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Effect of Restoration of Euthyroidism on Bone Mineral Density in Hypothyroid Patients

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Abstract

Osteoporosis is a condition characterized by low bone mass, resulting in decreased bone strength and an increased risk of fracture. The purpose of this study was to examine the effect of Thyroid hormone replacement on bone mineral density (BMD) in newly diagnosed cases of hypothyroidism in individuals without diabetes. This is a clinical trial study during which 80 postmenopausal females were enrolled. The first group = 40 females (Hypothyroid group) received the intervention which is Levothyroxine sodium anhydrous (Eltroxin™) and Vit-D and calcium replacement according to NOF (National osteoporosis foundation), The second group = 40 females received Vit-D and calcium replacement (euthyroid group). The Hypothyroid group had a greater percentage change in TSH, total calcium, and Vit. D levels than the Control group (p=0.001). Regarding DEXA scan measurement parameters, FraxTM major fracture measurement was significantly higher in the hypothyroid group than in the Control group which indicates that treatment of hypothyroidism in postmenopausal females with evidence of osteoporosis has a positive correlation with bone health on the long run. Both groups show significant increase in Ionized serum calcium and Vit. D levels after replacement compared to their levels before therapy. Among hypothyroid females, there is significant decrease in DEXA scan of FraxTM major osteoporotic after thyroid hormone replacement compared to its value before replacement, no significant differences in DEXA scan of Left femur score or Frax major osteoporotic before and after treatment in the Control group. Hypothyroid postmenopausal females showed significant increase in total serum Calcium, ionized serum calcium and Vit. D levels post replacement compared to their levels before therapy.

Keywords: Euthyroidism; Bone Mineral Density; Hypothyroid, Osteoporosis, postmenopausal, Dexa Scan

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1. Introduction

Hypothyroidism tends to develop slowly, and its symptoms tend to worsen over time [1-2]. The symptoms of hypothyroidism can range from mild to severe, depending on how old the patient is when they were diagnosed [3].

Primary hypothyroidism occurs in 5% of individuals. and more common in females [4]. Rarely occurring secondary and tertiary hypothyroidism is typically attributable to pituitary gland and hypothalamic dysfunction [5]. An abnormally high TSH level almost often confirms the presence of primary hypothyroidism [6]. Systemic consequences of severe hypothyroidism can be treated with hormone replacement therapy to make up for the lack of endogenous thyroid hormone synthesis [7]. The preferred hormonal formulation is levothyroxine sodium (henceforth thyroxine) [8]. Primary hypothyroidism patients can have their thyroxine dosage determined by measuring their thyroid stimulating hormone levels. 4–6 weeks after starting treatment [3]. There are a number of methods for determining Bone mineral density (BMD), but DEXA provides the most accurate measurements at a variety of bone sites with the least amount of radiation. All women over the age of 65 should be evaluated for osteoporosis using bone densitometry, according to guidelines [9]. Women under 65 whose estimated fracture risk is at least that of a 65-year-old woman without additional risk factors are encouraged to undergo screening by the United States Preventive Services Task Force and the National Osteoporosis Foundation (NOF) Guideline, respectively [10]. BMD strongly predicts fracture risk. Fracture risk doubles for each standard deviation BMD below the peak bone mineral age average [11]. For example, BMD in the hip is the strongest predictor of hip fracture, although BMD measured anywhere predicts overall fracture risk [12]. Osteoporosis can be described as a BMD result that is 2.5 standard deviations (SD) or more below the average value for a person at the age of peak bone mineral content (a T-score of -2.5 or lower). Osteopenia can be described as a BMD result between -1.0 and -2.5 standard deviations (T-score) below the mean [13]. Vitamin D refers to both ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3), two related steroids. Both are synthesized via photolysis from sterol precursors found in nature. Until recently, vitamin D2 was the only type of vitamin D used in medicine or supplements, the availability of formulations with high vitamin D3 doses (e.g.,10,000-50,000 units) is beginning to alter this [14]. 7-dehydrocholesterol, a kind of cholesterol found in abundance in the skin, is the precursor to vitamin D3 [11]. These characteristics cause vitamin D2 to be metabolized differently from vitamin D3, yet both are ultimately converted to the active forms of vitamin D, 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D [11]. Sunlight exposure is the primary catalyst in the synthesis of pre-vitamin D3 during endogenous vitamin D synthesis. 1,25D (1,25 hydroxyvitamin D) is the physiologically active form of vitamin D, acting at target locations in bone and immune cells, as well as liver cells, after being hydroxylated in the liver and subsequently the kidney [15]. The purpose of this study was to examine the effect of Thyroid hormone replacement on bone mineral density (BMD) in newly diagnosed cases of hypothyroidism in individuals without diabetes.

2. Subjects and methods

This is a clinical trial study during which 80 postmenopausal females were enrolled. The female cohort were divided into two equal group. The first group = 40 females (Hypothyroid group) received the intervention which is Levothyroxine sodium anhydrous (Eltroxin™) and Vit-D and calcium replacement; Group 2 included 40 = females received Vit-D and calcium replacement only. The study was approved by the Ethical Review Board of the School of Medicine at Beni-Suef University (--). After the objectives of the study were explained, all participants voluntarily gave their written informed consent to participate. In case of vitamin D deficiency cholecalciferol was prescribed as one of the following: Vitamin D3 10,000units: Dose 5 capsules (50,000units) weekly. Calcio carbonate 2,500 mg (1,000 mg elemental calcium) in cases of calcium shortage (normally 10 ml/kg of this preparation will enhance serum calcium by 0.3-0.5 mmol/l; dose based on manufacturer's recommendations) [16]. Osteoporotic patients were treated according to guidelines by vitamin D & calcium replacement and Ipandroinic acid 150mg once weekly is the first-line treatment. Patients should comply with administration instructions to minimize esophageal irritation. (Dose according to manufacturer) [17].

2.1. Inclusion criteria

Patients diagnosed as hypothyroid nondiabetic patients, whether these patients are diagnosed as vitamin D & calcium deficit or not.

2.2. Exclusion criteria

Past history of malignancy and degeneration disease of the nervous system, other endocrine diseases which affect bone metabolism e.g., Cushing disease, Acromegaly, Chronic diseases e.g., Liver cirrhosis, chronic kidney disease, autoimmune diseases e.g., systemic lupus erythematosus & rheumatoid arthritis patients, History of drug use i.e., steroids.

2.3. 5-Statistical analyzes

Data was collected and entered to Excel® sheet then data exported to SPSS statistical package software for data analysis. All data were expressed as means ± standard deviations of the mean (SD). Independent t-test (two- sided), or Mann-Whitney U-test in the case of nonparametric distributions, were used to identify demographic variables showing differences among the groups, and to compare two groups after the intervention. To compare study variables during study periods, paired t-test or Wilcoxon signed-rank test for non-parametric distribution was used. Significance was defined as p- value equal or less to 0.05.

- All participants were subjected to the following before starting treatment & one years after reaching euthyroid state.
- The following data were collected, age, weight and BMI.

2.4. Laboratory investigations

Laboratory investigations include Total and ionized calcium, phosphorus, Vit D and Hb level, Albumin level, Alanine transaminase (ALT), Aspartate transaminase (AST), Alkaline phosphatase, urea, and creatinine.

2.5. Parathyroid hormone level (PTH)

2.5.1. Thyroid profile

Thyroid profile including Thyroid stimulating hormone (TSH), Free triiodothyronine (FT3) & Free Tetra-iodothyronine (FT4) Levels.

2.5.2. The dual-energy X-ray absorptiometry (DEXA)

The dual-energy X-ray absorptiometry (DEXA) to assess the level of bone mineral density once at diagnosis & after one year.

2.5.3. Fracture Risk Assessment Tool (FRAX) Score

For untreated patients between the ages of 40 and 90, FRAX can estimate the 10-year probability of hip fracture and major osteoporotic fracture (hip, clinical spine, proximal humerus, or forearm) using readily available clinical risk factors for fracture, with or without femoral neck BMD.

3. Results

The mean age in hypothyroid group was 57±10 yrs. and the mean age in the control group was 55±10 yrs. The mean weight was 64±6 and 66±3 and the mean BMI was 24.5±1.1 and 24±1.2 in the hypothyroid group and control group respectively (Table1). No significant difference between the two groups regarding baseline parameters; free T4, calcium level, phosphorus, Vit D., Hb, albumin, ALT, AST, alkaline phosphatase, urea, creatinine (Table 2), or AP spine score, Left Radius T-score, and Frax™ Hip fracture (Table 3). After intervention; the measurement of free T3 and T4, total calcium level and VIT. D level was significantly higher in the hypothyroid group and p-value was (0.001, 0.047. 0.001 and 0.002 respectively) (Table 4). Before treatment, Frax™ major measurement was significantly higher in the hypothyroid group (3.00± 1.55) than in the Control group (1.85±0.89) and p-value was significant at (0.001) (Table 4). When comparing the hypothyroid group to the control group, the hypothyroid group had a greater percentage change in TSH, total calcium, and VIT D levels before and after treatment (p=0.001) (Table 5 & Figure 1). Frax™ major showed a substantially larger percentage change (0.00 ±0.01) in the hypothyroid group compared to the control group (-0.01 ±0.02), with a p-value of 0.031 (Table 6 & Figure 2). Among hypothyroid females, there is significant decrease in DEXA scan of Frax™ major osteoporotic after thyroid hormone replacement compared to its value before replacement, while there are no significant differences in DEXA scan of AP spine, left femur score, Left radius T score or Frax™ hip fracture before and after replacement therapy (Table 7). Among the Control group, there are significant decreases in DEXA scan of AP spine, Left radius T-score and Frax hip fracture after Control. while there are no significant differences in DEXA scan of Left femur score or FraX score (Table 8).

4. Discussion

This study shows the difference between parameters measurement after the intervention in both groups. The measurement of free T3 and T4, total calcium level and VIT. D level was significantly higher in the hypothyroid group and p value was (0.000, 0.047. 0.001 and 0.002 respectively) Our study is supported by that of Salvatore Benvenga et al., (2017) which reveal that postmenopausal hypothyroid patient level of vitamin D and calcium has a positive impact with thyroid hormone replacement [18]. As the level of vitamins has a negative correlation with the level of TSH in the case of hypothyroid patients, our study shows that the percentage change in TSH, total calcium level, and VIT D level was significantly higher in the Hypothyroid group than in the Control group and p-value was significant at 0.001, this is supported by findings reported by Salvatore Benvenga et al., (2017) [18]. However, the results of a case-control study by Ishag Adam et al. contradict ours, showing no significant difference in vitamin D levels between women with hypothyroidism and the control group [18]. Regarding DEXA scan measurement parameters, Frax™ major fracture before treatment was significantly higher in the hypothyroid group (3.00±1.55) than in the Control group (1.85±0.89) and p-value was significant at (0.001), after treatment the percent of improvement of FraxTM major fracture in the hypothyroidism group was higher comparing to the control group this support the approach to treat hypothyroidism in postmenopausal females with osteoporosis prior to Vit. D and calcium supplementation. This might have a positive correlation with bone health on the long run and this is supported by Lia Mara Montagner Ross et al., (2018) [19-20]. Our study shows that among hypothyroid postmenopausal females, there is significant increase in total serum Calcium, Ionized serum calcium and Vit. D levels after replacement compared to their levels before therapy, while there are no significant differences in serum phosphorus level or PTH level before and after therapy this is supported by study by Deborah Agostini et al., (2018) [20].

Table 1: Demographic characteristics of the studied patients.

Variable	**Hypothyroid group (n. 40)** Mean ± SD	**Non -Thyroid (control) Group (n. 40)** Mean ± SD	**P value**
Age in years	57±10	55±10	0.234
Weight in Kg	64±6	66±3	0.465
BMI	24.5±1.1	24±1.2	0.756

N: number.

Table 2: Baseline measurement before treatment with hypothyroid group (n=40) or Control (n=40).

Characteristics	Group		p-value
	hypothyroid group Mean ±SD	**control group** Mean ± SD	
TSH	59 ±29.0	3.7±1.4	0.004*
FreeT4	0.66±0.116	0.67 ±0.116	NS
Total Calcium	8±0.0	8±0.0	NS
Ionized Calcium	4±0.0	4±0.0	NS
Phosphorus	4±0.0	4±0.0	NS
Vit. D	13±5.0	13±6.0	NS
PTH	47±12.0	51±14.0	0.034*
Hb	12 ±1.0	12±1.0	NS
Albumin	4 ±1.0	4±0.0	NS
ALT	38 ±4.0	43±22.0	NS
AST	38 ±4.0	38 ±3.0	NS
Alkaline phosphatase	81 ±37.0	70±21.0	NS
Urea	33 ±6.0	32±6.0	NS
Creatinine	1 ±0	1 ±0	NS
AP spine T score	-1±1	-1±2	NS
Left Radius T-score	-2±2	-2 ±2	NS
Frax^{TM} Major osteoporotic	1.79 ±1.07	1.55 ±1.19	0.003*
Frax^{TM} Hip fracture	.59 ±1.43	0.59 ±0.99	NS

TSH; thyroid stimulating hormone, T3; T4; VITD; vitamin D, PTH; parathyroid hormone, HB; hemoglobin, ALT; alanine transaminase, AST; aspartate transaminase, AP spine T score; Anteroposterior spine T score, Fra^{xTM}; Fracture risk assessment tool.

Table 3: DEXA scan parameters before treatment with Thyroid replacement therapy between Hypothyroid GROUP (n=40) and Control (n=40).

Parameters	Hypothyroid group	Control group	P value
AP spine T score	-1 ±1	-1 ± 1	0.364
Left femur score	-1±1	0 ±1	0.545
Left radius T-score	-1± 1	-1 ±1	0.929
Frax^{TM} major osteoporotic	3.00± 1.55	1.85±0.89	0.001*
Frax^{TM} hip fracture	0.23 ± 0.34	0.15 ±0.15	0.188

AP spine T score; Anteroposterior spine T score Frax^{TM}; Fracture risk assessment tool.

Table 4: Parameters after treatment in Hypothyroid group (n=40) and Control (n=40).

Parameters	Group		P value
	hypothyroid group Mean ± SD	Control group Mean± SD	
TSH	3±1	3 ± 1	0.369
FreeT4	1.33± 0.26	1.23 ± 0.19	0.047*
Calcium total	9.2± 0.1	8.71 ±1.2	0.001*
Calcium ionized	5.1 ± 0.21	5.03 ± 0.43	0.800
Phosphorus	4.06 ± 0.012	4.01 ± 0.023	0.314
Vit. D	28.7± 4	20.1 ± 4	0.002*
PTH	44 ± 9	46 ± 5	0.269
Hb	12.1 ±1.0	12.3± 1.09	0.580
Albumin	4.13 ±1	4.10 ± 0.89	>0.999
AlT	38 ± 4	38 ± 3	0.532
AST	38 ± 4	38 ± 4	0.684
Alkaline phosphatase	71 ± 18	75 ± 21	0.357
Urea	33 ± 6	32 ± 6	0.925
Creatinine	1 ± 0	1± 0	0.807

TSH; thyroid stimulating hormone, T3; T4; VITD; vitamin D, PTH; parathyroid hormone, HB; hemoglobin, ALT; alanine transaminase, AST; aspartate transaminase.

Table 5: Mean percent of change in TSH, T4, total calcium, VIT D and PTH parameters after treatment.

Mean percent of change	Hypothyroid group Mean ±SD	Control Group Mean ±SD	P-value
TSH	0.56 ±.29	0.34 ±.14	0.001*
Free T4	0.01 ±.00	0.01 ±.00	0.055
Total calcium	0.01 ±.00	0.00 ±.01	0.001*
VIT.D	0.15 ±.07	0.07 ±.08	0.001*
PTH	0.00 ±.01	0.00 ±0.01	0.229

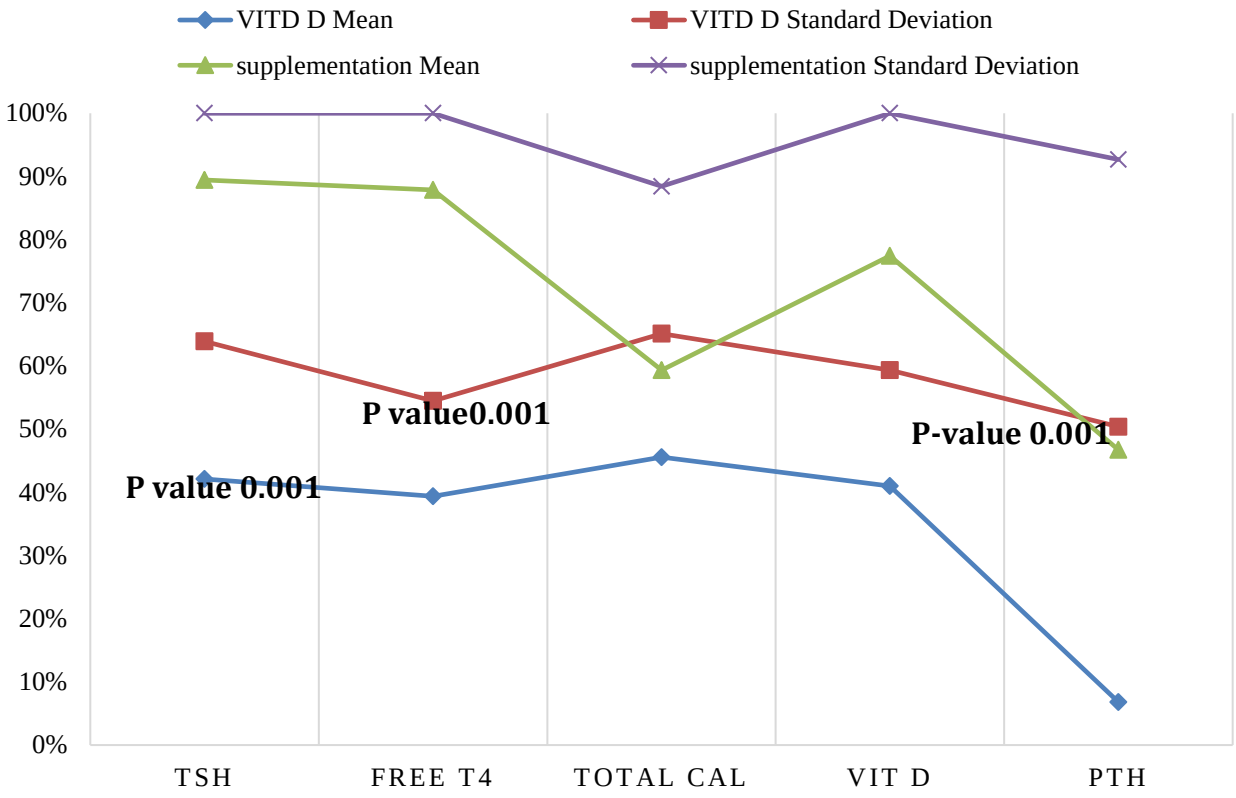

Figure 1: Percent of change in the TSH, Free T4, Total Ca, VIT D and PTH measurement.

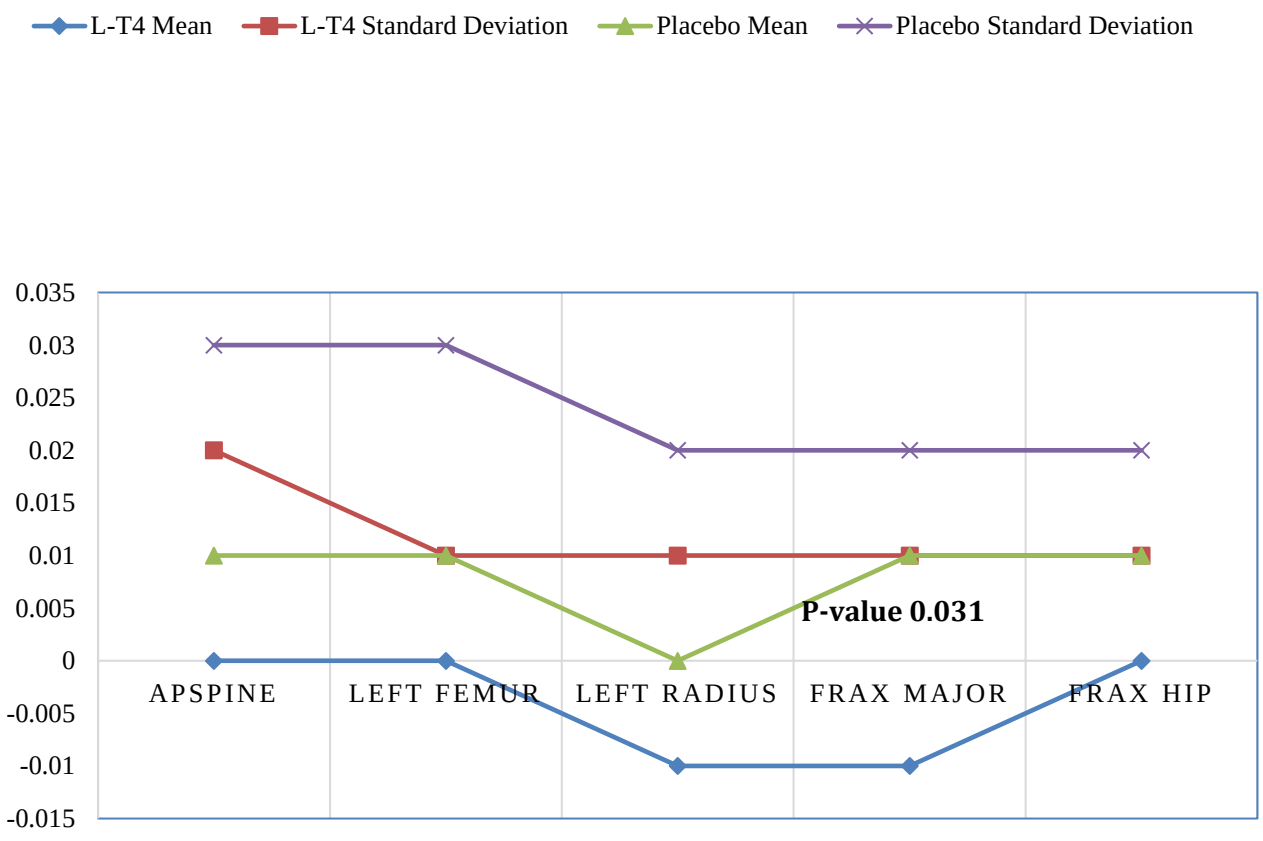

Figure 2: Percent of change in the DEXA scan measurement.

Table 6: Mean percent of change in DEXA scan.

Mean percent of change	Hypothyroid group Mean ±SD	Control Group Mean ±SD	P-value
AP spine T score	0.00 ± 0.02	-0.01 ± 0.02	0.269
Left femur T score	0.00 ± 0.01	0.00 ± 0.02	0.771
Left radius	-0.01± 0.02	-0.01± 0.02	0.523
Frax™ Major	0.01 ± 0.02	-0.00 ± 0.01	0.031*
Frax™ hip	0.00 ± 0.01	0.00 ± 0.01	0.786

Table 7: Differences in DEXA scan before and after Replacement in hypothyroid females.

Hypothyroid group (N=40)	Pre	Post	P-value
AP spine	1.22±1.3	1.00±1.0	0.382
Left femur score	0.91±1.2	0.58±1.0	0.166
Left radius T score	1.90±2.0	1.36±1.3	0.132
Frax™ major osteoporotic	3.00±1.5	1.79±1.0	0.001*
Frax™ hip fracture	0.58±1.4	0.22±0.3	0.135

Table 8: Differences in DEXA scan before and after in the Control group.

Control group	Pre	Post	P.value
AP spine	1.43 ± 1.5	0.78 ± 1.0	0.038*
Left femur score	0.88 ± 1.2	0.45 ± 0.8	0.080
Left radius T score	2.21 ± 2.0	1.34 ± 1.3	0.023*
Frax™ major osteoporotic	1.54 ± 1.1	1.85 ± 0.8	0.179
Frax™ hip fracture	0.58 ± 0.9	0.15 ± 0.1	0.010

Our study reveals that among hypothyroid females, there is significant decrease in DEXA scan of Frax™ major osteoporotic after thyroid hormone replacement compared to its value before replacement, while there are no significant differences in DEXA scan of AP spine, left femur score, Left radius T score or Frax™ hip fracture before and after replacement therapy these results not the same with Kristi Tough DeSapri & Rachel Brook, this may be due to our small study population ethnicity so that we need further assessment and follow-up over a large scale of population [21]. Among the Control group our study shows, there are significant increases in Ionized serum calcium and Vitamin D levels after treatment while PTH level significantly decreased after treatment, However, there are no significant differences in Total serum Calcium level or Serum phosphorus level before and after treatment of control group, Raposo et al.'s (2017) study in Portugal supports this [22]. Our study shows that among the Control group, there are significant decreases in DEXA scan of AP spine, Left radius T-score and Frax hip fracture after Control. while there are no significant differences in DEXA scan of Left femur score or Frax major osteoporotic before and after Control so these results statistically significant however with the use of FRAX score it's negligible. Patricia Barrionuevo et al., (2019) supports these results [23].

5. Conclusions

In conclusion we found that, treatment of hypothyroidism in postmenopausal females with evidence of osteoporosis has a positive correlation with bone health on the long run. Hypothyroid postmenopausal females showed significant increase in total serum Calcium, ionized serum calcium and Vit. D levels post replacement compared to their levels before therapy. Frax™ major fracture measurement was significantly higher in the hypothyroid females (3.00±1.55). Hypothyroid postmenopausal females showed no significant differences in serum phosphorus level or PTH level before and after therapy. Among hypothyroid females, there is a significant decrease in DEXA scan of Frax™ major osteoporotic after thyroid hormone replacement compared to its value before replacement. Among hypothyroid females, there are no significant differences in DEXA scan of AP spine, left femur score, Left radius T score or Frax™ hip fracture before and after replacement therapy in this study due to smaller population ethnic. This Study alarming that all postmenopausal females are in a needy situation for free T3, freeT4 & THS levels measurements periodically to help themselves for keeping a healthy life without risky unfavorable problems.

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Conflict of interest

We have no conflict of interest to declare.

Authors contribution

M.A.M conceived the idea of the study, collected data, contributed to the statistical analysis of the data, and wrote the first draft, M.F.K conceived the idea of the study, and substantively revised the work. All other authors were involved in the acquisition of data and revised the work. All authors approved the submitted version. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

Ethical approval

The study was approved by the ethical review boards in Faculty of Medicine Beni Suef University, Approval No. FWA 00015574.

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