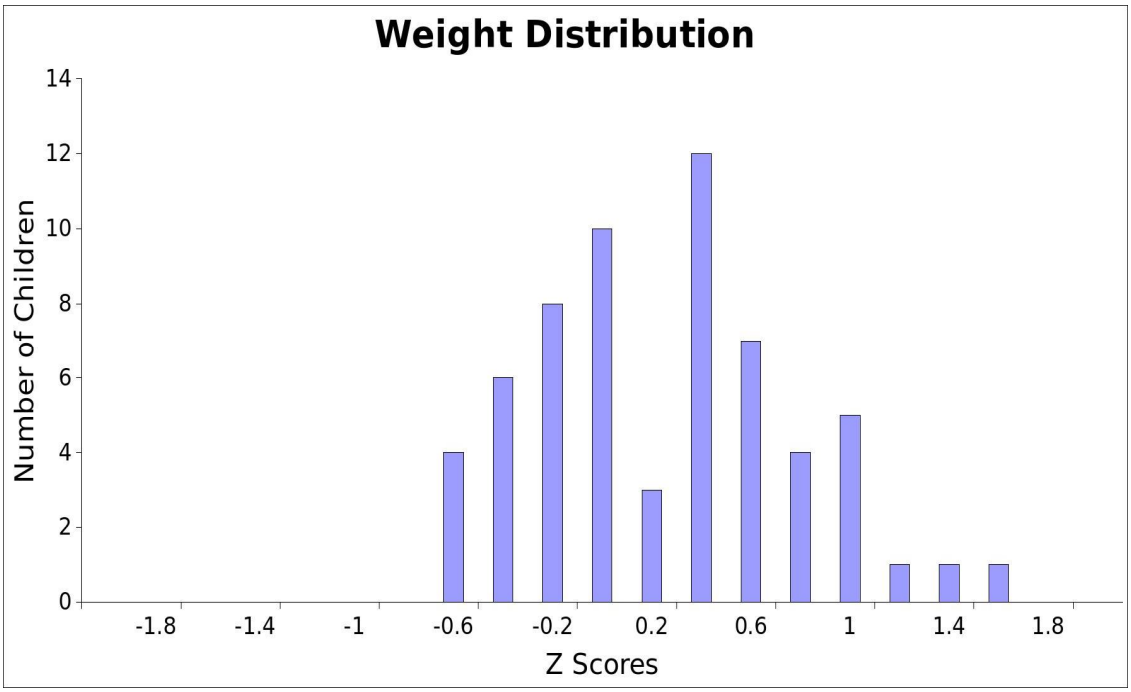
One Sample T-Test:

Maximum value	1.52	p =0.832
Minimum value	-1.6	
Mean	-0.016	
95% CI	-0.16 to 0.135	

Mean Z score for height of the study group is (-0.016) below population mean (Z=0), and it is statistically not significant (p=0.832).

WEIGHT

CHART-9



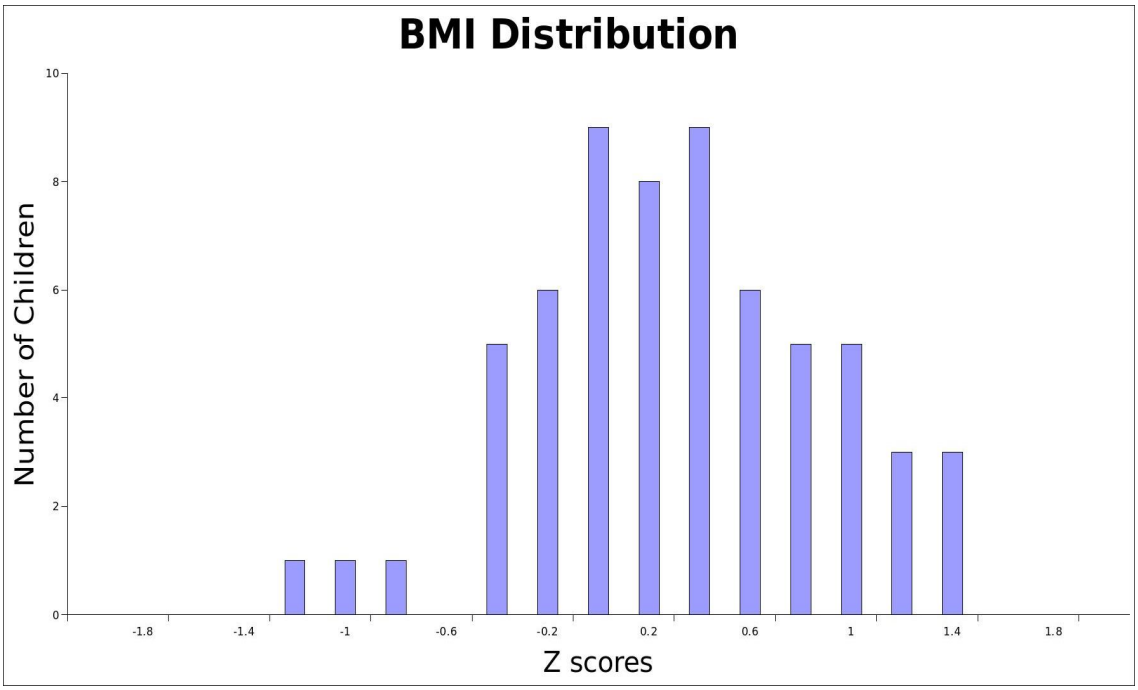
One Sample T-Test:

Maximum value	1.42	p=0.023
Minimum value	-0.78	
Mean	0.154	
95%CI	0.022-0.029	

Mean Z score for weight of the study group is (0.154) above the population mean (Z=0), and it is statistically significant (p=0.023).

BMI

CHART-10



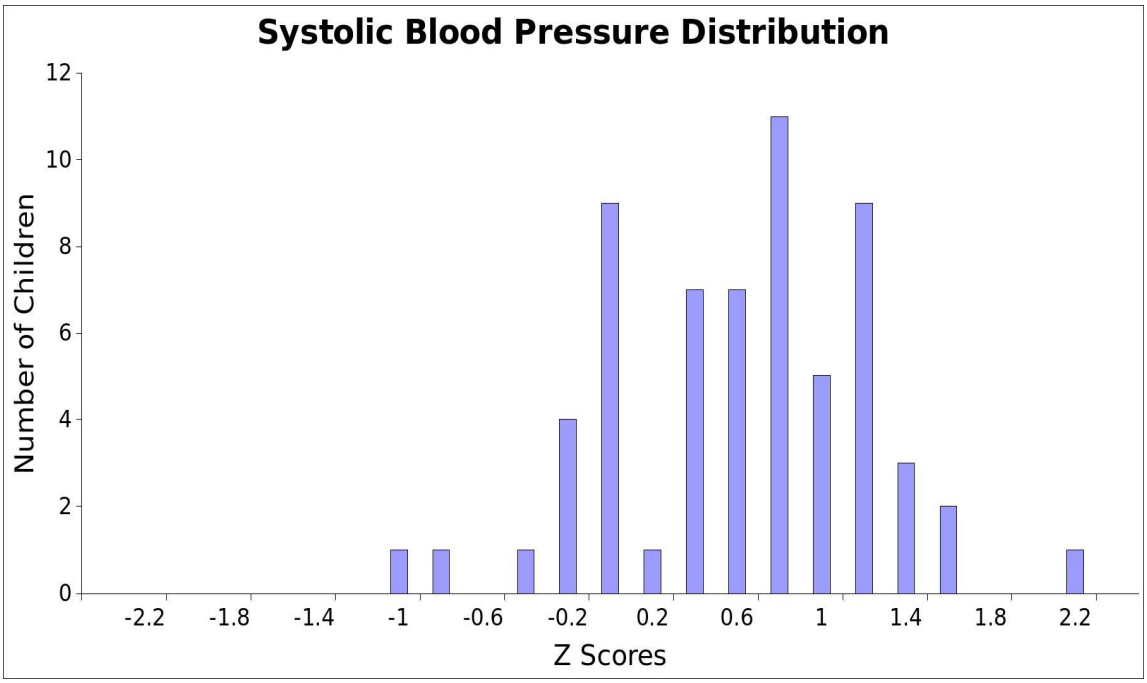
One Sample T-Test:

Minimum value	-1.26	p=0.004
Maximum value	1.4	
Mean	0.216	
95%CI	0.07-0.36	

Mean Z score for BMI of the study group is (0.216) above the population mean (Z=0), and it is statistically significant (p=0.004).

SYSTOLIC BLOOD PRESSURE

CHART-11



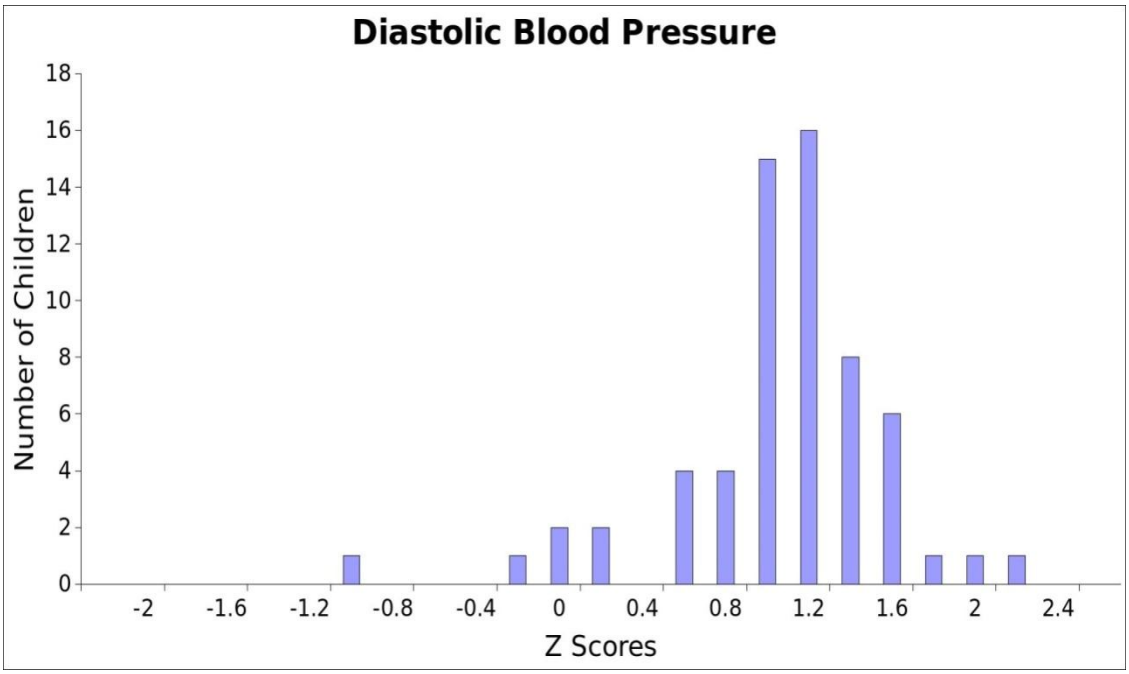
One Sample T-Test:

Maximum value	2.03	p=<0.0001
Minimum value	-1.04	
Mean	0.526	
95% CI	0.37-0.68	

Mean Z score for SBP of the study group is (0.526) above the population mean (Z=0), and it is statistically significant (p<0.0001).

DIASTOLIC BLOOD PRESSURE

CHART-12



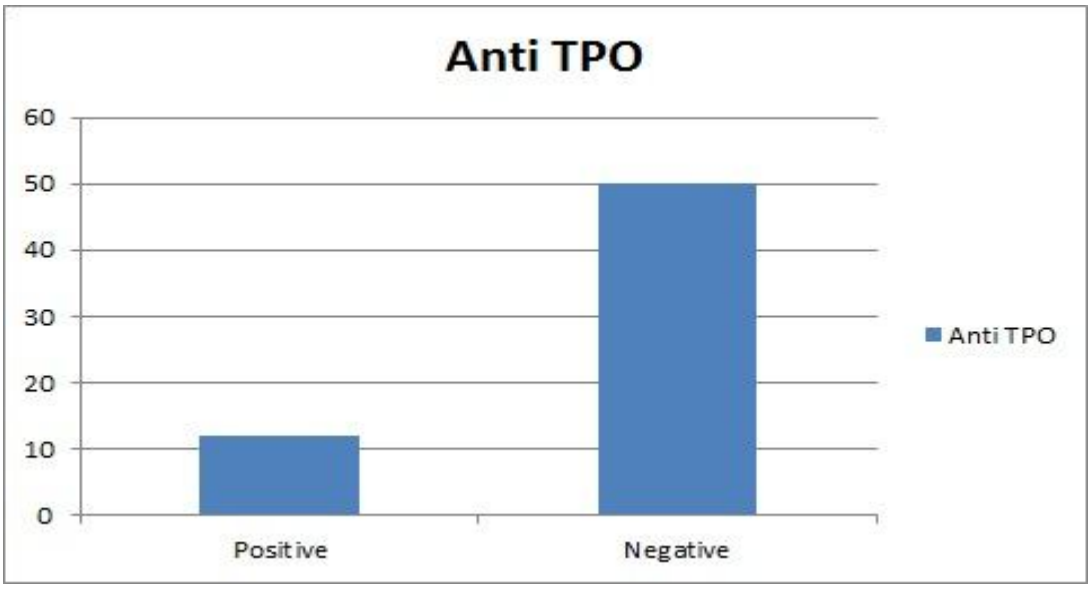
One Sample T-Test:

Maximum value	2.17	p<0.0001
Minimum value	-1.14	
Mean	0.96	
95% CI	0.83-1.08	

Mean Z score for DBP of the study group is (0.96) above the population mean (Z=0), and it is statistically significant (p=0.0001).

ANTI-TPO

CHART-13

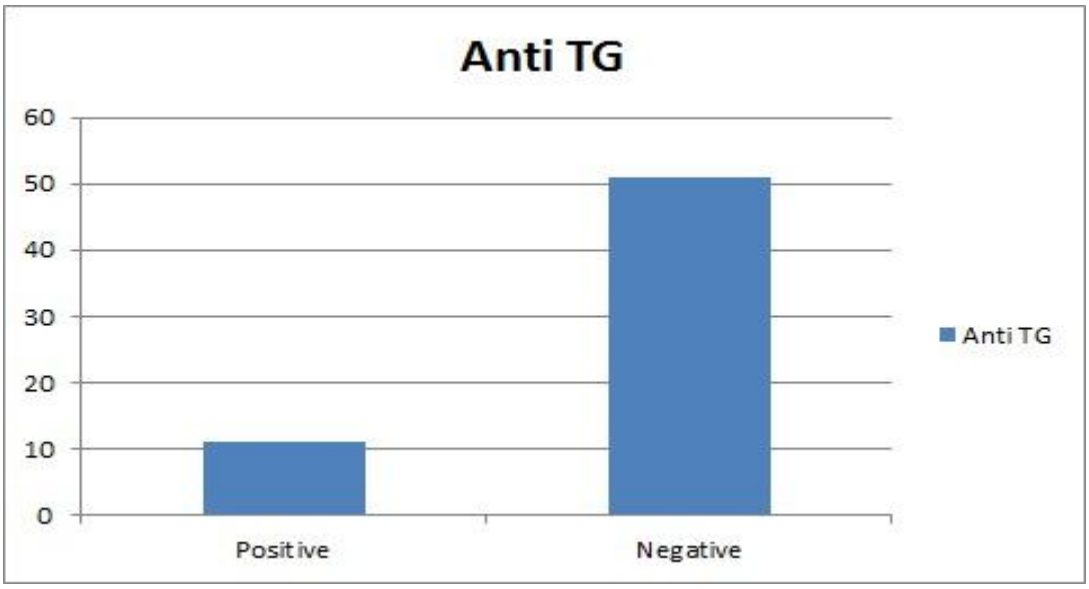


12(19.35%) subjects were positive for Anti-TPO antibodies.

The mean value of TSH with normal titer of Anti-TPO antibody (7.235) is lower than mean value of TSH with high titer of Anti-TPO antibody (7.918). This increase in TSH value in patients with high titer of Anti-TPO is statistically significant (p=0.036).

ANTI-TG

CHART-14

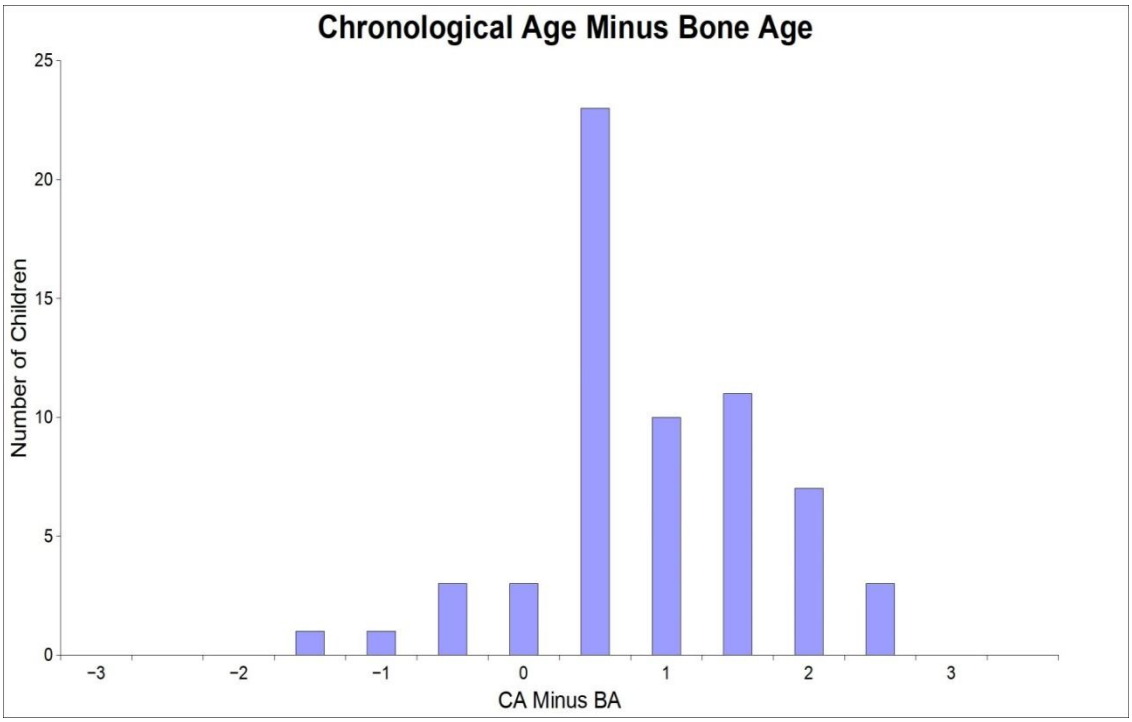


11(17.74%) subjects showed positive Anti-TG antibody titers.

The mean value of TSH with normal titer of Anti-TG antibody (7.216) is lower than mean value of TSH with high titer of Anti-TG antibody (8.07). This increase in TSH values in patients with high titer of Anti-TG is statistically significant (p=0.008).

X-RAY BONE AGE

CHART-15

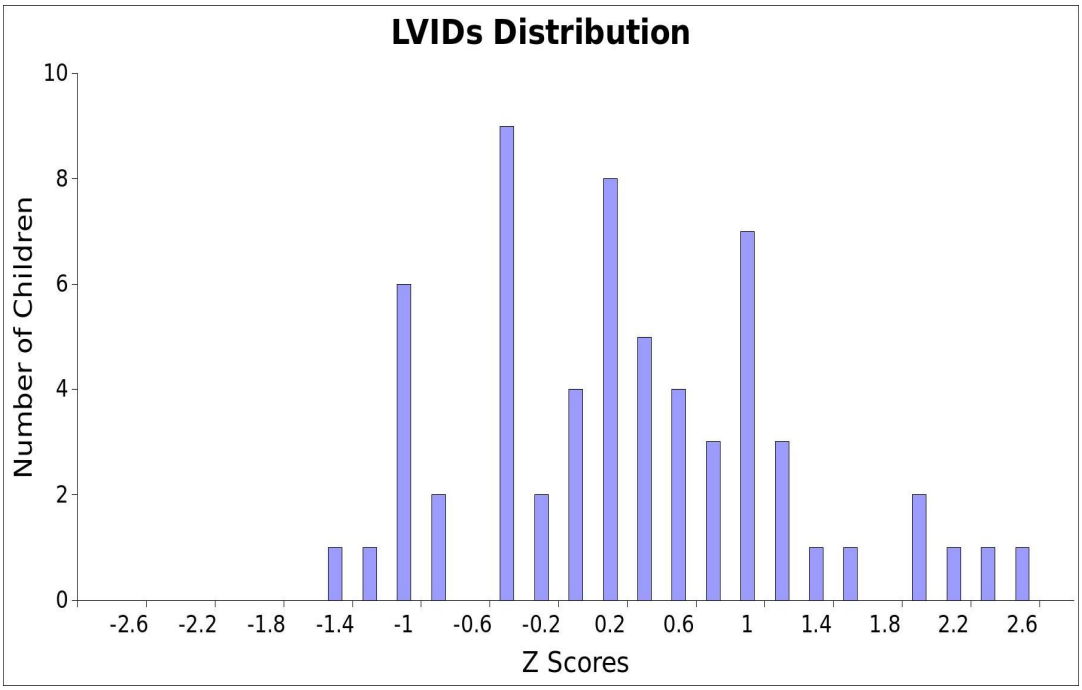


Significant delay of bone age (> 2 years) was observed in 3 (4.8%) subjects.

Remaining 59 children did not have discrepancy between chronological age and bone age.

LVIDs

CHART-16



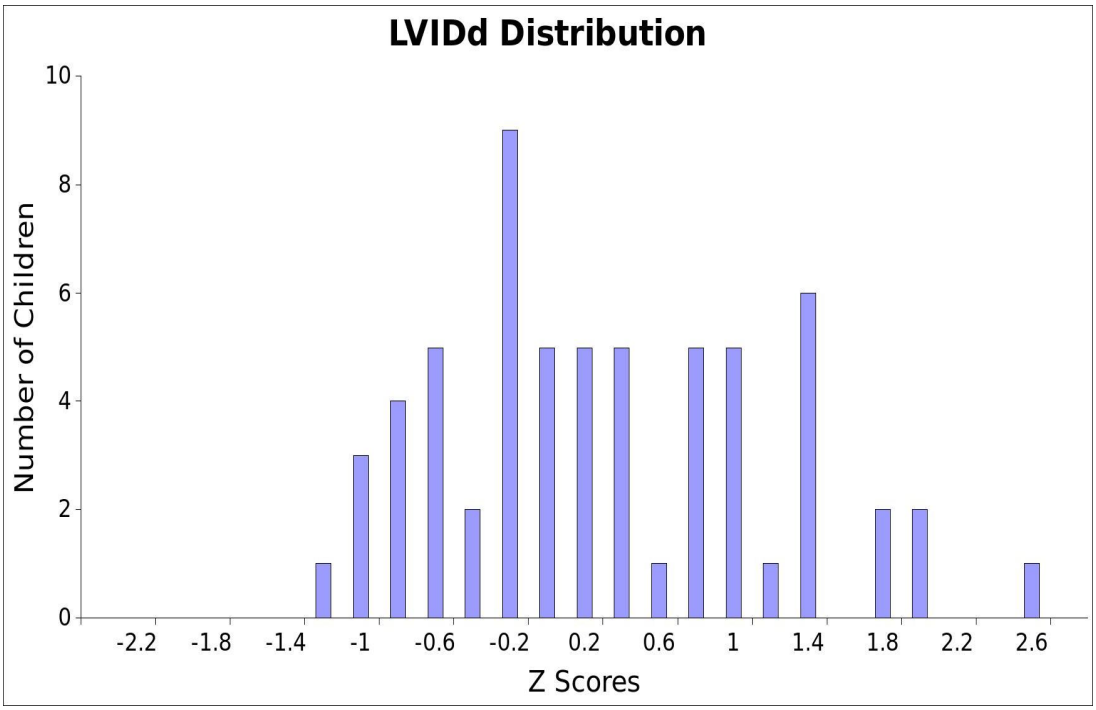
One Sample T-Test:

Maximum value	2.43	p=0.093
Minimum value	-1.48	
Mean	0.2	
95% CI	-0.34 to 0.433	

Mean Z score for LVIDs of the study group is (0.2) above the population mean (Z=0), and it is statistically not significant (p=0.093).

LVIDd

CHART-17



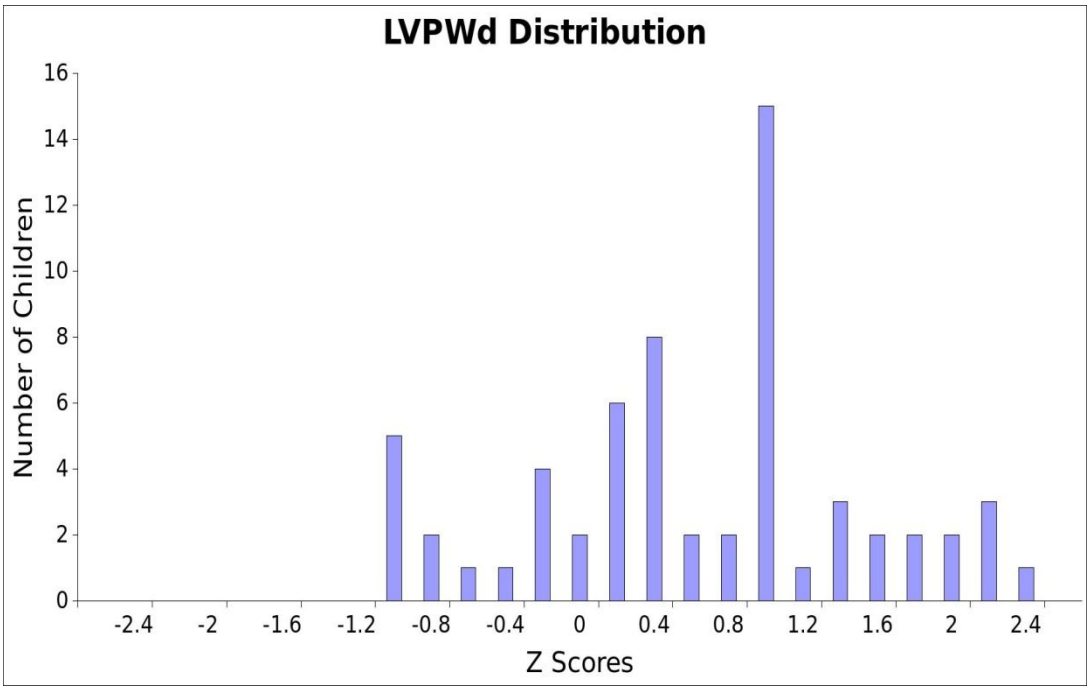
One Sample T-Test:

Maximum value	2.59	p=0.067
Minimum value	-1.23	
Mean	0.21	
95% CI	-0.015 to 0.435	

Mean Z score for LVIDd of the study group is (0.21) above the population mean (Z=0), and it is statistically not significant (p=0.067).

LVPWd

CHART-18



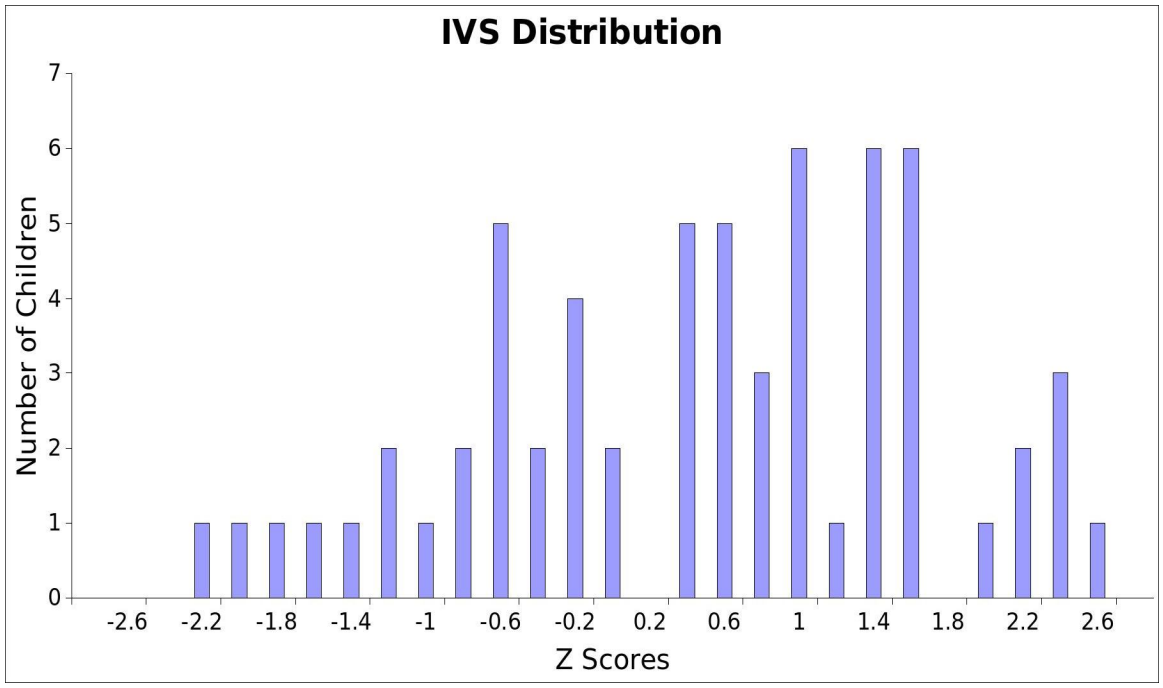
One Sample T-Test:

Maximum value	2.25	p<0.0001
Minimum value	-1.08	
Mean	0.56	
95% CI	0.337 to 0.784	

Mean Z score for LVPWd of the study group is (0.56) above the population mean (Z=0), and it is statistically significant (p<0.0001).

IVS

CHART-19



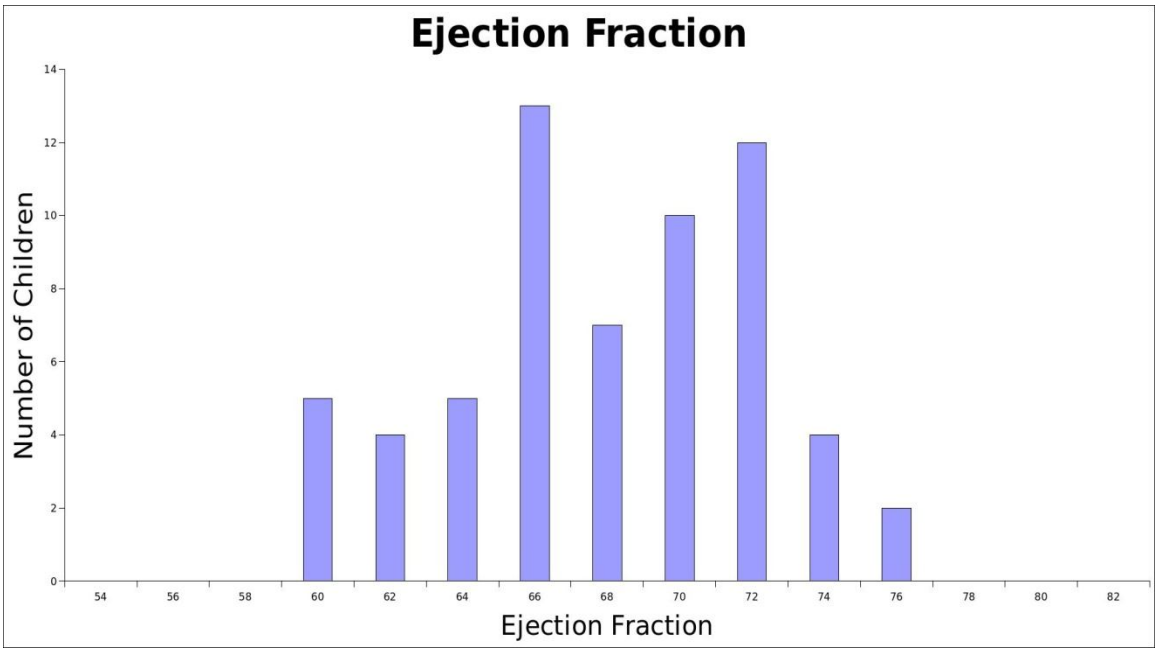
One Sample T-Test:

Maximum value	2.56	p=0.011
Minimum value	-2.3	
Mean	0.39	
95% CI	0.094 to 0.696	

Mean Z score for IVS of the study group is (0.39) above the population mean (Z=0), and it is statistically significant (p=0.011).

EJECTION FRACTION

CHART-20

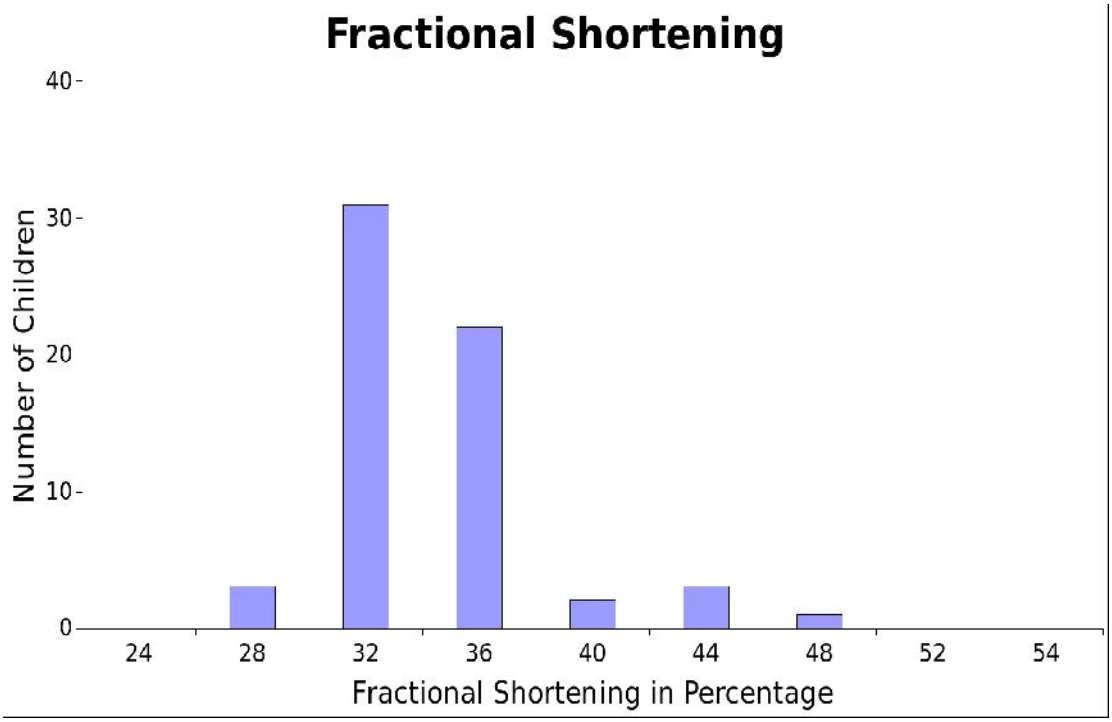


Mean	67.63
Standard error	0.55
95% CI	66.54 to 68.73
Maximum value	75
Minimum value	59

All children had normal ejection fraction.

FRACTIONAL SHORTENING

CHART-21

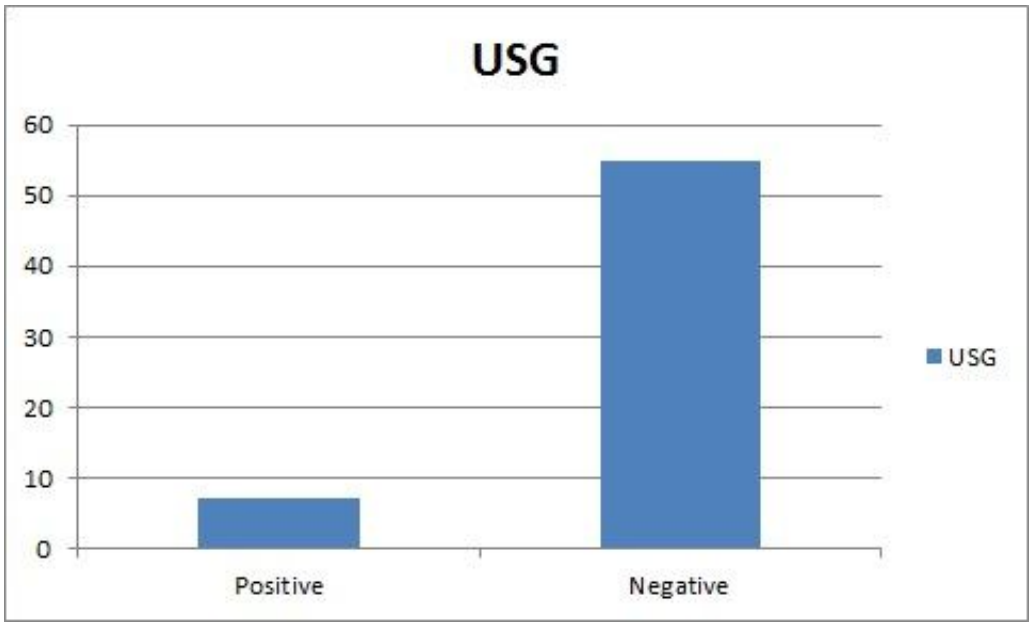


Mean	32.84
Standard error	0.43
95% CI	31.98 to 33.7
Maximum value	46
Minimum value	28

All children had normal Fractional shortening.

USG THYROID

CHART-22



USG finding of Auto-immune thyroiditis was seen in 7 (11.29%) subjects.

All these patients had elevated Anti-TPO and Anti-TG antibodies.

LIPID PROFILE

HDL

TABLE 1:

		Mean	95% CI	p value
Male	**5-9 years**	38.25	34.53-41.96	<0.0001
	10-14 years	38.7	34.65-42.74	<0.0001
Female	**5-9 years**	37.33	34.58-40.07	<0.0001
	10-14 years	36	33.82-38.17	<0.0001

As the standard population estimates for lipid profile were not available in less than 5 year old children they were excluded from the analysis.

In male children aged 5-9 years mean value of HDL is (38.25) below the population mean (55), and it is statistically significant ($p<0.0001$). In male children aged 10-14 years mean value of HDL is (38.7) below the population mean (55), and it is statistically significant ($p<0.0001$).

In female children aged 5-9 years mean value of HDL is (37.33) below the population mean (52), and it is statistically significant ($p<0.0001$). In female children aged 10-14 years mean value of HDL is (36) below the population mean (52), and it is statistically significant ($p<0.0001$)

CHOLESTEROL

TABLE-2:

		Mean	95% CI	p value
Male	**5-9 years**	171.25	165.77-176.72	<0.0001
	10-14 years	171.4	164.36-178.43	0.008
Female	**5-9 years**	170.33	166.13-174.52	0.005
	10-14 years	173.64	169.18-178.7	<0.0001

In male children aged 5-9 years mean value of cholesterol is (171.25) above the population mean (153), and it is statistically significant ($p<0.0001$). In male children aged 10-14 years mean value of cholesterol is (171.4) above the population mean (161), and it is statistically significant ($p=0.008$).

In female children aged 5-9 years mean value of cholesterol is (170.33) above the population mean (164), and it is statistically significant ($p=0.005$). In female children aged 10-14 years mean value of HDL is (173.64) above the population mean (159), and it is statistically significant ($p<0.0001$).

TRIGLYCERIDES

TABLE-3:

		Mean	95% CI	p value
Male	**5-9 years**	69.91	61.7-78.12	0.0001
	10-14 years	85.9	68.89-102.9	0.005
Female	**5-9 years**	80.88	72.7-89.07	<0.0001
	10-14 years	73.77	66.85-80.7	0.096

In male children aged 5-9 years mean value of triglycerides is (69.91) above the population mean (48), and it is statistically significant (p=0.0001). In male children aged 10-14 years mean value of triglycerides is (85.9) above the population mean (58), and it is statistically significant (p=0.005).

In female children aged 5-9 years mean value of triglycerides is (80.88) above the population mean (57), and it is statistically significant (p<0.001). In female children aged 10-14 years mean value of triglycerides is (73.77) above the population mean (68), and it is statistically significant (p<0.0001).

RESULTS

This study was conducted to understand the symptomatology, clinical and biochemical profile of Subclinical hypothyroidism in children who attended the Endocrinology OPD of Institute of Child Health and Hospital for Children.

A total of 62 children were enrolled for the study which included 37 (59.7%) girls and 25 (40.3%) boys. Average age of presentation in our study is 8.42 years.

Of 62 children 35 (56.45%) had sought medical advice for complaint of excessive weight gain, 28 (45.16%) had neck swelling as their principal symptom. 9 (14.51%) children had symptom of generalized weakness, 5(8%) children had history of difficulty in swallowing, 4 had history of head ache. 1.6% children had decreased appetite, constipation, generalized swelling, these symptoms were mainly in association with above mentioned principal symptoms.

Family history of thyroid disease was elicited in 7 (11.3%) children, and family history of autoimmune disease was elicited in 3 (4.84%) children.

It was found that all children who had positive family history of thyroid disease and autoimmune disease were females.

11(17.74%) children had goiter of which 9 (81.82%) were female and 2 (18.2%) were male. 7 (11.29%) children had features of thyroiditis in USG neck, all had elevated autoimmune antibodies.

Mean Z-score for height of the study group (-0.016) is lower than population mean which is not statistically significant (p=0.832). Mean Z-score for weight (0.154) and mean BMI (0.216) of the study population is significantly higher with p values of 0.023 and 0.004 respectively. It implies that significant difference in height is not observed in SCH children. However these children had higher weight and BMI.

Heart rate of the study population is well within the reference range for all age groups.

Mean Z-score for SBP (0.526) and mean Z-score for DBP (0.96) of the study population is significantly high with p<0.0001. This high value of Z-scores implies that these children are at higher risk of hypertension.

Among children with positive anti-thyroid antibodies Anti-TPO and Anti-TG, it was found that this group of children had high mean TSH when compared to children with normal titers of Anti-TPO and Anti-TG which was statistically significant. Implying SCH children due to autoimmune etiology tends to have high TSH when compared to other non-autoimmune etiology.

No significant discrepancy is observed between chronological age and bone age in 59 (95.16%) children. Significant delay of bone maturation (>2 years) is seen in 3 children which constitutes <5% of study population.

In left ventricular internal dimensions three LVIDs values and one LVIDd value is observed away from normal distribution. Mean Z-score for both LVIDs (0.2) and LVIDd (0.21) is positive, but statistically not significant. (p value 0.093 and 0.067 respectively). It implies that LV diameters were not found to be altered.

Left ventricular systolic function parameters like ejection fraction and Fractional shortening were found to be within reference range implying normal Left Ventricular systolic function in SCH children.

Mean HDL value is significantly low in all children with p value of <0.0001. Mean total cholesterol is significantly high in all children. Though mean Triglycerides of 10-14 year old female children is high it is not statistically significant (p=0.096), but remaining subjects have significantly high levels of Triglycerides. It implies that SCH is associated with adverse pro atherogenic lipid abnormalities.

DISCUSSION

The study sample is representative of Subclinical Hypothyroidism children attending Endocrinology OPD in a tertiary care center in south India.

In this study mean age of presentation is 8.42 years. Female children are largely affected (Female: Male ratio of 1.48:1).

Major symptoms the children had were weight gain, neck swelling, and generalized weakness which are consistent with symptom description by David S Cooper[8] in his review article.

11.29% of children had family history of thyroid illness, 4.8% of children had family history of autoimmune disease.

Goiter was noted in 17.74% of cases, majority of them being females (90.9%). Among the children with goiter, 81.8% had positive Anti-thyroid antibody implying goitrous autoimmune thyroid disease. It was found that only one male child had goitrous autoimmune thyroid disease.

In our study 19.35% of children had positive Anti-TPO antibodies, 17.74% had positive Anti-TG antibodies. These Children had significantly higher mean level of TSH when compared to the children with normal titers. These children must be followed up regularly with TSH monitoring as they have higher chance of future development of hypothyroidism. Radetti et al[26] in their study had found that presence of goiter and elevated TG-Abs at presentation along with increase in TPO-Abs predicts future development of

hypothyroidism. Similarly Zois et al[27] also showed that elevated TPO-Abs can be considered as a predictive factor for impending thyroid failure. Gopalakrishnan et al[28] in their study had concluded that subjects with goitrous autoimmune thyroiditis need periodic monitoring of thyroid function as development of thyroid dysfunction is insidious.

All children had normal heart rate according to their age.

Mean Z-scores of both SBP and DBP is high in the study group, implying these children are at increased risk of hypertension. Similar finding was obtained in a Chinese study by Chen et al[24] where increase in BP was associated with high TSH without overt thyroid disease. Ittermann et al[25] also found positive relationship between serum TSH with SBP and DBP.

95.16% of study subjects had no significant discrepancy in chronological age and bone age. It shows that majority of SCH children do not have significant delay in bone maturation. Similar observation was made by Di Mase et al[23] where they had arrived at a conclusion that neither the duration of SCH nor TSH levels had significant impact on bone health.

Mean left ventricular wall thickness (IVS and LVPW) of study patients as obtained by M-mode measurements were significantly higher when compared to population mean.

Statistically significant increase in Left Ventricular wall thickness in our study group was obtained as a one point measurement. Serial monitoring of

these children will be needed to ascertain the clinical and hemodynamic significance of this study.

Left ventricular dimensions during both phases of cardiac cycle were within normal limits.

Left ventricular systolic functions which were measured by after load dependent parameters like Ejection fraction and Fractional shortening were also within normal range. Decreased FS can be seen in poorly compensated LV function regardless of the cause.

Mean values of Cholesterol and Triglycerides were significantly elevated and mean value of HDL was significantly low in our study group. Implying these children had an abnormal lipid profile. Similar observation was made by Cerbone et al[29] where SCH children had significantly high atherogenic index and Triglyceride/HDL ratio indicating pro atherogenic lipid abnormalities.

CONCLUSION

- Subclinical hypothyroidism is more common in female children.
- Principal complaints in these children are Neck swelling and weight gain.
- Subclinical hypothyroidism children do not have significant alteration in bone maturation.
- Goitrous autoimmune disease presenting as subclinical hypothyroidism is more common in female children.
- Significant number of children have positive Anti-thyroid antibody titers. These children should be followed up regularly so as to recognize the onset of overt hypothyroidism early.
- Mean TSH value of patients with positive Anti-thyroid antibody is higher when compared to patients with negative titers.
- Subclinical hypothyroid children have normal heart rate. Both Systolic and diastolic blood pressures are high in these children.
- Subclinical hypothyroid children have adverse proatherogenic lipid profile.

LIMITATIONS

- Our cross sectional study was done on a small sample of children (n=62). As the prospective follow up is missing natural course of the disease could not be studied.
- Children with clinical symptoms were conveniently included in the study. Ideally sample should have been selected from population after screening.
- Diastolic function was not measured in study population.

RECOMMENDATION

This study puts forth many important queries which may provide scope for future research.

First, regular follow up of these children for cardiovascular and lipid abnormalities is essential as they have higher risk of atherosclerosis which increases cardiovascular mortality and morbidity. Regular monitoring of subclinical hypothyroid children with positive anti-thyroid antibodies is necessary as they have higher risk of progression to overt thyroid disease. Prospective follow up of these children will help in studying the natural course of the disease.

Second, to ascertain whether these changes are reversed by treatment with L-thyroxine, randomized controlled trials are to be conducted. If proven L-thyroxine treatment may significantly reduce the adverse cardiovascular consequences associated with Subclinical Hypothyroidism.

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INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

EC Reg No.ECR/270/Inst./TN/2013
Telephone No. 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To

Dr.Poornachand.V.
Post Graduate in M.D.(Paediatrics)
Madras Medical College
Chennai 600 003

Dear Dr. Poornachand.V,

The Institutional Ethics Committee has considered your request and approved your study titled **"STUDY OF CLINICAL AND BIO-CHEMICAL PROFILE OF SUB-CLINICAL HYPOTHYROIDISM IN CHILDREN AGED TWO TO TWELVE YEARS " No. 34102015.**

The following members of Ethics Committee were present in the meeting held on 06.10.2015 conducted at Madras Medical College, Chennai-3.

1. Prof.C.Rajendran, M.D., : Chairperson
2. Prof.R.Vimala, M.D., Dean, MMC, Ch-3 : Deputy Chairperson
3. Prof.Sudha Seshayyan, M.D. Vice-Principal,MMC,Ch-3: Member Secretary
4. Prof.B.Vasanthi, M.D., Professor Pharmacology, MMC : Member
5. Prof.P.Ragumani, M.S., Professor, Inst.of Surgery, MMC : Member
6. Prof.K.Ramadevi, Director, Inst.of Biochemistry, MMC : Member
7. Prof.Saraswathy, M.D., Director, Inst. Of Pathology, MMC: Member
8. Prof.Srinivasagalu, Director, Inst.of Inter Med. MMC : Member
9. Tmt. Rajalakshmi, Jr. Administrative Officer : Lay Person
10. Thiru S.Govindasamy, B.A., B.L., : Lawyer
11. Tmt.Arnold Saulina, M.A., MSW., : Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

PROFORMA

1. Study Id:

2. Name:

3. OP Number:

4. Age: DOB-

Actual age- _____ years_____months

5. Sex: A) Male B) Female

SYMPTOMS OF HYPOTHYROIDISM

6. Weight gain: Y/N

7. Decreased appetite: Y/N

8. Cold intolerance: Y/N

9. Swelling of feet: Y/N

10. Dry, cold skin: Y/N

11. Loss of hair and thinning of hair: Y/N

12. Hoarseness of voice: Y/N

13. Headache: Y/N

14. Neck swelling: Y/N

15. Difficulty in swallowing: Y/N

16. Generalized weakness: Y/N

17. Lassitude: Y/N

18. Constipation: Y/N

19. Any other complaints: Y/N

20. Other autoimmune diseases (Type 1 DM/RA/MS): Y/N

21. Family h/o hypothyroidism/probable autoimmune disease: Y/N

(Diagnosis if available:_____)

22. Medication/other treatment history:

23. Thyroid surgery: Y/N

24. Antithyroid drugs: Y/N

25. Other medications:

ANTHROPOMETRY

26. Height/Length for age: A) Actual-

B) Z-score

27. Weight for age: A) Actual-

B) Z-score

28. BMI:

Z-score:

EXAMINATION

29. Pallor:

30. Oedema:

31. Skin:

32. Pulse rate:

33. Blood pressure: Z-scores:

34. Goitre: Y/N

35. Respiratory system:

36. Cardiovascular system:

37. Per abdomen:

38. Central nervous system:

INVESTIGATIONS

39. TSH:

40. Free T4:

41. Free T3:

42. Anti-Thyroid peroxidase Ab: Positive/Negative, Value if positive _____

43. Anti-Thyroglobulin Ab: Positive/Negative, Value if positive _____

44. HDL

45. TG

46. X ray bone age:

47. M mode echo:

தகவல் படிவம்

ஆய்விடம் அரசு குழந்தைள் நல மருத்துவமனை மற்றும் ஆராய்ச்சி நிலையம்

ஆய்வாளர் மருத்துவர் : வே.பூர்ணசந்
பங்கு பெறுபவரின் பெயர் : வயது: பாலினம் :

மருத்துவமனை எண்.

1. ஆய்வுதலைப்பு : 2 முதல் 12 வயது வரை உள்ள குழந்தைகளுக்கு தைராய்டு சுரப்பி குறைவதால் (Subclinical Hypothyroidism) உடலில் ஏற்படும் மாற்றங்கள் மற்றும் வேதியல் மாற்றங்கள் பற்றிய ஆய்வு.
2. தங்கள் குழந்தையும் இந்த ஆய்வில் பங்கு பெற கேட்டுக் கொள்கின்றோம்.
3. குழந்தையைப் பற்றிய விவரங்கள் கேட்டு அறியப்படும் மருத்துவ பரிசோதனை மேற்கொள்ளப்படும். இரத்தப் பரிசோதனை மற்றும் XRay, Echo எடுக்கப்படும்.
4. இந்த ஆய்வில் பங்கு பெறுவது உங்கள் தனிப்பட்ட விருப்பமே. ஆய்வு ஆரம்பித்த பின் விருப்பம் இல்லை என்றால் தாங்கள் விலகிக் கொள்ளலாம். அவ்வாறு விலகுவதானது தங்கள் குழந்தையின் சிகிச்சைக்கு எவ்வித பாதிப்பையும் உருவாக்காது.
   ஆய்வின் முடிவுகள் ஆய்வு நடக்கும் போதோ (தேவை ஏற்படின்)
5. உங்களுக்கு இந்த ஆய்வில் பங்கு பெறுவதால் எந்த பயனும் இல்லை. ஆனால் இந்த ஆய்வில் வரும் முடிவுகளை வைத்து மற்ற குழந்தைகளுக்கு கிடைக்கும் சிகிச்சைமுறை மேம்படுத்தப்படும்.
6. இந்த ஆய்வில் உங்கள் குழந்தையைப் பற்றிய தனிப்பட்ட விவரங்கள் யாருக்கும் தெரிவிக்காமல் பாதுகாக்கப்படும்.
7. உங்கள் குழந்தையைப்பற்றிய விவரங்கள் தெரிய வேண்டுமென்றால் ஆய்வு செய்யும் மருத்துவரை அணுகவும்.
   மருத்துவ ஆய்வாளர் : வே.பூர்ணசந் (போன் 9566808101)

ஆய்வாளரின் கையொப்பம் பெற்றோரின் கையொப்பம்

நாள் :
இடம் :

PATIENT INFORMATION SHEET

Place of study: Institute Of Child Health And Hospital for Children, Egmore, Chennai-8.

Name of Investigator: Dr. POORNACHND V

Name of Participant: **Age**: **Sex**:

Hospital No:

Study title: STUDY OF CLINICAL AND BIOCHEMICAL PROFILE OF SUBCLINICAL HYPOTHYROIDISM IN CHILDREN

We request your child to participate in the study.

Aim of the study-

To study clinical and biochemical profile in children with subclinical hypothyroidism in children

Methods- Clinical history will be collected. Detailed clinical examination including anthropometry will be done. Vitals noted including BP. Blood samples collected for thyroid function test, lipid profile, Anti TPO and Anti TG antibodies, X ray for bone age will be taken and left ventricular function will be assessed using M mode echo.

Participation in the study is purely voluntary. You may refuse to participate or withdraw from the study at any time. In both cases the treatment and care your child receives from this hospital will not be affected in any manner.

Your child will not benefit directly by participating in this study. But by way of participating in this study, your child is contributing to updation of science which may benefit her/him and all other patients with this disease in future.

Confidentiality-

The data collected from the study will be used for the purpose of study only. The results of the study will be published. Personal information of the children participating in the study will be kept confidential. There will not be any disclosure about your child's information without your permission.

Subject rights-

If you wish further information regarding your child's rights as a research participant, you may contact the principal investigator in the mobile number or address mentioned below.

Principal Investigator – Dr POORNACHAND V

Mobile number - 9566808101

Contact Address - MD Post Graduate, Institute of Child Health and Hospital for Children, Halls road, Egmore, Chennai.

Place:

Date: Signature of Parent

ஒப்புதல் படிவம்

ஆய்விடம் அரசு குழந்தைள் நல மருத்துவமனை மற்றும் ஆராய்ச்சி நிலையம்

ஆய்வாளர் மருத்துவர் : வே.பூர்ணசந்
பங்கு பெறுபவரின் பெயர் : வயது: பாலினம் :

மருத்துவமனை எண்.

ஆய்வுதலைப்பு : 2 முதல் 12 வயது வரை உள்ள குழந்தைகளுக்கு தைராய்டு சுரப்பி குறைவதால் (Subclinical Hypothyroidism) உடலில் ஏற்படும் மாற்றங்கள் மற்றும் வேதியல் மாற்றங்கள் பற்றிய ஆய்வு.

1. இந்த ஆய்வைப்பற்றிய அனைத்து தகவல்களும் எனக்கு தெரிவிக்கப்பட்டது.
2. இதில் பங்கு பெறுவதற்கான ஒப்பந்த படிவமும் எனக்கு விவரிக்கப்பட்டது.
3, ஆராய்ச்சியின் தன்மையும் எனது உரிமைகளும் எடுத்துரைக்கப்பட்டது.
4. இந்த ஆய்வினால் எனது குழந்தையின் நலனுக்கு எந்த தீங்கும் இல்லை என்பதை தெரிந்து கொண்டேன்.
5. இந்த ஆய்வில் எனது குழந்தை பங்கு பெற எனது மனமார்ந்த ஒப்புதலை தருகிறேன்.
6. இந்த ஆய்வில் உங்கள் குழந்தையைப் பற்றிய தனிப்பட்ட விவரங்கள் யாருக்கும் தெரிவிக்காமல் பாதுகாக்கப்படும்.

7, இந்த ஆய்வில் பங்கு பெறுவது உங்கள் தனிப்பட்ட விருப்பமே. ஆய்வு ஆரம்பித்த பின் விருப்பம் இல்லை என்றால் தாங்கள் விலகிக் கொள்ளலாம். அவ்வாறு விலகுவதானது தங்கள் குழந்தையின் சிகிச்சைக்கு எவ்வித பாதிப்பையும் உருவாக்காது.

பெற்றோரின் கையொப்பம் சாட்சியின் கையொப்பம்
நாள் :
இடம் :

INFORMED CONSENT FORM

Study place: Institute Of Child Health And Hospital For Children,
Egmore, Chennai-8.

Title of the study: STUDY OF CLINICAL AND BIOCHEMICAL PROFILE OF SUBCLINICAL HYPOTHYROIDISM IN CHILDREN

Name of the investigator: Dr. POORNACHAND V

Name of the Participant: **Age**: **Sex**:

Hospital number:

1. I have read and understood the patient information sheet provided to me regarding the participation of my child in the study.

2. I have been explained about the nature of the study and had my questions answered to my satisfaction.

3. I have been explained about my rights and responsibilities by the investigator.

4. I will allow my child to cooperate with the investigator and undergo clinical tests subjected during the study whole heartedly.

5. I have been advised about the risks associated with my child's participation in this study.

6. I am aware of the fact that I can opt out of the study at any time without having to give any reason and this will not affect my child's future treatment in this hospital.

7. I hereby give permission to the investigators to release the information obtained from my child as result of participation in this study to medical journals/conference proceedings.

8. I understand that my child's identity will be kept confidential if my child's data are publicly presented/ published.

9. I have decided my child can participate in the research study. I am aware that if I have any question during this study, I should contact the investigator.

10. By signing this consent form I attest that the information given in this document has been clearly explained to me and understood by me, I will be given a copy of this consent document.

Name and signature / thumb impression of the parent/guardian

Name _____ Signature_____

Date_____

Name and Signature of the investigator

Name _____ Signature_____

Date_____

Name and Signature of impartial witness 1:

Name _____ Signature_____

Date_____

Name and Signature of impartial witness 2:

Name _____ Signature_____

Date_____

KEY TO MASTER CHART

A. Sex : 1-Male; 2-Female

B. Symptoms : 1- Weight gain; 2- Neck swelling; 3- Head ache; 4- Difficulty in swallowing; 5- Generalized weakness; 6- Decreased appetite; 7- Constipation; 8- Generalized swelling; 9- Nonspecific.

C. Family history of autoimmune disease: 1- Yes; 2- No.

D. Family history of thyroid disease: 1- Yes; 2- No.

E. Thyroid surgery: 1-Yes; 2- No.

F. Anti-thyroid drugs: 1- Yes; 2- No.

G. Goiter: 1- Yes; 2- No.

H. USG features of autoimmune disease: 1- Yes; 2- No.

I. Anti-TPO antibodies: 1- Positive; 2- Negative.

J. Anti-TG antibodies: 1-Positive; 2- Negative.

MASTER CHART

sl. no	name	age	sex	symotoms	autoimmune disease	familhistory	height	weight	bmi	pulse	sbp	dbp	goitre	tsh	anti_tpo	anti_tg	hdl	cholesterol	triglycerides	x ray_ba	ivs	lvids	lvidd	lvpwd	lad	ef	fs	usg	ca-ba
1	Mythli	9	2	2,3	2	2	0.39	0.45	0.34	88	-0.04	-0.016	1	8.19	339.58	45.99	32	165	56	10	-1.89	0.55	1.91	1	0.53	74	43	1	-1
2	lingeshwaran	9.5	1	1	2	2	-0.4	-0.23	-0.048	96	-1.04	-0.21	2	8.3	<3	<3	38	175	85	9	-0.2	0.9	1.62	1.01	0.6	74	32	2	0.5
3	Gayatri	6	2	1	2	2	0.85	1.28	1.29	102	-0.19	-0.13	2	5.8	<3	<3	36	177	89	6	0.22	0.21	0.44	1	0.58	70	30	2	0
4	Sri nidhi	5.25	2	2,5	2	2	0.52	0.87	0.91	110	2.03	1.5	2	9.5	<3	<3	30	181	66	7	1.33	0.65	0.34	2.12	0.9	72	34	2	-1.75
5	jeevanandam	8.32	1	9	2	1	0.28	0.0004	-0.41	94	0	-1.14	2	6.8	<3	<3	48	166	88	8	1.33	1.04	0.34	-0.24	0.73	60	32	2	0.32
6	Kavipriya	8.9	2	1	2	2	0.32	1.19	1.26	100	-0.96	0.77	2	8.42	11.4	93.26	41	162	79	9	0.84	-1.39	0.86	1.22	-0.1	70	30.5	2	-0.1
7	Srividya	7.5	2	4,5,9	2	2	-0.1	0.51	0.74	82	1.12	1.25	2	8.33	<3	<3	49	159	85	6	0	0.88	0.89	0.94	0.36	72	34	2	1.5
8	Samiya	5.56	2	2,8	2	2	-1.1	-0.25	0.58	108	1.14	1.03	1	6.26	29.94	3.24	41	163	68	4	2.3	0.37	-0.14	1	0.26	75	33	2	1.56
9	shanthini	11	2	2	2	2	-1	-0.05	0.51	90	0.58	1.05	2	8.65	<3	<3	36	173	69	10	-0.21	2.43	1.91	-1.08	0.43	59	31	2	1
10	Monisha	7	2	2	2	2	0.26	-0.6	-1.18	98	0.14	0.79	1	7.15	<3	<3	38	161	74	6	1.33	-0.5	-0.28	0.94	0.56	70	33	2	1
11	Dilipan	4.5	1	1,5	2	2	-0.2	-0.6	-0.82	102	0.63	0.83	2	6.3	<3	<3	35	164	63	4	2.03	0.93	-0.57	1.6	0.82	70	32	2	0.5
12	Sasibalaji	3.5	1	7	2	2	-0.2	-0.18	-0.11	108	0.55	1.43	2	7.3	0.3	1.17	36	163	81	1.5	2.12	1	0.71	1.87	-0.2	65	32	2	2
13	Dhanushree	10.1	2	2,5	2	2	-0.1	0.5	0.71	90	0.99	0.99	2	7.25	<3	<3	36	158	60	10	-1.78	0.86	2.59	1	1.1	70	32	2	0.1
14	Keerthana	9.8	2	1	2	2	0.67	0.24	-0.1	102	-0.1	0.1	2	8.75	<3	<3	32	170	70	9	2.25	-0.56	-0.19	2.25	0.35	71.1	31.5	2	0.8
15	Abinaya	10.9	2	2	2	1	-0.6	-0.42	-0.18	84	1.02	1.64	1	8.62	78.96	24.61	33	168	82	10	1.33	-1.17	-1.03	1	0.45	74	32	2	0.9
16	Sadhana	5	2	1	2	2	0.35	0.73	0.84	108	0.76	1.37	2	8.8	<3	<3	41	166	74	6	1.07	1.04	0.65	2.12	0.64	72	28	2	-1
17	Anandhi	9.1	2	1	2	2	0.09	0.94	1.16	96	-0.36	0.97	2	7.42	<3	<3	40	192	79	9	0.84	-1.14	-0.99	0.17	0.8	70	31	2	0.1
18	Ashrath	8.5	1	1,2,4	2	2	0.14	0.27	0.38	92	1.06	1.35	2	7.33	<3	<3	46	186	58	8	1	-1.48	0.06	0.38	0.4	68	34	2	0.5
19	Palani	5.16	1	2,3	2	2	0.4	0.7	0.52	106	-0.26	1.01	2	6.2	<3	<3	37	172	59	5	-0.27	0.5	1.29	1.88	0.13	66	28	2	0.16
20	Dravid	12	1	1	2	2	0.07	-0.1	-0.19	96	0.34	1.37	2	6.15	<3	<3	31	165	130	11	-0.84	1.33	1	-1.08	-0.37	66	36	2	1
21	Srikanth	9.25	1	1	2	2	0.57	0.21	-0.29	92	0.45	0.99	2	6.99	<3	<3	38	191	114	9	-1.26	0.17	1	-1.08	0.51	69	38	2	0.25
22	Teja	11.6	2	2	2	2	-0.1	-0.49	-0.57	82	-0.37	0.85	2	6.36	<3	<3	48	187	58	10	-1.22	-1.15	-0.66	-1	0.24	65	32	2	1.6
23	Rakesh	5.3	1	1	2	2	0.59	0.86	0.61	98	-0.29	1.12	2	8.16	<3	<3	36	162	71	5	-0.88	-0.28	0.71	1.24	-0.41	64	32	2	0.3
24	Kavitha	8.9	2	1,2	1	1	-0.3	0.5	0.82	84	-0.07	0.84	1	6.94	>1000	18.7	36	168	90	7	0.78	0.059	0.15	0.09	0.2	63	34.5	1	1.9
25	Senthila	10.4	2	2,5	2	2	-0.3	-0.058	0.08	82	-0.08	0.91	1	9.03	<3	<3	33	176	79	10	-2.3	0.21	-0.74	0.27	0.53	60	30.9	2	0.4
26	Rakshana	11.4	2	2	2	2	-0.2	-0.22	-0.15	86	1.58	1.23	1	9.6	>1000	168.7	39	170	120	10	-0.13	0.12	-0.39	1.33	0.37	63	33.2	1	1.4
27	Pavithra	10	2	1,2	2	2	-0.4	0.67	1.05	100	0.93	1	2	7.76	<3	<3	32	174	60	10	-2.11	0.86	-0.36	0.45	-0.06	59	28.9	2	0
28	Dinesh	11.1	1	2,3	2	2	-0.4	-0.35	-0.27	96	0.51	0.97	2	6.82	<3	<3	48	169	67	11	-0.67	-1.02	0.14	-1	0.43	65	35	2	0.1

29	Daneeshwaran	10.9	1	2	2	2	0.45	-0.64	-1.26	94	1.26	2.17	1	7.52	210.63	770.3	34	183	55	12	-0.67	-0.48	-1.18	1	0.83	63.5	33.6	1	-1.1
30	Nivedha	9.25	2	2	2	2	1.52	0.6	0.13	92	0.64	0.78	2	7.3	<3	<3	34	168	64	9	0.67	-0.48	-0.74	0.18	0.56	67	36.3	2	0.25
31	Princy	8.8	2	1	2	2	0.7	0.4	0.07	100	0.62	1.25	2	8.2	<3	<3	25	172	126	8	2.56	-1.04	-0.85	2.09	0.45	71.7	46	2	0.8
32	murali	8	1	1	2	2	-0.4	0.22	0.63	106	1.4	1.03	2	7.2	<3	<3	35	187	83	8	1.44	-0.93	-0.36	0.82	-0.39	72	41	2	0
33	fazil	9.1	1	5	2	2	-0.3	-0.33	-0.24	96	0.9	1.14	2	6.33	<3	<3	42	160	58	8	2.25	-1.08	-1.23	0.38	0.17	68	33.1	2	1.1
34	Nakul	6	1	2	2	2	-0.2	0.35	0.52	102	0.23	1.09	2	7.32	<3	<3	36	168	76	5	0.27	0.69	0.95	0.71	0	68	29	2	1
35	Danush	11	1	1	2	1	0.45	0.37	0.25	92	0.28	1.04	2	7.15	<3	<3	36	172	98	10	-0.74	0.64	0.75	-0.25	-0.04	66	36	2	1
36	Santhosh	8.25	1	1	2	2	0.67	0.25	-0.04	96	1.15	1.42	2	6.9	<3	<3	32	171	64	8	0.44	1.93	0.3	0.64	0.35	68	35	2	0.25
37	Tarun	11	1	2	2	2	-0.6	-0.27	0.014	82	-0.18	0.83	2	6.56	<3	<3	48	166	86	10	0.22	-0.48	-0.74	-0.64	-0.52	66	34	2	1
38	Ramesh	6	1	1,2	2	2	0.57	0.75	0.53	96	0.71	1.14	2	7.16	<3	<3	31	164	71	6	0.5	0.12	0.71	-0.19	0.43	65	32	2	0
39	Deepa	8	2	1,2	1	2	0.41	0.89	0.94	86	0.92	1.23	1	8.14	>1000	38.7	30	194	91	6	0.22	-0.14	-0.03	-0.82	0.17	60	28	1	2
40	Senthil	10	1	2	2	2	-0.2	0.13	0.3	90	0.46	1	2	8	<3	<3	36	173	76	10	-1.58	-0.43	-0.41	-0.08	-0.84	61	31.2	2	0
41	Nandini	6.25	1	1	2	2	1	1.42	1.4	100	0.31	0.6	2	6.5	<3	<3	38	160	85	6	1.56	0.86	1.28	0.27	-0.26	71	28.3	2	0.25
42	Navneeth	4	1	1,2	2	2	-0.3	-0.16	0.03	102	1.06	1.046	2	6.3	<3	<3	36	167	59	3	1.87	0.04	0.14	1.6	0.65	66	31	2	1
43	Kowshik	5.16	1	1	2	2	-0.6	-0.18	0.12	102	0.71	0.65	2	7.3	<3	<3	32	176	48	5	1.6	0.26	0.27	1.73	0.26	69	31.2	2	0.16
44	Divya	10.1	2	2	2	2	-0.1	-0.15	-0.19	90	1.55	1.18	2	6.5	<3	<3	35	165	72	8	1	-0.28	0.06	0.29	-0.27	66	32	2	2.1
45	Rakshitha	10.1	2	2	1	1	-0.8	-0.48	-0.21	96	0.74	1.13	1	9.1	>1000	68.8	36	184	76	9	0.56	0.57	-1.02	0.18	-0.16	61	31	1	1.1
46	Kaviya	10.5	2	2	2	2	-0.9	-0.16	0.33	90	0.53	1.48	2	7.65	<3	<3	38	170	69	10	0.22	2.28	1.62	-0.82	-0.28	62	36	2	0.5
47	Danshika	6.16	2	2,4,9	2	2	-0.3	0.35	0.73	102	1.09	1.41	2	6.76	<3	<3	40	169	90	6	0.93	-0.5	-0.28	0.94	0	75	32.5	2	0.16
48	Elakiya	7.6	2	4,5,6	2	2	0.02	-0.28	-0.46	86	0.8	0.85	2	7.33	<3	<3	39	170	82	8	1.33	-0.12	-0.28	1.76	0.8	70	33	2	-0.4
49	Amudha	8.6	2	1	2	2	0.09	0.93	1.16	98	-0.48	0.54	2	7.42	8.1	103.6	36	174	97	8	0.84	-0.93	-0.93	-0.25	0.07	72	33.5	2	0.6
50	shanthi	11.5	2	2	2	2	-0.8	-0.34	0.08	94	0.37	1.04	2	6.28	<3	<3	42	176	80	10	-0.21	-0.07	-0.99	-0.42	-0.28	66	32	2	1.5
51	Sabitha	10.2	2	2	2	2	-0.9	-0.108	0.41	96	0.54	1.86	2	6.52	<3	<3	34	170	72	10	-0.44	-0.14	-0.74	0.09	-0.41	64	32	2	0.2
52	Nithin	8	1	2	2	2	1.21	0.23	-0.52	98	1.31	0.99	2	7.2	<3	<3	43	168	56	8	0.67	0.14	-0.03	1	0.77	66	33	2	0
53	Nivedha	5	2	2,4,5	2	1	-0.4	0.45	0.99	108	1.13	1.54	2	8.8	<3	<3	36	172	84	5	-0.67	0.14	-0.36	1	0.48	72	31	2	0
54	Vendamani	9	2	1,2	2	2	-0.5	-0.41	-0.26	106	0.27	0.89	2	6.76	<3	<3	42	178	70	10	-1	0.5	-0.03	0.27	-0.48	61	29	2	-1
55	Bhanu	8.8	2	2,3	2	2	0.24	0.4	0.36	86	0.21	0.06	2	7.19	320.5	43.9	40	169	54	7	1.33	0.21	1.03	1	0.1	72	41	1	1.8
56	Siju	8	1	9	2	1	0.26	-0.17	-0.42	92	-0.18	0.81	2	6.84	<3	<3	45	175	80	8	1.6	1.81	1.26	-0.24	1.4	66	32	2	0
57	dhanshika	9.5	2	2,5	2	2	-0.7	-0.52	-0.32	92	0.75	1.21	2	7.12	<3	<3	38	166	62	9	-0.67	1.57	1.28	1	0.94	68	32.3	2	0.5
58	Karthika	10.15	2	1	2	2	-1.6	-0.58	0.27	104	-0.01	0.44	2	6.7	<3	<3	32	194	74	9	0.44	-0.43	-0.3	0.27	0.71	72.2	32.5	2	1.15
59	Aarthi	9.75	2	2	2	2	-0.9	-0.78	0.12	86	0.95	1.02	1	7.62	124.96	34.8	30	170	82	8	1.56	-0.57	-0.36	0.09	0.61	72	31	2	1.75
60	Selvi	8.3	2	1	2	2	0.4	0.37	0.21	98	0.64	1.09	2	6.42	<3	<3	40	166	81	8	0.44	0.14	0.3	0.55	1.03	72	33	2	0.3
61	Saranya	4.75	2	1	2	2	0.6	0.56	0.3	108	1.07	1.11	2	7.2	<3	<3	36	178	84	4	1.47	1.04	1.34	0.94	0.56	68	30	2	0.75
62	Akash	9.75	1	1	2	2	0.31	0.11	-0.018	94	0.77	0.53	2	6.3	<3	<3	36	160	90	10	-0.52	2.12	1.35	0.29	1.4	70	30.3	2	-0.25