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Effect of TSH Suppression Therapy on levels of TSH, T_4 and T_3

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Abstract

Objectives *– To find the effect Of TSH suppression therapy on levels of TSH, T_4 and T_3 in hypothyroidism.*

Methods *- The study comprised of 40 subjects, classified into 2 groups each, with 20 subjects. Group I – 20 (Healthy individuals) controls aged between 20 – 45 years with euthyroid status. Group II- 20 Hypothyroid subjects with suppressed levels of TSH aged between 20 to 45 years. The parameter like T3, T4, TSH measured.*

Results – *The mean value of TSH were 2.42±1.08 in controls and 0.15±0.00 in hypothyroid treated, the mean value of T_4 were 98.45±21.92 in controls and 139.65±37.90 in hypothyroid treated, the mean value of T_3 were 1.25±0.33 in controls and 1.36±0.48 in hypothyroid treated.*

Conclusion *- The Mean value of TSH is much less in subjects and is statistically significant. Serum T_4 and T_3 levels are higher in subjects compared to controls and serum T_3 changes are not significant. Serum T_4 changes are significant. As a result of treatment with L-thyroxine there is an high levels of serum T_4 and T_3.*

Key Words – TSH, T3, T4, Hypothyroidism, Thyroid.

INTRODUCTION

Thyroid disease is one of the most common endocrine problems managed by general physicians in the endocrinology out patient department. Hypothyroidism as a clinical syndrome was recognized even later than hyperthyroidism and at first its cause was equally obscure. First defined in London in the 1870s what we call hypothyroidism was named Myxedema because of swollen skin and its excess content of mucin. Common causes of Hypothyroidism are Iodine deficiency, Auto immunity like Atrophic Thyroiditis, Hashimoto's thyroiditis, Drug-Induced Hypothyroidism[1].

In hyperthyroid patients giving radioactive iodine therapy can eventually develop hypothyroidism. Spontaneous atrophic hypothyroidism, thyroid failure following or surgical treatment of hyperthyroidism and hypothyroidism of Hashimoto's thyroiditis account for over 90% of cases in those parts of the world which are not iodine deficient. The prevalence of primary hypothyroidism is 10/1000 but increases to 50/1000 if patients with sub-clinical hypothyroidism. It is more common in women (in the age between 20-45 years) than men. The ratio of female to male is approximately 6:1.The life time prevalence for an individual is higher perhaps as high as 9% for women and 1% for men with mean age at diagnosis around 60 years[2]. The common symptoms of hypothyroidism are tiredness, weight gain, cold intolerance, goiter, puffy eyes, dry coarse skin, muscle weakness, constipation, menorrhagia, psychosis, peri-orbital edema, slow relaxing reflexes, poor libido, poor memory etc. The diagnosis is based on signs and symptoms and is confirmed by measuring serum TSH,T_4 and T_3 levels by RIA techniques. Serum TSH concentration are usually in excess of 20mu/L in patients with primary hypothyroidism defined as high serum TSH and low T_4 concentration. The increase in TSH secretion in these patients is accompanied by hypertrophy and hyperplasia of the thyrotrophs which is sufficiently intense to cause enlargement of pituitary. Measuring of serum T_3 are not indicated in evaluating patients with hypothyroidism[3]

Hypothyroidism should be treated with levothyroxine, which is available as 25,50and 100µg tablets. It starts slowly and a dose of 50 µg per day and should be given for 3 weeks, increasing thereafter to 100 µg / day for a further 3 weeks and finally to 150 µg / day.[11] After initiation of therapy in patients with hypothyroidism. Serum TSH concentrations fall slowly as serum T_4 concentration rise. The correct does of thyroxin is that which restores serum TSH to normal. Patients taking thyroxin have a low serum TSH concentration and feel better than when the concentration is normal[3]. In hypothyroidism, lack of thyroid hormones results in reduced cardiac function and an increase of systemic vascular resistance. Hemodynamic regulation in subjects with subclinical hypothyroidism defined as mildly elevated thyrotropin [TSH] despite free thyroxin [T_4] and triiodothyronine [T_3] estimates within reference range would benefit from levothyroxine (LT_4) substitution[4].

The name 'thyroid' was introduced by Thomas warton in 1656. It is derived from the Greek thyreos ,a shield. The human thyroid gland begins to develop about 4 weeks after conception when the embryo is 3.5 to 4.0 mm long. During the first 10-12 wks fetal growth and development takes place without the need for thyroid hormones. After 12 weeks small amounts of thyroid hormones are formed, and from 20-22 wks fetal TSH secretion and Thyroid hormone secretion increase steadily till the end of pregnancy. Thyroid hormones are required particularly for normal foetal bone formation and for normal development of central nervous system. Thyroid tissue is present in all vertebrates. The normal adult thyroid is the largest endocrine gland weighing about 15-25 gms. In mammals

the thyroid originates from an evagination of the floor of the pharynx and a thyroglossal duct marking the path of the thyroid from the tongue to the neck & it sometimes persists in the adult. The two lobes of the human thyroid are connected by a bridge of tissue, the thyroid isthmus, and closely attached to the anterior and lateral aspects of the upper part of the trachea. The gland is well vascularized and the thyroid has one of the highest rates of blood flow per gram of tissue of any organ in the body. It is estimated about 4-6 ml/g/min excludes even with that of kidney.It has a large lymphatic drainage through which part of the stored large molecular thyroglobulin may enter the circulation. Thyroid is innervated by sympathetic system which probably supplies only blood vessels[5]. The thyroid gland is covered by a fibrous capsule. Septa extending into the gland from capsule divide it into lobules. Light microscopy shows the gland to consist of about three million spherical follicles which vary in diameter from 50 to 500 µm.Some 40 follicles are grouped together to form a lobule. The wall of each follicle is lined by a cuboidal epithelium whose height varies with the degree of glandular stimulation. When inactive the cells are flat/squamous and the follicles are distended with abundant colloid. When cells are highly active they become columnar and colloid is scanty & the edge of colloid different follicles is scalloped forming many small reabsorption lacunae may show differing levels of activity[6]. Each follicle contains a clear viscid proteinaceous amber colored colloid which normally comprises the greater part of thyroid mass. The colloid consists mainly of thyroglobulin. The thyroid is peculiar among endocrine glands in that its product is not stored intracellular but is secreted through the apex of the follicular cell for extracellular storage in the follicular lumen. Electron microscopy shows that the cells have cytological features of protein secreting cells combined with structures concerned with absorption of colloid and the release of thyroid hormones from thyroglobulin.The apical end of follicular cell shows numerous microvilli projecting into the colloid and canaliculi extend into them. There is a prominent endoplasmic reticulum, a feature common to most glandular cells, and a prominent supranucelar golgi complex. Lysosomes, microtubules & microfilaments are also present[7]. Secretory droplets of thyroglobulin are seen at the apical part of the cell. The individual thyroid cells rest on the basal lamina that separate them from the adjacent capillaries. The capillaries are fenestrated, like those of other endocrine glands. Between the follicles there are parafollicular or 'C' cells which originate in neural crest and then migrate to ultimobranchial bodies which fuse with the thyroid in mammals. The follicular cells secrete the iodine containing compounds L-Thyroxine (T_4) and L-Triiodo thyronine (T_3) these are thyroid hormones[5].

Formation & secretion of thyroid hormones:

- Thyroid hormones are unique in that they incorporated an inorganic element, iodine, into an organic structure made up of two molecules of the amino acid tyrosine.
- The secretory products of thyroid gland are known as iodothyronines.
- The major product is 3,5,3^1,5^{1-} tetraiodothyronine, known as thyroxine & referred to as T_4. This molecule functions largely as a circulating prohormone.
- Secreted in much less quantity is 3,5, 3^{1-} tri iodo thyronine known simply as triiodothyronine & referred as T_3
- T_3 is more active than T_4.
- A trivial secretory product with no identified hormonal action is 3, 3^1, 5^1 triiodothyronine, known as reverse T_3 (r T_3) because it differs from T_3 only in the location of one of the three iodine atoms. This is an alternative product of the prohormone T_4 and is produced when less thyroid hormone action is needed[8].

Thyroid Hormone Synthesis:

- Synthesis of T_4 and T_3 by the thyroid gland involves six major steps
- Active Transport of I^- across the basement membrane into the thyroid cell (Trapping)
- Oxidation of iodide and iodination of tyrosyl residues in thyroglobulin (Organification)
- Linking pairs of iodotyrosine molecules within thyroglobulin to form the iodothyronines T_3 and T_4 (Coupling)
- Proteolysis of thyroglobulin, with release of free iodothyronines & iodotyrosines into the circulation.
- Deiodination of iodotyrosines within the thyroid cell, with conservation and reuse of the liberated iodide.
- Intrathyroidal 5^1 – deiodination of T_4 to T_3. Thyroid hormone synthesis requires sodium I symport, thyroglobulin & the enzyme thyroid peroxidase[9].

Thyroid hormone homeostasis is meticulously controlled by the hypothalamus and pituitary. TRH is synthesized by the medial basal hypothalamus and secreted into the hypophyseal portal system from where it travels to the anterior pituitary to bind to receptors on thyrotropic cells, stimulating both synthesis and release of thyroid stimulating hormone (TSH). TSH acts to stimulate the thyroid cells and to increase the synthesis and release of T_4 & T_3. These hormones in turn, feed back on the pituitary thyrotroph, where T_4 is converted to T_3 and intracellularly acts to suppress synthesis of TSH. Dopamine & somatostatin also act on pituitary to inhibit the release of TSH[10]. Thyroid autoregulation may be defined as the capacity of the thyroid gland to modify its function to adapt to changes in the availability of iodine, independent of pituitary TSH.Humans can maintain normal thyroid hormone secretion with iodide intake varying from 50ug to several milligrams per day. The Major adaptation to low iodide intake is the preferential synthesis of T_3 rather than T_4, increasing the metabolic effectiveness of secreted hormone. Iodide excess, inhibits iodide transport, CAMP formation, peroxide generation, hormone synthesis & secretion. The ability of the normal thyroid to "escape" from these inhibitory effects (Wolff-chaikoff effect) allows the gland to continue to secrete hormone despite a high

dietary iodide intake. It is different from therapeutic effect of iodide in treatment of Grave's disease. Here, the high levels of iodide persistently inhibit thyroglobulin endocytosis & lysosomal activity, decreasing thyroid hormone release & lowering circulating hormone levels[9]. Most cells of the body are targets for the action of thyroid hormones. The sensitivity or responsiveness of a particular cell to thyroid hormones correlates to some degree with the number of receptors for these hormones. Thyroid hormone receptors (TR) are located in the nuclei of target cells bound to thyroid hormone response elements (TRE) in the DNA. TR's are protein molecules of about 50K Da that are structurally similar to the nuclear receptors for steroid hormones and vitamin D. The free forms of T_3 & T_4 are taken up by target cells from the blood through a carrier mediated process that requires ATP. Once inside the cell, T_4 is deiodinated to T_3 which enters the nucleus of the cell and binds to its receptor in the chromatin. There are two human TR genes; an α receptor gene on chromosome 17 and a β receptor gene on chromosome 3. By alternative splicing, each forms at least two different mRNA'S and therefore two different receptor proteins. TR's bind to DNA as monomers, homodimers and heterodimers with other nuclear receptors, particularly the retinoid x receptor (RxR). This activates transcription, as a result the production of m-RNA for certain proteins is either increased or decreased, changing the cell's capacity to make these proteins. There are also coactivator and corepressor proteins that affect the actions of the TR's. In most of its actions, T_3 acts more rapidly and is three to five times more potent than T_4. This is because it is less tightly bound to plasma proteins but binds more avidly to thyroid hormone receptors. RT_3 is inert[11].

Growth in human beings is intimately intermingled with, the development. The thyroid hormones affect the physical, mental & sexual growth. The most spectacular example is the process of metamorphosis in non human vertebrates. Endogenous thyroid hormone levels are very low in amphibians, until just before the major stage of metamorphosis. At this point, the hormone levels increase sharply and parallel the rapid change from the larval to adult form, after which the levels again decline. Thyroid hormone accelerates all aspects of tadpole metamorphosis, including limb growth, tail resorption, shortening of gastro intestinal tract and induction of hepatic ureagenesis. Thyroid hormone is essential for development of central nervous system & must be present in adequate amount at the time of birth & during the first year. In its absence, irreversible mental retardation occurs. Myelination is also delayed. The frequency of α waves in electro encephalogram is increased in hyperthyroidism and decreased in hypothyroidism. TH's also maintain a normal reaction time of the jerks. Thyroid hormones increase the activities of the heart as a whole due to increased responsiveness to catecholamines. This is due to increased number of β – adrenergic receptors. It leads to positive inotropic, chronotropic, bathmotropic & dromotropic effects. It increases the production of myosin with a high ATPase activity in both cardiac & skeletal muscle. The thyroid hormones increase the resting respiratory rate, minute ventilation and the ventilatory responses to hypercapnia and hypoxia. These actions maintain a normal arterial PO_2 when O_2 utilisation is increased, and a normal PCO_2 when CO_2 production is increased. Red cell mass increases slightly and thereby enhances the oxygen carrying capacity. Thyroid hormones affect the expression of the MHC genes in skeletal as well as cardiac muscle. Muscle weakness occurs in most patients with hyperthyroidism (Thyrotoxic myopathy) and when it is severe & prolonged, the myopathy may be severe & this is due to increased protein catabolism. Hypothyroidism is also associated with muscle weakness, cramps & stiffness. Optimal amount of thyroxine is necessary for normal gonadal function. Thyroid gland is larger at puberty & in pregnant women. In hyperthyroidism there is an increased appetite, increased motility of gut and diarrhoea. In hypothyroidism there is a decreased appetite & constipation also[12]. Diseases of the thyroid are manifested by qualitative or quantitative alterations in hormone secretion, enlargement of the thyroid or both. Insufficient hormone secretion results in hypothyroidism or myxedema, in which decreased caloric expenditure is a principal feature. Conversely excessive secretion of hormones results in hypermetabolism & other features, together termed hyperthyroidism or thyrotoxicosis. Enlargement of thyroid gland is called goiter. Goiters may be associated with increased, normal or decreased hormone secretion. Any goiter may compress adjacent structures in the neck or mediastinum.

According to Leese G.P.,et al Serum T_4 and TSH assays, clinical assessment scores, and admission records with regard to ischemic heart disease, overall fractures, fractured neck of femur and breast carcinoma. Over one year, 1180 patients on thyroxine replacement had clinical and biochemical assessment, 59% had a suppressed TSH and 38% normal TSH. Patients with a suppressed TSH exhibited higher median serum thyroxine levels (146 nmol./L, range 77-252 vs 119 nmol/L,58-224; $P<0.001$).Patients under the age of 65 yrs on L-thyroxine had an increased risk of ischaemic heart disease compared to the general population[female 27 vs 0.7%,p,0.001;male 64 vs 17%,p,001], but the risk was no different between those with suppressed and normal TSH. There was no increase in risk for overall fracture, fractured neck of femur or breast carcinoma in those on thyroxine with suppressed or normal TSH. They concluded that patients under the age of 65 years on L-Thyroxine had an increased risk of ischaemic heart disease. There was no excess of fractures in patients on L-Thyroxine even if the TSH is suppressed[13].

According to Sijanovic S & Karner I the effects on bone metabolism of long-term treatment with thyroid hormone given at suppressive doses have been debated. Determined whether long term thyroxine therapy in the premenopausal period is a risk factor for the development of secondary osteoporosis and whether women receiving this therapy have increased bone loss during the premenopausal period. The study enrolled a select group of 19 premenopausal women of mean ages 39 +/- 8 years suffering from differentiated thyroid gland carcinoma. All subjects had undergone total thyroidectomy and subsequently initiated thyroxine suppressive therapy. At the begining of their

study, the women had been on suppressive therapy for 9.4 +/- 6.4 years. Laboratory results were performed to exclude other possible factors for secondary osteoporosis. This prospective study of bone mineral density was conducted over a 4–year period on all subjects using the method of dual photon X-ray absorptiometry of the spine and the femoral neck and also by the method of single – Photon absorptiometry of distal radius. At the beginning of this study, 2 subjects had osteopenia in the spine and 2 had osteopenia in the femoral neck; they had been on suppressive thyroxine therapy for 10 years. Osteopenia in the distal radius was found in 4 subjects. Overall, 8 of the 19 women had osteopenia at the beginning of the study. One year later, after the second BMD measurements, no statistically significant loss of bone mass occurred in any region of the skeleton in any of the patients. However, a review of the individual scores revealed osteopenia in 6 patients at the distal radius; bone loss also occurred at the spine and the femoral neck in several women, but not to the extent that would establish osteopenia. After the 4 years, BMD measurements indicated significant bone loss. Concluded that women who begin long term(~10years) thyroxine therapy in the premenopausal period can develop osteopenia by the beginning of menopause[14]. The main aim of study is to estimate the levels of serum TSH, T_4 and T_3 by radioimmuno assay for diagnosing hypothyroidism.

MATERIALS AND METHODS

The present study is carried out in Department of Endocrinology of Sri Venkateswara Institute of medical sciences, Tirupathi. The study comprised of 40 subjects, classified into 2 groups each, with 20 subjects, Group I is composed with 20 healthy individuals considered as controls aged between 20 – 45 years and Group II composed with 20 Hypothyroid subjects. The Hypothyroidism with suppressed levels of TSH is diagnosed by endocrinologist on the basis of clinical history, clinical examination and biochemical levels of T_3, T_4, TSH. Data of these patients is compared with age matched controls. Results were statistically analyzed by applying student 'T' test.

Assessments:-Assessment of T_3, T_4, TSH in serum:

Sample collection and preparation:-

5 ml of blood is collected with out anticoagulant in a glass vial or in a test tube. The blood is allowed to clot at room temperature. Rim the clot, centrifuge and the serum is collected. Store at 2^0c to 8^0c for assay on the same day or -20^0c if the storage is expected to be more than a day. The sample is allowed to thaw prior to assay, mix thoroughly met erogeneity of serum has been shown to result in misleading assay values. Haemolysed and lipemic samples should be avoided.

Estimation of T_3:

Intended use :- RIAK-4/4 A kit is to be used for the quantitative measurement of T_3 in human serum by RIA unlabelled endogenoust T_3 competes with Radiolabel led T_3 for the limited binding sites on the antibody made specifically for T_3. The antibody is in the form of complex with second antibody. At the end of incubation, the T_3 (Ag) bound to antibody second antibody complex and free T3 are separated by the addition of polyethylene glycol. The amount bound to the antibody complex in the assay tube is compared with values of known T_3 standards and the T_3 concentration in the patient sample can be calculated. 8 anillinol – naphthalene sulphoinic acid (ANS) is used in this kit for displacing T_3 bound to TBG. This test is performed with 50 ml of the serum volume and covers a sample range of 0-4.8 ng/ml.

RIAK – 4/4 A kit is stable until the stated expiry date when stored at 2^0c to 8^0c on receiving the kit. Aliquoted samples from a prepared pool are stable up to six months when stored below -20^0c. Do not refreeze samples for later used.

Estimation of T_4:-

RIAK – 5/5 A kit is to be used for the quantitative measurement of T_4 in human serum by RIA.

Principle :-

Unlabelled endogenous T_4 competes with radiolabel led T_4 for the limited binding sites on the antibody made specifically for T_4 at the end of the incubation the T_4 bound to antibody (Ag-Ab) and free T_4 are separated by the addition of poly ethylene glycol. The amount bound to the antibody in the assay tube is compared with values of known T_4 standards and the T_4 concentration in the patients sample can be calculated. 8–anilino – 1 – naphthalene sulphonic acid is used in this kit for displacing T_4 bound to TBG. This test is performed with 10 ml of the serum volume and covers a sample range of 0-200ng/ml.

Estimation of TSH:-

Intended use :- IRMAK-9, IRMA kit for h TSH, is specifically designed to quantitate human thyroid stimulating hormone (HTSH) in serum or plasma sample.

Principle:- In Immunoradiometric assay (IRMA) two antibodies generated against different portions of the same antigen are used. One antibody is bound to a solid phase, usually a tube, while the other antibody is labelled with 1-125. Thus when an antigen is present, it simultaneously binds both antibodies in a "bridge" or "Sand wich" fashion This entire complex remains bound to the tube. The radioactivity in the bound fraction may be quantitiated using a gamma counter. IRMAK – 9 kit enables the practice of such immuno radio metric assay technique to quantitate human thyroid stimulating hormone in serum sample.

RESULTS

The mean value of TSH were 2.42$\pm$1.08 in controls and 0.15$\pm$0.00 in hypothyroid treated, the mean value of T_4 were 98.45$\pm$21.92 in controls and 139.65$\pm$37.90 in hypothyroid treated, , the mean value of T_3 were 1.25$\pm$0.33 in controls and 1.36$\pm$0.48 in hypothyroid treated (Table 1).

Table 1. Comparison of TSH, T_4 and T_3 levels of serum in controls and subjects.

	Controls		Subjects		't'	'P'
	Mean	SD	Mean	SD		
TSH	2.42	1.08	0.15	0.00	9.39	<0.001
T_4	98.45	21.92	139.65	37.90	4.20	<0.001
T_3	1.25	0.33	1.36	0.48	0.84	0.40

DISCUSSION

The present study is to find out the effect of TSH suppression therapy on TSH, T_4 and T_3 levels in hypothyroidism. Hypothyroidism is diagnosed on the basis of serum TSH, T_4 and T_3 levels which are estimated by Radio Immuno Assay Technology using IRMAK – 9, RIAK – 5/5 A, RIAK – 4/4 A Kits respectively. The clinical features of hypothyroidism are not appreciably observed in patients as all of them are on treatment for hypothyroidism . Almost all the selected patients are women in the age group of 20-45 years. In the selection of subjects, above 45 years of women are excluded because of menopausal changes and osteoporosis is common in that age due to decrease in estrogen levels.

Serum TSH, T_4 ,T_3 levels are compared between controls and subjects. Only TSH & T_4 are found to be significant, but not T_3 in this study. The negative feedback effect of thyroid hormones on TSH secretion may be exerted in part at the hypothalamic level, but it must be mainly on the pituitary, since T_4 and T_3 block the increase in TSH secretion produced by TRH. Infusion of T_4 as well as T_3 reduces TSH, and there is a measurable decline in the level of TSH within 1 hour. Similar results are found by Leese G.P. et al [13]. TSH levels are less than 0.15 suggesting TSH suppression therapy.

The serum Cholesterol levels are compared between controls and hypothyroid subjects. The serum Cholesterol levels are higher in hypothyroid subjects but not significant statistically because the subjects are under treatment. Thyroid hormones lower circulating cholesterol levels. The decrease in plasma cholesterol concentration is due to increased formation of LDL receptors in the liver, resulting in increased hepatic removal of cholesterol from the circulation. In hypothyroidism there is a decreased formation of LDL receptors, resulting in increased plasma cholesterol concentration[6].

In the present study there is random selection of patients who are on treatment with levothyroxine for 6 months / 2 years. All subjects are women aged between 20 to 45 years and are screened for thyroid function tests. The serum TSH levels are suppressed i.e., less than 0.15 in subjects when compared to normals. The serum T_4 and T_3 are increased in subjects compared to normals and in these only TSH and T_4 are found significant statistically but not T_3. These values indicate hypothyroidism with suppressed levels of TSH in subjects. The effect of TSH suppression therapy induces a risk of osteoporosis on bone. The patients on long term treatment of drugs like levothyroxine, inspite of treating hypothyroidism there is a loss of bone mineral density although not with a higher fracture rate due to suppression of TSH levels (<0.15).

Mosekilde L, et al studied effects of Thyroid hormones on bone and mineral metabolism, because of pronounced symptoms and early detection, severe hyperthyroidism is usually treated before skeletal symptoms are evident. However, previous hyperthyroidism may involve a risk of later postmenopausal or senile osteoporosis. since some of bone loss apparently is irreversible. Border line hyperthyroidism in clinically euthyroid patients may induce accelerated bone loss and there by increase the risk of low –energy fractures. From these considerations it appears that disturbed thyroid function may be involved in the pathogenesis of osteoporosis, one of the major health problems in western hemisphere[15].

Paul T.L. et al (1988) studied long term L-thyroxine therapy is associated with decreased hip bone density in premenopausal women. The effect of long term L-thyroxine (L-T_4) therapy on axial skeleton bone density was studied in 31 premenopausal women, the bone densities of these women were compared with the bone densities of 31 age and weight matched women without thyroid or bone abnormalities. The women receiving L-T_4 therapy had been receiving the medication for a minimum of five years. There was no difference in calcium intake or excretion between the L-T_4 treated women and the controls. Women receiving L-T_4 had increased serum thyroxine concentrations (134 +/-5 vs 95 +/-3 nmol/L, [10.4 +/-0.4 vs7.4 +/-0.2 µgms/dL]), an increased free thyroxine index (9.4+/-0.4 vs 6.8 +/- 0.2) and decreased serum TSH concentrations (0.9+/-0.2 mu/L vs 2.1+/-0.3mu/L [0.9 +/-0.2 vs 2.1 +/- 0.3 µu/ml]).Serum triodothyronine concentrations were normal and were similar in both groups. Women treated with L-T_4 had a 12.8% lower bone density at the femoral neck and a 10.1% lower bone density at the femoral trochanter compared with matched controls. In contrast, lumbar spine bone density was similar in two groups.The data suggested that long term L-T_4 therapy, which is often given at supraphysiologic dosages, may predispose patients to decreased bone density in the hip and may increase the risk of age – related bone loss. They employed a dosage of L-T_4 that is carefully monitored to avoid the long term use of dosages that are excessive for the thyroid condition being treated[16].

Susan L- et al(1999) studied the effect of thyroid hormone on skeletal Integrity , to review evidence on the effect of thyroid hormone on skeletal integrity. Cross sectional studies, longitudinal studies, and meta analyses that had appropriate control groups (Patients matched for age, sex and menopausal status) made comparisons with established data bases, or defined thyroid state by TSH level or thyroid hormone dose were reviewed. Observed from their studies, in premenopausal women, six cross sectional & two longitudinal studies have shown a negative effect on bone resulting from partial or complete TSH suppression; in post menopausal women, seven cross sectional studies & 3 longitudinal studies have demonstrated such an effect. Although a roughly equal number of studies has shown that TSH suppression has no effect on bone. Their interpretation of these studies suggested that physicians should assess bone mass in both premenopausal and post menopausal women who are not receiving hormone replacement therapy and have been receiving thyroid hormone replacement therapy with full TSH suppression. Thyroid hormone suppression of TSH for thyroid cancer, goiter or nodules seems to have on adverse effect on bone, and this effect seems to be greater in post menopausal women. It also seems to be greater in cortical than in trabecular bone. Thyroid hormone replacement therapy, resulting in normal serum TSH levels seems to have minimal or no effect on bone[17].

In this study serum calcium level is decreased in hypothyroid subjects. Serum ALP and phosphorus levels

are high in hypothyroid subjects though these are not significant statistically. The serum PTH is decreased & 25-OH Vit-D_3 is increased in hypothyroid subjects when compared to controls. Then values are not significant statistically. The similar results are found by Stall GM et al[18].

The major effect of PTH is to maintain normal ionized serum calcium concentration. PTH stimulates the bone resorption releasing calcium into ECF. When PTH is increased more calcium is reabsorbed in distal nephron whereas when PTH is decreased less calcium is reabsorbed and urinary calcium excretion rises. The reabsorption of phosphate which occurs in proximal tubule is controlled by PTH. PTH decreases proximal tubular reabsorption of phosphate so that increased urinary excretion of phosphate occurs. Sustained elevation in PTH thus results in hypophosphatemia in addition to hypocalcemia[19]. 25-OH Vit-D_3 increases intestinal phosphorus absorption by increasing the active transport of phosphorus. So, in this study, the PTH decreases the serum calcium along with increase in serum phosphorus of hypothyroid subjects. 25-OH Vit-D_3 also increases serum phosphorus.The serum ALP is the commonly used bone formation marker because there is a relationship between increases in serum ALP and increases in osteoblastic activity.25-OH Vit-D_3 increases ALP enzyme activity in osteoblast like cells. Mineral and hormonal changes described above may cause bone changes. Almost all hypothyroid patients of this study complain of knee joint pain and backache. This initiates further investigation of bone changes.

CONCLUSION

The Mean value of TSH is much less in subjects and is statistically significant. Serum T_4 and T_3 levels are higher in subjects compared to controls and serum T_3 changes are not significant. Serum T_4 changes are significant. As a result of treatment with L-thyroxine there is an high levels of serum T_4 and T_3

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