EVALUATION OF EFFECT OF BRAINSTEM EVOKED RESPONSE AUDIOMETRY IN SUBCLINICAL HYPOTHYROID PATIENTS IN CORRELATION WITH THYROGLOBULIN ANTIBODY, THYROID PEROXIDASE ANTIBODY AND LIPID PROFILE

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MAY 2018

CERTIFICATE

This is to certify that the dissertation entitled **"Evaluation of effect of brainstem evoked response audiometry in subclinical Hypothyroid patients in correlation with thyroglobulin antibody, thyroid peroxidase antibody and lipid profile" by Dr.P.SENTHAMIL PAVAI,** for M.D Physiology is a bonafide record of the research done by her during the period of the study (2015-2018) in the Institute of Physiology and Experimental Medicine, Madras Medical College, Chennai- 600 003.

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ABBREVIATIONS

1.	TSH	-	Thyroid stimulating hormone
2.	TPO	-	Thyroid peroxidase
3.	DM	-	Diabetes Mellitus
4.	T_g	-	Thyroglobulin
5.	BERA	-	Brainstem evoked response audiometry
6.	SNHL	-	Sensorineural hearing loss
7.	LDL	-	Low density lipoprotein
8.	ms	-	milliseconds
9.	T_4	-	Thyroxine
10.	T_3	-	Triiodothyronine
11.	RT_3	-	Reverse triiodothyronine
12.	TRH	-	Thyrotropin releasing hormone
13.	OL	-	Oligodendrocyte
14.	TH	-	Thyroid hormone
15.	TR	-	Thyroid hormone receptor
16.	CNS	-	Central nervous system
17.	OPC	-	Oligodendrocyteprecursorscells
18.	OHCs	-	Outer hair cells
19.	BMI	-	Body Mass Index
20.	FNAC	-	Fine needle aspiration cytology
21.	SCTD	-	Subclinical thyroid disease
22.	HDL	-	High density lipoprotein
23.	TGL	-	Triglycerides
24.	ABR	-	Auditory brainstem response
25.	BAEP	-	Brainstem auditory evoked potential

CERTIFICATE

This is to certify that this dissertation work titled "**EVALUATION OF EFFECT OF BRAINSTEM EVOKED RESPONSE AUDIOMETRY IN SUBCLINICAL HYPOTHYROID PATIENTS IN CORRELATION WITH THYROGLOBULIN ANTIBODY, THYROID PEROXIDASE ANTIBODY AND LIPID PROFILE"** of the candidate **Dr.P.SENTHAMIL PAVAI** with registration Number **201515005** for the award of **M.D** in the branch of **PHYSIOLOGY**.I personally verified the urkund .com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows **1 percentage** of plagiarism in the dissertation.

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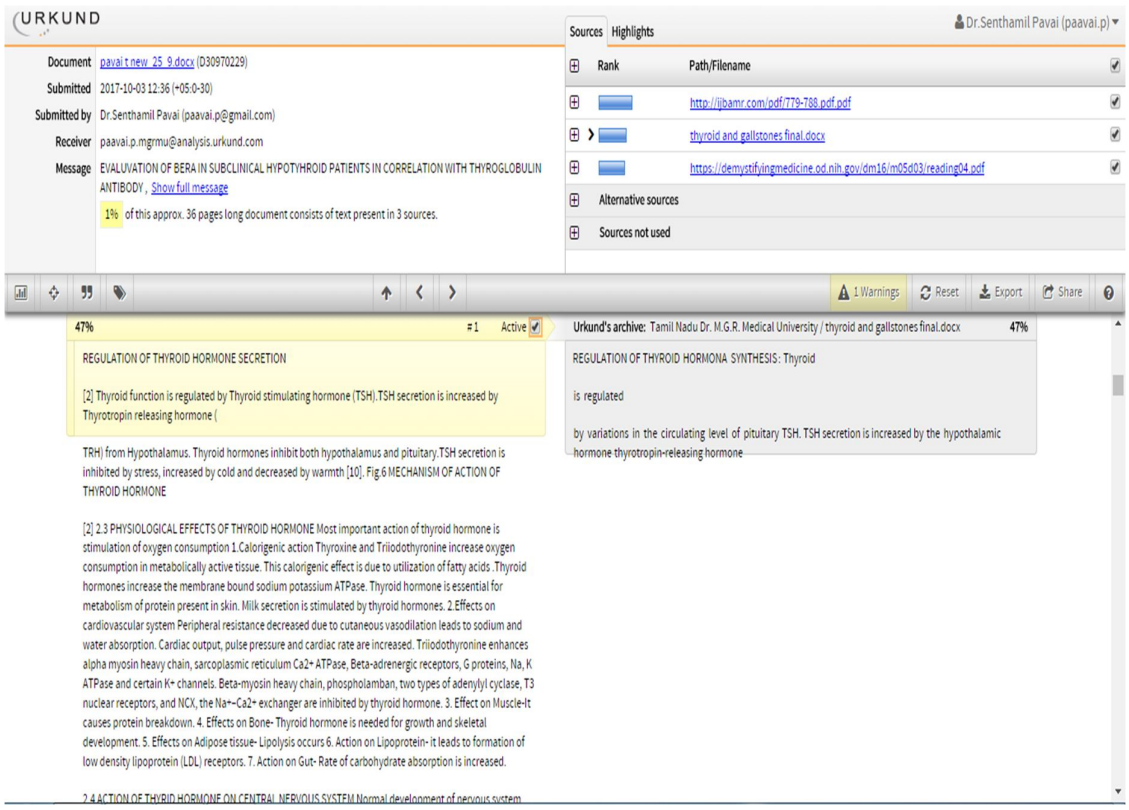


Introduction

1. INTRODUCTION

Thyroid gland is an endocrine gland which is located in anterior aspect of neck between cricoid cartilage and suprasternal notch. The two lobes of thyroid gland are connected by isthmus. Weight of the gland is 15-20gm. It develops from the floor of primitive pharynx at 3rd week along with thyroglossal duct and it migrates from floor of tongue to neck. Thyroid hormone synthesis begins at 11th week of gestation. Disorders of thyroid gland are very common [1].

One of the most important disorders of the thyroid gland is hypothyroidism. In adults with hypothyroidism, the onset in usually so insidious that typical manifestation take months or years to appear or may go unnoticed. The gradual development of the hypothyroid state is the result of slow progression of thyroid hypofunction, hypothyroidism continues to be diagnosed at earlier stages. Based on the most recent data, subclinical or early hypothyroidism is approximately 14 times more common that overt hypothyroidism. Subclinical hypothyroidism is seen in children and adolescents. Those who are affected are either obese or have family history of thyroid disease.

Subclinical hypothyroidism is defined as high serum TSH (Thyroid stimulating hormone) concentration and normal serum thyroxine and triiodothyronine. Considerable controversy exists regarding the definition of a high serum TSH concentration, the biologic significance of Subclinical hypothyroidism and indication of treatment [2].

TSH values between 4.2 & 5mU/L are slightly normal. In my study TSH level>5.1mIU/L is taken. Subclinical hypothyroidism is more prevalent in patients with Down syndrome, type 1 DM (Diabetes mellitus) and other auto immune disease. About 2% of pregnant women have Subclinical hypothyroidism. Among those pregnant women have, about 58% have positive anti-TPO (Thyroid peroxidase).

In a Michigen outpatient practice 54% patients with Subclinical hypothyroidism had chronic autoimmuethyroiditis. In a community survey in Whickham England, 67% of women and of 40% men have high serum concentration of TSH and TPO. Inadequate thyroid hormone therapy leads to overt hypothyroidism.

Thyroid peroxidise is an enzyme, Microsomal antigen and membrane associated glycoprotein. It catalyzes the iodination of tyrosine residues and their coupling to form thyroid hormone. TPO-Ab(Thyroid peroxidase antibody)is found in serum of auto immune hypothyroidism. It shows high affinity for an immune dominant region of TPO moleucules.

TPO-Abs is positive in 10% of individuals who do not display obvious clinical thyroid tissue.100% positive Anti-TPO is seen in patients suffering from auto immune hypothyroidism and 80% positive in Graves ‘s disease.

Anti-Tg (Thyroglobulin) is found in auto immune hypothyroidism, but its function is unclear. It is identified by chemiluminescence immune assay. Primary

use of TgAb (Thyroglobulin antibody) with serum Tg levels is to differentiate the various types of thyroid cancer.

High TgAb is seen in papillary carcinoma and lymph node metastasis [2].Subclinical hypothyroidism is commonly accompanied by dyslipidemia; the total cholesterol level is higher and leads to risk of arthrosclerosis.

"Hypothyroidism facilitates lipid peroxidation, which leads to free radical production causing tissue damage" byMarjam et al., 2008 [3].

"Dyslipidemia of total cholesterol and low density lipoprotein is seen in subclinical hypothyroidism with TSH values >6mu/L" by (Mansourian et al.,2008)[3].LDL-cholesterol lipoprotein (a) concentration(Low density lipoprotein) is also increased [3].Thyroid hormone reduces the plasma levels of Cholesterol, Triglycerides and Phospholipids levels .Reduced hormone increases the above mentioned compound levels in plasma leading to atherosclerosis which causes deafness and peripheral vascular diseases. Thyroid hormone increases the number of LDL receptors in liver cells thereby reducing the plasma LDL levels [1].

Ritter,1967 et al Congenital and acquired hypothyroidism are accompanied by hearing impairment[4]. Sensorineural hearing loss(SNHL) is the most common sensory deficit associated with communication difficulties[4].

Pathophysiology of SNHL is immuomediated, Hashimoto's thyroiditis (HT) being, an autoimmune disorder, also leads to hearing dysfunctions[4].

Hypothyroidism shows elevated concentration of antithyroid antibodies. Interaction between genetic susceptibility and environmental factors precipitates thyroid autoimmunity.

The pathophysiology mechanisms of hearing loss in hypothyroid individuals are not yet discovered. In this condition, there is reduced cell metabolism with reduced microcirculation and this affects metabolism and oxygenation of various organs. The striavascularis and organ of corti in the inner ear are found be involved.

Thyroid hormones are concerned with myelin formation and lipid concentration in Central nervous system. Thyroxine is a neurotransmitter by itself so it is obvious that hearing loss in hypothyroid individuals is of central nervous system origin involving the structures of the inner ear[5].

Synaptic transmission in auditory pathway is affected by reduced calcium absorption in hypothyroidism[5].ATP deficiency causes impaired function of sodium –potassium pump .It causes reduced axonal transport in nerve fires[5].Increased glycogen and glucosaminoglycans in cell causes the neuropathy by compression due to myxeoedematous deposits[5].

Conductive type of hearing loss is due to oedema and hypertrophy of mucosal lining of Eustachian tube and middle ear .Tympanic membrane is also thickened[5]. In hypothyroidism, changes in ossicles in oval and round window

cause obliteration of oval and round window, crystallised consistency of bone and fusion and distortion of incus[5].

Thornton and Jarvis et al evaluated the effect of hypothyroidism on auditory pathway by using Brainstem evoked response audiometry(BERA). In brainstem evoked response audiometry, stimulus is given to record the electrical potential from nervous system by non invasive method. It was done by Dawson for the first time in 1947.The evoked response is interpreted by measuring amplitudes and latencies in millisecond (ms) domain [5].

Brain stem evoked response audiometry is used to detect the auditory pathway in brainstem. Electrodes are kept in vertex and mastoid region. Electrical stimulation is given to record the conduction of auditory pathway up to midbrain. If sound enters the cochlea, production of electrical impulse passes to the auditory cortex by the following pathway:

First order neuron is bipolar cells of spiral ganglion which end in Ventral and Dorsal cochlear nuclei in brainstem. Axons of Second order neurons from cochlear nuclei pass in the dorsal part of pons. The crossing fibres of two sides form Trapezoid body. Third order neurons have their cell bodies in Superior olivary nucleus and Trapezoid body and lateral lemniscus in midbrain .The fibres of lateral lemniscus ascend to the mid brain and terminate in the inferior colliculus. Fourth order neurons have their cell bodies in inferior colliculus in midbrain and fibres arising from this region reach Medial geniculate body in Thalamus. Fifth order neurons have their cell bodies in Medial geniculate body

and fibres from this region reach form acoustic radiation which ends in Auditoryarea in cerebral cortex[6].

The normal BERA recordings consists of five or more vertex positive and vertex negative waves arising within 10ms (milliseconds) of auditory stimulus. Some studies reported the prolongation of both peripheral and central conduction time in hypothyroidism.

- Wave I-Peripheral portion of the VIII nerve
- Wave II-Cochlear nucleus
- Wave III-Superior olivary nucleus
- Wave IV-Lateral Lemniscus
- Wave V-Inferior colliculus[7].

Central and peripheral nervous system will be affected in Hypothyroidism[8].

Absolute peak latencies of waves I, II, III, IV and V together with IPLs I-III, III-V, were recorded.

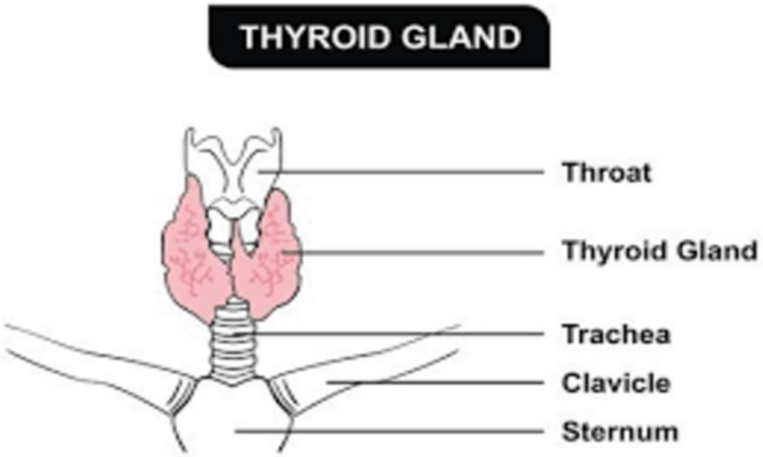
In my study by simple non invasive method (BERA)I am going to detect central nervous system dysfunction and hearing impairment in earlier stages in subclinical hypothyroid patients and evaluate the cause of subclinical hypothyroidism by doing anti-TPO and anti-Tg levels and find the correlation of BERA with Thyroid antibodies and lipid profiles.

Review of literature

2. REVIEW OF LITERATURE

The thyroid gland is situated below the larynx on either side of and anterior to trachea between cricoid cartilage and suprasternal notch which is one of the biggest endocrine gland. The thyroid gland secretes THYROXINE (T_4) and TRIIODOTHYRONINE (T_3). Both the hormones increase the basal metabolic rate of the body. Thyroid gland secretion is under control of Thyroid stimulating hormone (TSH) secreted by anterior pituitary. The thyroid gland also secretes calcitonin, a hormone that controls calcium metabolism .The thyroid gland is made up of large numbers of closed follicles containing colloid .Thyroid follicles are lined with cuboidal epithelial cells that secrete into the interior of the follicles. These cells contain numerous granules, endoplasmic reticulum, Golgicomplex and lysosome. The colloid contains thyroglobulin molecule. Thyroid hormones are present in the colloid. Once the secretion has entered the follicles, it must be absorbed back through the follicular epithelium into the blood before it can function in the body. The thyroid gland receives blood supply of five times the weight of the gland[1].

Fig.1



2.1 History

1811 - Bernard Courtosis-discovered iodine

1907 - David Marine –iodine is necessary for thyroid function

1909 - Theodor Kocher -Physiology, Pathology and surgery of thyroid gland

1927 - Thyroxine was synthesized

1970 - Conversion of Thyroxine to Triiodothyroxine

1970 - TRH was discovered by Andrew Schally

1988 - Beta subunit gene for TSH was identified

1989 - TSH receptor gene was cloned [9]

Fig.2 THYROID CELL

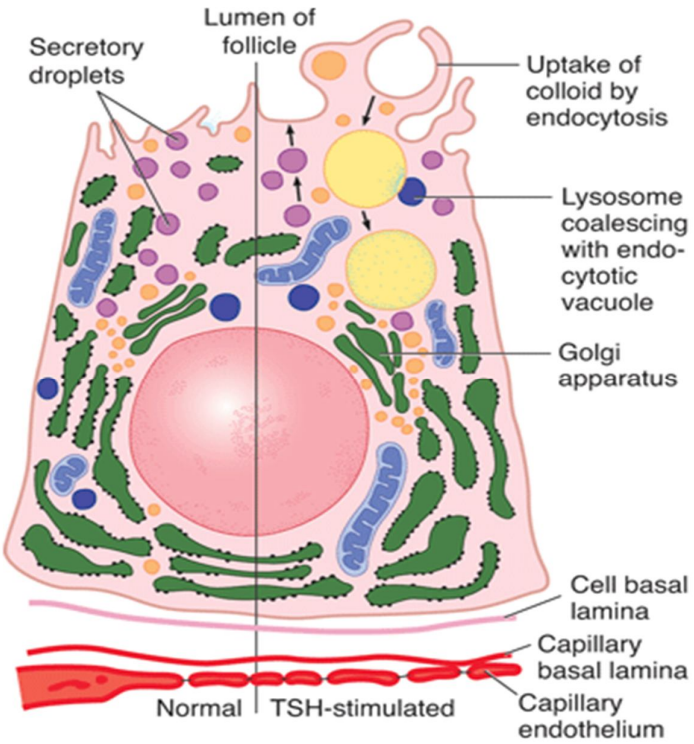


Fig.3 THYROID HISTOLOGY[10]

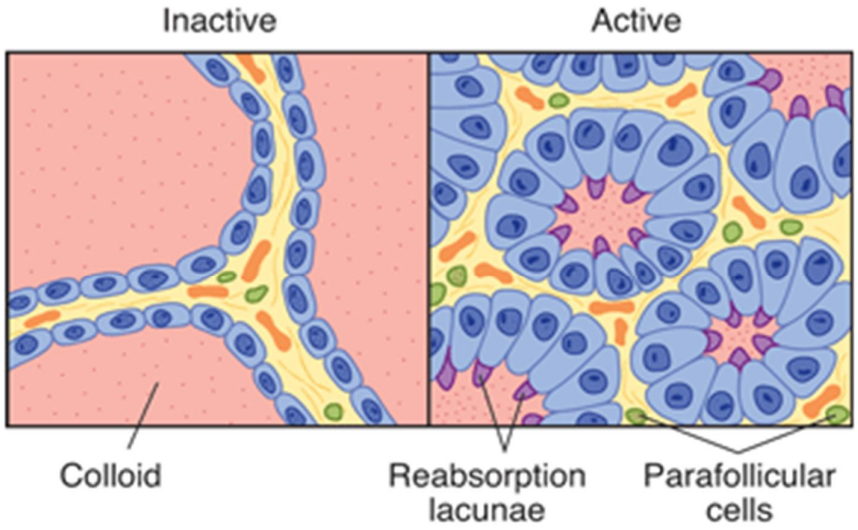
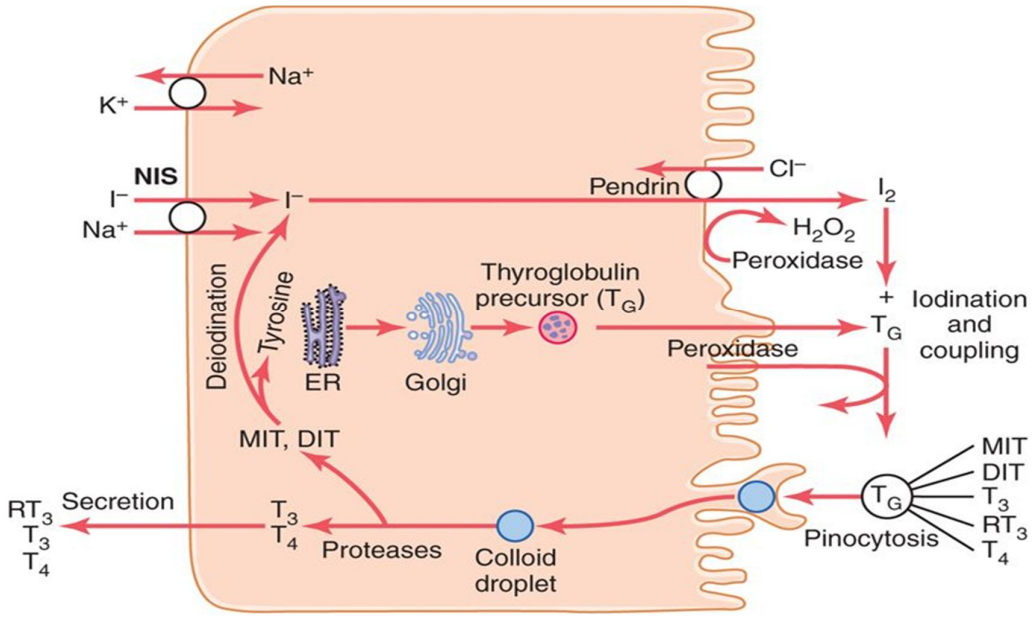


Fig.4 STEPS IN THYROID HORMONE SYNTHESIS[1]



Iodine is needed for formation of Thyroxine.

Iodine is absorbed from GIT in the form of Iodide. One year iodine requirement is 50mg. One week required amount is 1mg/week. This is the amount of iodine needed for normal thyroid function[1].

2.2 SYNTHESIS OF THYROID HORMONE

1. Iodide trapping

Active transport of iodide from circulation into the colloid of thyroid follicle (Secondary active transport) occurs. Iodide is transported along with sodium.TSH induces expression and retention of Na^+/I^-symporter in basolateral membrane and it leads to continuous iodide uptake. Sodium is pumped into interstitium by sodium potassium pump. Resting membrane potential is -50mV in thyroid cell. Iodide is pumped into the cell against electrical gradient. Iodide concentration is very high inside the follicular cell. Iodide is going inside the cell against chemical gradient.

II. Conversion reaction

Iodide is converted into iodine by oxidation. Thyroid peroxidase enzyme is needed for this reaction.

III. Thyroglobulin synthesis

Thyroglobulin is a glycoprotein molecule .It contains 2 subunits .Molecular weight is 660 kDa. About 123 Tyrosine residues are present in thyroglobulin molecule.

Thyroglobulin molecule is synthesized in endoplasmic reticulum and packing occurs in Golgi apparatus and secreted into colloid by exocytosis. Thyroid peroxidase enzyme is needed for this reaction. Thyroid hormone is produced in the thyroglobulin molecule and present inside the molecule until secreted.

IV. Organification of thyroglobulin molecule

Iodine is bound to tyrosine molecule which is present inside the thyroglobulin molecule. This reaction is facilitated by Thyroid peroxidase enzyme[11].

V. Coupling Reaction

Iodine binds with tyrosine at 3rd position form monoiodotyrosine. Another one molecule is added at 5th position form diiodotyrosine. Two diiodotyrosine molecules unite to form thyroxine molecule by oxidative condensation method.

1. Intramolecular coupling

Coupling occurs with both diiodotyrosine molecule attached to thyroglobulin.

2. Intermolecular coupling

Diiodotyrosine molecule which forms the outer ring is detached from thyroglobulin molecule.

This coupling reaction is facilitated by thyroid peroxidase enzyme.

One monoiodotyrosine and one diiodotyrosine molecule unite to form Triiodothyronine(T_3).

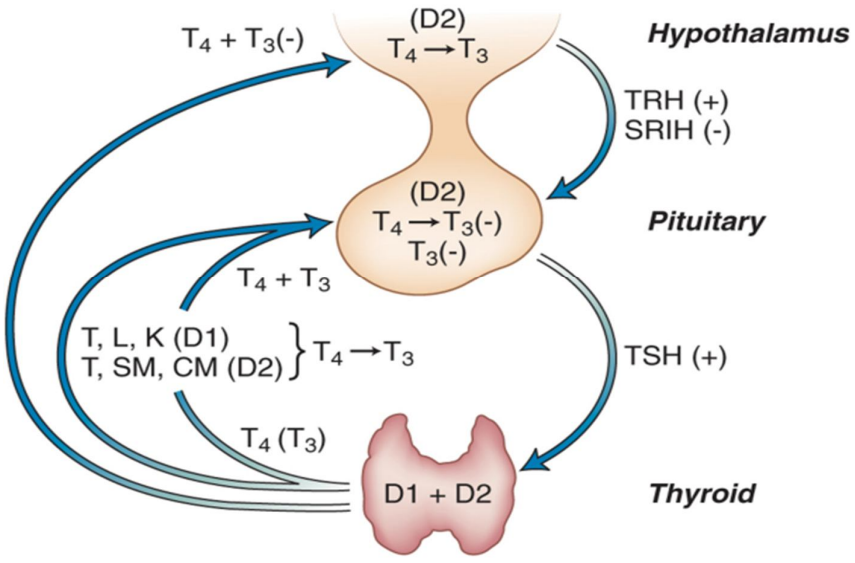
But condensation between diiodotyrosine and monoiodotyroine form reverse triiodothyronine (RT_3)[10].

VI. Secretion of Thyroid hormones

Thyroid follicular cell extends pseudopodia like extensions for uptake of colloid by endocytosis to form pinocytic vesicles. Pinocytic vesicle combines with lysosomes to form digestive vesicle. It contains protease enzyme that is mixed with colloid and digests the thyroglobulin molecule and releases thyroid hormone in free form directly into capillaries.

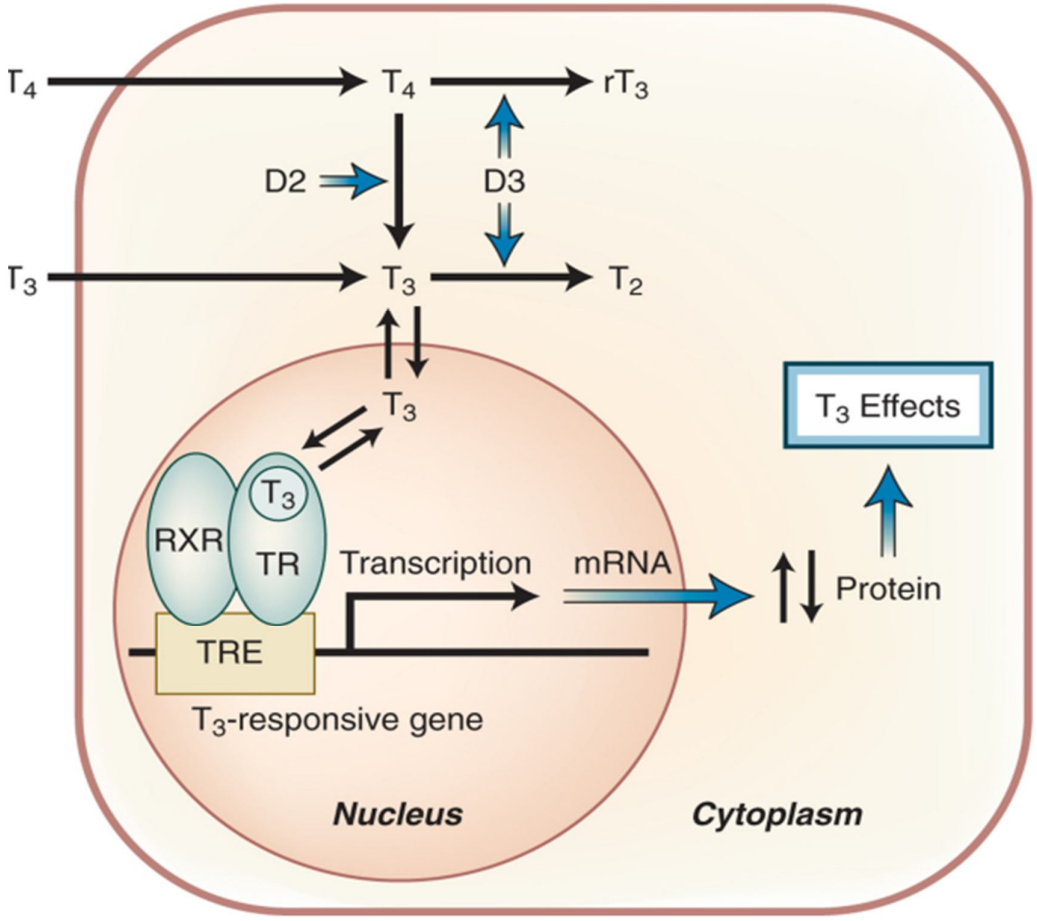
Some part of iodinated tyrosine in the thyroglobulin molecule never becomes thyroid hormone but remains as monoiodotyrosine and diiodotyrosine . Enzyme deiodinase cleaves the iodine molecule that is recycled for thyroid hormone synthesis again [1].

Fig.5 REGULATION OF THYROID HORMONE SECRETION



Thyroid function is regulated by Thyroid stimulating hormone (TSH).TSH secretion is increased by Thyrotropin releasing hormone (TRH) from Hypothalamus. Thyroid hormones inhibit both hypothalamus and pituitary.TSH secretion is inhibited by stress, increased by cold and decreased by warmth [10].

Fig.6 MECHANISM OF ACTION OF THYROID HORMONE



2.3 PHYSIOLOGICAL EFFECTS OF THYROID HORMONE

Most important action of thyroid hormone is stimulation of oxygen consumption

1.Calorigenic action

Thyroxine and Triiodothyronine increase oxygen consumption in metabolically active tissue. This calorigenic effect is due to utilization of fatty acids .Thyroid hormones increase the membrane bound sodium potassium ATPase. Thyroid hormone is essential for metabolism of protein present in skin. Milk secretion is stimulated by thyroid hormones.

2. Effects on cardiovascular system

Peripheral resistance decreased due to cutaneous vasodilation leads to sodium and water absorption. Cardiac output, pulse pressure and cardiac rate are increased.Triiodothyronine enhances alpha myosin heavy chain, sarcoplasmic reticulum Ca^{2+} ATPase, Beta-adrenergic receptors, G proteins, Na, K ATPase and certain K^{+} channels. Beta-myosin heavy chain, phospholamban, two types of adenylyl cyclase, T_3 nuclear receptors, and NCX, the Na^{+}–Ca^{2+} exchanger are inhibited by thyroid hormone.

3. Effect on Muscle-It causes protein breakdown.

4. Effects on Bone- Thyroid hormone is needed for growth and skeletal development.

5. Effects on Adipose tissue- Lipolysis occurs

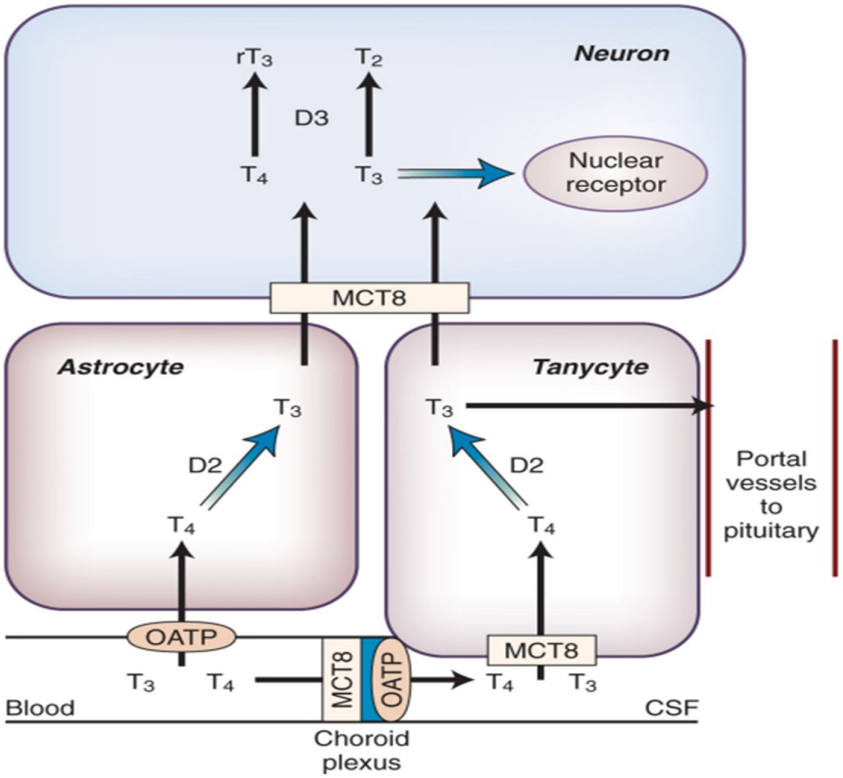
6. Action on Lipoprotein- it leads to formation of low density lipoprotein (LDL) receptors.

7. Action on Gut- Rate of carbohydrate absorption is increased.

2.4 ACTION OF THYRID HORMONE ON CENTRAL NERVOUS SYSTEM

Normal development of nervous system depends on thyroid hormone. The parts of brain most affected are cerebral cortex, Basal ganglia and Cochlea. Mental retardation, motor rigidity, and deaf–mutism occur due to deficiency of thyroid hormones during development[10].

Fig.7 THYROID HORMONE ENTRY INTO CENTRAL NERVOUS SYSTEM



MCT8- is a T-type amino acid transporter belonging to the monocarboxylate transporter family expressed in the brain, heart, kidney, liver, and skeletal muscle. It facilitates transport of T_3, T_4, rT_3 and T_2 across cell membranes in vitro. It is encoded by X chromosome [12].

T_4, OATP1C1 (a member of the organic anion transporting polypeptide family) is involved in the transport of T_4 across the blood-brain barrier. Thyroid hormone (TH) is essential for myelination explained by Bernal 2002, 2007, Zoeller&Rovet 2004, Darras 2008.

Synthesis of oligodendrocyte(OL) from multi potent neural stem cells depend on thyroid hormone . Development and maturation of OL needs thyroxine. TH act as an instructive agent, triggering OPCs (oligodendrocyteprecursorscells) cell cycle exit in close cooperation with platelet-derived growth factor (PDGF). T_3 regulates OPC proliferation and differentiation through a mitogen-dependent intrinsic cell timer. They become sensitive to T_3 after eight cell divisions (or corresponding time) because of a cell cycle-dependent expression of TRs (Thyroid hormone Receptors). Cellular programming, micro-environmental signals and cell cycle are controlled by thyroid hormone. A cell cycle dependent balance among the different TR iso forms could regulate the differential hormonal sensitivity and thus the transcriptional response to T_3 in the different phases of the cell cycle which also occurs in mature CNS. OPCs progress toward myelinating OLs stage TRa expression is decreased. Terminal maturation mainly depends on TRb1. THs stimulate the morphological and functional maturation of OLs. It is

done by thyroid hormones by inducing different genes, like myelin-OL glycoprotein, myelin basic protein (MBP) and glutamine synthese.

TH and CNS Remyelination

Miller &Mi 2007 et al reported that remyelination is a recapitulation of developmental myelination and thyroid hormone has a role in remyelination.

Schenker et al in 2002 proposed that cytoskeleton protein expression during axon growth and regeneration are accelerated by thyroid hormone.

Berbel et al. 1994, Guadan ˜o Ferraz et al in 1994 expressed that White matter growth and organization are controlled by thyroid hormone due to its modulator action on axon-OL.

Trentin 2006 told that astrocyte differentiation and maturation is regulated by TH by promoting the production of extracellular matrix proteins and growth factors. These proteins are responsible for neuronal growth and neuritogenesis.

Mendes-de-Aguiar et al in 2008 told that extracellular matrix proteins like laminin, fibronectin and syndecan synthesis is altered by T_3.

Process of myelinization via peripheral Schwann cells and central oligodendrocytes were accelerated by neuronal activity.

Schaeren-Wiemers and Gerfin-Moser, 1993, Lees and Brostoff, 1984; Lemke, 1988, 1995 et al reported that peripheral protein zero (P0) and the myelin basic

protein (MBP) were used as marker in the peripheral nervous system and proteolipid protein (PLP) and MBP for the central nervous system.

Campagnoni and Hunkeler, in 1980 demonstrated that mRNA of these marker appearances corresponds to that of myelination. Peripheral and central myelin markers appeared in the intra dural part of the cochlea depends on thyroid hormone. In auditory system, the evoked auditory brainstem responses need rapid and synchronized activation of neuronal pathways. Moore et al in 1995 told that Synchronized conduction depends on myelinogenesis[13].

2.5 Action on auditory system

Cochlea is a receptor organ for hearing. Hair cells act as receptors. Primary sensory receptors are inner hair cells. They are responsible for production of action potential which depends on the movement of fluid. Outer hair cells respond to sound in which depolarization causes shortening and hyper polarization produces lengthening. Outer hair cells cause amplification of sound waves reaching the cochlea. This action is due to changes in membrane protein called PRESTIN. This is a motor protein in outer hair cell [10].

Voltage-dependent conformational changes of motor proteins that are densely packed in the lateral plasma membrane cause electromotility.

Zheng et al reported that Prestin a putative motor protein was invented by cDNA library subtraction procedure.

Outer hair cells (OHCs) have a property to change their length in higher frequencies. Also they contain frequency resolving capacity. Prestin is a sulfate anion transport protein which is present in outer hair cell. Prestin ATG codon contains TH response element in the first intron. PrestinTRE (Thyroid response element) binds TH receptors as a monomer or presumptive heterodimer and mediated a triiodothyronine-dependent transactivation of a heterologous promotor in response to triiodothyronine receptors and Retinoid X receptor had an additive effect. Prestin mRNA and Prestin protein levels are reduced in unavailability of thyroid hormone. Immature prestin is present in hypothyroidism. Transcriptional regulator of the motor protein prestin is thyroid hormone [14].

2.6 THYROID FUNCTION TESTS

Tests for thyroid function come under five headings.

1. Tests to asses Hypothalamo-Pituitary –Ovarian axis
2. Tests to asses Thyroid hormones Levels in blood.
3. Tests to investigate about thyroid autoimmune disease.
4. Tests to asses Thyroid iodine metabolism
5. Tests to investigate about effect of thyroid hormone on tissues.

Examples

1. Measurment of BMR(Oxygen consumption)
2. Estimation of protein bound iodine
3. Radioactive iodine uptake(RAIU)
4. Serum T3 , T4 , TSH-estimation –best test

5. Ultrasonagraphy (B scan) of thyroid gland
6. Thyroid scan (iodine, Tchnetim99) with radioactive elements
7. Antithyroid antibodies
8. FNAC[6]

Estimation of Thyroid stimulating hormone level is a highly sensitive and specific test. It gives information about negative feedback regulation of thyroid hormone synthesis. Thyroid hormones control pituitary TSH release.

TABLE NO.1Normal values of Thyroid profile [2]

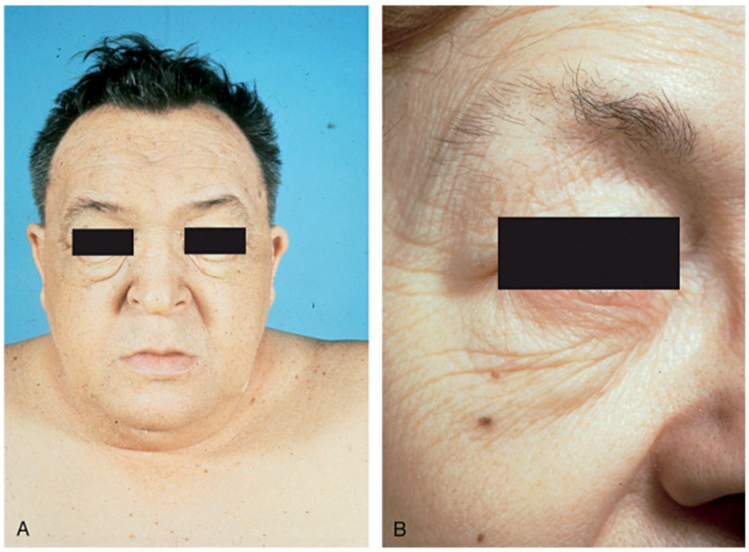
TSH	0.4-4.2mIU/ml
Free T3	0.2-0.5ng/dl
Free T4	0.7-2.5ng/dl
Total T3	70-190 ng/dl
Total T4	5-11µg/dl

2.7 HYPOTHYROIDISM

Production of reduced thyroid hormone is known as Hypothyroidism. Any destruction or loss of thyroid tissue due to autoimmunity or radiation injury causes primary hypothyroidism. Defect in Hypothalamus or pituitary or Thyroid stimulating hormone leads to secondary hypothyroidism. Temporary or transient hypothyroidism is due to sub acute thyroiditis. Any condition leading to reduced thyroid hormone levels causes enlargement of thyroid gland.

Hypothyroidism affects all organs. Clinical manifestations depend on the thyroid hormone levels. 'Myxedema' word denotes appearance of the skin and subcutaneous tissues in hypothyroid patients. Severe hypothyroidism with this clinical picture is rarely seen now days. Myxedema terminology is used to describe the clinical signs of Hypothyroidism.

FIG.8. MYXEDEMA AND LOSS OF LATERAL ASPECT OF EYEBROW



2.7.1 Changes in Skin and appendages

Hypothyroidism causes accumulation of hyaluronic acid and chondroitin sulphate in dermis. These substances are bound with protein to form tissue gel, which increases the fluid in interstitial space. Due to this gel nature interstitial fluid is immobile, so edema is non pitting in nature.

2.7.2 Cardiovascular system

Cardiac output is decreased due to decrease in heart rate and stroke volume. Blood volume is decreased and peripheral resistance is increased.

Peripheral cutaneous circulation is diminished which is responsible for cold skin. Heart rate is diminished due to pericardial effusion. Thyroid hormones have an effect on angina pectoris and coronary artery disease. Electrocardiographic picture shows sinus bradycardia, prolongation of the PR interval, low amplitude of the P wave and QRS complex, alterations of the ST segment, and flattened or inverted T waves. Echocardiogram reflects resting left ventricular diastolic dysfunction in overt, and in some studies, subclinical hypothyroidism.

2.7.3 Respiratory system

Pleural effusions, alveolar hypoventilation and carbon dioxide retention

2.7.4 Gastrointestinal system

Weight gain (accumulation of fluid in interstitial space due to hydrophilic glycoprotein), decreased appetite, Decreased peristalsis activity, Constipation and adynamic ileus.

2.7.5 Central and Peripheral nervous system

Thyroid gland is needed for growth of brain in early life. Reduced level of this hormone causes defect in cortical neurons, myelination and vascularity. If damage is not corrected in earlier stage it leads to permanent defect. Speech, thought and movement are reduced. Lethargy and sleepiness and delayed relaxation of ankle jerk will be present. Entrapment of peripheral nerves by ground substance causes carpal tunnel syndrome.

2.7.6 Reproductive system

Menorrhagia, infertility and galactorrhoea,

2.7.7 Blood - Anemia

2.7.8 Treatment

Replacement of thyroid hormone is in the form of L-Thyroxine[2].

2.8 SUBCLINICAL HYPOTHYROIDISM

Subclinical hypothyroidism is a biochemical condition. Thyroxine and Triiodothyronine levels are normal but thyroid stimulating hormone level is elevated. SCTD (Subclinical thyroid disease) is identified in young, middle and old age population. Due to presence of high prevalence it progresses to overt hypothyroidism, SCTD is considered as a significant clinical condition. Regarding SCTD symptoms and signs are different in each tissue of our body. At which level of TSH we have to give treatment is also controversial. The prevalence of SCTD is 4-10%. About 20% prevalence is seen in women older than 60 years. The various names of SCTD are compensated hypothyroidism, preclinical hypothyroidism, mild thyroid failure, and mild hypothyroidism.

SCTD is a TSH abnormality in which upper limit is not fully explained. It is reduced from 10mIU/liter to about 4.0–4.5 mIU/liter by TSH RIAs (Radio immune assay) and thyroid antibody tests.

Now days we are using monoclonal antibodies. It will detect various isoforms of TSH.

National Health and Nutritional Examination (NHANES) III survey shows 10% prevalence of anti thyroglobulin antibody (TgAb) and 12% prevalence of detectable thyroid peroxidase (TPO) levels is seen community [15].

National Academy of Clinical Biochemistry criteria as well as sonographic confirmation of a normal thyroid gland study in reference shows, the reference range for the lower limit of TSH increased from 0.3 to 0.4 mIU/liter and 4.1 to 3.7 mIU/liter is used as higher level [16].

Serum TSH of 0.25–2.12 mIU/liter is used as a reference level in iodine - deficient area (western Pomerania, northeast Germany)[17].

In iodine deficient village of southern Italy, TSH concentration in the adult population was 1.4 ±1.1 mIU/liter in goitrous subjects and 2.0 ±2.4 mIU/liter in nongoitrous subjects [18].

Whickham survey shows that TSH >2mIU/liter has increased chance of getting Hypothyroidism. If they are positive for thyroid peroxidase antibody, they have more chance of becoming hypothyroid.

Epidemiological evidence reveals that TSH between 3 and 4.5 mIU/liter and those having positive anti thyroid antibodies have increased chance of getting hypothyroidism. Additional importance should be given to these persons and continuous follow up should be given [19].

Serum FT_4 and TSH are specific for each person. These levels are monitored by hypothalamic-pituitary-thyroid axis "set-point [20].

Individual variation in hypothalamic-pituitary-thyroid axis set-point depends on genetics of particular individuals [21, 22].

The action of thyroid hormone depends on presence of T_3, it's level is controlled by type 1, 2, and 3 iodotyrosinedeiodinases (D1, D2, and D3).If serum T_4 level decreased there is increased change of T_4 to T_3 by D2 [23].

Biological activity of thyroid hormone is influenced by polymorphisms in genes involved in thyroid hormone metabolism [24].

Deiodinase enzyme has tissue specific action, and its level is controlled by feedback regulation [25].

Subclinical hypothyroidism is classified into two groups .First one has TSH level between 4.5 and 10 mIU/liter. Another group has TSH level >10 mIU/liter[26].

The cause of subclinical hypothyroidism is like that of overt hypothyroidism [27].

The most common cause of subclinical hypothyroidism is autoimmune disorders of thyroid gland. Examples are goitrous Hashimoto's thyroiditis and atrophic thyroiditis.

Treatment which causes destruction of thyroid tissue like radioactive iodine treatment or external radiation therapy produces primary hypothyroidism. This frequently occurs if radiation is given over head and neck region and is a dose dependent effect [15].

Chemotherapy is also a cause of hypothyroidism [28].

Women with breast cancer have increased risk of developing subclinical hypothyroidism. After subacute, postpartum, or painless thyroiditis and partial thyroidectomy also can cause subclinical hypothyroidism [29, 30].

Subclinical or overt hypothyroidism is caused by drugs like iodine-containing compounds, lithium carbonate, cytokines, and interferon. Amiodarone is prescribed to treat tachyarrhythmias. It stops the thyroid hormone production[15].

Amiodarone treated persons have an increased risk of Iodine-induced subclinical or overt hypothyroidism. Mild or transient hypothyroidism may be produced by excess dietary iodine, medication, topical antiseptics and iodine contrast agents used for diagnostic procedures [31].

Manic-depressive disorders are treated by Lithium carbonate. It produces goitre and hypothyroidism. These patients also have underlying Hashimoto thyroiditis [32, 33].

Interferon alfa and IL-2 cause autoimmune thyroiditis [34].

Subclinical hypothyroidism is common in multiple sclerosis patients after starting treatment [35].

Sunitinib, a drug used to treat gastrointestinal stromal tumour and renal cell carcinoma can cause TSH elevation. Increased risk of hypothyroidism is seen in Postpartum period. Autoimmune thyroiditis is a part of other endocrine disorders, like polyendocrine failure syndrome type I. It contains hypoparathyroidism, adrenal insufficiency, and chronic mucocutaneous candidiasis.

Poly endocrine failure type 2 is a combination of adrenal insufficiency, type 1 diabetes mellitus and primary ovarian failure.

Patients with overt hypothyroidism those who are getting improper treatment is a cause for subclinical hypothyroidism. It can also occur due to drug interactions or if treatment is not monitored properly [36].

Inadequate thyroid hormone supplementation is a reason for subclinical hypothyroidism between 17.6 and 30% of patients with overt thyroid failure [37].

Genetic mutation in TSH receptor can produce subclinical hypothyroidism [38, 39].

2.8.1 Differential diagnosis of subclinical hypothyroidism

1. Transient subclinical hypothyroidism following sub acute, painless, or postpartum thyroiditis [15]
2. After withdrawal of thyroid hormone therapy in euthyroid patients [15]

3. Laboratory analytical problem (assay variability, heterophilic antibodies)[40]
4. Impaired renal function [15]
5. Recovery phase of euthyroid sick syndrome [15]
6. Untreated adrenal insufficiency[41]
7. TSH-secreting pituitary adenoma [42]
8. Isolated pituitary resistance to thyroid hormone

Old age, female sex and TPO antibodies positive with increased TSH values are increased risks of having overt hypothyroidism.

If the person has elevated TSH and positive TPO antibodies, chance of getting overt hypothyroidism is 4.3%. In women, 3% chance of becoming hypothyroid if the person has only elevated TSH. About 2% of persons become overt hypothyroid only if anti thyroid antibodies are positive. If serum level of TSH is more than 2 mIU/ litre, they have increased risk of becoming overt hypothyroidism [19].

Thyroid auto antibodies were used as a prognostic relevance in elderly subjects. Geriatric patients become overt hypothyroid in a follow up period of some years.

If the TSH value is more than 20mIU/litre, surely they will become overt hypothyroid. About 80% of Anti microsomal antibodies positive persons become overt hypothyroid irrespective of TSH value [43].

Pregnant women with asymptomatic autoimmune thyroiditis have increased risk to become overt hypothyroid [44].

2.8.2 Symptoms of subclinical Hypothyroidism

A Colorado study which showed 17 thyroid symptoms express a clear correlation between the type of symptoms, number and elevated TSH(dry skin, poor memory, slow thinking, muscle weakness, fatigue, muscle cramp, cold intolerance, puffy eyes, constipation, and hoarseness).

Of euthyroid persons who had 12.1% of all listed symptoms, about 16.6% become overtly hypothyroid and about 13.8% ended up with mild hypothyroidism [45, 46].

Zulewski et al introduced new clinical score which contains 14 symptoms. He revealed good correlation between this score, FT_4 and TSH in patients with subclinical hypothyroidism [47].

Subclinical hypothyroid patients showed an increased prevalence of symptoms than euthyroid[15].

Among subclinical hypothyroid patients, about 83% expressed fatigue and about 80% showed weight gain and some persons showed elevated anxiety scores [48].

Impaired memory is also seen in subclinical hypothyroid patients [49].

2.8.3 Cardiovascular dysfunction in subclinical hypothyroidism

Prolonged isovolumetric relaxation time and an impaired time to peak filling rate were seen in subclinical hypothyroidism. These parameters are used to assess left ventricular diastolic function. It is due to reduced levels of sarcoplasmic reticulum calcium ATP ase. It causes reduced calcium uptake into sarcoplasmic reticulum and there is impaired diastolic relaxation [50-56].

The systolic time interval alterations were seen in subclinical hypothyroid patients [57, 58].

Cardiac volumes and systolic performance were changed in subclinical hypothyroidism. End diastolic volume was reduced and the Systemic vascular resistance was elevated, which leads to reduced cardiac performance [59].

2.8.4 Vascular system and Subclinical hypothyroidism

T_3 causes vascular smooth-muscle cells relaxation. It reduces systemic vascular resistance by tissue thermo genesis and metabolic activity [60, 61]

.

Sub clinical hypothyroidism is associated with hypertension. Increased peripheral vascular resistance, increased arterial stiffness, and endothelial dysfunction may be the causes of hypertension [62, 63].

Increased arterial stiffness in subclinical hypothyroidism is identified by pulse wave analysis. Subclinical hypothyroid persons showed an increase in diastolic blood pressure and brachial-ankle pulse wave velocity in TSH values of 6.9 ±0.82 mIU/litre [63].

Endothelium dependent vasodilatation is impaired in TSH levels between4.01and10mIU/litre and also when it is greaterthan10mIU/litre [64].

Endothelial dysfunction was due to reduced level of NO availability. Low-grade chronic inflammation may be a cause for endothelial dysfunction and impaired NO availability by a cyclooxygenase(COX-2)-dependent pathway. Subclinical hypothyroid patients showed an increased oxidative stress in Hashimoto's thyroiditis [65].

2.8.5 Subclinical hypothyroidism and neuromuscular dysfunction

Subclinical hypothyroidism is associated with neuromuscular dysfunctions.Impaired glycogenolysis[66, 67] changes in myosin heavy chain expression [68]and decreased mitochondrial activity may be the causes for neuromuscular dysfunction[69,70].

The amplitude of the stapedial reflex is abnormal in subclinical hypothyroidism. It gives information about neuromuscular status [71].

Distal motor latencies, motor and sensory amplitudes and nerve conduction velocities are normal in mild thyroid hormone deficiency [72].

Peripheral nerves or brainstem auditory evoked potential is normal in subclinical hypothyroidism of short duration [8].

2.8.6 Effect of replacement therapy

Levothyroxine is used in Hashimoto's thyroiditis to reduce the size of the thyroid gland**.**

One study showed that thyroid volume was decreased in 77% of Subclinical hypothyroid patients with Hashimoto's thyroiditis after treatment with Levothyroxine therapy [73].

Levothyroxine therapy reduces the thyroid peroxidase antibodies and other thyroid antibodies in Hashimoto thyroiditis or idiopathic myxedema

Levothyroxine treatment can normalize cardiac hemodynamic alterations produced by subclinical hypothyroidism [74].

2.8.7 Maternal and Fetal risk in subclinical hypothyroidism

Thyroid autoimmunity is a cause for recurrent miscarriage [75, 76 and 77]. La Franchi SH et al described that preterm births are seen in 6% of women with Subclinical hypothyroidism which increases to 20% in overt disease. Gestational hypertension was present in 11% of subclinical hypothyroid and 23% of overt hypothyroidism.

Perinatal mortality occurred in 2.9 of subclinical hypothyroidism and 7% in overt hypothyroidism [15].

Inadequate levothyroxine treatment was given for 114 primary hypothyroidism patients and they showed the following results.

TABLE.2 Outcome of inadequate levothyroxine in pregnancy

Outcome	Subclinical Hypothyroidism	Overt Hypothyroidism
Abortion	71.4%	60%
Preterm Delivery	7.2%	20%
Term delivery	21.4%	20%

If adequate treatment was given, 100% of overt hypothyroidism and 90.5% of subclinical hypothyroidism patients had full term delivery and no incidence of abortion occurred [15].

Fetal brain development and maturation need maternal FT_4 [78, 15].

In 1969, Man and Jones reported that Children of hypothyroid mothers, who were not properly treated, showed reduced IQ [79].

2.8.8 Subclinical hypothyroidism in elderly

Subclinical hypothyroidism is more common in elder population [15].

Autoimmne thyroiditis and treatment of hyperthyroidism are causes for subclinical hypothyroidism in older group [80].

In older persons subclinical hypothyroidism is not recognized and it is considered that these changes are due to ageing [81, 82].

2.8.9Treatment

Subclinical hypothyroidism is a biochemical disorder. Lifelong levothyroxine therapy is debatable. Treatment is given for two reasons:

1) To prevent progression to overt hypothyroidism
2) To prevent thyroid hormone deficiency symptoms

Treatment for subclinical hypothyroidism is not explained clearly [83, 84].

A panel of 13 experts (eight had expertise in thyroid disease, and eight had expertise in cardiology, epidemiology, biostatistics, evidence-based medicine, health service research, general internal medicine, and clinical nutrition) explained treatment for patients with TSH values between 4.5 and 10 mIU/litre should be monitored for 6-to12-month.Dyslipidemia was present only in patients with TSH values above 10 mIU/ litre. Treatment was given in these patients due to high rate of progression to overt hypothyroidism [85].

The three societies (the American Association of Clinical Endocrinologist, The Endocrine Society, and the ATA) recommended routine treatment of patients with subclinical hypothyroidism those who had serum TSH levels of 4.5–10 mIU/litre [86, 87].

Younger patients should be treated correctly than older patients [88].

2.9THYROGLOBULIN AND THYROID PEROXIDASE ANTIBODY IN SUBCLINICAL HYPOTHYROIDISM

Anti thyroperoxidase antibody (TPOAbs) and anti thyroglobulin antibody (TgAb) are most common auto antibodies which are expressed in patients with autoimmune thyroid diseases [89].

Thyroglobulin molecule is a 660kDa protein, which is a precursor of thyroid hormone [90].

Autoantibodies to thyroglobulin molecule and thyroperoxidase molecule are present in 10% of healthy individuals. The actions of these antibodies were not fully understood [89].

Thyroglobulin antibodies do not fix complement or participate in antibody-dependent cellular cytotoxicity [90].

Thyroid peroxidase (TPO) is very important for synthesis of thyroid hormones [91].

TPOAb and TgAb levels were increased in patients with elevated TSH values.

Thyroid antibodies were more present in a moderate iodine deficiency area (MUI45g/liter) (MUI-Median urinary iodine) than an area with mild iodine deficiency (MUI 61 g/liter) [89].

Of high-iodine diet fed animals almost 100% of genetically susceptible animals became TgAb positive. Positive TgAb and positive TPOAb patients showed thyroid dysfunction [89].

In patients with Hashimoto's thyroiditis, autoantibodies to Thyroglobulin antibodies appear in the three important immunoglobulin classes. Pressman et al., 1957 Korngold, Van Leeuwen&Brener, 1959, Fahey & Goodman, 1960 explained that centrifugation, gel diffusion and column chromatography methods are used to separate physically 7S and 19S fractions of serum. Both 19S and 7S antibodies were present in three experiments.

By zone ultracentrifugation, Torrigiani&Roitt (1963) demonstrated that macroglobulin class appeared in <1I% of the total antibodies to thyroglobulin.

With the help of radio immune electrophoresis Fahey & Goodman (1964) and Goodman, Exum& Robbins 1964 demonstrated thyroglobulin antibodies. It is present in IgG, IgA and IgM classes of antibodies.

Chronic thyroiditis patients showed the presence of antibodies to thyroglobulin in IgG1, IgG2 and IgG3 in serum. It was explained by Terry & Fahey (1964) and Lichter (1964).

Quantitative coprecipitation techniques were used by Torrigiani, Roitt&Doniach (1968)to measure the amount of antibodies to thyroglobulin in the IgG, IgA and IgM classes.

Thyroid peroxidase is auto-antigen, which is present in thyroid cell surface and cytoplasm .Anti-TPO is expressed in serum of autoimmune thyroid disorder patients [92].

Autoantibodies against TPO are present in 90% of Hashimoto's thyroiditis . Thyroid cell destruction occurs by cytotoxic mechanisms mediated by effector cells and/or complement activation. Antibody dependent cytotoxicity in Hashimoto's thyroiditis was first demonstrated by Bogner et al.

TPO antibodies belong to IgG1 subclass explained by Guo et al.

Cell surface TPO activates complement. It causes the cell lysis by complement –mediated cytotoxicity explained by Blanchin et al.

Mononuclear cell accumulation is seen in autoimmune thyroiditis. One study demonstrated human anti thyroid antibodies against thyroid peroxidase. They were isolated from patients who had autoimmune thyroid disease. It caused destruction of thyroid cell by peripheral blood mononuclear cell (HL-60 and THP-1)by Antibody dependent cytotoxicity. These reactions are due to Fc γ RI and Fc γ RII expressed on these cells.

Flow cytometric analysis was done to compare the binding of human anti-TPO Abs by their Fc region on HL60, THP-1and PBMCs.

Important feature of autoimmune thyroid disease is accumulation of the thyroid gland with lymphocytes and monocytes / macrophages.

Thyroid dysfunction induction, amplification and progression of autoimmune disease by cytotoxic mechanism were done by Anti-TPO. It is explained by Weetman AP et al[93]

Hypothyroidism occurs in Hashimoto's thyroiditis in iodine deplete individuals. Repletion of iodine in deficiency and increased iodine intake are cause for autoimmunity**.**

Thyroid autoimmunity is also produced by exposure to environmental chemicals and radiation exposure.

In Cochin study Hypothyroidism prevalence was 3.9% but about 9.4% persons had subclinical hypothyroidism and about 53% of subclinical hypothyroidism patients showed positive Anti-TPO.

Large doses of ingested iodine combines with thyroglobulin molecule to produces change in stereochemical conformation and leads to loss of antigenic epitopes to cause new iodine containing compound. This molecule is presented to T or B lymphocytes by antigen presenting cell which causes production of autoimmunity.

Second mechanism is that the increased iodine directly damages thyrocytes by a process of oxidative stress. Increased iodine is oxidised by TPO in the hyperplastic thyrocytes to produce oxidative metabolites of iodine. These compounds are reactive and bind with proteins, nucleic acids and membrane lipids

and iodo compounds are produced. It causes destruction of thyroid cell and mitochondrial membrane integrity. Thyroid cell necrosis occurs by the production of free radicals. During this process autoantigen is released. Thyrocyte apoptosis is caused by excessive iodine intake and development of thyroid autoimmunity.

Interpretation of Anti TPO antibody : <50IU/L-Negative

>50IU/L-Positive (Thomas et al)

Interpretation of Anti Thyrglobulin antibody

< 115 IU/mL (AyseArduc et al)

The production of autoimmunity may be predisposed by genetic factors**,** advancing age, environmental factors such as stress, infections, trauma, smoking andfemale sex due to hormonal influences. De Benoistet al demonstrated that Iodine plays a key role in the manifestation of autoimmune thyroiditis [94].

2.10 LIPID PROFILE IN SUBCLINICAL HYPOTHYROIDISM

Flower and swale et al explained that in middle of 20th century thyroid hormone assessment was not as easy as lipid measurement. Estimation of lipid profile, especially serum cholesterol level, was used as an indicator of thyroid hormone deficiency. Lithell et al said that Low density lipoprotein levels were elevated in subclinical hypothyroidism. Hypothyroidism causes lipid peroxidation and free radical formation leads to tissue damage [3].

Autoimmune thyroidits causes decreased transcription, expression and function of LDL receptor, impaired cholesterol degradation due to inhibition of cholesterol 27 –hydroxylase anti-cholesterol antibody [95].

Efstathiadou et al proposed that apolipoprotein b and lipoprotein levels were increased in subclinical hypothyroid patients but no change occurs in triglycerides (TGL) and high density lipoprotein (HDL), but significant increase in total cholesterol and low density lipoprotein is noted [3].

One analysis revealed that in subclinical hypothyroidism patients, Levothyroxine therapy reduces total cholesterol and low-density lipoprotein cholesterol (LDLc).

Caron et al reported that increase in ApoA and HDLc levels after Levothyroxine therapy. TOTAL CHOLESTEROL/HDLc ratio became normal.

There are reductions in LDLc, ApoB and the TOTAL CHOLESTEROL /HDL ratio after levothyrxine therapy in Subclinical hypothyroid patients with TSH level > 16.6 mIU/litre.

Levothyroxine therapy leads to reduced LDL cholesterol levels and improve the symptoms of subclinical hypothyroidism if TSH >12 mIU/litre.

Meier et al study reported that improvement in TOTAL CHOLESTEROL and LDLc levels in subclinical hypothyroid patients if TSH levels >6 mIU/litre.

Law MR et al study proposed that LDLc levels decreased in subclinical hypothyroidism treated by levothyroxine therapy. It is useful to reduce the risk for coronary heart disease.

Manninen et al Helsinki Heart Study reported that 7% reduction in LDLc levels leads to 15% reduction in the incidence of coronary heart disease [96].

The prevalence of subclinical hypothyroidism in dyslipidemic population was 1.4-11.2%.

Miura et al study demonstrated that subclinical hypothyroidism patients showed an increase in either total cholesterol (TC) and/or low-density lipoprotein (LDL) cholesterol.

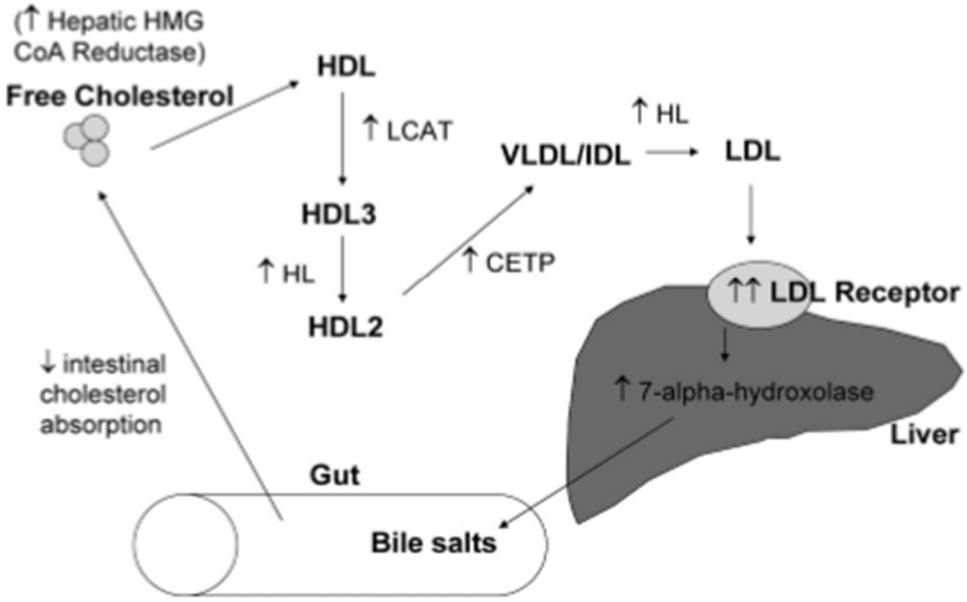
Kung AW, Althaus BU, Lam KS et al studies have showed that subclinical hypothyroidism patients had decreased levels of HDL.

Two of the 6 randomized studies support a favourable effect of thyroxine replacement. Caraccio et al reported that in patients with subclinical hypothyroidism, total cholesterol (208.8 ± 23.2 vs. 181.7 ± 23.2 mg/dL; $p < 0.01$), LDL (131.5 ± 38.7 vs. 112.1 ± 19.3 mg/dL; $p = 0.01$) and apolipoprotein B (107.4 ± 26.1 vs. 88.0 ± 19.7 mg/dL; $p = 0.001$) levels were increased. But other lipid parameters did not reveal any difference. Levothyroxine therapy for 6 months gave good results. No changes in other lipid parameters were seen. Elevated TSH value patients had increased reduction in total cholesterol and low density lipoprotein [97].

Biondi et al studies revealed that subclinical hypothyroidism should be treated if TSH value is <10mIU/L, because it is associated with lipid abnormalities.

Changes in cholesterol synthesis, metabolism, and mobilization of lipids may cause increase in total cholesterol and low-density lipoprotein cholesterol (LDL-C) [95].

FIG.9 EFFECT OF THYROID HORMONE ON CHOLESTEROL METABOLISM



HL - Hepatic lipase

LCAT - Lecithin –cholesterol acyltransferase

HDL-C - High density lipoprotein cholesterol

LDL - Low density lipoprotein

Hepatic HMG - Hydroxy methyl glutaryl coenzyme

The hepatic expression of hydroxyl methyl glutaryl coenzyme A reductase stimulated by thyroid hormone leads to increased cholesterol synthesis. Hepatic cholesterol synthesis is decreased in overt hypothyroidism. Expression of cell surface LDL-C receptors expressed in fibroblasts, liver, and other tissues is increased by thyroid hormone. Presence of high intracellular cholesterol levels regulates the LDL-C receptor levels by negative feedback mechanism. This action is due to the presence of sterol regulatory element-binding protein-2 (SREBP-2).

T_3 regulates the SREBP-2 gene. The decrease in LDL-C receptors leads to reduced Clearance of LDL-C from the serum.

Hypothyroidism causes an increase in the intestinal cholesterol absorption, because thyroid hormone acts on Niemann-Pick C1-like 1 protein in the gut.

Cholesterol from high-density lipoprotein to LDL-C and very low density lipoprotein is transferred by Cholesteryl ester transfer protein (CETP).

In hypothyroidism, Plasma CETP concentrations are decreased which produce changes in HDL-C. Hepatic lipase is regulated by thyroid hormone.

Lipoprotein lipase reduces triglyceride levels through hydrolysis of triglyceride-enriched lipoproteins. It causes transfer of cholesterol from these lipoproteins to HDL-C. Thyroid hormone increases Lipoprotein lipase activity.

In overt hypothyroid condition, serum triglycerides are elevated because of their lower lipoprotein lipase activity. Cholesterol is converted to bile acids and

excreted in faeces. Fecal excretion is an important mechanism for the removal of cholesterol from the body.

Kanaya AM et al study shows that an average of 9 mg/dl elevation of total cholesterol occurs if Serum TSH values exceeds 5.5 mIU/litre.

Canaris et al demonstrated that in Subclinical hypothyroid patients, fasting total cholesterol, triglyceride and LDL-C levels were increased.

Bell RJ et al study among a community-based sample survey in Australian women, total cholesterol, LDL-C, triglycerides, and HDL-C were equal between subclinical hypothyroid and euthyroid women.

Lai Y et al chinese adults survey showed that higher triglycerides and lower HDL-C were seen in subclinical hypothyroidism.

Monzani et al told that concentrations of apolipoproteinB (ApoB),which was present in LDL-C and VLDL, were increased in subclinical hypothyroidism

Perez et al, Ito M et al study revealed that$L\text{-}T_4$ treatment gave good results.

Weintraub et al proposed that T_4 causes an increase in the clearance of chylomicron remnants from serum.

Ito m et al demonstrated that Hypothyroidism is associated with elevated serum concentrations of remnant lipoproteins. Post prandial lipidemia is elevated (defined as an increase of 80% or more in serum triglycerides 4–6 h after eating)

in both overt and subclinical hypothyroidism. L-T_4 treatment gives positive results[99].

Duntas et al reported that oxidized LDL-C levels were increased in patients with subclinical hypothyroidism than in euthyroid. Oxidative LDL-C is responsible for initiation of atherosclerosis. In overt and subclinical hypothyroidism, size of lipid sub particle is altered [98].

Increased lipid concentration and diastolic pressure are seen in young women with Subclinical hypothyroidism. It is associated with hypertension, hyper triglyceridaemia and elevated TGL/HDL ratio which may increase the risk of accelerated atherosclerosis [99].

Triglycerides levels are elevated and HDL-C levels are decreased in subclinical hypothyroidism [100].

Fremantle Diabetes study showed that in the presence of insulin resistance, association between TSH and lipid profile is increased.

Hyperlipidemia and subclinical hypothyroidism are present in community. Ineck et al reveals that prevalence of subclinical hypothyroidism in dyslipidemia patients ranges from 4to11.2%

Ladenson et al reported thatthyroid function test should be done in adults more than 35 yrs of age.

For patients with subclinical hypothyroidism and hyperlipidemia, Life style changes are recommended and lipid-lowering drugs should be given irrespective of thyroxine therapy. Smoking and insulin resistance add to the effects of subclinical hypothyroidism on serum lipid values [99].

Hypercholesterol levels in subclinical hypothyroidism is treated with thyroxine therapy for restoration of euthyroidism, for improvement of lipid levels and to prevent progression to overt hypothyroidism[101]

TABLE NO.3 Normal values of Lipid Profile [102]

LDL	
<70 mg/dL	Therapeutic option for very high risk patients
<100 mg/dL	Optimal
100–129 mg/dL	Near optimal/above optimal
130–159 mg/dL	Borderline high
160–189 mg/dL	High
190 mg/dL	Very high
TOTAL CHOLESTEROL	
<200 mg/dL	Desirable
200–239 mg/dL	Borderline high
240 mg/dL	High
HDL CHOLESTEROL	
<40 mg/dL	Low
60 mg/dL	High

2.11 BRAINSTEM EVOKED RESPONSE AUDIOMETRY

Hypothyroidism is associated with hearing impairment. Kemp first explained this defect in severe hypothyroid patients (myxedema). Hearing loss in

acquired hypothyroidism was explained by Hilger. Some authors have explained that there is prolongation of both central and peripheral conduction time in hypothyroidism patients. There is a presence of conductive, sensorineural and mixed hearing loss.

2.11.1 Structure of inner ear

Inner ear is made up bony labyrinth which is located in the petrous part temporal bone and it contains perilymph. Membraneous labyrinth is located inside the bony labyrinth and it contains endolymph.

It has three components

Cochlea-It contains hair cells, the receptors for hearing.

Semi circuar canal- It contains hair cells. It responds to head rotation

Otolith organ-It contains hair cells. It responds to changes in gravity and head tilt.

Basilar and Reissner's membrane divide the cochlea into three chambers. Upper chamber is ScalaVestibuli and lower chamber is Scala Tympani. Both of them contain Perilymph. Both of them communicate with each other at the apex of cochlea through small opening which is known as helicotrema. Middle chamber is Scala Media, which contains Endolymph. The Organ of Corti extends from the base to the apex of the Cochlea which contains the hair cells.

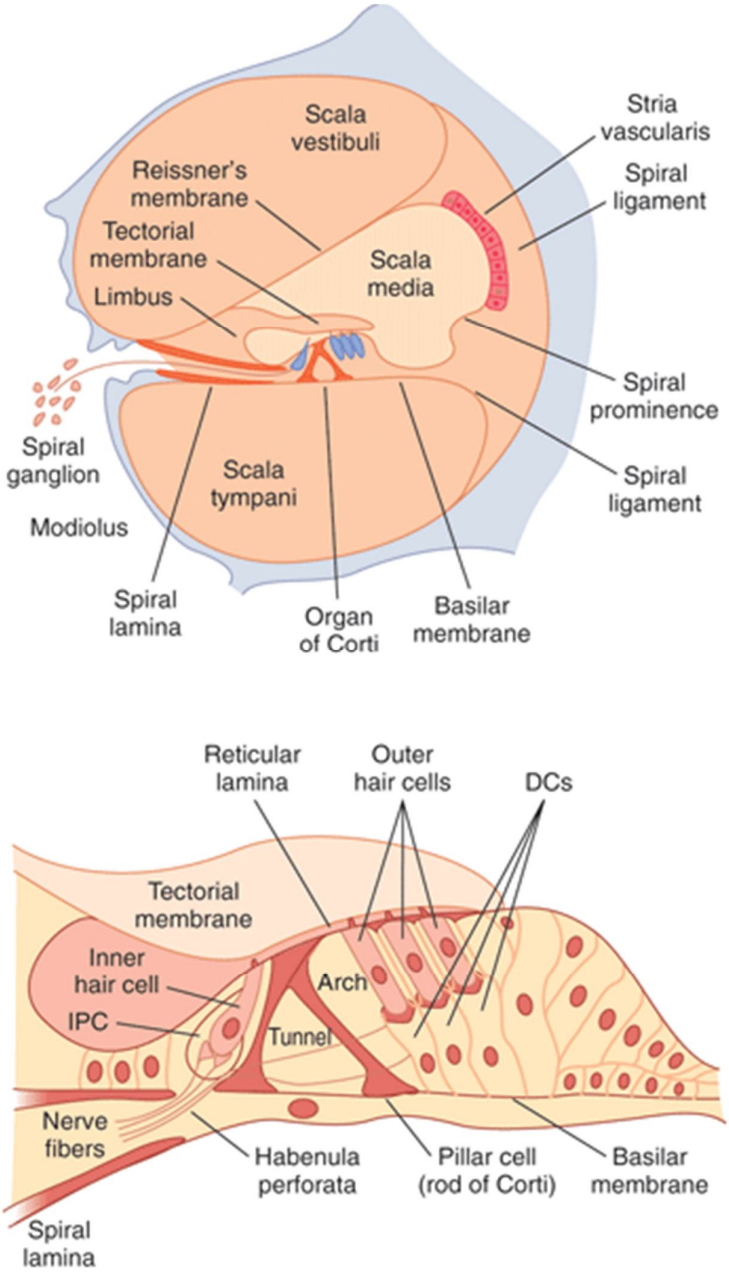
These hair cells act as the sensory receptors of auditory system. They are also known as mechanoreceptors which are responsible for hearing. It is a type of Mechanotransduction. They detect movement in the environment and convert them into electrical potentials.

Two types of hair cells are arranged in four rows. Outer hair cells are arranged in three rows and inner hair cells are arranged in single row. Cochlea contains 20,000 outer hair cells and 3500 inner hair cells. The tips of outer hair cells embedded in tectorial membrane. Sensory neurons to the hair cells arborise at their bases and their cell bodies are located in the spiral ganglion. The efferents from the hair cells are forming the cochlear division of the vestibulocochlear nerve.

The tight junctions between the hair cells prevent the endolymph reaching their base of cells. Basilar membrane is permeable to perilymph and bases of hair cells are bathed in peilymph. So the hair cell processes project into the endolymph formed by the striavascularis of the scala media .It contains high concentration of potassium ions.

2.11.2 Structure of Hair cell

Fig.10. Cross-section of the cochlea and Structure of the organ of Corti



About 30-150 rod shaped hairs project from the apical surface of each hair cell into the fluid of cochlear duct called as stereocilia. It contains actin coated with myosin.

Their heights are increased in a progressive manner. Tiplinks connect tip of this Stereocilium to the adjacent higher stereocilia. Cation channels are present at this junction in the taller Stereocilia.

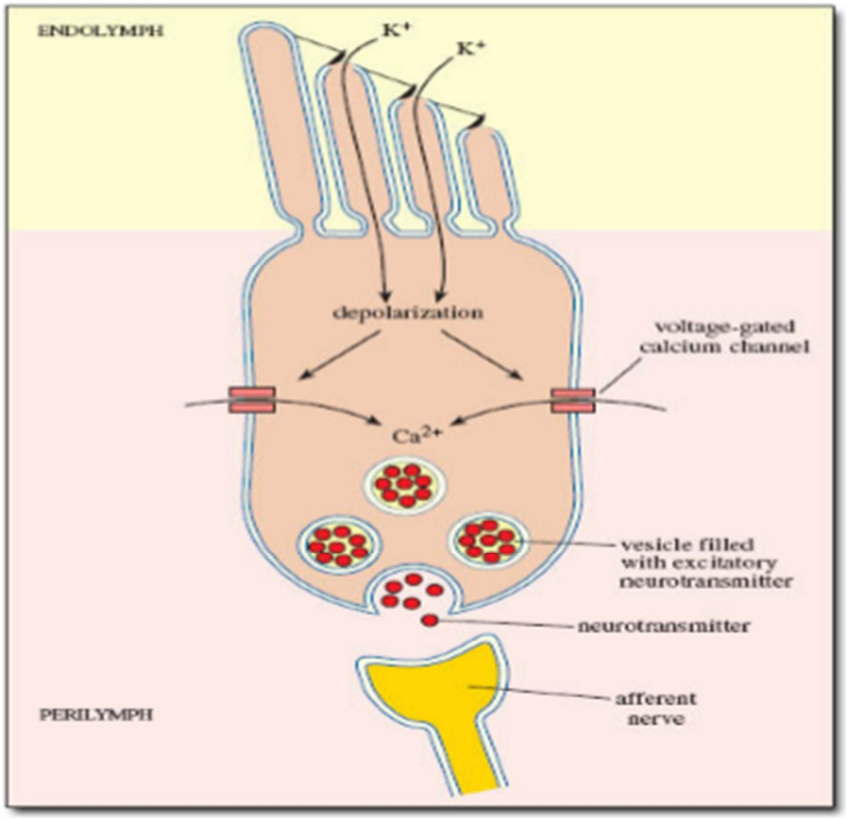
2.11.3 Function of the hair cells

The inner hair cells act as sensory receptors of hearing .Sound vibration stimulate the inner hair cells which causes the movement of fluid in inner ear. Action potentials are produced in inner hair cells and transmitted to the auditory nerve followed to brainstem. Outer hair cells are responsible for sound amplification and sound clarity. Outer hair cells contain prestin, which is a membrane motor protein and is responsible for changes in outer hair cells.

2.11.4 Mechanism of action

The deflection of the shorter stereocilium towards the larger ones opens voltage gated cation channels. It is responsible for an influx of Potassium and Calcium ions followed by depolarisation of the cell. The resting membrane potential of the hair cell is -60 mV. It decreases to -50 mV during depolarisation. It produces endocochlear potential. It opens more number of calcium channels and release of Glutamate. This neurotransmitter also stimulates the adjacent neurons and triggers the action potentials in the auditory nerve.

Fig.11 Receptor potential in hair cell



When stereocilium moves in opposite direction it produces hyperpolarization .

2.11.5 Clinical significance

Hearing sensitivity is reduced if hair cells are damaged. Hair cells cannot regenerate and produces permanent hearing loss resulting in defective action potential production and delayed transmission to higher centre [10].

Evoked potentials

"The electrical potentials generated from the nervous system of animal or human beings on application of a stimulus are called as Evoked potentials".

Brainstem evoked action potentials are recorded from the ear and vertex in response to auditory stimulation. It gives information regarding the auditory pathway up to midbrain. It contains 5 or more waves or more waves. These waves are produced within 10minutes of stimulus.

2.11.6 Uses

1. Identification of hearing impairment in uncooperative patients
2. To measure the hearing in Young children
3. To assess the severity of hearing deficits in infants
4. To know the function of the middle portion of the brainstem
5. To differentiate lesions of central auditory apparatus and peripheral organs
6. To assess the maturity of the central nervous system in new born
7. To know the prognosis in comatosed patients,
8. Diagnosing brain death

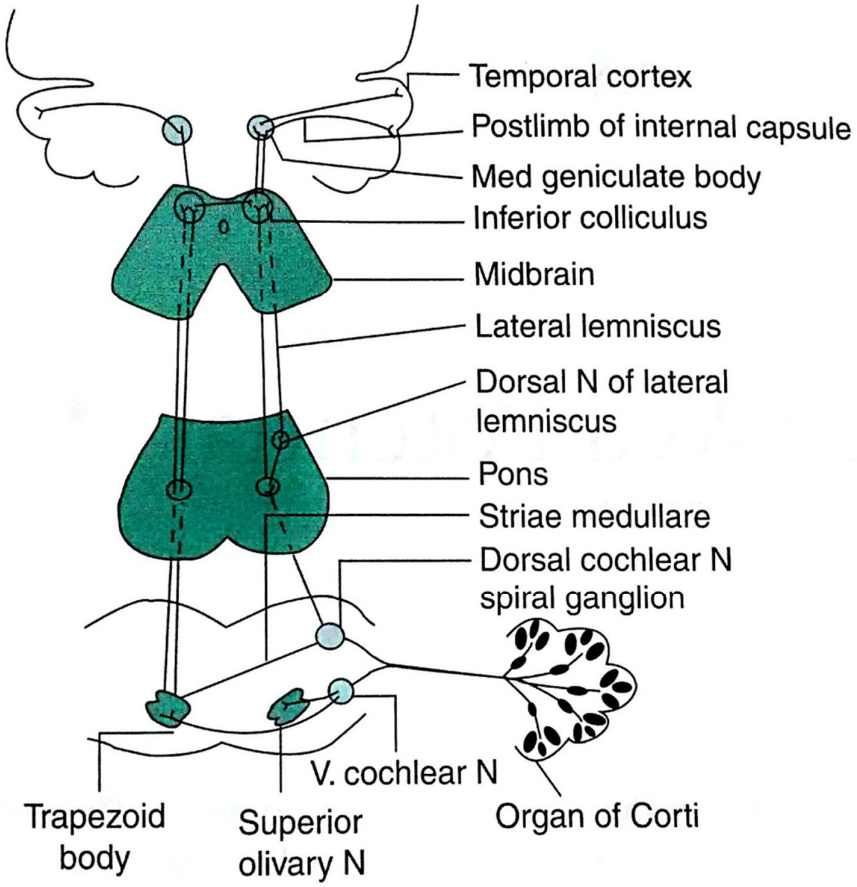
"It is the recording of the activity initiated at the base of cochlea which moves towards the apex within 4ms period of time". The parameters seen are

Amplitude	-	Number of firing neurons
Latency	-	Transmission speed
Inter peak latency	-	Time between peaks
Inter aural latency	-	Difference in wave latency between ears

2.11.7 Anatomical and Physiological basis of BAEPs

External and middle ear transmit the sound waves to the inner ear. Receptor organ for hearing is organ of corti which is located in cochlea. Cochlea is a coiled structure which rests on basilar membrane. Hair cells are receptor cells. Each hair cell contains 60 stereocilia, which are embedded in a gelatinous tectorial membrane overlying the organ of corti. The high frequency sounds affect the basal end of cochlea and low frequencies affect the apical end of cochlea. The amplitude of movement is related to the intensity of the acoustic signals.

Fig12 Auditory Pathway



Basilar membrane is supplied by eighth cranial nerve. Vibrated basilar membrane stimulates the eighth nerve. The latency of eighth nerve discharges following an acoustic signal will be shorter from the basal compared to apical end of cochlea. Eighth nerve has bipolar neuron. It is situated in spiral ganglion. Dendrites of the nerve go to hair cells and its axon goes to cochlear nucleus. Three sub nuclei are present in cochlear nuclei.

1. Anterior ventral cochlear nucleus(AVCN)
2. Posterior ventral cochlear nucleus(PVCN)
3. Dorsal cochlear nucleus(DCN)

The fibres from AVCN pass through the ventral acoustic striae form trapezoid body which terminate in superior olivary nuclei and inferior colliculus. AVCN neurons discharge at short latency to acoustic stimuli with a pattern like eighth nerve.

Fibres from PVCN pass through ventral and middle acoustic striae. These fibres terminate in superior olivary nucleus and inferior colliculus.

Fibres from DCN go to superior olivary nucleus and contralateral inferior nucleus through dorsal striae. Discharges from this neuron have long latency. The cochlear nucleus terminates in superior olivary nucleus and contains medial and lateral part, which is located at the base of pons.

Medial superior olivary nucleus= ipsilateral + contralateral AVCN→Excitatory

Lateral superior olivary nucleus= ipsilateral excitatory from AVCN and PVCN+

Inhibitory input from contralateral AVCN and PVCN

Olivary nucleus→Inhibitory and contralateral lateral lemnnisci→Inferiorcolliculi

↓

Neurons are affected in a nonlinear manner to binaural stimulation.

The inferior colliculi and lateral lemniscal nuclei converges the input from contralateral cochlear nucleus and superior olivary nucleus.

Inferior colliculi→ Medial geniculate body→ Auditory cortex (Superior temporal gyrus and upper bank of sylvian fissure including the frontal and parietal opercula).

The orientation of the neurons in DCN, medial superior olivary and lateral superior olivary nuclei results in summation of synaptic potentials to result in high amplitude electrical fields. The nuclei are connected by large myelinated fiber tracts and their synchronous discharges also generate cohesive voltage fields.

Brainstem electrical activity and its correlation with BAEP

In first 10minutes after acoustic stimulus, recordings are done from different levels of subcortical auditory pathways. Potential corresponding to continuous activation of peripheral, pontomedullar, pontine, and midbrain portion of audiotory pathways can be recorded. The acoustic nerve and brainstem auditory potentials are volume conduction to surface recording electrodes. Vertex positive

and vertex negative waves are formed from vertex and earlobe. These waves are known as BAEPs. The peak to peak amplitude of these waves picked from scalp are only 1/100 the amplitude of ongoing spontaneous EEG activity.

Within 10minutes of auditory stimulus, five or more waves are recoded.

TABLE NO.4 Generators of BAEPs (Chiappa et al ,1990)

WAVEFORM	GENERATORS
I	Peripheral portion of VIII cranial nerve adjacent to cochlea
II	Cochlear nucleus
III	Suprior olivary nucleus
IV	Lateral lemiscus
V	Inferior colliculi

Alternate source of waves

(**Moller et al., 1988)** II-Originate from the intracranial but extra medullary portion of VIII nerve

(**Richter et al.,1983)** III- medial nucleus of trapezoid body

(Picton et al.,1981) IV- originate from Lateral lemiscus but independent of Inferior colliculi

V- Originate from high pons or low midbrain

Brain structure responsible for production of waves from III-V is closely packed brainstem structure. Only 2.5-4cm distance is present between entry point of VIII nerve and inferior colliculi [103].

METHODS

Fig.13 ELECTRODE PLACEMENT FOR BAEP

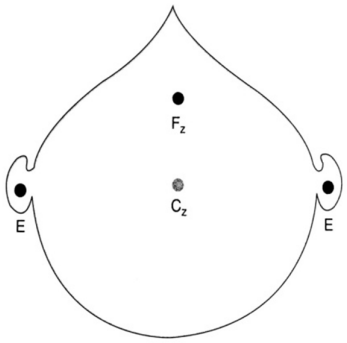


Fig.14 NORMAL BAEP WAVES

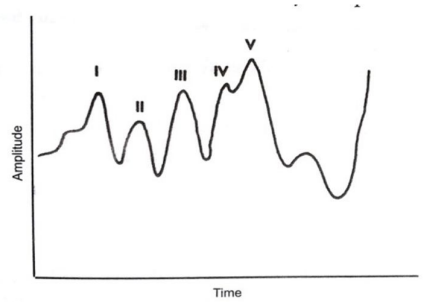


Fig.15 NORMAL VALUES OF BAEP[103]

Wave (latency ms)	Chiappa et al. (1979)	Misra and Kalita (n = 30 pts, 15–68 years)
I	1.7 ± 0.15	1.67 ± 0.17
II	2.8 ± 0.17	2.78 ± 0.21
III	3.9 ± 0.19	3.65 ± 0.22
IV	5.1 ± 0.24	5.0 ± 0.30
V	5.7 ± 0.25	5.72 ± 0.3
VI	7.3 ± 0.29	7.2 ± 0.48
I–III IPL	2.1 ± 0.15	1.99 ± 0.25
III–V IPL	1.9 ± 0.18	2.08 ± 0.30
I–V IPL	4.0 ± 0.23	4.04 ± 0.25

History of Brainstem evoked response audiometry

- 1967- **Sohmer and Feinmesser** –ABRs(Auditory brainstem response) recorded with surface electrodes in humans and cochlear potentials was done by non invasive method

- 1971- **Jewett and Williston**--- Description of the human ABR and interpreted the later waves as arriving from the brainstem
- 1974,-**Hecox and Galambos** --- ABR could be used for threshold estimation in adults and infants.
- In 1975- **Starr and Achor**---first to report the effects on the ABR of CNS pathology in the brainstem
- 1977-**Selters and Brackman---** published landmark findings on prolonged inter-peak latencies in tumour cases (greater than 1 cm) [104].

2.11.8 PATHOPHYSIOLGY OF HEARING IMPAIRNMENT

A.Uziel et al explained that deficiency of thyroid hormone causes defects in morphological and neuronal development of organ of corti.

Hearing impairments in acquired hypothyroidism are due to deterioration of oxygenation and metabolism in the organ of corti and stria vascularis. It also produces changes in protein synthesis, enzymes action and myelin production. Some conditions like Hypertension, Hyperlipidemia and electrolyte imbalance lead to hearing impairment. It was reported by K.T. sanos et al.

J.R. Berrocal et al proposed that autoimmue mechanism is responsible for sensoneural hearing loss in Hashimotos's thyroiditis. Possible mechanism is mainly vascular. It is also due to neuronal degenaration, endolymphatic edema and fibrous tissue proliferation, compression of perilymphatic sac and atrophy of the organ of corti due to the vascular and inflammatory processes of autoimmune damage.

Gawron et al evaluated hearing function in children with Hashimotos's thyroiditis showed that hearing disturbances in auditory nerve and brainstem neural conduction in brain auditory evoked potential. He found that positive correlation is between anti-TPO levels and extent of hearing defects in Hashimotos's thyroiditis.

There is also a positive association with anti-Tg levels [105].

Hypothyroidism causes atherosclerosis which leads to peripheral vascular disease, deafness and coronary artery disease [1].

Figueiredo et al found that subclinical hypothyroid patients showed marked difference in the absolute latencies of waves III and V and interpeaks LI-III, LIII-V, and LI-V [106].

Cristiane et al found out that inter peak latency was increased in subclinical group [107]

2.12 Dyslipedemia and hearing loss

"Cochlea- the lipid composition, fluidity, and stiffness of the outer hair cell lateral wall membrane have been shown to be important to its electromotile

function and the cochlear amplifier". The lateral wall plasma membrane of the outer hair cell has less cholesterol than other cells.

Hypercholesterolemia reduces cochlear vascularity leads to hearing loss. M. Bradley Evans et al explained that chronic dyslipidemia and elevated triglycerides decrease the auditory function.

Rosen et al demonstrated that reduced hearing occurs in dyslipidemia. But other studies do not show any significant relation between cholesterol and hearing loss [108].

2.13 Thyroid antibodies and hearing loss

Gawron et al. reported that subclinical Hashimoto encephalopathy produced changes in central part of auditory organ. Positive correlation exists between the anti-TPO levels and the changes in the central part of the hearing organ [109]. İlhan documented that abnormal BERA findings were due to autoimmunity which was shown by presence of correlation between elevated anti-Tg and anti-TPO and BERA parameter [110]. Leventrenda documented that antibodies directed against spiral ligament, striavasculris and supporting cells[111].

Naemaismail reported that autoimmunity was a cause for hypothyroidism. Auditory system affected due to endolymphatic edema, neuronal degeneration, fibrous tissue proliferation, atrophy of organ corti. He found that statistically insignificant correlation between thyroid peroxidase antibody and changes in auditory brainstem response [112].

Aim and objectives

3. AIM AND OBJECTIVES OF THE STUDY

Aim:

- To evaluate the audiologic function in newly diagnosed subclinical hypothyroidism patients by BERA

Objective:

1. To assess Age, Sex, Height, Weight, BMI
2. To assess the levels of TSH, fT_4, fT_3 in newly diagnosed subclinical hypothyroid patients
3. To assess levels of Thyroglobulin antibody and Thyroid peroxidase antibody if TSH>5.1mIU/L,fT_4>0.93 to 1.7 ng/dl, fT_3- >3.1 to 6.pmol/L
4. To assess the serum lipid profile
5. To do Brainstem evoked response audiometry to rule out changes in peripheral and central auditory pathway
6. Compare all the parameters with healthy age and sex matched controls.
7. To do correlation of Brainstem evoked response audiometry (BERA) with thyroid antibodies and lipid profile

Materials and Methods

4. METHODOLOGY (MATERIALS & METHODS)

The study was conducted in the year between 2016-2017 in the Institute of Physiology and Experimental medicine, Madras Medical College. This study was done after getting approval from Institutional Ethics committee, Madras Medical College, Chennai.

4.1Subject Selection:

Thirty newly diagnosed patients of subclinical Hypothyroidism of both sexes, in the age group below 60 years were included in the study. They were selected from the Medical Endocrine Clinic, Rajiv Gandhi Government general Hospital, Chennai.

Thirty control subjects of both sexes, in the age group below 60 years with normal thyroid profile were selected.

4.2 Inclusion Criteria:

Patients are both men and women in the age group below 60 years with TSH >5.1mIU/L, fT_4>0.93 to 1.7 ng/dl, fT_3- >3.1 to 6.8pmol/L

4.3 Exclusion Criteria:

Patients with:

- Neurological or psychiatric illness
- Altered sensorium
- Any other medical disorder that can affect hearing like diabetes

mellitus, anemia, hypertension, chronic obstructive pulmonary disease, acute or chronic liver disease, and acute or chronic renal disease

- Malignancy
- History of drug abuse and alcoholism
- Above 60 years
- Pregnancy

4.4 STUDY CENTRE

Institute of Physiology and Experimental Medicine, Medical endocrine Clinic, Rajiv Gandhi Government General Hospital, Madras Medical College, Chennai- 3.

4.5 STUDY DESIGN: Case control study

4.6 EXAMINATIONS

A. General examination

B. Examination of thyroid gland

C. Specific ENT examination

Both the control and study group individuals were subjected for basic ENT examination. It includes external ear examination, tuning fork tests like rinne's test and weber's test, Otoscopic examination.

Pure tone audiometry

Pure tone audiometry examination was done in both control and subclinical hypothyroid patients. To find out;

1. Hearing threshold of the subjects
2. To find out external or middle ear pathology

D.Brainstem Auditory Evoked Potential

The patients with subclinical hypothyroidism and controls were subjected to the non invasive assessment of hearing by Brainstem Evoked Response Audiometry (BERA). It was done by Computerised Neurostim, Medicaid system.

1. Apparatus for BERA

"The apparatus for eliciting brainstem evoked response audiometry are set as per the "Recommended standards for the clinical practice of evoked potentials" which is introduced in Guideline 9A: Guidelines on evoked potential, by American society of Clinical Neurophysiology."

Pulse generator

The stimulusis given in the form of in the form of clicks or tone pips. It is conducted in to the ear through the transducer placed in the headphone.

Recording electrodes

Three recording electrodes are placed as per the International 10-20 electrode placement system.

1. Active electrode- placed on the ipsilateral mastoid process

2. Reference electrode- placed on the vertex and a
3. Ground electrode-placed in front of reference electrode

There are two varieties are electrodes are used during recording processes.

1. Needle electrodes
2. Surface electrodes

The surface electrodes are commonly used. It does not produce pain sensation and infection rate also reduced. Ask the subject to take head bath before coming for examination for easy application of electrodes. Disc electrodes of 1cm size and with conducing jelly or paste are used. <5 kilo ohms of electrical impedance are used for good recording.

Filters

Filter is a device that restricts selectively the frequency domain of the signal. Frequency band pass means frequency range of a signal transmitted through the filter.

- Stop band means signal rejected in that particular frequency range.
- Transition lies between the frequency and stop band.

Uses

1. Noise elimination

2. Optimal recording

3. To obtain typical wave forms

I. Low frequency filter-It removes slowly changing low frequency and allows higher frequencies. It also known as high pass filter.

II. High frequency filter- It removes rapidly changing high frequency and allows low frequencies. It is also known as low pass filter.

Amplifier

500000 times of amplification is needed before displayed due to following reasons.

1. Biological signals are small
2. Intrinsic impedance of electrode. It changes with frequency and electrode type used.
3. Impedance of electrode- skin

   For the measurement of any electrical activity including action potential which is generated in central nervous system, nerve or muscle should flow through the ground lead.

Electrode impedance produces a drop in the amplitude of the action potential. It amplifies the attenuated action potential. Action potential reaching the amplifiers is attenuated action potential. The impedance of the amplifiers should be greater than electrode impedance to reduce this attenuation. A100:1 ratio of electrode to amplifier impedance is maintained across the range of frequencies in the waveform under study.

1. Due to amplification waveforms distortion are minimized
2. Improves noise rejection.

Signal average

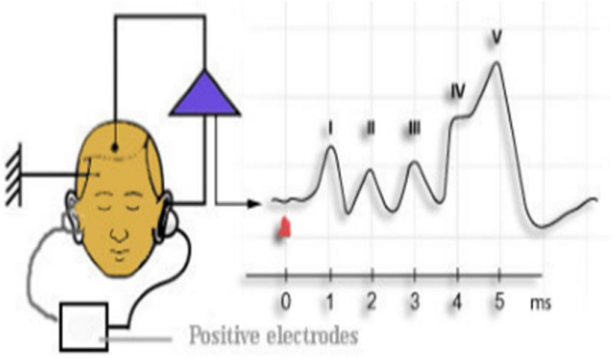
It is difficult to measure electrical activity of brain using sound stimuli given to the ear. Because spontaneous electrical activity is generated within the brain (Back ground potential).So the electrical activity set up in the brain in response to sound stimulus gets masked by spontaneous electrical activity occurring in the brain.

It used to extract small signals. Because it is hidden by large noise like evoked potential buried in EEG. Evoked electrical activity is time specific which occurs at a fixed point of time after the sound stimulation but spontaneous electrical activity occurring randomly not time specific. By averaging, the time-locked signals become prominent and stored in machine. If noise occurs which is cancelled or time –locked and rejected subsequently.

Electrical safety; All instruments should be checked periodically. It helps to protect from shock during power fluctuations.

2. Recordings procedure of BERA

Fig .16Recordings for BAEP waveforms



The recording was done in semi darkened and quiet room. The patient is advised to take head bath before recording. Electrodes placing areas are cleaned. Active, reference & ground electrodes are kept in a appropriate places. Below 5 kilo ohms levels of resistance are used. Auditory stimulus consists of clicks of 100µsec are given in one ear .It is given through electrically shielded ear phones at the rate of11.1 clicks/sec.

Another ear is masked by pure white noise of 40dB.It is used to prevent false BAEP response. To filter out undesirable frequencies in the surroundings we had to use band pass of 150-3000 Hz. Responses to 2000 clicks presentations were averaged.

A graph is plotted to show the result. X-axis contains time (in milliseconds from the onset of stimulus).Y-axis contains amplitude (in µvolts).5-7wave or peaks are seen within 8-10 milliseconds. It is marked with Roman numerals.

Waveforms were analyzed for the following characters.

- Latency
- Amplitude
- Morphology

It gives information about cochlear and retro cochlear function.

Wave I

It gives information about potentials generated in the peripheral part of 8th cranial nerve. It is a prominent initial peak confined to ipsilateral ear and is absent in

contralateral ear. It appears 1.5 ms after the application of stimulus .It is decreased in patients with peripheral hearing impairment

Wave II

It is appears as small peak.It appears 2.8ms after application of stimulus. It is absent in lesions of the cochlear nucleus.

Wave III

Itis a prominent peak followed by a prominent trough. It appears 3.9 ms after the click stimulus. It is absent in superior olivary nucleus lesion.

Wave IV

It appears as peak in the up going slope of after 5.1ms. Wave IV is absent in lateral lemniscus lesion

Wave V

Itis the most prominent peak. It appears 5.5 msec after the stimulus.It is absent inferior colliculi lesions. This wave component is analysed most often in clinical applications

Wave VI and VII

These waves are origin from subcortical structures like medial geniculate body and auditory radiation. It appears 7.3 and 9.6 ms after initiation of stimulus.

3. Wave forms interpretation

The parameters taken into consideration for studying the waveforms of BAEPs are

Absolute latency; It is the time interval and it is measured by milliseconds. It is starting point of stimulus to the peak of the wave.

Absolute amplitude; It is measured in microvolt. It is marked as the height from the peak of the wave to its trough. It is measured by microvolt. Amplitude of the waves is not as constant as latency and not reliable.

Inter peak latency (IPL): The duration between two different waves in the same ear is known as inter peak latency. It is also known as inter peak latency or inter wave latency. There are three inter peak latency most commonly used.

1. I-V----latency difference between wave V and I. It denotes the conduction from proximal VIII nerve through pons to midbrain. Normal duration is 4msec. It is shorter in young women and in older men becomes longer. It is prolonged in demyelination, ischemia, tumours, brain damage due to hypoxia.
2. I-III- it is a latency difference between wave I and III .It denotes conduction from VIII nerve across subarachnoid space. Normal is 2.1msec.It is prolonged in tumour or inflammation affecting the proximal portion of the VIII nerve.
3. III-V—It denotes conduction from lower pons to midbrain .Normal duration is 1.9msc

Amplitude ratio of wave V/I: Wave I is generated outside and wave v is generated inside the central nervous system. This is used to compare the relationship of the expected signal amplitude. Normal ratio is 50 %and 300%

If ratio exceeds 300%,it shows peripheral hearing impairment. If ratio is lower than 50%, it denotes central hearing loss.

Inter aural latency difference: It should be less than 0.5msec.It is the time interval between the two ears for same wave during supra threshold stimulus[113]

4. Technical factors

Stimulus rate: Number of clicks is given. It is 10-70times/seconds

Intensity of the sound stimulus; High intensity- wave I is decreased with prolonged I-V IPL. With decreasing intensity-I, III, V waves are present. Still lower intensity (10dBSL) V wave is seen.

Stimulus phase or polarity: The pulse can move towards or away from the ear. The ear phone movement toward the ear is called condensation phase moves away from the ear it is called as rarefaction phase.

Filter; lower frequency filter -100 or 150 Hz

High frequency filter- 3000 Hz

Nature of sound: Click stimulus was given for 1ms duration. The stimulus applied is usually square wave pulse. The sound stimuli delivered at 50-60 db above the hearing threshold.

Binaural/monaural stimulation: In clinical studies, monaural stimulation is recommended. If both ears are stimulated the amplitude of the waves III, IV, V are increased[114].

5.Nontechnical factors

Age; Older adults have longer I-V IPL by 0.1-0.15ms

Temperature: The absolute latency (7% for 1 celsius) and IPL are prolonged on lowering body temperature.

Hearing status; Ear canal examination and hearing should be tested.

Drugs: "BAEPs are resistant to the effect of drugs, but a slight prolongation of V wave latency with barbiturates or alcohol is attributed to the lowering of temperature"

6. Terminologies used in evoked potential study

Hearing level

It refers to the number of decibels of intensity compared to the threshold of hearing in a group of normal persons. Zero means threshold at which a normal subject can just perceive 50% of stimuli.

Sensory level (dB SL)

Zero is defined as the point at which the individual can barely appreciate the stimulus.

Decibel (dB=1/10 Bel)

It is defined as '20 log (P1/P2)', where P1 is the intensity of the sound to be measured andP2 is the intensity of the reference sound[103].

4.7. SAMPLE COLLECTION

After obtaining informed consent, under aseptic precautions, 5-10ml of blood would be taken for estimation of TSH ,fT_4,fT_3,(ElectroChemiluminescence immunoassay),Thyroglobulin antibody (Anti-Tg Elecsys e 100 kit),Thyroid peroxidase antibody(Anti-TPO Elecsyscobas kit) and lipid profile

4.8 STATISTICAL ANALYSIS

1. Using unpaired t test the mean variables between the normal and subclinical hypothyroid patients are compared. SPSS version 17 was used for data analysis.

2. Pearson's coefficient was done to find out the correlation between BERA with thyroglobulin antibody, thyroid peroxidase antibody and lipid profile in subclinical hypothyroid patients.

Results

5.RESULTS

All the Subclinical hypothyroid patients and controls enrolled for the present study had clinically no evidence of hearing deficit.

5.1 Characteristics of study and control subjects

Our study population consists of 30 subclinical hypothyroid patients in the age group 20-60 years without any clinical evidence hearing impairment. The control subjects were 30 in number belonging to the age ranging from 20-60 years.

5.2 Levels of Thyroid antibodies and lipid profile

The difference in the mean values of thyroid antibodies and lipid profile between controls and subclinical hypothyroid patients are given in table 9 and 10.

5.3 Brainstem auditory evoked potential parameters

Variable pertaining to BERA between normal and are subclinical hypothyroid patients are given in the tables 11-34 and also represented in graph (10-20). BERA parameters are utilized for evaluating the integrity of auditory pathway.

TABLE NO.5 Comparison of mean values of Height between controls and subclinical hypothyroid patients

	GROUPING	N	Mean	Std. Deviation	Std. Error Mean	t	DF	p Value
HT (m)	CONTROL GROUP	30	1.639	0.12067	0.02203	1.541	58	0.129
	STUDY GROUP	30	1.5943	0.10321	0.01884			

pvalue –not significant

TABLE NO.6 Comparison of mean values of weight between controls and subclinical hypothyroid patients

	GROUPING	N	Mean	Std. Deviation	Std. Error Mean	t	DF	p Value
WT (kg)	CONTROL GROUP	30	59.6	9.999	1.825	-3.867	58	0.000*
	STUDY GROUP	30	69.63	10.101	1.844			

pvalue – significant

TABLE NO.7 Comparison of mean values of body mass index between controls and subclinical hypothyroid patients

	GROUPING	N	Mean	Std. Deviation	Std. Error Mean	t	DF	p Value
BMI	CONTROL GROUP	30	22.148122	2.7366318	0.4996383	-5.945	58	0.000*
	STUDY GROUP	30	27.498865	4.1004333	0.7486333			

p value – significant

TABLE NO.8 Comparison of mean values of Free T_3, Free T_4 and thyroid stimulating hormone levels between controls and subclinical hypothyroid patients

	GROUPING	N	Mean	Std. Deviation	Std. Error Mean	T	DF	p Value
T_3 (pmol/L)	CONTROL GROUP	30	4.53	0.92295	0.16851	0.197	58	0.844
	STUDY GROUP	30	4.4867	*0.77417*	0.14134			
T_4 (ngm/dl)	CONTROL GROUP	30	1.2273	0.25308	0.04621	2.354	43.987	0.023
	STUDY GROUP	30	1.1043	0.13354	0.02438			
TSH (µIU/ml)	CONTROL GROUP	30	3.5267	0.48703	0.08892	-10.295	29.528	0.000*
	STUDY GROUP	30	13.1673	5.10568	0.93217			

p value –not significant in Free T_3, Free T_4

p value –significant in thyroid stimulating hormone

TABLE NO.9 Comparison of mean values of thyroglobulin antibody and thyroid peroxidase antibody between controls and subclinical hypothyroid patients

	GROUPING	N	Mean	Std. Deviation	Std. Error Mean	t	DF	p Value
Anti-Tg (IU/ml)	CONTROL GROUP	30	29.334	33.43902	6.1051	-5.453	31.863	0.000*
	STUDY GROUP	30	182.6353	150.31079	27.44287			
Anti-TPO (IU/ml)	CONTROL GROUP	30	55.5687	116.06911	21.19122	-5.424	41.497	0.000*
	STUDY GROUP	30	323.0273	243.87572	44.52541			

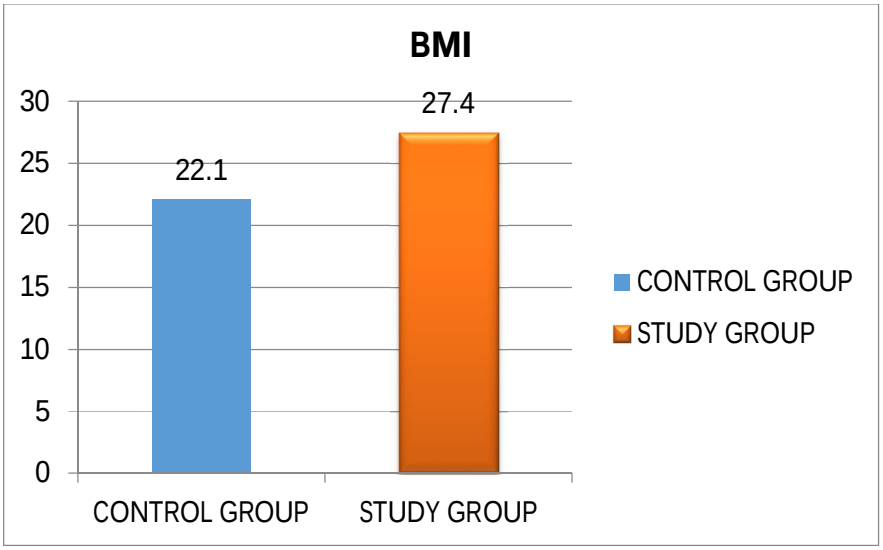
p value–significant in Anti-Tg, Anti-TPO

TABLE NO.10 Comparison of mean values of lipid profile between controls and subclinical hypothyroid patients

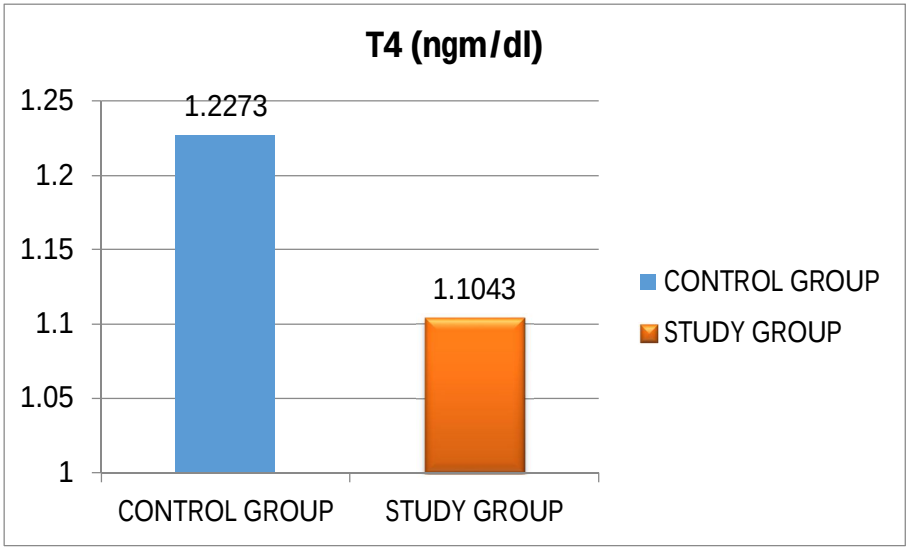
	GROUPING	N	Mean	Std. Deviation	Std. Error Mean	t	DF	p Value
TOTAL CHOLESTEROL (mg/dl)	CONTROL GROUP	30	174.7	18.234	3.329	-2.982	38.17	0.005*
	STUDY GROUP	30	201.27	45.266	8.264			
HDL (mg/dl)	CONTROL GROUP	30	52.9	7.48	1.366	1.933	42.827	0.06
	STUDY GROUP	30	47.03	14.85	2.711			
TGL mg/dl	CONTROL GROUP	30	143.67	8.193	1.496	-0.383	29.592	0.704
	STUDY GROUP	30	149.37	81.099	14.807			
VLDL mg/dl	CONTROL GROUP	30	28.733333	1.6386145	0.2991687	-0.383	29.592	0.704
	STUDY GROUP	30	29.873333	16.2197396	2.9613058			
LDL mg/dl	CONTROL GROUP	30	93.066667	16.9846449	3.1009577	-3.742	38.017	0.001*
	STUDY GROUP	30	124.36	42.5399253	7.7666922			
LDL/ HDL	CONTROL GROUP	30	1.795321	0.4117805	0.0751805	-3.04	30.716	0.005*
	STUDY GROUP	30	3.142826	2.3926494	0.436836			
TGL/ HDL	CONTROL GROUP	30	2.771594	0.4437766	0.0810222	-1.869	30.606	0.071
	STUDY GROUP	30	3.693572	2.6659285	0.4867297			

p value –significant in total cholesterol LDL and LDL/HDL

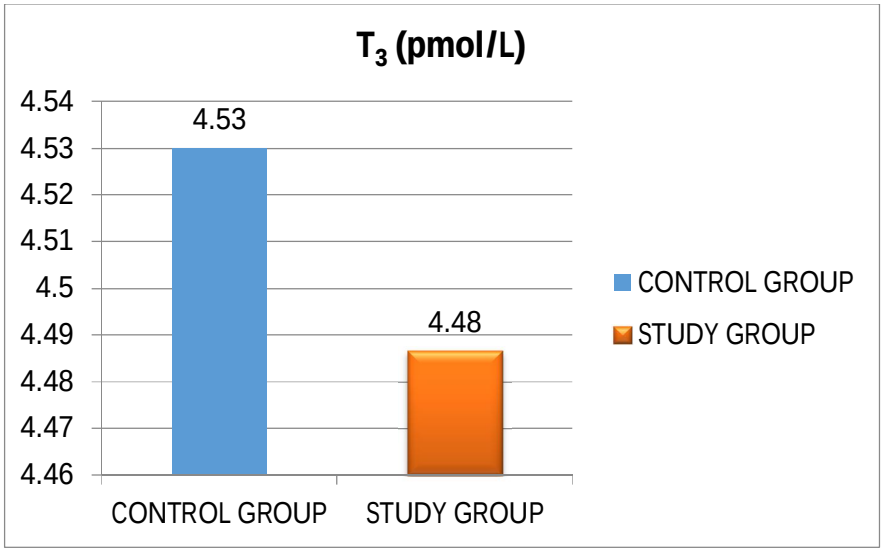
Graph 1.Comparison of mean values of BMI between controls and subclinical hypothyroid patients



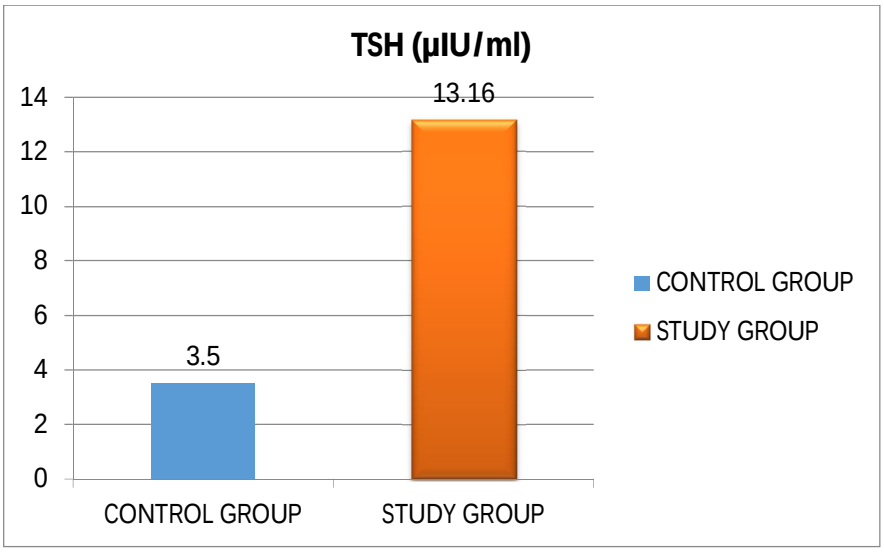
Graph.2 Comparison of mean values of T_4between controls and subclinical hypothyroid patients



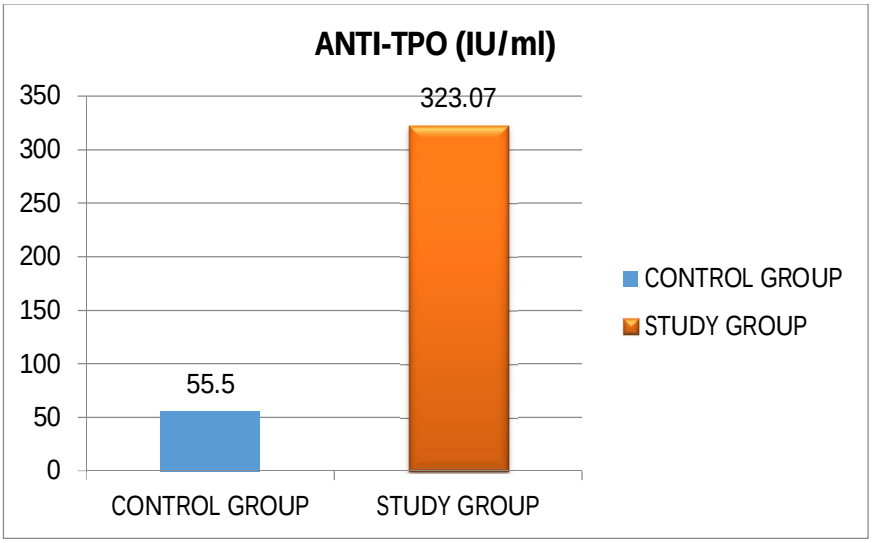
Graph. 3 Comparison of mean values of T_3between controls and subclinical hypothyroid patients



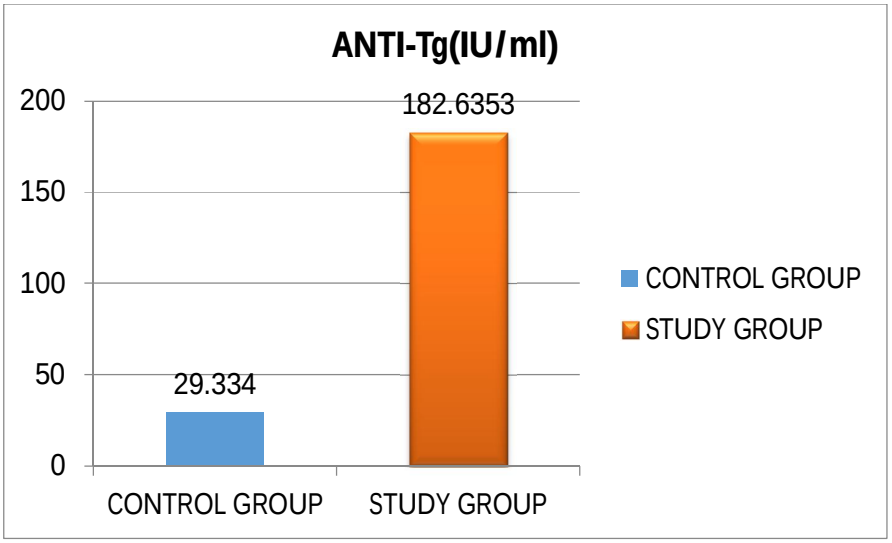
Graph.4 Comparison of mean values of TSH between controls and subclinical hypothyroid patients



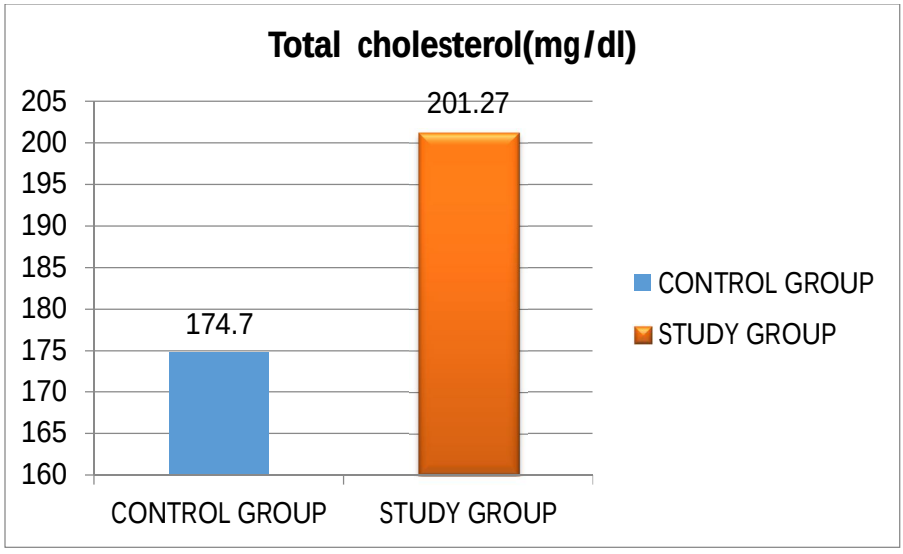
Graph .5Comparison of mean values of Anti-TPO between controls and subclinical hypothyroid patients



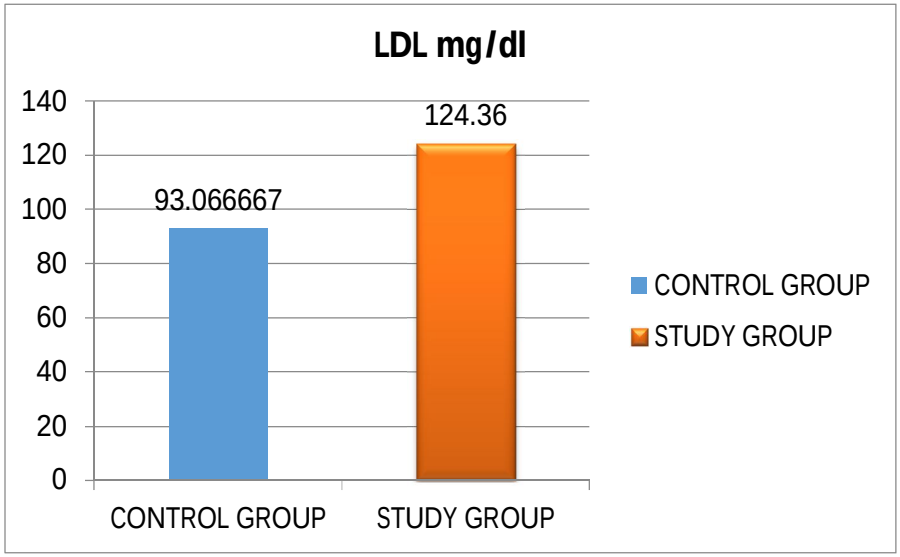
Graph.6 Comparison of mean values of Anti-Tgbetween controls and subclinical hypothyroid patients



Graph. 7Comparison of mean values of Total Cholesterol between controls and subclinical hypothyroid patients



Graph .8Comparison of mean values of LDL between controls and subclinical hypothyroid patients



Graph .9Comparison of mean values of TGL/HDL between controls and subclinical hypothyroid patients

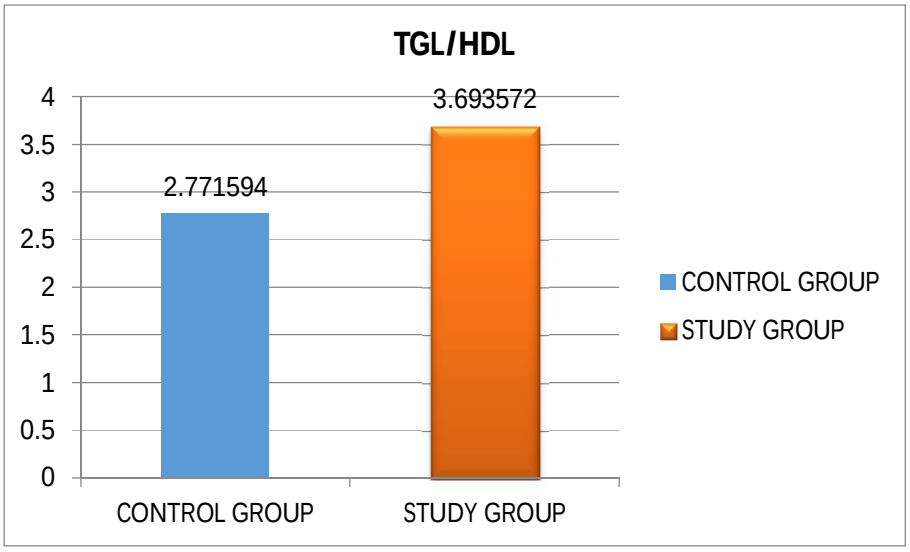


TABLE NO.11 Comparison of the mean values of absolute latencies of wave I between controls and subclinical hypothyroid patients in the right ear.

	GROUPING	N	Mean	Std. Deviation	Std. Error Mean	t	DF	p Value
Right Ear wave I	CONTROL GROUP	30	1.691	.11	.02008	.0408	58	.968
	STUDY GROUP	30	1.69	.077	.01406			

p value-not significant

TABLE NO.12 Comparison of mean values of absolute latencies of wave I between controls and subclinical hypothyroid patients in the left ear

	GROUPING	N	Mean	Std. Deviation	Std. Error Mean	T	DF	p Value
Left ear Wave I	CONTROL GROUP	30	1.6517	.17360	.03170	-.396	58	.693
	STUDY GROUP	30	1.6713	.20921	.03820			

p value-not significant

TABLE NO.13 Comparison of mean values of absolute latencies of wave II between controls and subclinical hypothyroid patients in the right ear

	GROUPING	N	Mean	Std. Deviation	Std. Error Mean	t	DF	p Value
Right Ear Wave II	CONTROL GROUP	30	2.7530	.06929	.01265	-.270	58	.788
	STUDY GROUP	30	2.7573	.05413	.00988			

p value-not significant

TABLE NO.14 Comparison of mean values of absolute latencies of wave II between controls and subclinical hypothyroid patients in the left ear

	GROUPING	N	Mean	Std. Deviation	Std. Error Mean	t	DF	p Value
Left ear Wave II	CONTROL GROUP	30	2.7137	.17431	.03182	-.886	58	.379
	STUDY GROUP	30	2.7553	.18957	.03461			

p value-not significant

TABLE NO.15 Comparison of mean values of absolute latencies of wave III between controls and subclinical hypothyroid patients in the right ear

	GROUPING	N	Mean	Std. Deviation	Std. Error Mean	t	DF	p Value
Right ear Wave III	CONTROL GROUP	30	3.6687	.14638	.02672	-.739	58	.463
	STUDY GROUP	30	3.6987	.16735	.03055			

p value-not significant

TABLE NO.16 Comparison of mean values of absolute latencies of wave III between controls and subclinical hypothyroid patients in the left ear

	GROUPING	N	Mean	Std. Deviation	Std. Error Mean	t	DF	p Value
Left ear Wave III	CONTROL GROUP	30	3.7117	.19785	.03612	-.629	58	.532
	STUDY GROUP	30	3.7460	.22391	.04088			

p value-not significant

TABLE NO.17 Comparison of mean values of absolute latencies of wave IV between controls and subclinical hypothyroid patients in the right ear

	GROUPING	N	Mean	Std. Deviation	Std. Error Mean	t	DF	p Value
Right Ear Wave IV	CONTROL GROUP	30	4.8320	.08961	.01636	-.235	58	.815
	STUDY GROUP	30	4.8370	.07484	.01366			

p value-not significant

TABLE NO.18 Comparison of mean values of absolute latencies of wave IV between controls and subclinical hypothyroid patients in the left ear

	GROUPING	N	Mean	Std. Deviation	Std. Error Mean	t	DF	p Value
Left ear Wave IV	CONTROL GROUP	30	4.7420	.20965	.03828	-.804	58	.425
	STUDY GROUP	30	4.7880	.23301	.04254			

p value-not significant

TABLE NO.19 Comparison of mean values of absolute latencies of wave V between controls and subclinical hypothyroid patients in the right ear

	GROUPING	N	Mean	Std. Deviation	Std. Error Mean	t	DF	p Value
Right Ear Wave V	CONTROL GROUP	30	5.6727	.16328	.02981	-2.116	45.494	0.040*
	STUDY GROUP	30	5.8020	.29228	.05336			

p value-significant

TABLE NO.20 Comparison of mean values of absolute latencies of wave V between controls and subclinical hypothyroid patients in the left ear

	GROUPING	N	Mean	Std. Deviation	Std. Error Mean	t	DF	p Value
Left ear Wave V	CONTROL GROUP	30	5.6250	.12913	.02358	-2.804	39.792	0.008*
	STUDY GROUP	30	5.7893	.29393	.05366			

p value- significant

TABLE NO.21 Comparison of mean values of I-III IPL between controls and subclinical hypothyroid patients in the right ear.

	GROUPING	**N**	**Mean**	**Std. Deviation**	**Std. Error Mean**	**T**	**DF**	**p Value**
Right Ear IPL I-III	CONTROL GROUP	30	1.9780	.17065	.03116	-.706	58	.483
	STUDY GROUP	30	2.0090	.16961	.03097			

p value-not significant

TABLE NO. 22 Comparison of mean values of I-III IPL between controls and subclinical hypothyroid patients in the left ear

	GROUPING	**N**	**Mean**	**Std. Deviation**	**Std. Error Mean**	**t**	**DF**	**p Value**
Left ear IPL I-III	CONTROL GROUP	30	2.0600	.22364	.04083	-.242	58	.810
	STUDY GROUP	30	2.0747	.24611	.04493			

p value-not significant

TABLE NO.23 Comparison of mean values of III-V IPL between controls and subclinical hypothyroid patients in the right ear

	GROUPING	N	Mean	Std. Deviation	Std. Error Mean	t	DF	p Value
Right Ear IPL III-V	CONTROL GROUP	30	2.0040	.18906	.03452	-1.446	46.590	.155
	STUDY GROUP	30	2.1033	.32523	.05938			

p value-not significant

TABLE NO.24 Comparison of mean values of III-V IPL between controls and subclinical hypothyroid patients in the left ear

	GROUPING	N	Mean	Std. Deviation	Std. Error Mean	t	DF	p Value
Left ear IPL III-V	CONTROL GROUP	30	1.9133	.26084	.04762	-1.651	58	.104
	STUDY GROUP	30	2.0433	.34336	.06269			

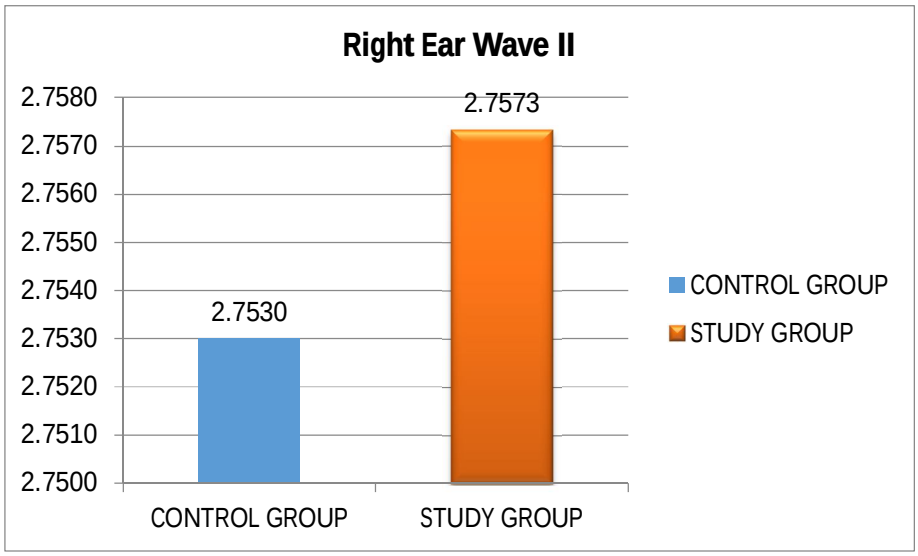
p value-not significant

TABLE NO.25 Comparison of mean values of I-V IPL between controls and subclinical hypothyroid patients in the right ear

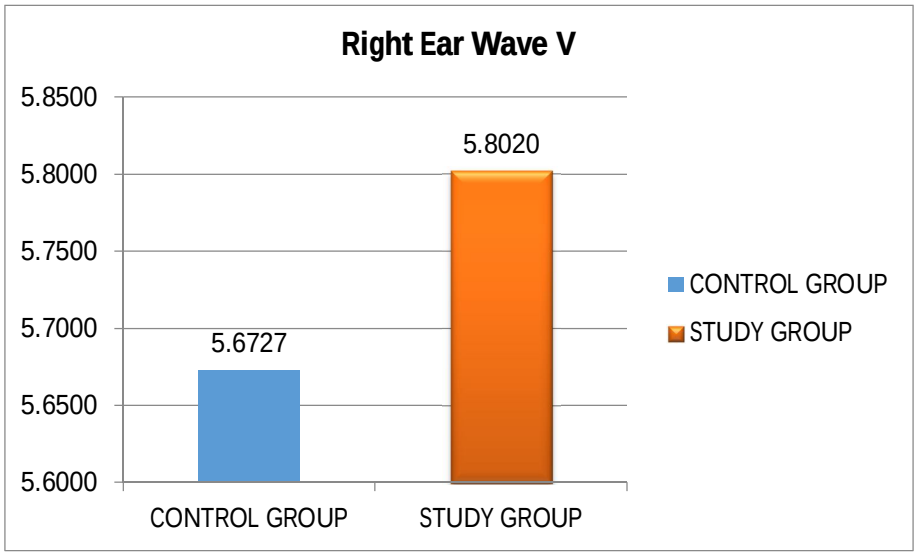
	GROUPING	N	Mean	Std. Deviation	Std. Error Mean	T	DF	p Value
Right Ear IPL I-V	CONTROL GROUP	30	3.9820	.21661	.03955	-1.985	58	.052
	STUDY GROUP	30	4.1123	.28712	.05242			

p value-not significant

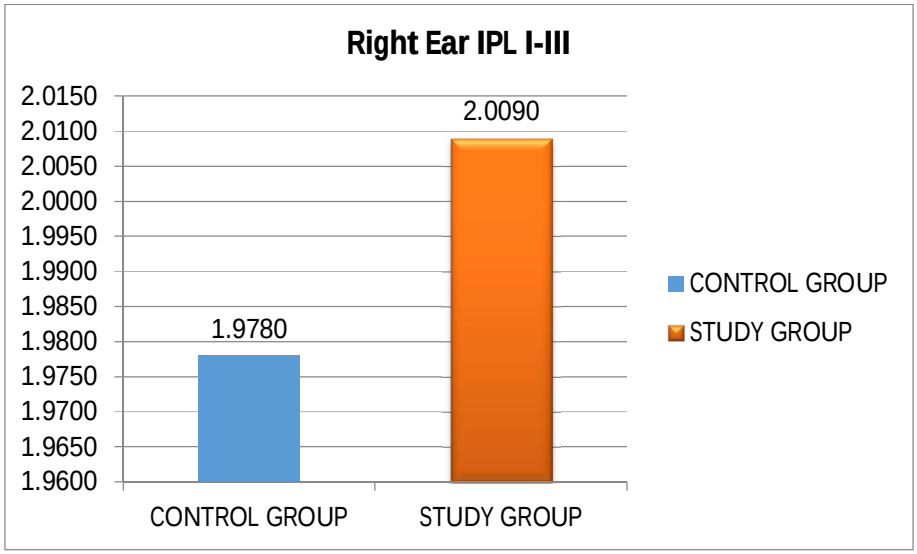
Graph.10 Comparison of mean values of absolute latencies of wave II between controls and subclinical hypothyroid patients in the right ear



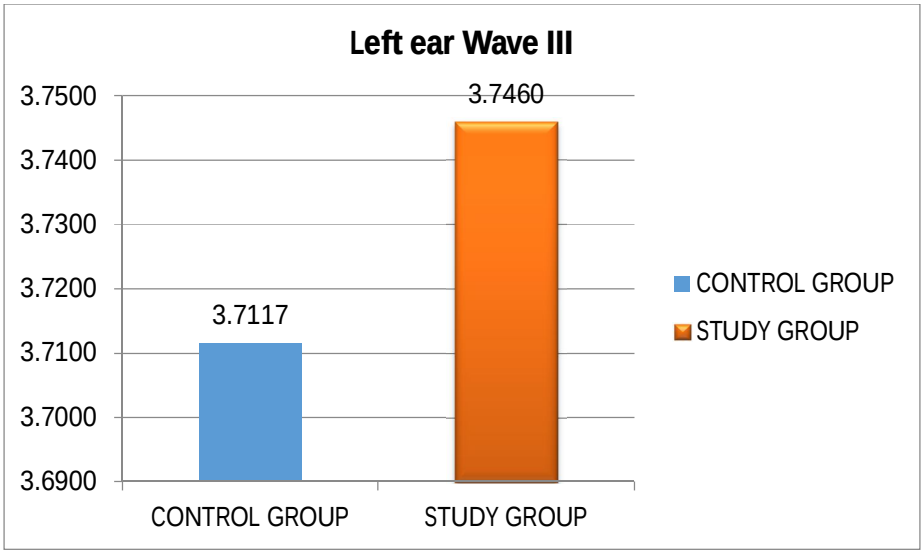
Graph.11 Comparison of mean values of absolute latencies of wave V between controls and subclinical hypothyroid patients in the right ear



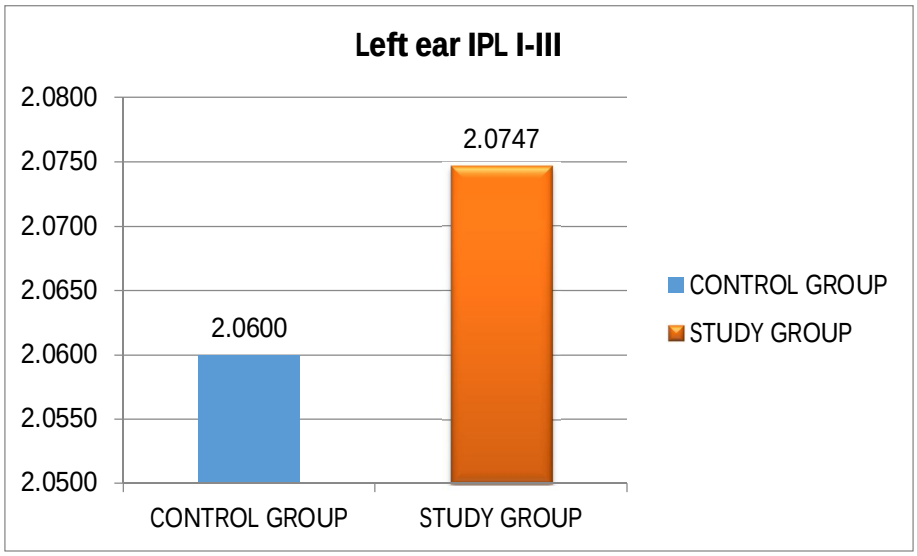
Graph.12Comparison of mean values I-III IPL between controls and subclinical hypothyroid patients in the right ear.



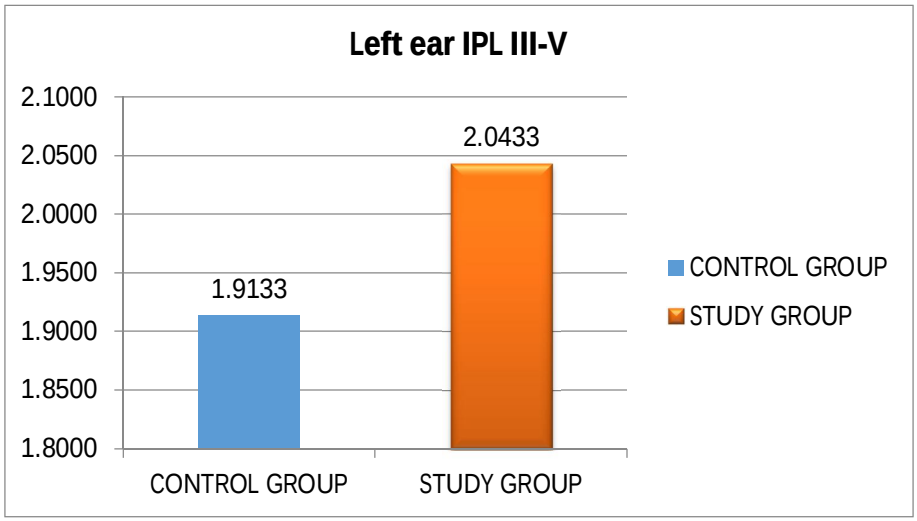
Graph.13Comparison of mean values of absolute latencies of wave III between controls and subclinical hypothyroid patients in the left ear



Graph.14Comparison of mean values I-III IPL between controls and subclinical hypothyroid patients in the left ear.



Graph.15Comparison of mean values III-V IPL between controls and subclinical hypothyroid patients in the left ear.



Graph.16Comparison of the mean values of I-V IPL between controls and subclinical hypothyroid patients in the left ear.

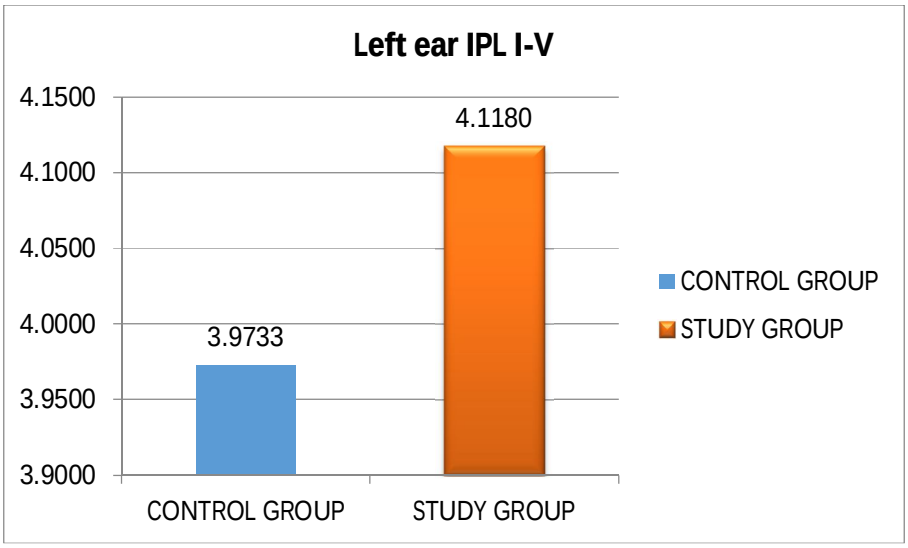


TABLE NO.26 Comparison of mean values of I-V IPL between controls and subclinical hypothyroid patients in the left ear

	GROUPING	N	Mean	Std. Deviation	Std. Error Mean	t	DF	p Value
Left ear IPL I-V	CONTROL GROUP	30	3.9733	.24055	.04392	-1.915	58	.060
	STUDY GROUP	30	4.1180	.33673	.06148			

p value-not significant

TABLE no.27 Correlation between Anti-Tg and Right Ear BERA Wave V in subclinical hypothyroid patients

Right Ear Wave V Vs. Anti-Tg (IU/ml)			
	Mean	**Std. Deviation**	**N**
Right Ear Wave V	5.8020	.29228	30
Anti-Tg (IU/ml)	182.6353	150.31079	30
Pearson Correlation	0.32172	p VALUE	0.083
*p Value Significant at the level <0.05			

Positive correlation, p value is not significant

TABLE NO.28 Correlation between Anti-Tg and left Ear BERA Wave V in subclinical hypothyroid patients.

Left Ear Wave V Vs. Anti-Tg (IU/ml)			
	Mean	Std. Deviation	N
Left ear Wave V	5.7893	.29393	30
Anti-Tg (IU/ml)	182.6353	150.31079	30
Pearson Correlation	0.216093	p VALUE	0.251425
*p Value Significant at the level <0.05			

Positive correlation, p value is not significant

TABLE NO.29 Correlation between the Anti-TPO and Right Ear BERA Wave V in subclinical hypothyroid patients.

Right Ear Wave V Vs. Anti-TPO (IU/ml)			
	Mean	Std. Deviation	N
Right Ear Wave V	5.8020	.29228	30
Anti-TPO (IU/ml)	323.0273	243.87572	30
Pearson Correlation	0.286752	p VALUE	0.1245
*p Value Significant at the level <0.05			

Positive correlation, p value is not significant

TABLE NO.30 Correlation between Anti-TPO (IU/ml) and left Ear BERA Wave V in subclinical hypothyroid patients.

Left ear Wave V Vs. Anti--TPO (IU/ml)

	Mean	**Std. Deviation**	**N**
Left ear Wave V	5.7893	.29393	30
Anti-TPO (IU/ml)	323.0273	243.87572	30
Pearson Correlation	0.126845	p VALUE	0.5042
*p Value Significant at the level <0.05			

Positive correlation,p value is not significant

TABLE NO.31 Correlation between Total Cholesterol and Right Ear BERA Wave V in subclinical hypothyroid patients.

Right Ear Wave V Vs. Total cholesterol (mg/dl)

	Mean	Std. Deviation	N
Right Ear Wave V	5.8020	.29228	30
Total cholesterol(mg/dl)	201.27	45.266	30
Pearson Correlation	-0.16	p VALUE	0.400
*p Value Significant at the level <0.05			

Negative correlation, p value is not significant

TABLE NO.32 Correlation between Total cholesterol and left Ear BERA Wave V in subclinical hypothyroid patients

Left ear Wave V Vs. Total Cholesterol (mg/dl)			
	Mean	Std. Deviation	N
Left ear Wave V	5.7893	.29393	30
Total Cholesterol(mg/dl)	201.27	45.266	30
Pearson Correlation	-0.237	p VALUE	0.208
*p Value Significant at the level <0.05			

Negative correlation, p value is not significant

TABLE NO.33 Correlation between LDL and Right Ear BERA Wave V in subclinical hypothyroid patients

Left ear Wave V Vs. LDL mg/dl			
	Mean	Std. Deviation	N
Right Ear Wave V	5.8020	.29228	30
LDL mg/dl	124.360000	42.5399253	30
Pearson Correlation	-0.256	p VALUE	0.172
*p Value Significant at the level <0.05			

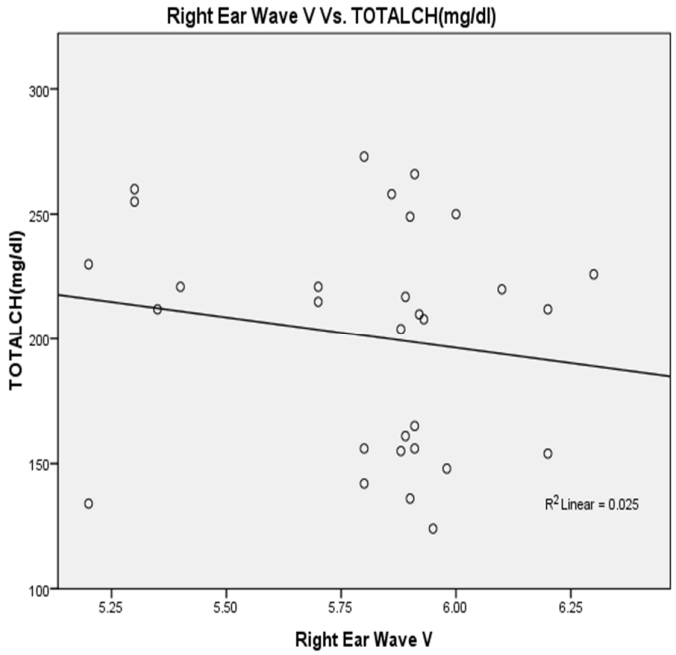
Negative correlation, p value is not significant

TABLE NO.34 Correlation between LDL and left Ear BERA Wave V in subclinical hypothyroid patients

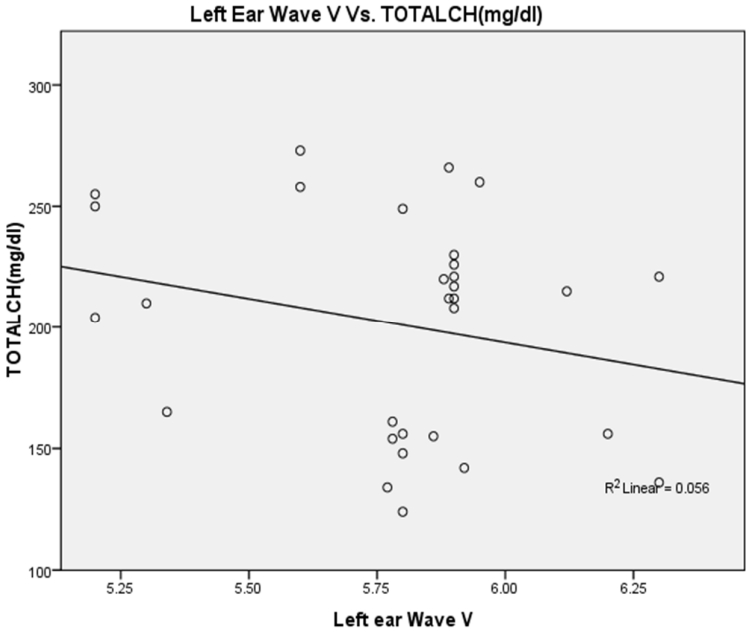
Left ear Wave V Vs. LDL mg/dl			
	Mean	Std. Deviation	N
Left ear Wave V	5.7893	.29393	30
LDL mg/dl	124.360000	42.5399253	30
Pearson Correlation	-0.328	p VALUE	0.077
*p Value Significant at the level <0.05			

Negative correlation, p value is not significant

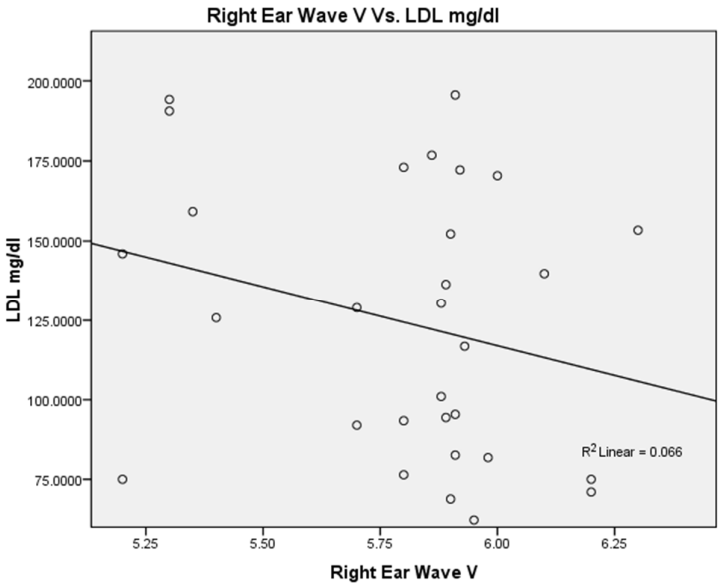
GRAPH.17 Correlation between Total Cholesterol and Right Ear BERA Wave V in subclinical hypothyroid patients.



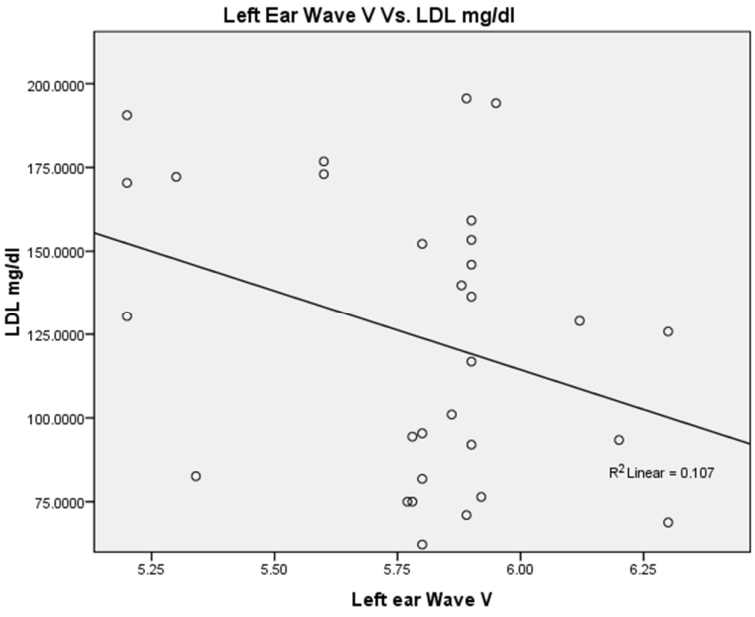
GRAPH.18 Correlation between Total Cholesterol and left Ear BERA Wave V in subclinical hypothyroid patient



GRAPH.19 Correlation between LDL and Right Ear BERA Wave V in subclinical hypothyroid patients



GRAPH. 20 Correlation between LDL and left Ear BERA Wave V in subclinical hypothyroid patients



Discussion

6. DISCUSSION

Central nervous system dysfunction and hearing loss are seen in subclinical hypothyroidism patients. Sensorineural deafness is the most common manifestation due to dysfunction of thyroid gland. Few studies reveal that brainstem evoked response audiometry shows changes in subclinical hypothyroidism.

Thomas cyriac reported that prevalence of subclinical hypothyroidism and hypothyroidism is 15% and 11.7% respectively [94].

Danese et al suggested that periodic examination of TSH should be done after 35 years of age [115].

About 30 newly diagnosed hypothyroid patients and 30 controls are included in my study in the age group of below 60 years.

Characteristic of parameters between cases and controls

6.1 Age

My present study shows that there is no specific difference in age group between subclinical hypothyroidism patients and controls. My study has similar findings with **kirti Sharma** study but **Samuels et al** reported that hypothyroidism is most common in elderly women, particularly in the presence of thyroid autoantibodies[107, 116].

Unnikrishnan AG and VanderpumpMP. T reported that increased prevalence of hypothyroidism is seen in age group of 46-54 years (13.1%) [117].

6.2 Gender

Most of the patients in my study are females. My study is supported by **Sangeeta Gupta et al, UnnikrishnanAG andVanderpump MP. T.** They reported that Subclinical hypothyroidism is more common in females [118,117].

6.3 Height

On comparing the height between subclinical hypothyroidism patients and controls, it is observed that there exists (**p value=0.129**) no significant difference between the both groups.**Kirti Sharma** study has the same finding like my study [107]. **p Value is statistically not significant.**

6.4 Weight

On comparing the weight between subclinical hypothyroidism patients and controls, it shows that weight gain **(p= 0.000)**is present in subclinical hypothyroid patients. **p Value is statistically significant.**

My findings are supported by **Mario Rotondi,** he reported that lipid deposition occurs along with increase in TSH levels. Free thyroid hormone controls TSH secretion from pituitary by negative feedback mechanism. This feedback mechanism fails in obesity [119].

6.5 Body mass index (BMI)

On analysing the present data, it is obvious that subclinical hypothyroid patients have significant increase in body mass index **(p value=0.000)**. p Value is statistically significant.

Gauravgupta study reported that increased weight gain is seen in subclinical hypothyroid patients and changes in basal metabolic rate and environmental factors leads to obesity by unknown biological mechanism [120].

Milionis A, Milionis C reported that environmental factors contribute to weight gain in Subclinical hypothyroid patients [121].

Controversy to my study was explained by **Kirti Sharma,** he reported that no difference in body mass index between the study and control group [107].

Zhang J study showed that increased chance of weight gain is seen in subclinical hypothyroidism Chinese adolescents[122].

6.6 Free T_3, Free T_4

No signifying difference between T_3, T_4 levels in control and study group**. (p Value=0.844, pValue=0.023).** p Value is statistically not significant for T_3, T_4 Subclinical hypothyroidism T_3, T_4 levels are normal.

6.7 Thyroid stimulating hormone

Thyroid stimulating hormone levels are elevated in subclinical hypothyroidism patients **(p Value =0.000). p Value is statistically significant**

My present study shows that 22 persons have TSH value of >10mIU/L. About 8persons have TSH value between5.1mIU/L and 10mIU/L.

Hamilton et al reported the upper reference limit for TSH is 4.1 mIU/L[123].

Vahab reported that follow up should be given if TSH value is 3-5mIU/L with positive antithyroid antibodies[124].

6.8 Thyroglobulin antibody

In the present study, the analysis revealed that there is an increase in Anti-Tg levels in subclinical hypothyroid patients.

Normal anti-Tg level is (**Harrison's**) <40IU/mL[125].

Hollowell,Surks MI et al reported that anti-thyroid antibodies levels are increased as age advances and is also associated with parallel increase in serum TSH levels. It is responsible for increased occurrence of acquired autoimmune thyroid disease [126,127].

6.9 Thyroid peroxidase antibody

My study shows that thyroid peroxidase antibody levels are increased in **(p Value=0.000)** subclinical hypothyroidism patients. **p Value is statistically significant**. The same finding was explained by following authors. **AnnemiekeRoos et al** reported that positive relationship exists between the TPO-Abs and TSH. Both of them predict the development of hypothyroid state

and“presence of TPOAbs necessitating a compensatory increase in levels of TSH for maintenance of euthyroidism, even in the euthyroid range” [128].

Normal range in humans for anti-TPO (**Harrison**) <35IU/mL[125].

Vanderpump MP reported that presence of anti-TPO in subclinical hypothyroidism has increased chance of getting overt hypothyroidism later in life.

Thomas cyric reported that about 68.9% of subclinical hypothyroidism patients had positive TPO-Abs.

Thomas cyric and Ghoraishian SM explained that positive correlation exists between TSH and TPO-Abs.

Zois andJaksi et al reported that all subclinical hypothyroid patients had positive anti-thyroid antibodies [129, 130].

Controversy to my study was explained by Zimmermann. He reported that no relation exists between subclinical hypothyroid patients and anti-thyroid antibodies [131].

6.11Lipid profile

The present study reveals that elevated levels of total cholesterol, low density lipoprotein and LDL/HDL ratio is seen subclinical hypothyroid patients. But triglycerides, HDL and TGL/HDL ratio are normal in my study.

My study was supported by **A. IQBAL et al**. He revealed that serum TSH levels and Total Cholesterol and LDL-C levels are positively correlated. Thyroxine reduces these lipids levels [132].

Azad reza et al reported that subclinical hypothyroidism was associated with dyslipedemia.

BeataAIneck et al reported that subclinical hypothyroidism has little effects on Triglycerides level and favours my study.

Miura et al reported similar findings like that of my study. They concluded that subclinical hypothyroidism associated with elevated levels of total cholesterol and LDL-cholesterol [3].

Ph. Caron et al report does not support my study. He revealed that total cholesterol, triglycerides and apolipoprotein levels are normal in subclinical hypothyroidism patients[133].

Kung et al reported that subclinical hypothyroidism patients had increased LDL- cholesterol and reduced HDL cholesterol [134].

BeataAIneck et al reported that subclinical hypothyroidism leads to pro-atherogenic lipid profile in patients with elevated TSH. Thyroxine treatment reduces the total cholesterol and low density lipoprotein but has no effects on triglycerides. Further studies needed to prove the effects on HDL and lipoprotein levels.

10. Brainstem evoked response audiometry-Earlier identification of neurological changes in subclinical hypothyroidism is done by using BERA.

Brainstem audiotory evoked potential evaluates the audiotory nerve, brainstem and subcortical structures by using audiotory stimulation.

It is a simple,non invasive method to detect the abnormalities in neuronal pathway of hearing from inner ear to auditory cortex.

Kirti Sharma et al reported that hearing loss is seen in hypothyroidism and studies reveal that prolongation of both central and peripheral conduction time in hypothyroidism. Conductive, sensorineural and mixed type of hearing loss is seen.

Sangeetagupta et al strongly suggests that abnormal BERA waves are seen in subclinical hypothyroidism. He reported that prolongation of both absolute latency of waves and IPLs (III-V and I-V).

Sangeetagupta et al reported that some studies did not show any alternation in BERA in subclinical hypothyroidism.

Ozata M et al study reported that Abnormal BAEPs in subclinical hypothyroidism have not been reported.

Sharma K et al reported that prolongation of wave V latencies is seen in subclinical hypothyroidism.

Figueiredo LC et al showed that prolongation of absolute latencies of waves III and V in the subclinical hyporhyroidism [135].

6.12. Interpretation of BERA waves

Wave I abnormality shows involvement of peripheral nervous system. Other waves reports that abnormal involvement of central nervous system.

a.Wave-I

Right ear p Value =0.968. p Value is statistically not significant.

Left ear p Value =0. 693. pValue is statistically not significant.

My study reveals that no significant change in absolute latency of wave-I between subclinical hypothyroidism patients and control group in both ears.

It shows that absence of peripheral hearing impairment in subclinical hypothyroid patients. **Kirit Sharma and Ozata et al** reported the similar findings i.e there is absence of changes in brainstem auditory evoked potential in subclinical hypothyroid patients.

Sangeetagupta et al study reveals controversy findings in subclinical hypothyroid patients and reported that prolongation of absolute latency of wave 1 in BERA.

b. Wave II

The Present study shows that no change in absolute latency of wave II between control and study group in both ears

Right ear p Value =0. 788. pValue is statistically not significant.

Left ear p Value =0. 379. pValue is statistically not significant.

c. Wave III

Absolute latency of wave III means onset of stimulus to peak of wave III. It is measured in milliseconds. It is normal in both ears.

Right ear p Value =0. 463. pValue is statistically not significant.

Left ear p Value =0. 532 .pValue is statistically not significant.

Kirit Sharma and Ozata et al reported the similar findings i. e there is absence of changes in brainstem auditory evoked potential in subclinical hypothyroid patients.

Sangeetagupta et al study reveals controversy findings to my study in subclinical hypothyroid patients and reported that prolongation of wave III in BERA.

Figueiredo LC et al concluded that prolongation of absolute latency of wave III in subclinical hypothyroid patients.

d.Wave IV

Right ear p Value =0. 815. pValue is statistically not significant.

Left ear p Value =0. 425. pValue is statistically not significant.

The Present study shows no significant changes in absolute latency of wave IV between control and study group in both ears.

e.Wave V

Right ear p Value =0. 040. pValue is statistically significant.

Left ear p Value =. 008. pValue is statistically significant.

The present study shows that prolongation of absolute latency of Wave V in subclinical hypothyroid patients in both ears which means onset of stimulus to peak of wave V.

Kirit Sharma et al reported the similar findings i.e there is prolongation absolute latency of wave V in brainstem auditory evoked potential in subclinical hypothyroid patients in both ears.

Figueiredo LC et al concluded that prolongation of absolute latency of wave Vin subclinical hypothyroid patients.

IPLI-III

Right ear p Value =0. 483. pValue is statistically not significant.

Left ear p Value =0. 810.pValue is statistically not significant.

Inter peak latencies I-III in the present study, reflects that there is no significant changes in both ears and conduction time between cochlea and caudal pons is normal.

Cristiane et al reported controversy findings to my study i.e increase in IPL I-III in subclinical hypothyroidism group in both ears.

Kirit Sharma and Ozata et al reported no specific changes in IPLI-III in both ears like my study.

f.Inter Peak Latency III-V

Right ear p Value =0. 155. pValue is statistically not significant.

Left ear p Value =0. 104. pValue is statistically not significant.

Inter peak latencies III -V in the present study is found to be normal in both ears.

Cristiane et al and **SangeetaguPta et al** reported controversy findings to my study i.e increase in IPL III-V in subclinical hypothyroidism group in both ears.

g. Inter Peak Latency I-V

Right ear p Value =0. 052. pValue is statistically not significant.

Left ear p Value =0. 060. pValue is statistically not significant.

Inter peak latencies I -V in the present study is found to be normal in both ears.

Cristiane et al, and SangeetaguPta et al reported controversy findings to my study i.e increase in IPL I-V in subclinical hypothyroidism group in both ears.

6.13 Correlation of variables

There was positive correlation between Anti-Tg and Anti-TPO in the both ear and negative correlation between total cholesterol and LDL values in both ears.

Wojeiech et al reported that positive correlation present between anti-thyroid peroxidase antibody levels in blood and changes in the central part of hearing organ[109].

Aysearduc demonstrated that thyroid autoimmunity is responsible for reduced hearing ability[111].

Ilhan reported that there is a correlation between increased levels of thyroid antibodies and BAEP parameter and it is related to autoimmue mediated mechanism[110].

LeventRenda reported that atoimmune antibodies produces changes in inner ear it leads to sensorineural hearing loss.

First time Lehnardt explained about antigen antibody reaction was seen sensorineural hearing loss.

Antibodies act against inner ear structure like spiral ligament, striavascularis and supporting cells. The following autoimmue mechanism is involved like intolerance, cross-reactions and genetic factors.

LeventRenda study reported that circulating antithyroid antibodies is a cause for hearing impairment[111].

My study shows that increased antibody levels produces changes in Brainstem evoked potential which is correlating with Wojeiech et al [109].

Conclusion

7. CONCLUSION

Functional integrity of the central nervous system and hearing status is evaluated in newly diagnosed subclinical hypothyroid patients by brainstem evoked response audiometry.

The central nervous system is affected in subclinical hypothyroidism. It is expressed by an increase in the latency of BERA wave V in both ears. Subclinical hypothyroidism leads to overt hypothyroidism. Early identification of thyroid hormone deficiency prevents further progression of disease and its related morbidity. Autoimmunity is the most probable factor for subclinical hypothyroidism. It is clearly shown by elevated levels of thyroid peroxidase antibody and thyrglobulin antibody. Elevated level of low density lipoprotein and total cholesterol is seen in patients with subclinical hypothyroidism.

Increased levels of antibody is the cause for changes in BERA, it leads to central nervous system dysfunction and hearing defects. It is clearly shown by positive correlation exists between thyroid antibodies BERA changes. Increased cholesterol may be a contributing factor. Thyroxine treatment may be given to prevent disease progression and hence central nervous system dysfunction and audiological dysfunction in earlier stages itself.

Limitations of the study

However, the study has got its own limitation and a larger sample size is needed to confirm the findings. Further research is needed to confirm the correlation between thyroid antibodies and other waves and the inter peak latency of BERA.

Summary

8. SUMMARY

Hypothyroidism is one of the important disorders of thyroid gland. Hearing defects are also common in hypothyroidism. Subclinical hypothyroidism is a clinical condition associated with elevated level of thyroid stimulating hormone with normal levels of thyroxine(T_4) and triiodothyronine(T_3) is present. Subcinical hypothyroidism becomes overt hypothyroidism. This study aimed to identify central nervous system dysfunction and hearing defects by using brainstem evoked response audiometry in subclinical hypothyroid patients.

30 newly diagnosed subclinical hypothyroid patients were selected, brainstem evoked response audiometry, thyroid peroxidase antibody and thyroglobulin antibody levels and lipid profile was done. All these procedure was done in control subject also.

My study shows that elevated level of thyroid peroxidase antibody and thyroglobuin antibody is present in patients with subclinical hypothyroidism. Also Low density lipoprotein and total cholesterol are increased in subclinical hypothyroidism patients. BERA results showed that V wave latency is increased in subclinical hypothyroidism patients.

BERA results showed that auditory pathway is affected in subclinical hypothyroidism due to defect in brain structure. Audiological impairment occurs along with central nervous system dysfunction.

Autoimmunity is a cause for subclinical hypothyroidism, because elevated levels of antibody is present. The pathophysiological cause for hearing defects in hypothyroidism is deterioration of oxygenation and metabolism in the organ of corti and striavascularis. It leads to changes in protein synthesis, enzymes action and myelin production. Hyperlipidemia also leads to hearing impairment.

Increased level of thyroid antibodies is responsible for changes in brainstem evoked potential.

By using simple non-invasive method (BERA) we can identify central nervous system dysfunction at earlier stages in subclinical Hypothyroidism.

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Annexures

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To
Dr.P.Senthamil pavai
Post Graduate in M.D.Physiology
Institute of Physiology and Experimental Medicine
Madras Medical College
Chennai 600 003

Dear Dr.P.Senthamil pavai,

The Institutional Ethics Committee has considered your request and approved your study titled **" EVALUATION OF EFFECT OF BRAINSTEM EVOKED RESPONSE AUDIOMETRY IN SUBCLINICAL HYPOTHYROID PATIENTS IN CORRELATION WITH THYROGLOBULIN ANTIBODY, THYROID PEROXIDASE ANTIBODY AND LIPID PROFILE" NO. 20062016.**

The following members of Ethics Committee were present in the meeting hold on **07.06.2016** conducted at Madras Medical College, Chennai 3

1.Dr.C.Rajendran, MD.,	:Chairperson
2.Dr.Isaac Christian Moses,MD.Ph.D.Dean(FAC)MMC,Ch-3	:Deputy Chairperson
3.Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	:MemberSecretary
4.Prof.B.Vasanthi,MD., Prof.of Pharmacology.,MMC,Ch-3	: Member
5.Prof.P.Raghumani,MS, Prof. of Surgery,RGGGH,Ch-3	: Member
6.Prof.Baby Vasumathi, Director, Inst. of O&G,Ch-8	: Member
7.Prof.K.Ramadevi,MD, Director,Inst.of Bio-Chem,MMC,Ch-3	: Member
8.Prof.M.Saraswathi,MD.,Director, Inst.of Path,MMC,Ch-3	: Member
9.Tmt.J.Rajalakshmi, JAO,MMC, Ch-3–	: Lay Person
10.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
11.Tmt.Arnold Saulina, MA.,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.

28/6/16

Member Secretary - Ethics Committee
MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

INFORMATION TO PARTICIPANTS

Investigator: Dr. P. Senthamil pavai

Name of Participant:

Title:"Evaluation of effect of brainstem evoked response audiometry in subclinical Hypothyroid patients in correlation with Thyroglobulin antibody, Thyroid peroxidase antibody and Lipid profile"

You are invited to take part in this research/ study /procedures. The information in this document is meant to help you decide whether or not to take part. Please feel free to ask if you have any queries or concerns.

You are being asked to participate in this study being conducted in Medical Endocrine clinic, Rajiv Gandhi Govt. General Hospital, Madras Medical College, Chennai – 3 and Institute of Physiology and Experimental Medicine, Madras Medical College, Chennai - 3.

What is the Purpose of the Research?

The purpose of this study is to evaluate the effectiveness of a BERA in early identification of hearing loss and CNS dysfunction in Subclinical Hypothyroidism patients by non-invasive method.

The Study Design -Case control study

The Study Procedures: Blood investigation for **Thyroglobulin antibody, Thyroid peroxidase antibody and Lipid profile"**and **BERA** to rule out hearing and CNS dysfunction.

Possible Risks to you - Nil

Possible benefits to you- Earlier identification of hearing and CNS dysfunction due to Subclinical hypothyroidism by non invasive method.

Possible benefits to other people:

The result of the research may provide benefits to the society in terms of advancement of medical knowledge and/or therapeutic benefits to future patients.

Confidentiality of the information obtained from you

You have the right to confidentiality regarding the privacy of your medical information (personal details, results of physical examinations, investigations, and your medical history). By signing this document, you will be allowing the research team investigators, other study personnel, sponsors, IEC and any person or agency required by law like the Drug Controller General of India to view your data, if required.

The information from this study, if published in scientific journals or presented at scientific meetings, will not reveal your identity.

How will your decision do not participate in the study affect you?
Your decisions of not participating in this research study will not affect your medical care or your relationship with investigator or the institution. Your doctor will still take care of you and you will not lose any benefits to which you are entitled.

Can you decide to stop participating in the study once you start?
The participation in this research is purely voluntary and you have the right to withdraw from this study at any time during course of the study without giving any reasons. However, it is advisable that you talk to the research team before stopping the treatment.

INFORMED CONSENT FORM

Title of the study : "Evaluation of effect of brainstem evoked response audiometry in subclinical Hypothyroid patients in correlation with Thyroglobulin antibody, Thyroid peroxidase antibody and Lipid profile

Name of the Participant:

Name of the Principal Investigator: Dr. P. SENTHAMIL PAVAI

Name of the Institution: Institute of Physiology and Experimental Medicine,
Rajiv Gandhi Government General Hospital
Madras Medical College,
Chennai – 3

Documentation of the informed consent

I, _____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising my free power of choice, hereby give my consent to be included as a participant in

"Evaluation of effect of brainstem evoked response audiometry in subclinical Hypothyroid patients in correlation with Thyroglobulin antibody, Thyroid peroxidase antibody and Lipid profile"

1. I have read and understood this consent form and the information provided to me.
2. I have had the consent document explained to me.
3. I have been explained about the nature of the study.
4. I have been explained about my rights and responsibilities by the investigator.
5. I have been informed the investigator of all the treatments I am taking or have taken in the past _____ months including any native (alternative) treatment.
6. I have been advised about the risks associated with my participation in this study.
7. I agree to cooperate with the investigator and I will inform him/her immediately if I suffer unusual symptoms.
8. I have not participated in any research study within the past _____month(s).
9. 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 future treatment in this hospital.

10. I am also aware that the investigator may terminate my participation in the study at any time, for any reason, without my consent.

12. I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regulatory authorities, Govt. agencies, and IEC. I understand that they are publicly presented.

13. I have understand, that my identity will be kept confidential if my data are publicly presented.

14. I have had my questions answered to my satisfaction.

15. I have decided to be in the research study.

I am aware that if I have any question during this study, I should contact the investigator. 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.

For adult participants:

Name and signature / thumb impression of the participant (or legal representative if participant incompetent)

Name _____ Signature_____ Date_____

Name and Signature of impartial witness (required for illiterate patients):

Name _____ Signature_____ Date_____

Address and contact number of the impartial witness:

Name and Signature of the investigator or his representative obtaining consent:

Name _____ Signature_____ Date_____

ஆராய்ச்சி தகவல் படிவம்

ஆராய்ச்சி தலைப்பு : குணக்குறி தோன்றா தைராய்டு சுரப்பு குறைபாடு உள்ள நோயாளிகளின் செவித்திறனை மூளைத்தண்டு மீதூர்ந்து பதில் கேட்பளக்கும் (BERA) கருவியை கொண்டு ஆய்வு செய்தல்.

ஆராய்ச்சி நடக்கும் இடம் : சென்னை மருத்துவக் கல்லூரி

பெயர் :

வயது :

பாலினம் : ஆண் / பெண்

முகவரி :

பங்கு பெறுபவர் அடையாள எண் :

இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கமும் முழுமையாக எனக்கு தெரிவாக விளக்கப்பட்டது.

எனக்கு விளக்கப்பட்ட விஷயங்களை புரிந்து கொண்டு நான் எனது சம்மதத்தை தெரிவிக்கிறேன்.

இந்த ஆராய்ச்சியில் யாருடைய நிர்பந்தமுமின்றி சொந்த விருப்பத்தின் பேரில் சம்மதிக்கிறேன்.

குண்க்குறி தோன்றா தைராய்டு சுரப்பு குறைபாடு உள்ள நோயாளிகளின் செவிதிறனை மூளைத்தண்டு மீதூர்ந்து பதில் கேட்பளக்கும் குருவியை கொண்டு ஆய்வு செய்வதன் ஆராய்ச்சி விவரங்கள் கொண்ட தகவல்களை பெற்றுகொண்டேன்.

இரத்த பரிசோதனைகள் (Anti-TPO, Anti – TG Elipid profile) செய்து கொள்ளவும் சம்மதிக்கிறேன்.

நான் என்னுடைய சுய நினைவுடன் மற்றும் முழு சம்மத்துடன் ஆராய்ச்சிக்கு என்னை பரிசோதிக்க சம்மதிக்கிறேன்.

பங்கேற்பாளர் கையொப்பம்

நாள் :
இடம் :

நோயாளி ஒப்புதல் படிவம்

ஆராய்ச்சியின் விவரம்

ஆராய்ச்சி மையம்

நோயாளியின் பெயர் **நோயாளியின் வயது**

பதிவு எண்.

நோயாளி கீழ்கண்டவற்றுள் கட்டங்களை (√) செய்யவும்

1. மேற்குறிப்பிட்டுள்ள ஆராய்ச்சியின் நோக்கத்தையும் பயணையும் முழுவதுமாக புரிந்துகொண்டேன். மேலும் எனது அனைத்து சந்தேகங்களையும் கேட்டு அதற்கான விளக்கங்களையும் தெளிவுபடுத்திக் கொண்டேன்.

2. இந்த ஆராய்ச்சிற்கு எனது சொந்த விருப்பத்தின் பேரில் பங்கேற்கின்றேன் என்றும், மேலும் எந்த நேரத்திலும் எவ்வித முன்னறிவிப்புமின்றி இந்த ஆராய்ச்சியிலிருந்து விலக முழுமையான உரிமை உள்ளதையும், இதற்கு எவ்வித சட்ட பிணைப்பும் இல்லை என்பதையும் அறிவேன்.

3. ஆராய்ச்சியாளரோ, ஆராய்சி உதவியாளரோ, ஆராய்ச்சி உபயத்தாரோ, ஆராய்ச்சி பேராசிரியரோ, ஒழுங்குநெறி செயற்குழு உறுப்பினர்களோ எப்போது வேண்டுமானாலும் எனது மனுமதியின்றி எனது உள்நோயாளி பதிவுகளை இந்த ஆராய்ச்சிக்காகவோ அல்லது எதிர்கால பிற ஆராய்சிகளுக்காகவோ பயன்படுத்திக் கொள்ளலாம் என்றும், மேலும் இந்த நிபந்தனை நான் இவ்வாராய்ச்சியிலிருந்து விலகினாலும் தகும் என்றும் ஒப்புக்கொள்கிறேன். ஆயினும் எனது அடையாளம் சம்பந்தப்பட்ட எந்த பதிவுகளும் (சட்டபூர்வமாக தேவைகள் தவிர) வெளியிடப்படமாட்டாது என்ற உறுதி மொழியின் பெயரில் இந்த ஆராய்ச்சியிலிருந்து கிடைக்கப்பொறும் முடிவுகளை வெளியிட மறுப்பு தெரிவிக்கமாட்டேன் என்று உறுதியளிக்கின்றேன்.

4. இந்த ஆராய்ச்சிக்கு நான் முழுமனதுடன் சம்மதிக்கின்றேன் என்றும் மேலும் ஆராய்ச்சிக் குழுவினர் எனக்கு அளிக்கும் அறிவுரைகளை தவறாது பின்பற்றுவேன். என்றும் இந்த ஆராய்ச்சிகாலம் முழுவதும் எனது உடல் நிலையில் ஏதேனும் மாற்றமோ அல்லது எதிர்பாராத பாதகமான விளைவோ ஏற்படுமாயின் உடனடியாக ஆராய்ச்சி குழுவினரை அணுகுவேன் என்றும் உறுதியிளிக்கின்றேன்.

5. இந்த ஆராய்ச்சிக்குத் தேவைப்படும் அனைத்து மருத்துவப் பரிசோதனைகளுக்கும் ஒத்துழைப்பு தருவேன் என்று உறுதியளிக்கின்றேன்.

6. இந்த ஆராய்ச்சிக்கு யாருடைய வற்புறுத்தலுமின்றி எனது சொந்த விருப்பத்தின் பேரிலும் சுயஅறிவுடனும் முழுமனதுடனும் சம்பத்திக்கின்றேன் என்று இதன் மூலம் ஒப்புக்கொள்கிறேன்.

நோயாளியின் கையொப்பம் / பெருவிரல் கைரேகை

இடம் : தேதி : ஆராய்ச்சியாளரின் கையொப்பம்

PROFORMA

Name:

Age/ Sex:

Address:

OP No.:

Occupation:

Duration of any non specific symptoms

History of associated illness:

a. Hypertension
b. Ischemic heart disease
c. Bronchial asthma
d. Renal diseases

Investigations:

EXAMINATION

General examination:

Temperature:

Pulse rate:

Blood pressure:

Examination of Thyroid:

Systemic examination:

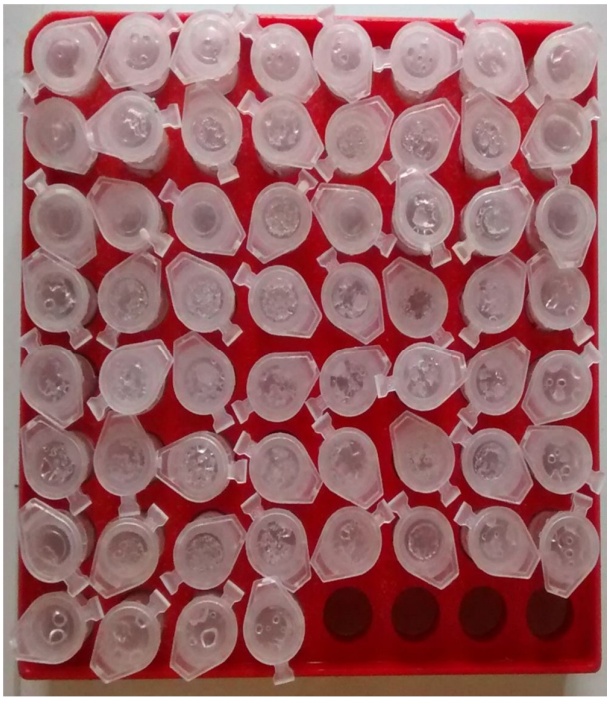
Cardiovascular system:

Respiratory system:

Gastrointestinal system:

Central nervous system:

1. Serum Samples



2.Anti-Tg and Anti-TPO

3. ElectroChemiluminescence immunoassay

4. Recordings of brainstem evokedresponse audiometry

CONTROL GROUP- THYROID PROFILE, ANTIBODY LEVELS & LIPID PROFIE																	
S.NO	AGE	SEX	HT (m)	WT (kg)	BMI	T_3	T_4	TSH	ANTI-Tg	ANTI-TPO	Total Cholesterol	HDL	TGL	VLDL	LDL	LDL/HDL	TGL/HDL
						(pmol/L)	(ngm/dl)	(µIU/ml)	(IU/ml)	(IU/ml)	(mg/dl)	(mg/dl)	mg/dl	mg/dl	mg/dl		
1	52	F	1.5	63	28	4.2	0.94	3	10.92	26.35	158	55	140	28	75	1	3
2	43	F	1.72	68	23	3.2	0.96	4	10.45	47.04	184	58	140	28	98	2	2
3	44	F	1.7	68	24	3.4	1.1	3.4	14.38	22.69	165	40	135	27	98	2	3
4	60	F	1.52	63	27	5	1	4.2	15.33	84.51	185	55	150	30	100	2	3
5	48	F	1.74	70	23	4.8	1.4	4.1	15.58	600	198	50	140	28	120	2	3
6	55	F	1.68	60	21	6	1.6	3.2	10	12.57	183	56	150	30	97	2	3
7	53	F	1.88	76	22	5.9	1	4.2	13.55	28.2	178	55	125	25	98	2	2
8	49	F	1.76	72	23	5.4	1.6	3.7	50	293.3	178	54	140	28	96	2	3
9	44	F	1.74	70	23	4.2	1	3	112.3	55	148	56	150	30	62	1	3
10	26	F	1.65	60	22	4.4	0.99	4	10	13.39	188	60	150	30	98	2	3
11	34	F	1.45	42	20	4	1.1	2.8	10.59	16.85	146	40	145	29	77	2	4
12	48	F	1.47	50	23	3	1.2	3.1	119.5	47.26	170	54	150	30	86	2	3
13	33	F	1.5	55	24	5.6	1.4	3	10	13.35	175	50	150	30	95	2	3
14	36	F	1.48	40	18	5.4	1.7	2.9	10	8.43	178	56	145	29	93	2	3
15	39	F	1.59	50	20	3.2	1.7	4	10	9.62	170	54	130	26	90	2	2
16	40	F	1.78	64	20	3.4	1	4.2	10	115.1	168	40	140	28	100	3	4
17	43	F	1.54	54	23	4	1.5	3.8	10	12.12	230	56	150	30	144	3	3
18	45	F	1.74	66	22	4.6	1	3.6	13.47	12.78	174	58	120	24	92	2	2
19	29	F	1.4	55	28	4.6	0.96	3.7	10	16.57	200	50	150	30	120	2	3
20	30	F	1.75	62	20	5.2	1.3	4.1	10	13.11	198	56	150	30	112	2	3
21	33	F	1.77	68	22	4	0.97	4.2	55	10.7	162	60	150	30	72	1	3
22	32	F	1.62	60	23	3.4	1.2	3.4	43.42	24.08	180	56	150	30	94	2	3
23	32	F	1.68	68	24	6	1.5	3.3	55	45	186	76	140	28	82	1	2
24	55	F	1.55	50	21	5.4	1.4	4	104.9	24.3	170	42	150	30	98	2	4
25	56	F	1.65	43	16	6	1	3	10	15.73	145	50	140	28	67	1	3
26	32	F	1.58	51	20	3.6	1	2.8	11.46	13.35	148	40	150	30	78	2	4
27	45	F	1.57	50	20	4.6	1.6	3.6	18.9	29.45	160	58	145	29	73	1	3
28	43	M	1.65	48	18	4	1.3	3.2	10	14.76	160	50	150	30	80	2	3
29	26	M	1.74	69	23	4.4	1.2	3.3	13.04	16.51	178	50	150	30	98	2	3
30	40	M	1.77	73	23	5	1.2	3	82.23	24.94	178	52	135	27	99	2	3

SUBCLINIAL HYPOTHYROIDISM - THYROID PROFILE,ANTIBODY LEVELS &LIPID PROFILE																	
S.NO	AGE	SEX	HT(m)	WT(kg)	BMI	T_3	T_4	TSH	ANTI-Tg	ANTI-TPO	Total cholesterol	HDL	TGL	VLDL	LDL	LDL/HDL	TGL/HDL
						pmol/l	ngm/dl	(µIU/ml)	(IU/ml)	(IU/ml)	mg/dl	mgm/dl	mg/dl	mg/dl	mg/dl		
1	41	F	1.58	68	27	4.9	1.2	5.8	11.57	17.16	212	20	164	33	159	8	8
2	52	F	1.56	63	26	4.6	1.2	17.9	120.2	11.12	204	53	103	21	130	2	2
3	55	F	1.54	68	29	4.56	1.11	9.13	10	155	217	57	118	24	136	2	2
4	46	F	1.49	58	26	2.3	1.4	15	396.5	250.1	249	34	314	63	152	4	9
5	27	F	1.7	80	28	5.3	1.1	17	400	600	156	42	93	19	95	2	2
6	20	F	1.58	54	22	4.3	1.1	12.8	170.3	593	208	47	221	44	117	2	5
7	30	F	1.58	68	27	2.49	0.98	16.98	190	243.2	148	43	116	23	82	2	3
8	22	F	1.62	64	24	5.4	1.2	6.6	102.6	668	154	62	85	17	75	1	1
9	45	F	1.35	50	27	4	1.4	22.47	400	322	155	40	70	14	101	3	2
10	43	F	1.68	79	28	4	1.4	10.49	145	14.2	136	46	106	21	69	1	2
11	40	F	1.5	92	41	5.3	1.1	6.4	185.7	600	266	50	102	20	196	4	2
12	36	F	1.78	73	23	4.8	1	13.4	69.2	600	210	13	124	25	172	13	10
13	44	F	1.75	76	25	4.4	1.2	26.8	400	8.99	212	91	250	50	71	1	3
14	43	F	1.6	54	21	4.6	1.2	14.31	221.7	372.7	124	28	169	34	62	2	6
15	27	F	1.56	78	32	4.6	1	11	10	7.9	134	37	110	22	75	2	3
16	32	F	1.48	75	34	5.3	1	16.8	19	81.53	255	44	102	20	191	4	2
17	47	F	1.58	68	27	4.4	1	7.57	120.2	138.2	221	48	405	81	92	2	8
18	55	F	1.58	63	25	5	1.1	12	432.5	600	215	59	135	27	129	2	2
19	27	F	1.7	88	30	4.7	1	16.4	123	600	220	46	171	34	140	3	4
20	24	F	1.64	68	25	4	1	14.88	401.1	421.7	161	42	123	25	94	2	3
21	28	F	1.62	70	27	4.4	1.2	15.12	319.6	23.3	221	64	156	31	126	2	2
22	24	F	1.62	58	22	5.5	0.9	13.2	92.36	250	226	36	183	37	153	4	5
23	27	F	1.68	69	24	4.4	1	6.34	150	596.5	273	34	330	66	173	5	10
24	31	F	1.36	58	31	4.5	1.2	16	57.89	309.6	258	47	171	34	177	4	4
25	24	F	1.78	80	25	5.3	0.98	17.6	10	115.3	230	64	100	20	146	2	2
26	20	F	1.58	68	27	5	1.1	17.7	467.7	600	142	51	73	15	76	1	1
27	36	F	1.58	83	33	3.05	0.98	7.63	257.7	230	165	58	122	24	83	1	2
28	42	M	1.48	68	31	4.7	0.98	5.7	61.83	600	156	44	93	19	93	2	2
29	29	M	1.6	70	27	4.8	1.1	10	123.4	61.32	250	64	78	16	170	3	1
30	44	M	1.68	78	28	4	1	12	10.1	600	260	47	94	19	194	4	2

BRAINSTEM EVOKED RESPONSE AUDIOMETRY -CONTROL GROUP																
	Right Ear								Left Ear							
S.NO	wave I	Wave II	Wave III	Wave IV	Wave V	IPL I-III	IPL III-V	IPL I-V	Wave I	Wave II	Wave III	Wave IV	Wave V	IPL I-III	IPL III-V	IPL I-V
1	1.63	2.84	3.65	4.8	5.61	2.02	1.96	3.98	1.53	2.83	3.85	4.87	5.6	2.32	1.75	4.07
2	1.67	2.89	3.81	4.8	5.72	2.14	1.91	4.05	1.55	2.8	3.68	4.86	5.9	2.13	2.22	4.35
3	1.68	2.78	3.86	4.88	5.73	2.18	1.87	4.05	1.6	2.81	3.62	4.81	5.8	2.02	2.18	4.2
4	1.76	2.68	3.94	4.89	5.56	2.18	1.62	3.8	1.51	2.91	3.9	4.88	5.6	2.39	1.7	4.09
5	1.66	2.79	3.87	4.76	5.79	2.21	1.92	4.13	1.52	2.67	3.55	4.79	5.54	2.03	1.99	4.02
6	1.59	2.68	3.97	4.9	5.73	2.38	1.76	4.14	1.55	2.78	3.56	4.68	5.6	2.01	2.04	4.05
7	1.62	2.83	3.64	4.67	5.6	2.02	1.96	3.98	1.57	2.77	3.5	4.97	5.59	1.93	2.09	4.02
8	1.7	2.78	3.67	4.68	5.55	1.97	1.88	3.85	1.7	2.89	3.44	4.69	5.9	1.74	2.46	4.2
9	1.94	2.78	3.67	4.9	5.53	1.73	1.86	3.59	1.64	2.68	3.79	4.8	5.57	2.15	1.78	3.93
10	1.65	2.67	3.4	4.88	5.65	1.75	2.25	4	1.88	2.71	3.9	4.78	5.55	2.02	1.65	3.67
11	1.64	2.69	3.68	4.79	5.7	2.04	2.02	4.06	1.77	2.69	3.98	4.45	5.6	2.21	1.62	3.83
12	1.65	2.78	3.65	4.9	5.6	2	1.95	3.95	1.54	2.9	3.98	4.99	5.8	2.44	1.82	4.26
13	1.66	2.8	3.5	4.9	5.6	1.84	2.1	3.94	1.78	2.55	3.55	4.6	5.7	1.77	2.15	3.92
14	1.65	2.75	3.4	4.9	5.61	1.75	2.21	3.96	1.55	2.42	3.8	4.97	5.7	2.25	1.9	4.15
15	1.68	2.77	3.77	4.75	6.2	2.09	2.43	4.52	1.99	2.83	3.69	4.55	5.54	1.7	1.85	3.55
16	1.6	2.63	3.6	4.8	5.6	2	2	4	1.4	2.55	3.5	4.5	5.6	2.1	2.1	4.2
17	1.7	2.67	3.73	4.73	5.6	2.03	1.87	3.9	1.87	2.85	3.9	4.8	5.54	2.03	1.64	3.67
18	1.63	2.68	3.64	4.86	5.62	2.01	1.98	3.99	1.88	2.73	3.79	4.69	5.67	1.91	1.88	3.79
19	1.62	2.78	3.6	4.9	5.77	1.98	2.17	4.15	1.57	2.74	3.7	4.99	5.5	2.13	1.8	3.93
20	1.77	2.9	3.7	4.88	5.3	1.93	1.6	3.53	1.46	2.5	3.34	4.3	5.6	1.88	2.26	4.14
21	1.64	2.85	3.4	4.76	5.6	1.76	2.2	3.96	1.48	2.47	3.6	4.88	5.68	2.12	2.08	4.2
22	1.65	2.7	3.5	4.97	5.67	1.85	2.17	4.02	1.8	2.7	3.75	4.75	5.7	1.95	1.95	3.9
23	2	2.7	3.76	4.97	5.7	1.76	1.94	3.7	1.98	2.99	3.7	4.88	5.6	1.72	1.9	3.62
24	1.68	2.7	3.73	4.74	5.6	2.05	1.87	3.92	1.43	2.99	3.99	4.99	5.58	2.56	1.59	4.15
25	1.59	2.8	3.55	4.89	5.59	1.96	2.04	4	1.42	2.42	3.44	4.44	5.69	2.02	2.25	4.27
26	1.61	2.7	3.79	4.88	6.1	2.18	2.31	4.49	1.65	2.9	3.3	4.3	5.6	1.65	2.3	3.95
27	2	2.75	3.65	4.68	5.62	1.65	1.97	3.62	1.8	2.75	3.9	4.77	5.21	2.1	1.31	3.41
28	1.78	2.68	3.65	4.68	5.63	1.87	1.98	3.85	1.7	2.3	3.88	4.41	5.55	2.18	1.67	3.85
29	1.6	2.76	3.73	4.94	5.8	2.13	2.07	4.2	1.9	2.65	3.89	4.88	5.54	1.99	1.65	3.64
30	1.67	2.78	3.55	4.88	5.8	1.88	2.25	4.13	1.53	2.63	3.88	4.99	5.7	2.35	1.82	4.17

BRAINSTEM EVOKED RESPONSE AUDIOMETRY -STUDY GROUP																
	Right Ear								Left Ear							
S.No	Wave I	Wave II	Wave III	Wave IV	Wave V	IPL I-III	IPL III-V	IPL I-V	Wave I	Wave II	Wave III	Wave IV	Wave V	IPL-I-III	IPL III-V	IPL I-V
1	1.75	2.65	3.45	4.9	5.35	1.7	1.9	3.6	1.88	2.99	3.58	4.55	5.9	1.7	2.32	4.02
2	1.74	2.67	3.84	4.7	5.88	2.1	2.04	4.14	1.89	2.68	3.8	4.99	5.2	1.91	1.4	3.31
3	1.78	2.69	3.89	4.89	5.89	2.11	2	4.11	1.87	2.55	3.8	4.8	5.9	1.93	2.1	4.03
4	1.66	2.77	3.72	4.71	5.9	2.06	2.18	4.24	1.6	2.44	3.41	4.4	5.8	1.81	2.39	4.2
5	1.87	2.8	3.71	4.91	5.91	1.84	2.2	4.04	1.48	2.48	3.4	4.3	5.8	1.92	2.4	4.32
6	1.79	2.7	3.86	4.92	5.93	2.07	2.07	4.14	1.5	2.5	3.5	4.56	5.9	2	2.4	4.4
7	1.7	2.8	3.7	4.99	5.98	2	2.28	4.28	1.3	2.98	3.6	4.96	5.8	2.3	2.2	4.5
8	1.65	2.77	3.74	4.9	6.2	2.09	2.46	4.55	1.78	2.96	3.99	4.87	5.78	2.21	1.79	4
9	1.65	2.78	3.55	4.8	5.88	1.9	2.33	4.23	1.7	2.9	3.98	4.97	5.86	2.28	1.88	4.16
10	1.7	2.77	3.65	4.9	5.9	1.95	2.25	4.2	1.9	2.93	3.96	4.99	6.3	2.06	2.34	4.4
11	1.76	2.78	3.88	4.79	5.91	2.12	2.03	4.15	1.89	2.91	3.96	4.8	5.89	2.07	1.93	4
12	1.7	2.8	3.5	4.9	5.92	1.8	2.42	4.22	1.87	2.93	3.6	4.7	5.3	1.73	1.7	3.43
13	1.7	2.82	3.87	4.87	6.2	2.17	2.33	4.5	1.85	2.94	3.89	4.68	5.89	2.04	2	4.04
14	1.68	2.77	3.76	4.85	5.95	2.08	2.19	4.27	1.89	2.93	4.1	4.98	5.8	2.21	1.7	3.91
15	1.74	2.77	3.76	4.75	5.2	2.02	1.44	3.46	1.3	2.95	3.97	4.55	5.77	2.67	1.8	4.47
16	1.65	2.65	3.33	4.8	5.3	1.68	1.97	3.65	1.65	2.88	3.55	4.5	5.2	1.9	1.65	3.55
17	1.68	2.79	3.85	4.79	5.7	2.17	1.85	4.02	1.88	2.89	3.6	4.5	5.9	1.72	2.3	4.02
18	1.69	2.78	3.65	4.8	5.7	1.96	2.05	4.01	1.68	2.55	3.88	4.78	6.12	2.2	2.24	4.44
19	1.66	2.78	3.58	4.91	6.1	1.92	2.52	4.44	1.99	2.58	3.92	4.99	5.88	1.93	1.96	3.89
20	1.78	2.77	3.99	4.9	5.89	2.21	1.9	4.11	1.55	2.5	3.76	4.98	5.78	2.21	2.02	4.23
21	1.63	2.71	3.78	4.78	5.4	2.15	1.62	3.77	1.44	2.79	3.55	4.99	6.3	2.11	2.75	4.86
22	1.55	2.8	3.5	4.76	6.3	1.95	2.8	4.75	1.5	2.75	3.99	4.97	5.9	2.49	1.91	4.4
23	1.65	2.8	3.75	4.74	5.8	2.1	2.05	4.15	1.45	2.78	3.83	4.99	5.6	2.38	1.77	4.15
24	1.6	2.88	3.71	4.89	5.86	2.11	2.15	4.26	1.68	2.56	3.4	4.4	5.6	1.72	2.2	3.92
25	1.54	2.77	3.87	4.8	5.2	2.33	1.33	3.66	1.67	2.74	3.83	5.1	5.9	2.16	2.07	4.23
26	1.7	2.75	3.79	4.76	5.8	2.09	2.01	4.1	1.4	2.4	3.2	4.99	5.92	1.8	2.72	4.52
27	1.67	2.76	3.78	4.96	5.91	2.11	2.13	4.24	1.54	2.8	3.75	4.5	5.34	2.21	1.59	3.8
28	1.77	2.75	3.6	4.8	5.8	1.83	2.2	4.03	1.8	2.88	3.88	4.9	6.2	2.08	2.32	4.4
29	1.73	2.65	3.3	4.8	6	1.57	2.7	4.27	1.33	2.89	3.8	4.99	5.2	2.47	1.4	3.87
30	1.52	2.74	3.6	4.84	5.3	2.08	1.7	3.78	1.88	2.6	3.9	4.96	5.95	2.02	2.05	4.07