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A Study on Effects of TSH Suppression Therapy in Hypothyroidism

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Abstract

Background: Thyroid disease is one of the most common endocrine problems managed by general physicians in the endocrinology practice. Hypothyroidism as a clinical syndrome was recognized even later than hyperthyroidism and at first its cause was equally obscure. Common causes of Hypothyroidism are Iodine deficiency, Auto immunity like Atrophic Thyroiditis, Hashimoto's thyroiditis, Drug Induced 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, Ca^{+2}, Po_4^{-3}, ALP, PTH and 25-OH Vit- Dmeasured. *Results:* The mean value of TSH was 2.42±1.08 in controls and 0.15±0.00 was in hypothyroid treated, the mean value of T4 was 98.45±21.92 in controls and 139.65±37.90 was in hypothyroid treated, the mean value of T3 was 1.25±0.33 in controls and1.36±0.48 was in hypothyroid treated.The mean value of mean bone mineral area in lumbar spine, femur neck and radius & ulna were 47.53±3.80, 4.47±0.35 and 4.50±0.45 respectively. The mean value of bone mineral area in lumbar spine is less compared to controls. Themean values bone mineral density of lumbar spine, femur neck, and radius & ulna were 39.47+5.07, 3.23+0.54 and 2.89+0.43 respectively. *Conclusion:* The patients on long term treatment of drugs likelevothyroxine, in spite of treating hypothyroidism there is aloss of bone mineral density although not with a higherfracture rate due to suppression of TSH levels.

Keywords: TSH; T3; T4; Hypothyroidism; Thyroid; Bone Sensity.

Introduction

The name 'thyroid' was introduced by Thomas warton in1656. It is derived from the Greek thyreos, a shield. Thehuman thyroid gland begins to develop about 4 weeks afterconception when the embryo is 3.5 to 4.0 mm long. Duringthe first 10-12 weeks foetal growth and development takes place without the need for thyroid hormones. After 12weeks small amounts of thyroid hormones are formed and from 20-22 weeks foetal 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 ofcentral nervous system[1].

Hypothyroidism, also called underactive thyroid or low thyroid, is a common disorder of the endocrine system in which the thyroid gland does not produce enough thyroid hormone [3]. It can cause a number of symptoms, such as poor ability to tolerate cold, a feeling of tiredness, constipation, depression, and weight gain [2]. In hyperthyroid patients giving radioactive iodine therapy can eventually develop hypothyroidism.

Spontaneous atrophic hypothyroidism, thyroid failure following orsurgical treatment of hyperthyroidism and hypothyroidism of Hashimoto's thyroiditis account for over 90% of cases inthose parts of the world which are not iodine deficient. The prevalence of primary hypothyroidism is 10/1000 butincreases 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.The common symptoms of hypothyroidism are tiredness, weight gain, cold intolerance, goiter, puffy eyes, dry coarseskin, muscle weakness, constipation,

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menorrhagia, psychosis, peri-orbital edema, slow relaxing reflexes, poorlibido, poor memory etc. The diagnosis is based on signsand symptoms and is confirmed by measuring serum TSH, T4 and T3 levels by RIA techniques.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 T3 are notindicated in evaluating patients with hypothyroidism [3]. Hypothyroidism should be treated with levothyroxine, which is available as 25,50 and 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 [3]. After initiation oftherapy in patients with hypothyroidism. Serum TSH concentrations fall slowly as serum T4 concentration rise. The correct does of thyroxine 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].

The mechanism of action as well as the clinical effects ofthyroid hormones on bone has been of interest for morethan a century. With the appearance of new treatment modalities for thyroid function disorders, the accompanying alterations in bone metabolism appeared to be rare. In endocrinology practice it is a regularprocedure to screen out the hypothyroid patients for bonechanges by densitometry. The bone fragility is determined not only by bone quantity but bone quality as well [4]. The development of non-invasive techniques for diagnosingbone loss and the availability of second and third generation assays for TSH led to a better understanding ofthe consequences of thyroid hormone over treatment withrespect to bone loss. However the consequences of over treatment were not fully appreciated until the late 1980'swhen Ross and colleagues reported significant reductionsin radial bone mineral density in pre menopausal women receiving suppressive doses of L-thyroxine [5]. Bone density is a medical term referring to the amount of matter per cubic centimetre of bones. A scanner used to measure bone density is dual energy X-ray absorptiometry or bone densitometry. It is an enhanced form of X-raytechnology that is used to measure bone loss. DEXA ismost often performed on the lower spine and hips. DEXAis most often used to diagnose osteoporosis a condition thatoften affects women after menopause osteoporosis involvesa gradual loss of calcium, as well as structural changes causing the bones to become thinner, more fragile & morelikely to break DEXA test can also assess an individuals risk for developing fractures. The most common sites tomeasure with DEXA are the spine, the hip and the distalforearm. BMD results are calculated as the bone mineral content divided by the area of bone measured. In lumbosacral spine measurements are generally made at the L1, L2, L3 & L4 vertebra & then averaged together for atotal spine score. At the hip, measurements are made at the femoral neck, greater trochanter, intertrochanteric area and wards triangle and then averaged. Results are generally scored by two measures the T-score and the z-Score. T-score: this number shows the amount of bone we have compared with a young adult of same gender with peak bone mass.

Normal T-score isgreater than-1, Osteopenia T-score is between 1 to 2.5 and Osteoporosis T-score less than-2.5.T-score is used to estimate our risk of developing of a fracture. Z-score reflects the amount of bone we hav ecompared with other people in ourage group and of the same size and gender. The benefits of DEXA is a simple, quick & non-invasive procedure. No anaesthesia is required. The amount of radiation used is extremely small. It is the most accurate method available for the diagnosis of osteoporosis. The risks is slight chance of cancer from excessive exposure to radiation.

No complication sare expected with the DEXA procedure. DEXA test can not predict who will experience a fracture but can provide indications of relative risk. Moreover, the DEXA, have better precision and reproducibility and can do cument differences better than the older techniques [6].

The present study undertaken for foll owing objectives to assess the bone mineral content, bone mineral density and osteoporotic changes in hypothyroidism with suppressed levels of TSH by using DEXA scan and to assess themetabolic bone disease by parameters like serum T3, T4, TSH, Ca^{+2}, Po_4^{-3}, ALP, PTH and 25-OH Vit- Dmeasured.

Materials and Methods

The present study is carried out in Department of Endocrinology of Sri Venkateswara Institute of medical sciences, Tirupati. The study comprised of 40 subjects, classified into 2 groups each, with 20 subjects, Group I iscomposed with 20 healthy individuals considered as controls aged between 20–45 years and Group IIcomposed with 20 Hypothyroid subjects. The Hypothyroidism with suppressed levels of TSH isdiagnosed by

endocrinologist on the basis of clinical history, clinical examination and biochemical levels of T3, T4, TSH, BMD & metabolic bone disease work up likeCa^{+2}, Po_4^{-3}, ALP, PTH and 25-OH Vit- Dis carried out for these patients.

Data of these patients is compared with age matched controls. Results were statistically analysed by applying student 'T' test.

Results

The levels of T4 and TSH were shown significant change between controls and treated groups (Table 1).

The results of serum cholesterol, Ca^{+2}, Po_4^{-3}, ALP, PTH, 25-OH Vit- Dand DEXA results were summarised following tables (Table 2,3,4,5,6).

Table 1: Comparison of TSH, T4 and T3 levels of serumin controls and subjects

	Controls Mean ± SD	Subjects Mean ± SD	t	p
TSH	2.42 ± 1.08	0.15 ± 0.02	9.39	<0.001
T4	98.45 ± 21.92	139.65 ± 37.90	4.20	<0.001
T3	1.25 ± 0.33	1.36 ± 0.48	0.84	0.40

Table 2: Comparison of serum calcium, phosphorus, Alkaline Phosphatase and cholesterol in controls and subjects

	Controls Mean ± SD	Subjects Mean ± SD	T	p
Ca^{+2}	10.02 ± 0.38	9.92 ± 0.33	0.88	0.37
Po_4^{-3}	3.48 ± 0.56	3.51 ± 6.68	0.15	0.88
ALP	75.3 ± 14.06	89.1 ± 33.93	1.68	0.10
Total Cholesterol	165.8 ± 19.24	181.0 ± 35.6	1.70	0.09
PTH	38.5 ± 10.71	28.94 ± 21.17	1.80	0.07
Vit D_3	17.5 ± 11.46	19.24 ± 11.12	0.47	0.64

Table 3: Comparison of Bone Mineral Area of Lumbar spine,Femur neck, Radius & Ulna in controls and subjects

	Controls Mean ± SD	Subjects Mean ± SD	T	p
Lumbar spine	51.21 ± 3.56	47.53 ± 3.80	3.16	0.003
Femur neck	4.44 ± 0.56	4.47 ± 0.35	0.20	0.84
Radius & Ulna	4.50 ± 0.41	4.50 ± 0.45	0.00	1.00

Table 4: Comparison of Bone mineral content of lumbarspine, femur neck, Radius and ulna in controls and subjects

	Controls Mean ± SD	Subjects Mean ± SD	T	p
Lumbar spine	54.95 ± 6.09	39.47 ± 5.07	8.73	<0.001
Femur neck	3.93 ± 0.57	3.23 ± 0.54	3.98	0.84
Radius & Ulna	3.23 ± 0.36	2.89 ± 0.43	2.71	1.00

Table 4: Comparison of bone mineral density of lumbar spine, femur neck, Radius & Ulna in controls and subjects.

	Controls Mean ± SD	Subjects Mean ± SD	T	p
Lumbar spine	1.07 ± 0.08	0.83 ± 0.08	9.48	<0.001
Femur neck	0.89 ± 0.10	0.72 ± 0.10	5.73	<0.001
Radius & Ulna	0.72 ± 0.05	0.64 ± 0.07	4.25	<0.001

Table 6: Comparison of 'T'-Score of Lumbar spine, Femur neck and Radius & ulna from BMD of controls and subjects

	Controls Mean ± SD	Subjects Mean ± SD	T	p
Lumbar spine	0.25 ± 0.71	-1.98 ± 0.73	9.73	<0.001
Femur neck	0.37 ± 0.91	-1.19 ± 0.94	5.33	<0.001
Radius & Ulna	0.72 ± 0.86	-0.73 ± 1.28	3.68	<0.001

Discussion

The present study is to find out the effect of TSH suppression therapy on TSH, T4 and T3 levels in hypothyroidism. Hypothyroidism is diagnosed on the basis of serum TSH, T4 andT3 levels. Serum TSH, T4,T3 levels are compared between controls and subjects. Only TSH & T4 are found to be significant, but not T3 in this study. The negative feedback effect of thyroid hormones on TSH secretion may be exerted in partat the hypothalamic level, but it must be mainly on the pituitary, since T4 and T3 block the increase in TSHsecretion produced by TRH. Infusion of T3 as well as T4 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 [7]. TSH levels are less than 0.15 suggestingTSH 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, resultingin increased hepatic removal of cholesterol from the circulation. In hypothyroidism there is a decreased formation of LDL receptors, resulting in increased plasma cholesterol concentration [8]. Bone changes reflect on serum calcium, phosphorus and alkaline phosphatase levels and these chemical changes regulate the secretion of PTH & 25-OH Vit Dby feedback mechanism. These hormones act on the bone andcause osteogenesis & osteoporosis. So in this study serumcalcium level is decreased in hypothyroid subjects. SerumALP and phosphorus levels are high in hypothyroid subjects though these are not significant statistically. The serum PTH is decreased & 25-OH Vit-D is increased in hypothyroid subjects when compared to controls. Thenvalues are not significant statistically. The similar results are found by Stall GM et al [9].

The major effect of PTH is to maintain normal ionized serum calcium concentration. PTH stimulates the bonereabsorption releasing calcium into ECF. When PTH is increased more calcium is reabsorbed in distal nephron whereas when PTH is decreased less calcium is reabsorbedand urinary calcium excretion rises. The reabsorption of phosphate which occurs in proximal tubule is controlled by PTH. PTH decreases proximal tubular reabsorption ofphosphate so that increased urinary excretion of phosphateoccurs. Sustained elevation in PTH thus results in hypophosphatemia in addition to hypocalcemia[10]. 25-OHincreases intestinal phosphorus absorption by increasing the active transport of phosphorus. So, in this study, the PTH decreases the serum calcium along withincrease in serum phosphorus of hypothyroid subjects. 25OH3, Vit-D also increases serum phosphorus. The serumALP is the commonly used bone formation marker becausethere is a relationship between increases in serum ALP andincreases in osteoblastic activity. 25-OH3Vit-D increasesALP enzyme activity in osteoblast like cells. Mineral and hormonal changes described above may cause bonechanges. Almost all hypothyroid patients of this studycomplain of knee joint pain and backache. This initiatesfurther investigation of bone changes. Bone mineral area of lumbar spine, femur neck, radius & ulna are compared between controls and subjects. The Bone mineral area of lumber spine is less compared tocontrols & it is significant statistically. The change is notmuch found in femur neck and radius & ulna, and is notsignificant statistically. Bone mineral content & Bonemineral density of lumbar spine, femur neck, radius & ulnaare compared between controls and subjects. The BMC & BMD of all these areas are less compared to controls is significant statistically. The similar results were found by Sijanovic S. et al [11]. The decrease in bone turnover in hypothyroidism explains the reduced responsiveness of bone to PTH, 25-OH, Vit-D and to calcitonin in affected patients. So, in this study the BMC & BMD decreases inhypothyroid subjects which are on treatment for above 2yrs. The T4 & T3 supplementation with TSH suppression has nodirect effect on bone metabolism. Administration of T4 in myxedema patients causes a marked diuresis with loss of calcium that may cause of hypocalcemia. In hypothyroid patients there is a positive balance of phosphate this is dueto metabolism of creatinine phosphate in muscle. Hyperthyroidism may produce vitamin D deficiency.Thyroid hormones stimulate metabolic process increases the demand of coefficient enzymes and vitamins. So inhyperthyroidism demand is greater than synthesis, Vit – Ddeficiency occurs where as in hypothyroidism there is anincrease in Vit-D. The 25-OH, Vit-Dalso increases theintestinal absorption of phosphorus. The PTH decreases in this study. This may be due to theeffect of decreased T4 action on secreting cells ofparathyroid gland. The cell membranes of both the osteoblasts and the osteocytes have receptor proteins forbinding PTH. PTH increases the calcium permeability ofthe bone fluid. Side of the osteocytic membrane, thusallowing calcium ions to diffuse into the membrane cellsfrom the bone fluid. On the other side of the membrane the calcium ions

transfer in the ECF [12]. Inhypoparathyroidism, osteoblastic activity decreases leads toosteoporosis. In osteoporosis the mineral and mass ratio isconstant, bone mass decreases. In this condition there is adecrease in bone formation or increase in bonereabsorption. T-score of lumbar spine, femur neck, radius & ulna are compared between controls and subjects. The T-Score ofall these areas are less compared to controls & is significantstatistically. The BMD decreases so the T-Score alsodecreases because the T-score is dependent on the subjects BMD when compared to that of healthy 30 yr old of same sex and ethnicity. Stall GM, et al [9] studied accelerated boneloss in hypothyroid patients over treated with L-Thyroxine of 361 women enrolled in a 2 year calcium supplementtrial, 18 received thyroxin for hypothyroidism. Of these, 10were considered overtreated, because they had low TSH levels. Rates of loss of bone mineral density from theradius, spine, and hip during 1.9+/-0.6 years were measuredby single & dual – Photon absorptiometry. Theyconcluded that thyroxine treated women with low TSH levels lose bone mineral from the spine more rapidly thando women without known thyroid disease. These patientsare therefore at increased risk for osteoporosis. Theabsence of detectable biochemical changes in women withlow TSH levels may result from their relatively modest degree of over treatment [9].

Ribot, C. et al, studied Bone mineral density and thyroidhormone therapy. The results suggested that in the case of primaryhypothyroidism even appropriate thyroid replacementtherapy could lead during the first year of treatment to asignificant reduction in vertebral & femoral BMD. However, the fact that an increased fracture rate has notbeen documented in long term treated patients, and the results of their cross-sectional study, suggested that this bone mass reduction could be transient and reversible dueto new bone formation at the end of the resorptive sequence [13]. Ongphiphadhanakul B, et al, studied effect of TSHsuppressive doses of levothyroxine on bone mineral densityin Thai women. In this study stated that TSH suppressive doses of thyroid hormone should only beprescribed when appropriate and no longer than necessaryto minimize this adverse effect of excessive doses of thyroid hormone on bone [14].

Salerno et al studied the effect of long term L-thyroxinetreatment on bone mineral density in young adults withcongenital hypothyroidism. They concluded that the careful monitoring of serumthyroid – stimulating hormone and adjustment of 1 thyroxinedosage avoided the significant deleterious effects of prolonged 1-thyroxine replacement therapy on bonetissue in adolescents and young adults with congenital hypothyroidism treated from the neonatal period[15]. Stepan JJ & Limanova Z studied biochemical assessment of bone loss in patients on long term thyroid hormone treatment. To test conditions under which thyroid hormone might be deleterious to bone, they studied a group of 58patients who had undergone thyroidectomy because ofthyroid cancer 1 to 21 years previously and were treatedwith steady doses of exogenous thyroid hormone. Vertebral bone density (BMD Z – score) was significantly reduced and biochemical indices of bone resorption and of osteoblastic activity as well as the calculated prevalence of boneresorption relative to osteoblastic activity (HBP) were significantly increased in thyroid hormone treated post menopausal women but not in men and pre menopausal women. The HBP as well as the biochemical indices of bone remodeling were significantly negatively correlated with serum TSH levels. In treated patients, BMD Z-scorewas significantly dependent on the HBP, menopausal state, duration of treatment and serum TSH levels. Theyconcluded that the further increase in bone resorption bythyroid hormone is predisposed by menopausal changes inbone turn over. The simultaneous evaluation ofbiochemical indices of bone resorption and formation improves the assessment of bone loss in patients treated with thyroid hormone in a suppressive dose [16]. The patients on long term treatment of drugs likelevothyroxine, inspite of treating hypothyroidism there is aloss of bone mineral density although not with a higher fracture rate due to suppression of TSH levels.

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