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Relationship of thyrotropin level and bone mineral density in adult females

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Abstract: Objective: objective we aimed to examine the association between bone mineral density (BMD) and serum TSH level in premenopausal Egyptian females receiving thyroxin treatment. **Methods** in this study a total of 90 women receiving thyroxin treatment. aged 35-45 years or older who underwent bone mineral density (BMD) measurement, thyroid function test, osteocalcin and deoxypyridinolin assessment; They were recruited from al Zahra university hospital outpatient endocrinology clinic. The 90 females were divided according to thyroid stimulating hormone (TSH) level into: Group 1: 30 females with low TSH level (suppressive therapy following surgical removal of thyroid cancer), Group 2: 29 females with normal TSH level (hypothyroid females on thyroxin replacement therapy (Controlled on treatment), Group 3: 31 females with High TSH level (hypothyroid females on suboptimum dose of thyroxin replacement therapy. **Results** there is no statistical significant difference between (weight, height, BMI and waist circumference) among the three groups, this could be explained by the selection criteria of the patients as our study population were not obese or having high body mass index being weight and BMI matched. There were high significant difference between Group 1, 2 and 3 as regard Z score femoral, humerous and spine, In the present study Z score was lower in Group 1 (low TSH) (differentiated thyroid cancer) in comparison to Group 2 & 3, although the overall reduction did not reach the osteoporotic level. Group 2 (women with normal TSH) had the most favorable BMD in comparison to Group 1 & 3. Also Group 3 (high TSH due to suboptimum dose of thyroxin) had better BMD in comparison to Group 1 (women having low TSH due to suppressive therapy). considering the whole studied population, TSH was not correlated with the Z score of femur, humerous or spine, but it was positively correlated with z score of humerous in Group 2 (Normal TSH). FT3 was negatively correlated with spine z score in Group 1 (low TSH). both humerous and spine have significant correlation with either TSH, Free T3 or free T4, although femur had no correlation with TSH, free T4 or Free T3. In the present study, FT4 was correlated negatively with spine Z score in all studied population in all study population. Also, it was correlated negatively with humerous z score in Group 1 (low TSH) and negatively with spine z score in Group 2. there were increase in osteocalcin in low TSH (Group 1) and high TSH (Group 3) than normal TSH (Group 2). it was higher in the low TSH (Group 1) with statistical significant difference. ($p<0.01$). ($p=0.007$). Group 1 has higher osteocalcin level than Group 2 and 3. Osteocalcin has positive relationship with serum TSH levels and indicators of the used bone formation marker (osteocalcin). We also found a negative correlation between FT3 and osteocalcin, In the present study, As regard deoxypyridinolin (DPD) we Found that there is high statistical significant difference between Group 1, 2 and 3 ($p<0.001$) (table) In this study DPD values were highest in Group 1 (low TSH), while being lowest in Group 3 (high TSH) Group , Receiver operating characteristic analysis (ROC) was mad between patients with osteoporosis and patients without osteoporosis to TSH, osteocalcin and DPD TSH cut off values were (=OR<0.05), (>9.7) and (=OR>3.5) previous values are accepted for screening the risk of osteoporosis in patient receiving thyroxin treatment.

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Keywords: Relationship; thyrotropin; level; bone; mineral; density; adult; female

1. Introduction:

Women are ten times more likely to suffer from thyroid diseases, for example, between 30 and 60 years of age, the prevalence of thyrotoxicosis is 1.4%. 3% of women over the age of 50 years receive thyroxin replacement for either primary hypothyroidism, following radioiodine treatment or after surgery for thyrotoxicosis, and at least one-fifth of these women are over-replaced 1. The clinical significance of osteoporosis lies in the fractures morbidity and mortality that arise.2. Thyroid disorders are considered to be one of the major common

disorders which have been linked to disturbed bone density. It has been shown that thyroid disturbance is a major cause of secondary osteoporosis.2. The potential of TSH to modulate bone remodeling, even independently of thyroid hormones, has been investigated and supported by the fact that TSH receptors are present both in osteoblasts and osteoclasts. The definite thyroid association with osteoporosis is a questionable issue as regard many aspects; moreover, few studies have been conducted in such topic.2.

2. Martial and Method:

In this study a total of 90 women receiving thyroxin treatment. aged 35-45 years or older who underwent bone mineral density (BMD) measurement, thyroid function test, osteocalcin and deoxypyridinolin assessment; They were recruited from al Zahra university hospital outpatient endocrinology clinic., they were divided into three groups according to thyrotropin (TSH) level. Group 1: 30 females with low TSH level (suppressive therapy following surgical removal of thyroid cancer), Group 2: 29 females with normal TSH level (hypothyroid females on thyroxin replacement therapy (Controlled on treatment). Group 3: 31 females with High TSH level (hypothyroid females on suboptimum dose of thyroxin replacement therapy there was no previous graves' disease in order to avoid other cause of osteoporosis. Does (150 - 200 ug /d) and duration of treatment (13 ±4 month) were matched in the three groups to avoid variability in thyroid profile throughout the treatment period.

3. Result:

There is no statistical significant difference between (weight, height, BMI and waist circumference) among the three groups. There were high significant difference between Group 1, 2 and 3 as regard Z score femoral, humerous and spine, Z score was lower in Group 1 (low TSH) (differentiated thyroid cancer) in comparison to Group 2 & 3, although the overall reduction did not reach the osteoporotic level. Group 2 (women with normal TSH) had the most favorable BMD in comparison to Group 1 & 3. Also Group 3 (high TSH due to suboptimum dose of thyroxin) had better BMD in comparison to Group 1 (women having low TSH due to suppressive therapy). Considering the whole studied population, TSH was not correlated with the Z score of femur, humerous or spine, but it was positively correlated with z score of humerous in Group 2 (Normal TSH). FT3 was negatively correlated with spine z score in Group 1 (low TSH). In the current study, both humerous and spine have significant correlation with either TSH, Free T3 or free T4, although femur had no correlation with TSH, free T4 or Free T3. FT4 was correlated negatively with spine Z score in all studied population in all study population. Also, it was correlated negatively with humerous z score in Group 1 (low TSH) and negatively with spine z score in Group 2. there were increase in osteocalcin in low TSH (Group 1) and high TSH (Group 3) than normal TSH (Group 2). it was higher in the low TSH (Group 1) with statistical significant difference. Group 1 has higher osteocalcin level than Group 2 and 3. Osteocalcin has positive relationship with serum TSH levels and indicators of the used bone formation marker (osteocalcin). We also found a negative correlation between FT3 and osteocalcin, As regard DPD there is high statistical significant difference between Group 1, 2 and 3, DPD values were highest in Group 1 (low TSH), while being lowest in Group 3 (high TSH) Group, supporting the anti resorpitive effect of TSH on bone tissue.

Table (1): Description of all studied population according to the demographic, clinical, biochemical and BMD result.

	Mean ± SD	Median (IQR)	Range
Does (ug/d)	176.67 ± 38	175 (150 - 200)	100 – 250
Duration (month)	13 ±4		
Age (yr)	30-45		
WC (cm)	90±3		
WT (kg)	72±4		
HT (cm)	168±4		
BMI (kg/m2)	25±3		
TSH (mU/l)	25±3		
FT3(pmol/l)	2.88 ± 1.66	2.6 (1.7 - 3.7)	0.001 - 100
FT4(pmol/l)	10.52 ± 3.75	11 (10 - 13)	0.5 – 17
Osteocalcin (ng/mL)	9.66 ± 0.94	9.6 (8.9 - 10.4)	7.8 - 11.7
DPD	1.5-6.9	3.97 ± 5.09	3.9 (2.13 - 4.7)
Femur Z	0.83 ± 1.74	1.4 (-1 - 2)	-4 - 3.3
Humerous Z	0.57 ± 1.67	1 (-1 - 1.8)	-3.5 - 3.1
Spine Z	0.8 ± 1.59	1.1 (-0.5 - 2)	-3.5 - 3.5

Receiver operating characteristic analysis (ROC) was mad between patients with osteoporosis and patients without osteoporosis to TSH, osteocalcin and DPD; TSH cut off values were (=OR<0.05), osteocalcin cut off values were (>9.7) and DPD cut off values were (=OR>3.5) previous values are accepted for screening the risk of osteoporosis in patient receiving thyroxin treatment.

This table shows Description of all studied population according to the demographic, clinical, biochemical and bone mineral density result.

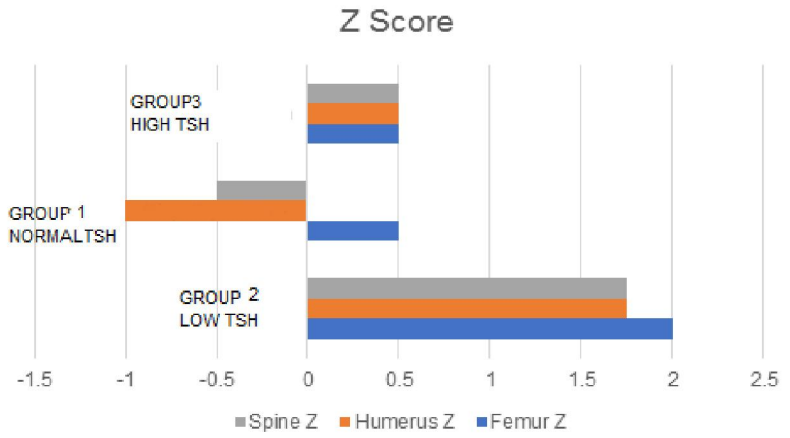

Figure (1): This table shows that there is high statistical significance between Group 1, 2 and 3 and Z score and T score of humerous, femur and spine.

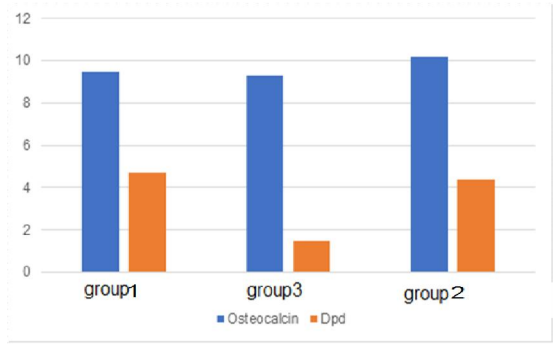

Figure (2): Shows that there is high statistical significance between Group 1, 2 and 3 as regard deoxypyridinolin and osteocalcin.

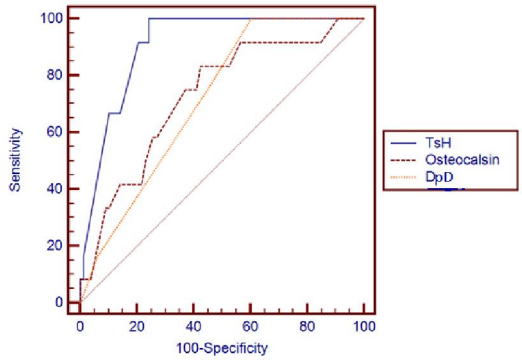

Figure (3): ROC curve analysis of TSH, Osteocalcin and DPD to detect Osteoporosis:

Among the whole sample

	AUC	95% CI	Cutoff point	Sensitivity	Specificity	+PV	-PV	p value	sig.
TSH	0.907	0.827 to 0.958	<=0.05	100	75.6	38.7	100	<0.001	S
DPD	0.714	0.609 to 0.804	>=2.5	100	39.7	20	100	<0.001	S
OC	0.728	0.624 to 0.817	>9.7	83.3	57.7	23.3	95.7	<0.004	S

4. Discussion

There is no statistical significant difference between (weight, height, BMI and waist circumference) among the three groups, this could be explained by the selection criteria of the patients as our study population were not obese or having high body mass index being weight and BMI matched.

In vitro studies suggest that TSH stimulates osteoblast differentiation, as shown by effects on alkaline phosphatase activity, osteocalcin expression, and mineralization. TSH itself possibly plays a favorable (anabolic) role influencing the bone mineral density even independently of thyroid hormones. This finding is confirmed by increased bone formation marker and bone formation process supporting the anabolic role of thyrotropin hormone. But it seems that it is not in unlimited fashion because high TSH results in low bone turnover with decreased osteoblastic bone

formation and reduced osteoclastic bone resorption. The prolonged bone remodeling cycle includes a longer period of secondary mineralization resulting in a net increase in bone mineralization and mass without a change in bone volume.

It seems that in adult patients with high TSH (hypothyroidism), bone density increases but bone quality is poor, High TSH causes an increase in the duration of the remodeling cycle and thus, leads to low bone turnover and enhanced mineralization, also, many population-based studies show that hypothyroid patients also have an increased risk of fracture even with high BMD3.

Because low TSH accelerates bone turnover and shortens the normal bone remodeling cycle, bone regeneration time are reduced significantly so that the negative balance between bone formation and bone resorption occurs. It was expected that suppressive therapy for post thyroidectomy in differentiated thyroid cancer may affect bone density (BMD) greatly giving osteoporosis.

However, suppressive thyroxin therapy for differentiated thyroid cancer have reported conflicting data, many investigators have concluded that recommended dose of thyroxin for postoperative therapy does not have negative effects on bone density. Also, [4] and Morris et al., (2007)[5] observed associations between low TSH levels and osteoporosis prevalence, together with a graded increase in a BMD with increasing TSH in premenopausal women. Pedro et al. 2014 6also observed a high prevalence of low BMD in patients having low TSH and treated with dose matched thyroxin. In agreement to our result eE. Tsourdi1 t al,.2015 7who stated that low TSH tends to reduce all BMD variables. In agreement with our results also, Grimnes et al., 2008 [8] reported that bone mineral density in women with elevated TSH levels was higher than in women with low TSH supporting the bone anabolic effect of thyrotropin.

On the other side [9], Murphy Williams.[10], 2004, Heemstra et al., 2006 [11] stated that women receiving suppressive doses of thyroxin treatment did not have any changes in BMD.

T3 hormone and its circulating concentrations are regulated by a classical endocrine negative feedback loop that maintains an inverse physiological relationship between TSH, and T4 and regulates the intracellular supply of the active hormone, T3, 13T3 then enters the nucleus where it binds and activates either thyroid hormone receptor α or β (TRα, TRβ). Thyroxin receptors are expressed in growth plate chondrocytes, bone marrow stromal cells, and bone-forming osteoblasts, T3 stimulates differentiation of hypertrophic chondrocytes to regulate ossification, bone growth and chondrocyte differentiation into osteoblast. [3] TRβ is the main receptor expressed in the hypothalamus and pituitary where it mediates negative feedback control of the HPT axis, whereas TRα is the main receptor expressed in the skeleton and mediates T3 action in bone and cartilage 3 TRα is the main receptor expressed in the skeleton and mediates FT3and FT4 action in bone and cartilage. In the skeleton, Levels of circulating free T4 in serum are 3–4-fold higher than free T3. T4 and T3 enter target cells by active uptake mediated by cell membrane involve interactions with key signaling pathways that known to regulate communication between osteoblast and osteoclast cell lineages within the bone marrow microenvironment. [3]. Bolanowski., 2017 [12] stated that, FT3 stimulates the IL-6 and IL-8, intensifies the effects of IL-1 and IL-6, increases proliferation, differentiation and apoptosis of osteoblasts. Van der Deure et al.., 2007 [13] observed a stronger effect of FT4 than TSH on BMD, supporting the importance of thyroid hormone effects on bone.

Being significantly correlated, humerous and spine Z score could give us a preferable site for assessing BMD in premenopausal women taking thyroxin especially low TSH patients.

Grimnes et al., 2008 8 also investigated the site of low BMD, reporting that low serum TSH had lower BMD at the humerous site.

Osteocalcin (bone formation marker) is released by osteoblasts and involved primarily in bone mineralization. It is the most abundant non-collagen protein found in bone and considered to be an important bone formation marker.14 (Farahm and P et al., 2013), 15 (Garnero P et al.,2014).

These interrelations are in agreement with van der et al., 2008, 13 observed a positive relationship between TSH and osteocalcin, independent of thyroid hormone levels. On the other hand, Jagoda et al., 2013 16 stated that Despite an upward trend in serum osteocalcin measurements with decreasing TSH concentrations, there was no significant difference in serum osteocalcin among normal or low TSH groups. We also found a negative correlation between FT3 and osteocalcin, these data are not in agreement with what elhadidy et al., 2011 [17] found as he found positive correlation between free T3 and osteocalcin as bone turn over maker.

The commonly used resorption marker Deoxypyridinolin (DPD) is formed during the maturation of bone collagen, present in significant amounts in bone, released during resorption of bone and excreted in urine in the free and peptide-bound forms without being metabolized [18] (Pennypacker BL et al., 2014).

[19] Ghonaim et al., 2011 who stated that patients having low TSH have significant bone loss with higher DPD. And it was significantly higher in low TSH than in age-matched controls.

With the positive relation between TSH and BMD and osteocalcin (minimal bone anabolic effect) and strong negative relation between TSH and DPD (bone anti resorpitive effect), We concluded that the normal up to high BMD is mainly due to the anti resorpitive effect of thyrotropin rather than the slight increased TSH anabolic effect.

This bone state is associated with increased fracture risk with faulty sensation of good bone health attributed by high BMD. This is due to bone anti resorption rather than bon forming effect of thyrotropin.

Meanwhile, the observed elevation in osteocalcin level with low TSH (Group 1) is attributed to the mutual action of osteoclast and osteoblast, as bone resorption is always associated with bone formation.

According to our data we can suggest that TSH is useful clinical marker for osteoporosis in patients taking thyroxin therapy.

This level is important to patients taking thyroxin to avoid being deceived by high BMD while the patient is already in an adynamic bone state and osteoporotic patient taking thyroxin could benefit from this cut off as controlling thyroid state with this cut of number or slightly higher, could give them good resorption lowering beside increasing their formation state a little bit.

According to our data we can suggest that osteocalcin is useful clinical marker for osteoporosis in patients with thyroxin therapy. as there were statistical significance between TSH level and osteocalcin level. According to our data we can suggest that DPD is useful clinical marker for osteoporosis in patients with thyroxin therapy, as there were high statistical significance between TSH and DPD level.

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