

Effect of TSH Suppression Therapy on Bone Density in Hypothyroidism.

Swathi K¹, Haseena S², Hussain Saheb Shaik³.

¹Tutor, Department Physiology, RIMS, Kadapa, India, Pin – 516004.

²Ph.D Scholar, BLDE University's Sri B.M Patil Medical College, Bijapur, India, Pin -586103.

³Assistant Professor, Department of Anatomy, JJM Medical College, Davangere, India, Pin – 577004.

Abstract

Objectives – To find the effect Of TSH suppression therapy on bone density in hypothyroidism on bone mineral content, bone mineral density and osteoporotic changes with suppressed levels of TSH by using DEXA scan and assessing of metabolic bone disease by parameters like serum Ca^{+2} , PO_4^{-3} , ALP, PTH and 25-OH Vit- D₃.

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- D₃ measured.

Results – 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. The mean values of lumbar spine, femur neck, and radius & ulna were 39.47 ± 5.07 , 3.23 ± 0.54 and 2.89 ± 0.43 respectively.

Conclusion - T-Score values indicate significant changes in BMC and BMD in all subjects when compared to controls. Bone changes are further confirmed by changes in serum Ca^{+2} , PO_4^{-3} , ALP and hormonal changes in blood like PTH and 25-OH Vit-D₃. Serum Ca^{+2} levels are decreased serum PO_4^{-3} and ALP levels are increased in subjects. The hormonal factors like serum PTH decreases and 25- OH Vit-D₃ increases in subjects. These changes are not significant statistically. The PTH decreases due to effect of decreased T₄ action on secreting cells of parathyroid gland. The cell membranes of both the osteoblasts and the osteocytes have receptor proteins for binding PTH. PTH increases the calcium permeability of bone fluid. The patients on long term treatment of drugs like levothyroxine, in spite of treating hypothyroidism there is a loss of bone mineral density although not with a higher fracture rate due to suppression of TSH levels.

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. 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. The common causes of hypothyroidism are Iodine deficiency, Auto immunity, Atrophic Thyroiditis, Hashimoto's thyroiditis and Drug-Induced Hypothyroidism[1].

In hyperthyroid patients giving radio active 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.¹¹ 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, 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 not indicated in evaluating patients with hypothyroidism[2]. Hypothyroidism should be treated with levothyroxine, which is available as 25,50 and 100 µg 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 of therapy in patients with hypothyroidism. Serum TSH concentrations fall slowly as serum T₄ concentration rise. The correct dose of thyroxine is that which restores serum TSH to normal. Patients taking thyroxine have a low serum TSH concentration and feel better than when the concentration is normal[2].

The mechanism of action as well as the clinical effects of thyroid hormones on bone has been of interest for more than 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 department it is a regular procedure to screen out the hypothyroid patients for bone changes 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 diagnosing bone loss and the availability of second and third generation assays for TSH led to a better understanding of the consequences of thyroid hormone over treatment with respect to bone loss. However the consequences of over treatment were not fully appreciated until the late 1980's when Ross and colleagues reported significant reductions in radial bone mineral density in premenopausal women receiving suppressive doses of L-thyroxine. The past decade has witnessed almost 100 studies attempting to explain the effect of thyroid hormone on skeletal integrity[5].

Thyroid hormone is necessary for normal bone development, as is evidenced by poor bone growth and mineralization, delayed bone age epiphyseal digenesis, and immature body proportions in children with hypothyroidism. Hypothyroidism decreases recruitment, maturation and activity of bone cells, leading to decreased bone reabsorption and bone formation, decreased in bone reabsorption trabecular bone volume and bone mineral density due to decrease in osteoblastic activity[6]. Biochemical markers of bone metabolism suggest that skeletal turnover is decreased in hypothyroidism[7]. Serum ALP concentrations are often low or decreased Urinary excretion of hydroxyproline is decreased[8]. Decreased bone reabsorption, decreases the serum calcium but calcium levels are usually normal. Serum IGF-I concentration tend to be low in patient Cortical thickness increases. Bone turnover is reduced & bone mass is normal or slightly increased. Thyroid hormone stimulates both osteoblast and osteoclast. However, the effect on osteoclast exceeds that of osteoblast resulting in a decrease in bone mass. TSH suppressive doses of levothyroxine with otherwise normal thyroid function, so called subclinical hyperthyroidism, has been reported to cause a reduction in bone mass however the sites of bone loss vary among studies. Moreover, the effect of menopausal status on thyroid hormone induced bone loss is inconclusive. Ethnic and geographical differences may modify the skeletal response to thyroid hormone. The mechanism of action as well as the clinical effects of thyroid hormones on bone has been of interest for more than a century[9].

Bone density is a medical term referring to the amount of matter per cubic centimeter 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-ray technology that is used to measure bone loss. DEXA is most often performed on the lower spine and hips. DEXA is most often used to diagnose osteoporosis a condition that often affects women after menopause osteoporosis involves a gradual loss of calcium, as well as structural changes causing the bones to become thinner, more fragile & more likely to break DEXA test can also assess an individuals risk for developing fractures. The most common sites to measure with DEXA are the spine, the hip and the distal forearm. 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 a total 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 is greater 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 have compared with other people in our age group and of the same size and gender. The benefits of DEXA is a Simple, quick & non-invasive procedure. No anesthesia 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 complications are expected with the DEXA procedure. DEXA test cannot predict who will experience a fracture but can provide indications of relative risk. More over, the DEXA, have better precision and reproducibility and can document differences better than the older techniques[10]. The present study undertaken for following 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 the metabolic bone disease by parameters like serum Ca⁺², Po₄⁻³, ALP, PTH and 25-OH Vit- D₃.

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 T₃, T₄, TSH. BMD & metabolic bone disease work up like Ca⁺²,PO₄⁻³,SAP,25-OH Vit-D₃, PTH etc. is carried out for these patients. Data of these patients is compared with age matched controls. Results were statistically analyzed by applying student 'T' test.

RESULTS

The mean values of TSH, T₄ and T₃ in controls were 2.42±1.08, 98.45±21.92 and 1.25±0.33 respectively and in hypothyroid treated samples were 0.15±0.00, 139.65±37.90 and 1.36±0.46. The mean values of serum calcium in controls and hypothyroid treated samples were 10.02±0.38 and 9.92±0.33 respectively, The mean values of serum phosphorus in controls and hypothyroid treated samples were 3.48±0.56 and 3.51±0.68 respectively, The mean values of serum ALP in controls and hypothyroid treated samples were 75.3±14.06 and 89.1±33.93 respectively, The mean values of serum cholesterol in controls and hypothyroid treated samples were 165.8±19.24 and 181.0±35.0 respectively, Mean value of serum calcium is less compared to that of controls & 'P' value is not significant. Mean values of serum phosphorus and serum ALP are increased in subjects & these changes are not

significant statistically. Changes in serum cholesterol in controls and subjects are not significant, the Mean value of serum PTH is less in subjects compared to that of controls. 'P' value is not significant statistically. The mean value of serum 25-OH Vit D₃ values are increased in subjects & 'P' value is not significant (Table 1).

Table-1: Comparison of serum calcium, phosphorus, Alkaline Phosphatase and cholesterol in controls and subjects.

	Controls		Subjects		't'	'P'
	Mean	SD	Mean	SD		
Serum Calcium	10.02	0.38	9.92	0.33	0.88	0.37
Serum Phosphorus	3.48	0.56	3.51	0.68	0.15	0.88
Serum ALP	75.3	14.06	89.1	33.93	1.68	0.10
Serum Cholesterol	165.8	19.24	181.0	35.0	1.70	0.09
Serum PTH	38.5	10.71	28.94	21.17	1.80	0.07
Serum 25-OH Vit D ₃	17.5	11.46	19.24	11.12	0.47	0.64

The mean values of Bone Mineral Area of Lumbar spine, Femur neck, Radius & Ulna in controls were 51.21±3.56, 4.44±0.56 and 4.50±0.41 respectively. The mean values of Bone Mineral Area of Lumbar spine, Femur neck, Radius & Ulna in hypothyroid treated 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 and 'P' value is statistically significant. The change is not much found in femur neck & Radius – ulna & 'P' value is not significant statistically (Table 2).

Table 2: Comparison of Bone Mineral Area of Lumbar spine, Femur neck, Radius & Ulna in controls and subjects

	Controls		Subjects		't'	'P'
	Mean	SD	Mean	SD		
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

The mean values of Bone mineral content of Lumbar spine, Femur neck, Radius & Ulna in controls were 54.95±6.09, 3.93±0.57 and 3.23±0.36 respectively. The mean values of Bone mineral content of Lumbar spine, Femur neck, Radius & Ulna in hypothyroid treated were 39.47±5.07, 3.23±0.54 and 2.89±0.43 respectively. The mean values of bone mineral content in lumbar spine, Femur neck, Radius + ulna are lower than controls & the 'P' value indicates statistically significant (Table 3).

Table 3: Comparison of Bone mineral content of lumbar spine, femur neck, Radius and ulna in controls and subjects.

	Controls		Subjects		't'	'P'
	Mean	SD	Mean	SD		
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	<0.001
Radius + ulna	3.23	0.36	2.89	0.43	2.71	0.01

The mean values of Bone mineral density of Lumbar spine, Femur neck, Radius & Ulna in controls were 1.07±0.08, 0.89±0.10 and 0.72±0.05 respectively. The mean values of Bone mineral content of Lumbar spine, Femur neck, Radius & Ulna in hypothyroid treated were 0.83±0.08, 0.72±0.10 and 0.64±0.07 respectively. The mean values of Bone mineral density of lumbar spine, Femur neck, Radius & Ulna are lower than controls & the 'P' value indicates statistically significant (Table 4).

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

	Controls		Subjects		't'	'P'
	Mean	SD	Mean	SD		
Lumbar spine	1.07	0.08	0.83	0.08	9.48	<0.001
Femur neck	0.89	0.10	0.72	0.10	5.37	<0.001
Radius + ulna	0.72	0.05	0.64	0.07	4.15	<0.001

The mean values of 'T'-Score of Lumbar spine, Femur neck and Radius & ulna from BMD of controls were 0.25±0.71, 0.37±0.91 and 0.54±0.86 respectively. The mean values 'T'-Score of Lumbar spine, Femur neck and Radius & ulna from BMD of hypothyroid treated were -1.98±0.73, -1.19±0.94 and -0.73±1.28 respectively. The mean values of T-score of Lumbar spine, femur neck, Radius & ulna are lower than controls. 'P' values are statistically significant. The mean values are between -1 to -2.5 indicates osteopenia, below -1 indicates normal and above -2.5 indicates osteoporosis (Table 5).

Table 5: Comparison of 'T'-Score of Lumbar spine, Femur neck and Radius & ulna from BMD of controls and subjects

	Controls		Subjects		't'	'P'
	Mean	SD	Mean	SD		
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	0.54	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 bone density 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[11]. TSH levels are less than 0.15 suggesting TSH suppression therapy (Thyroxine extract). Suppressed TSH is the risk for osteoporosis. In the present study, DEXA bone scan is used for assessment of bone changes.

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[12].

Bone changes reflect on serum calcium, phosphorus and alkaline phosphatase levels and these chemical changes regulate the secretion of PTH & 25-OH Vit D₃ by feedback mechanism. These hormones act on the bone and cause osteogenesis & osteoporosis. So 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-D₃ 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[13].

The major effect of PTH is to maintain normal ionized serum calcium concentration. PTH stimulates the bone reabsorption 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[14]. 25-OH

Vit-D₃ 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-D₃ 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-D₃ 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.

Bone mineral area of lumbar spine, femur neck, radius & ulna are compared between controls and subjects. The Bone mineral area of lumbar spine is less compared to controls & it is significant statistically. The change is not much found in femur neck and radius & ulna, and is not significant statistically. Bone mineral content & Bone mineral density of lumbar spine, femur neck, radius & ulna are 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[15]. The decrease in bone turnover in hypothyroidism explains the reduced responsiveness of bone to PTH, 25-OH Vit-D₃ and to calcitonin in affected patients. So, in this study the BMC & BMD decreases in hypothyroid subjects which are on treatment for above 2 yrs. The T_4 supplementation with TSH suppression has no direct effect on bone metabolism. Administration of T_4 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 due to 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 in hyperthyroidism demand is greater than synthesis, Vit – D deficiency occurs where as in hypothyroidism there is an increase in Vit-D. The 25-OH Vit-D₃ also increases the intestinal absorption of phosphorus.

The PTH decreases in this study. This may be due to the effect of decreased T_4 action on secreting cells of parathyroid gland. The cell membranes of both the osteoblasts and the osteocytes have receptor proteins for binding PTH. PTH increases the calcium permeability of the bone fluid. Side of the osteocytic membrane, thus allowing calcium ions to diffuse into the membrane cells from the bone fluid. On the other side of the membrane the calcium ions transfer in the ECF[16]. In hypoparathyroidism, osteoblastic activity decreases leads to osteoporosis. In osteoporosis the mineral and mass ratio is constant, bone mass decreases. In this condition there is a decrease in bone formation or increase in bone reabsorption.

T-score of lumbar spine, femur neck, radius & ulna are compared between controls and subjects. The T-Score of all these areas are less compared to controls & is significant statistically. The BMD decreases so the T-Score also decreases 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 studied accelerated bone loss in hypothyroid patients over treated with L-Thyroxine of 361 women enrolled in a 2 year calcium supplement trial, 18 received thyroxine for hypothyroidism. Of these, 10 were considered overtreated, because they had low TSH levels. Rates of loss of bone mineral density from the radius, spine, and hip during 1.9 \pm 0.6 years were measured by single & dual – Photon absorptiometry. When compared with women with no known thyroid disease, women with low TSH levels had greater annualized, adjusted mean rates of bone loss from the spine (-2.89% \pm 0.65% compared with -1.13% \pm 0.13%, $P=0.009$) and similar but not significant trends at the radius (-1.18% \pm 0.75% compared with -0.13% \pm 0.17%) and femoral neck (-1.39% \pm 0.80% compared with -0.28% \pm 0.19%). These means were adjusted for variables that affected the rate of loss in the control group. There were no statistical differences between the low TSH and control groups for any laboratory variables measured, including serum calcium, phosphorus, parathyroid hormone or alkaline phosphatase, plasma 25-OH Vit D or 1,25 – (OH)₂ Vit D, or 24 hour urine calcium –to-creatinine ratio. They concluded that thyroxine treated women with low TSH levels lose bone mineral from the spine more rapidly than do women without known thyroid disease. These patients are therefore at increased risk for osteoporosis. The absence of detectable biochemical changes in women with low TSH levels may result from their relatively modest degree of over treatment[13].

Gam AN, et al studied the effect of thyroxine therapy on bone metabolism in substituted hypothyroid patients with normal or suppressed levels of TSH to evaluate a possible relationship between the calcium and the thyroid metabolism, 29 women with thyroxine (T₄) substituted hypothyroidism were examined. They were separated into two groups, one with normal (0.15 to 6 mu/l) and one with suppressed TSH (less than 0.15 mu/l). All the women were judged euthyroid both by their T₄ & T₃ by their clinics. The daily dose of T₄ had been unchanged and TSH level had been stable during the previous six months. Bone mineral content of the lumbar spine, bone mineral density of left & right collum femoris, serum AP activity, serum concentration of osteocalcin and urinary excretion of Hydroxy proline/creatinine were similar in two groups. A significant positive correlation was found between serum ost and Hpr / Crea (P less than 0.05) indicating a balanced state where bone formation equals bone resorption. AP failed to correlate to Ost and Hpr/Crea because the AP raises from both bone & liver of bone & liver metabolism whereas the two others predominantly reflect bone metabolism. It was suggested that euthyroid, T₄ substituted patients had a normal calcium metabolism whether TSH levels were suppressed or not[17].

Ribot, c et al, studied Bone mineral density and thyroid hormone therapy. The purpose of their study was to evaluate prospectively the evolution of femoral and vertebral BMD in hypothyroid subjects treated with replacement doses (mean \pm SD dose of L-thyroxine =135 \pm 32 μ g/day) as compared to an untreated group. Vertebral bone density was also measured in other patients who had been treated for at least 2 years with either

suppressive (mean dose =154 \pm 36 μ g / day , n=28) or replacement doses (mean dose =104 \pm 52 μ g /day, n=21) according to the TSH response to the TRH administration. In primary hypothyroid patients, a mean decrease of 5.4% ($P<0.01$) for vertebral BMD, 7.3% ($P<0.01$) for trochanter and 7% ($P<0.001$) for femoral neck was observed after 1 year of treatment. This loss was unrelated either to age or to menopausal status. A clinical and hormonal state of euthyroidism was reached since the 3rd month of treatment. Fasting urinary calcium / creatinine excretion was increased significantly ($P<0.05$) at the 3rd month, and plasma osteocalcin (oc) increased significantly from the 3rd month onwards. ($P<0.05$) up to the 12th month ($P<0.025$). In the cross sectional study, vertebral BMD was not significantly different from age matched normal values in patients receiving either substitutive or suppressive doses of LT₄. The results suggested that in the case of primary hypothyroidism even appropriate thyroid replacement therapy could lead during the first year of treatment to a significant reduction in vertebral & femoral BMD. However, the fact that an increased fracture rate has not been 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 due to new bone formation at the end of the resorptive sequence[18].

Ongphiphadhanakul B, et al, studied effect of TSH suppressive doses of levothyroxine on bone mineral density in Thai women. Subjects consisted of 27 Thai females aged between 23-79 years. Eighteen were premenopausal and nine were post menopausal . All were attending the Thyroid clinic at Ramathibodi Hospital and had been on at least 150 micrograms/day of L-T₄ for the treatment of nodular thyroid diseases for more than 2 years with at least one TSH value during the follow-up period in the suppressive range. None of the subjects had a previous history of Grave's disease. BMD was determined by DEXA. Data of 54 age- matched healthy, controls were used for comparison. BMD values were converted to Z-scores before analyses. Data were expressed as mean \pm SEM compared to controls, post menopausal women on long term L-T₄ had decreased BMD at anteroposterior spine (-0.69 \pm 0.26 vs 0.05 \pm 0.17, $P<0.01$), femoral neck(-0.61 \pm 0.35 vs 0.18 \pm 0.24, $P<0.05$), Femoral trochanter (-0.64 \pm 0.37 vs 0.13 \pm 0.22, $P<0.05$) but not at ward's triangle. In contrast to the findings in post menopausal women there was no significant difference of BMD compared to controls in premenopausal women at the lumbar spine, wards femoral neck or femoral trochanter. Concluded that Thai postmenopausal women on long term TSH – suppressive doses of L-T₄ have reduced BMD at various skeletal sites which may increase fracture risks. TSH suppressive doses of thyroid hormone should only be prescribed when appropriate and no longer than necessary to minimize this adverse effect of excessive doses of thyroid hormone on bone[19].

Sijanovic S & Karner I studied Bone loss in premenopausal women on long term suppressive therapy with thyroid hormone. 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 beginning 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 (~10 years) thyroxine therapy in the premenopausal period can develop osteopenia by the beginning of menopause[15].

Salerno et al studied the effect of long term L-thyroxine treatment on bone mineral density in young adults with congenital hypothyroidism. Thirty seven subjects with congenital hypothyroidism, detected by neonatal screening and longitudinally followed from the time of diagnosis and treatment (26 +/- 4 days) up to the age of 17.8 +/- 1.0 years, were studied. Spinal (L₂-L₄) BMD measured by DEXA, and bone quality, measured as amplitude dependent speed of sound (Ad-SoS) by qualitative ultrasound, were evaluated. Z-score mean values (+/-S.d.) of BMD (0.3 +/- 0.7) and Ad-SoS (-0.7 +/- 1.1) were slightly below the average but within the normal range. Ad-SoS resulted in a Z-score below -1 in 38% of patients as compared with BMD which resulted in a Z - score below -1 in only 13.5% of subject. No significant differences were observed between males (BMD, -0.3 +/- 0.7; Ad-SoS, -0.9 +/- 1.0), and females (BMD, -0.3 +/- 0.7 ; Ad -SoS, -0.5 +/- 1.2) or when dividing patients on the basis of aetiological defects; Ectopic gland (BMD, -0.3 +/- 0.6; Ad-SoS, -0.8 +/- 0.9), athyreosis (BMD, -0.3 +/- 0.9, Ad-SoS, -0.8 +/- 1.0) and ectopic gland (BMD, -0.3 +/- 0.8, Ad-SoS, -0.4 +/- 1.3). No significant relationships were observed between BMD or Ad-SoS Z - score and hormonal status or 1-thyroxine dosages at the time of study or during the pubertal period. They concluded that the careful monitoring of serum thyroid - stimulating hormone and adjustment of 1-thyroxine dosage avoided the significant deleterious effects of prolonged 1-thyroxine replacement therapy on bone

tissue in adolescents and young adults with congenital hypothyroidism treated from the neonatal period[20].

Kung A.W. and Pun K.K studied bone mineral density in premenopausal women receiving long term physiological doses of levothyroxine. Total body and regional bone mineral density levels were determined in 26 premenopausal women with Hashimoto's thyroiditis receiving long term physiological doses of levothyroxine sodium replacement therapy. The BMD levels of each patient were compared with the mean of the BMD levels of age matched normal controls. The mean levothyroxine sodium dose was 111 +/- 6 µgms/d, and the mean duration of treatment was 7.5 +/- 5.3 years (range, 1 to 24 years). Dietary calcium intake was similar in both groups as were serum thyroxine, triiodothyronine, free thyroxine index, and thyrotropin levels. Women receiving the levothyroxine treatment had normal total body BMD levels but had significantly lower BMD levels at the femoral neck (-5.7%), femoral trochanter (-7.0%), wards triangle (-10.6%), both arms (right, -7.8%; left, -8.9%), and pelvis (-4.9%). In contrast, lumbar spine BMD levels were similar in two groups. There was no correlation between the total body or different regional BMD levels and the duration or dosage of levothyroxine treatment or thyroid function test results. However, the Z-score of the femoral neck of these patients showed a significant negative correlation with their serum free thyroxine index levels. They concluded that patients receiving physiological doses of levothyroxine may have decreased bone density. Thyroid functions in patients receiving long term levothyroxine treatment should be closely monitored and bone densitometry should be performed in patients at risk for osteoporosis[21].

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[22].

Paul T.L. et al studied long term L-thyroxine therapy is associated with decreased hip bone density in premenopausal women. The effect of long term L-thyroxine (L-T₄) 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-T₄ therapy had been receiving the medication for a minimum of five years. There was no difference in calcium intake or excretion between the L-T₄ treated women and the controls. Women receiving L-T₄ had increased serum thyroxine concentrations (134 +/- 5 vs 95 +/- 3 nmol/L, [10.4 +/- 0.4 vs 7.4 +/- 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 +/- 0.3 mu/L [0.9 +/-

0.2 vs 2.1 +/- 0.3 µg/ml). Serum triiodothyronine concentrations were normal and were similar in both groups. Women treated with L-T₄ 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-T₄ 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-T₄ that is carefully monitored to avoid the long term use of dosages that are excessive for the thyroid condition being treated[23].

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 58 patients who had undergone thyroidectomy because of thyroid cancer 1 to 21 years previously and were treated with steady doses of exogenous thyroid hormone. Vertebral bone density (BMD Z – score) was significantly reduced and biochemical indices of bone resorption (urinary hydroxyproline and plasma tartrate resistant acid phosphatase activity) and of osteoblastic activity (plasma osteocalcin and bone isoenzyme of serum alkaline phosphatase) as well as the calculated prevalence of bone resorption relative to osteoblastic activity (HBP) were significantly increased in thyroid hormone treated post menopausal women but not in men and premenopausal 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-score was significantly dependent on the HBP, menopausal state, duration of treatment and serum TSH levels. They concluded that the further increase in bone resorption by thyroid hormone is predisposed by menopausal changes in bone turn over. The simultaneous evaluation of biochemical indices of bone resorption and formation improves the assessment of bone loss in patients treated with thyroid hormone in a suppressive dose[24].

Susan L- et al 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 an 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[4].

CONCLUSION

The patients on long term treatment of drugs like levothyroxine, in spite of treating hypothyroidism there is a loss of bone mineral density although not with a higher fracture rate due to suppression of TSH levels.

REFERENCES

- Lewis E.Braverman, Robert D. Utiger, and Werner & Ingbar's; "The Thyroid a Fundamental and Clinical Text", 9th Ed. 2005, Ch-13:339.
- Davidson's "Principles and practice of medicine", 17th Ed. 1995, ch-12: 693.
- Iakatos. P. " Thyroid Hormones: Beneficial or Deleterious for bone ", *Calcif Tissue Int.*2003;73:205-209.
- Susan L. Greenspan and Francis S.Greenspan; "The effect of thyroid hormone on skeletal Integrity", *Ann Intern Med.* 1999, Vol 130, No 9:753.
- Eriksen. EF, Mosekilde.L, Melsen.F; "Kinetics of trabecular bone resorption and formation in hypothyroidism:Evidence for a positive balance per remodelling cycle", *Bone.* 1986, 7:101.
- Krolner B, Jorgensen JV, Nielsen SP; "Spinal bone mineral content in myxedema and thyrotoxicosis; Effects of thyroid hormone and antithyroid treatment", *Clin Endocrinol (OXf).* 1983; 18:439.
- Brixen K, Nielsen HK, Eriksen EF; "Efficiency of wheat germ lectin precipitated alkaline phosphatase in serum as an estimator of bone mineralization rate: Comparison to serum total alkaline phosphatase and serum bone Gla-protein", *Calcif Tissue Int.* 1989; 44:93.
- Charles P,Poser JW,Mosekilde L; "Estimation of bone turnover evaluated by ca – kinetics: Efficiency of serum bone gamma – carboxy glutamic acid – containing protein, serum alkaline phosphatase and urinary hydroxy proline excretion", *J Clin Invest.* 1985;76:2254.
- Mosekilde. L, Eriksen .EF, Charles. P; "Effects of thyroid hormones on bone and mineral metabolism", *Endocrinol Metab Clin North Am.* 1990; 19:35.
- Radiological Society of North America, Inc. (RSNA) oct 1, 2008.
- Leese G.P., Jung R.T., Guthrie. C, Waugh. N, Browning M.C.K; "Morbidity in patients on l-Thyroxine: a comparison of those with a normal TSH to those with a suppressed TSH", *Clin Endocrinol (OXf)*, 1992. Dec; 37(6): 500-3.
- Willian F. Ganong; "Review of Medical physiology", 22nd Ed. 2005, Ch-18: 317
- Stall GM, Harris S, Sokoll LJ, Dawson-Hughes B; "Accelerated bone loss in hypothyroid patients over treated with L-thyroxine", *Ann Intern Med.* 1991, Feb 15; 114(4): 339-40.
- Best and Taylors; "Physiological Basis of Medical Practice", 12th ed.1989, ch-56 : 836-838.
- Sijanovic S and karner I; "Bone loss in premenopausal women on long term suppressive therapy with thyroid hormone", *Medscape womens health.* 2001 oct; 6(5):3.
- Arthur C. Guyton and John E. Hall.; "Textbook of Medical Physiology", 10th Ed. 2005, ch-79: 901-903,907.
- Gam AN, Jensen GF, Hasselstorm K, Olsen M, Nielsen KS; "Effect of thyroxine therapy on bone metabolism in substituted Hypothyroid patients with normal or suppressed levels of TSH", *J.Endocrinol Invest.* 1991, Jun; 14 (6): 451 – 5.
- Ribot C, Tremollieres F, Pouilles JM, Louvet. JP; "Bone mineral density and thyroid hormone therapy", *Clin-Endocrinol (OXf).* 1990 Aug; 33(2): 143 – 53.
- Ongphiphadhanakul B,Puavilai G,Rajatanavin R; "Effect of TSH-Suppressive doses of levothyroxine on bone mineral density in thai women", *J med Assoc Thai,* 1996 Sep; 79(9):563-7.
- Salerno M, Lettierio T, Esposito-Del Puente A, Esposito V, Capalbo D, Carpinelli A, Padula S, Del Puente A; "Effect of long term L-thyroxine treatment on bone mineral density in young adults with congenital hypothyroidism", *European journal of Endocrinology.* Vol 151, Issue 6 : 689-694.

21. Kung A.W and Pun K.K; "Bone mineral density in premenopausal women receiving long-term physiological doses of levothyroxine", J.Am med Assoc.1991, Vol-265: No-20.
22. Mosekilde. L, Eriksen .EF, Charles. P; "Effects of thyroid hormones on bone and mineral metabolism", Endocrinol Metab Clin North Am. 1990; 19:35.
23. Paul T.L, Kerrigan J, Kelly A.M, Braverman L.E, Baran D.T; "Long term L-Thyroxine therapy is associated with decreased hip bone density in premenopausal women", JAMA, 1988 Jun 3; 259 (21) : 3137 -41.
24. Stepan JJ&Limanova Z; "Biochemical assessment of bone loss in patients on long term thyroid hormone treatment", Bone miner, 1992 Jun; 17(3): 377-88.