Assessment of Bone Mineral Density in Patients with Subclinical Hypothyroidism

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Abstract:

Background and Aim: Although overt hyperthyroidism and overt hypothyroidism have been linked to osteoporosis in both women and men, it is unclear whether subclinical thyroid dysfunction is also linked to osteoporosis. The current study evaluated the association between thyroid function parameters and bone densitometry.

Patients and Methods: In this study, we enrolled 20 patients with subclinical hypothyroidism (SCH) and 20 healthy subjects. In all participants, bone mineral density (BMD) was assessed. In addition, thyroid hormone profile, lipid profile, and serum vitamin D were also evaluated.

Results: The main findings of the current study were; 1) patients with SCH had significantly lower BMD (0.872 ± 0.123 vs. 0.991 ± 0.112 (g/cm); p= 0.003), and lower vitamin D (14.98 ± 6.62 vs. 34.68 ± 13.92 (ng/ml); $p < 0.001$) and significantly higher cholesterol (184.89 ± 25.91 vs. 165.78 ± 23.67 (mg/dl); p= 0.02) and low density lipoproteins (114.8 ± 29 vs. 94.78 ± 17.54 (mg/dl); p= 0.012). Also, 12 (60%) patients had no osteopenia or osteoporosis, while 2 (10%) patients had osteopenia and 6 (30%) patients had osteoporosis. At the cutoff point, thyroid-stimulating hormone > 9.45, had 95% accuracy for predicting bone mineral disorders in patients with SCH, with an area under the curve of 0.939.

Conclusion: Patients with SCH are vulnerable to developing osteopenia and osteoporosis with subsequent pathological fracture. Regular assessment of such patients should be considered. Future studies are warranted to confirm these findings.

Keywords: Accuray, DEXA, Osteomalacia.

Introduction:

Any changes in normal thyroid function and thyroid-stimulating hormones (TSH) directly affect the remodeling of bone through TSH receptors found on osteoblast and osteoclast precursor cells **(1)**. Subclinical hypothyroidism represents a state with increased values of thyroid-stimulating hormone (TSH) and normal values of thyroxine (T4) and triiodothyronine (T3) **(2).**

The current study aimed to evaluate BMD in patients with SCH. Also, to evaluate the association between thyroid function parameters and bone densitometry.

Patients and Methods

Study Setting and Design

This case-control study was carried out on patients with subclinical hypothyroidism attending Outpatient Clinics and Inpatient Endocrinology Clinics.

All patients signed informed consent. IRB; Faculty of Assiut Medicine approved the study with IRB: 17101461

Inclusion Criteria

All adult patients with subclinical hypothyroidism are defined as a condition in which increased serum TSH levels are accompanied by thyroid hormone serum concentrations within the normal population-based reference range, based on the definition, with none of the underlying exclusion criteria

Exclusion Criteria

diabetes mellitus, Cushing disease, parathyroid disorders, chronic kidney disease, or on corticosteroid therapy, inflammatory conditions as rheumatoid arthritis, systemic lupus, Crohn's disease, ulcerative colitis, and/or chronic liver disease

Study Groups

The study included two groups:

1- **Group I (case group):**

Twenty patients with subclinical hypothyroidism

2- **Group II (control group**):

Twenty patients with normal thyroid function were age and sex matched.

Methodology

Data Collection

At each comprehensive health examination, we collected data on demographic characteristics, smoking status, physical activity, medical history, and medication use through standardized, self-administered questionnaires.

Trained registered nurses measured smoking status, blood pressure, and anthropometry items as part of a health check-up program. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2) **(3)**. Laboratory data were recorded, including complete blood count, serum vitamin D, and random blood sugar.

SCH was defined as a TSH level < 0.27 μIU/mL, and subclinical hypothyroidism was defined as TSH > 4.2 μIU/mL, both with an fT4 level within the normal range (0.84–1.74 ng/dL). We defined euthyroid status based on the normal TSH reference range of 0.27–4.20 μIU/Ml **(4)**. BMD was measured by dual-energy X-ray absorptiometry (Lunar Prodigy; GE, Madison, WI, USA), and the results are expressed in g/cm^2.

Results

Demographic data of the two studied groups (Table 1):

There is a significantly higher systolic and diastolic blood pressure among the cases with SCH.

Laboratory parameters between the two studied groups (Table 2)

The cases group had significantly lower vitamin D in comparison to the control group (14.98 ± 6.62 vs. 34.68 ± 13.92 (ng/ml); $p < 0.001$).

Lipid profile and lipid profile between the two studied groups (Table 3):

Patients SCH had significantly higher total cholesterol (TC) (184.89 ± 25.91 vs. 165.78 ± 23.67 (mg/dl); $p= 0.02$) and low-density lipoproteins (LDL) (114.8 ± 29 vs. 94.78 ± 17.54 (mg/dl); $p= 0.012$) in comparison to the control group but both groups had insignificant differences as regard triglyceride (TGs) and high-density lipoproteins (HDL).

Bone mineral density between the two studied groups (Table 4):

Patients with SCH had significantly lower BMD (0.872 ± 0.123 vs. 0.991 ± 0.112 (g/cm); $p= 0.003$), T-score (−2.53 ± 0.618 vs. −0.392± 1.03; $p < 0.001$) and Z-score (−0.6 ± 1.36 vs. −0.2 ± 1.2; $p < 0.001$)

Frequency of osteoporosis and osteopenia prevalence among the case group (Table 5).

It was found that 12 (60%) patients had no osteopenia or osteoporosis, while 2 (10%) patients had osteopenia and 6 (30%) patients had osteoporosis.

disorders in patients with SCH, with an area under the curve of 0.939.

Accuracy of thyroid-stimulating hormone in the prediction of bone mineral disorders in patients with SCH (Table 6, Figure 1):

At the cutoff point, TSH > 9.45 had 95% accuracy in predicting bone mineral

Correlation between BMD and thyroid function in the case group (Table 7):

TSH and BMD have a significant negative correlation (r=-0.199, p= 0.044) and T score (r= -0.215, p= 0.006).

Legend of Tables

Table 1: Demographic data of the two studied groups

Variable		**Cases** (n=20)	**Controls** (n=20)	***P***
Age (years)		45.79 ± 9.42	44.37 ± 7.35	.598
Sex	Female	13 (65%)	11 (55%)	.519
	Male	7 (35%)	9 (45%)	
Body mass index (kg/m^2)		26.12 ± 3.57	24.53 ± 2.96	.134
Waist circumference (cm)		95.48 ± 13.22	86.98 ± 12.53	.071
Systolic blood pressure (mmHg)		125.78 ± 4.81	120.67 ± 2.74	.000
Diastolic blood pressure (mmHg)		87.89 ± 13.84	79.78 ± 3.53	.018

Data is expressed as frequency (percentage) and mean (SD). P-value was significant if < 0.05

Table 2: Laboratory parameters between the two studied groups

	Cases (n=20)	**Controls** (n=20)	***P***
Hemoglobin (g/dl)	11.55 ± 1.64	12.18 ± 1.43	.154
Leucocytes (10^3 /µL)	8.12 ± 2.32	6.87 ± 3.02	.107
Platelets (10^3 /µL)	273.44 ± 35.92	268.18 ± 37.87	.617
Random blood sugar (mg/dl)	116.14 ± 19.61	125.57 ± 16.84	.074
Serum Creatinine (mg/dl)	0.654 ± 0.154	0.712 ± 0.163	.202
Urea (mg/dl)	19.25 ± 5.27	17.32 ± 5.64	.217
Aspartate transaminase (U/L)	31.65 ± 8.56	33.38 ± 10.6	.529
Alanine transaminase (U/L)	30.09 ± 10.01	28.36 ± 9.11	.526
Sodium (mEq/L)	136.61 ± 5.27	138.74 ± 2.56	.112
Potassium (mEq/L)	4.72 ± 0.643	4.78 ± 0.684	.777
Calcium (mg/dl)	8.83 ± 1.26	9.38 ± 0.724	.099
Phosphate (mg/dl)	5.24 ± 1.08	4.93 ± 0.754	.299
Magnesium (mg/dl)	2.52 ± 0.716	2.29 ± 0.403	.218
Alkaline phosphates (U/L)	218.43 ± 83.22	205.19 ± 74.31	.599
1, 25 $(OH)_2$Vitamin D (ng/ml)	14.98 ± 6.62	34.68 ± 13.92	**<0.001**

Data expressed as mean (SD). P-value was significant if < 0.05.

Table (3): Lipid profile and thyroid function between the two studied groups

	Cases (n=20)	**Controls** (n=20)	***P***
Cholesterol (m/dl)	184.89 ± 25.91	165.78 ± 23.67	.020
Triglyceride (mg/dl)	134.53 ± 32.76	134.64 ± 31.31	.991
Low density lipoproteins (mg/dl)	114.8 ± 29	94.78 ± 17.54	.012
High density lipoproteins (mg/dl)	44 ± 13.36	43.78 ± 4.79	.945
Thyroid-stimulating hormone (mU/L)	10.05 ± 1.64	1.85 ± 0.46	<0.001
Free T4 (pmol/L)	14.42 ± 1.79	14.49 ± 1.91	.902
Free T3 (pmol/L)	7.41 ± 1.01	7.49 ± 1.14	.816

Data expressed as mean (SD). P-value was significant if < 0.05.

Table (4): Bone mineral density between the two studied groups

	Cases (n=20)	**Controls** (n=20)	***P***
Bone mineral density (g/cm^2)	0.872 ± 0.123	0.991 ± 0.112	0.003
T-score	−2.53 ± 0.618	−0.392± 0.03	<0.001
Z-score	−0.6 ± 1.36	−0.2 ± 0.02	< 0.001

Data expressed as mean (SD). P-value was significant if < 0.05. BMD: bone mineral density

Table (5): Osteoporosis prevalence among the case group.

	Cases (n=20)
Osteopenia	2 (10%)
Osteoporosis	6 (30%)
Normal	12 (60%)

Data expressed as frequency (percentage)

Table (6): Accuracy of thyroid-stimulating hormone in the prediction of bone mineral disorders in patients with SCH

	Indices
Sensitivity	97%
Specificity	90%
Positive predictive value	85%
Negative predictive value	98%
Accuracy	95%
Cutoff point	> 9.45
Area under the curve	0.939
P value	< 0.001

P-value was significant if < 0.05. SCH: subclinical hypothyroidism

Table 7: Correlation between BMD and thyroid function in the case group

	BMD	**T score**
Thyroid-stimulating hormone (mU/L)	-0.199 (0.044)	-0.215 (0.006)
Free T_4 (pmol/L)	0.13 (0.569)	0.12 (0.178)
Free T_3 (pmol/L)	0.10 (0.220)	0.09 (0.389)

Data expressed as *r* value (*p* value). BMD: bone mineral density

Legend of Figures

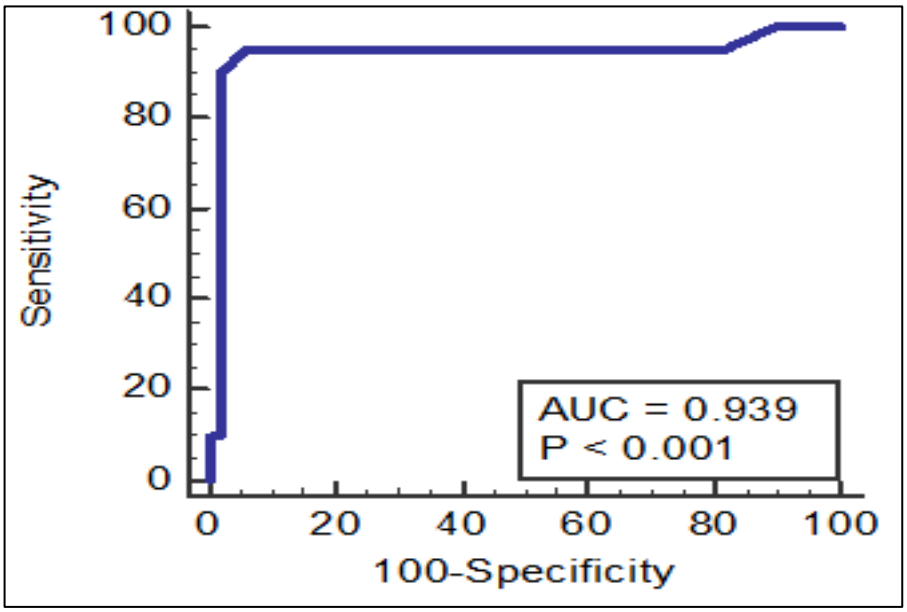

Figure 1: Accuracy of thyroid-stimulating hormone in predicting bone mineral disorders in patients with subclinical hypothyroidism. AUC: area under the curve

Discussion

The current study found no significant differences between the groups regarding baseline data, except for higher SBP and DBP among patients with SCH. In line with this study, previous research stated no significant differences between patients with SCH and those with normal thyroid function with regard to baseline data **(5)**. Also, **Garin et al.** found the same findings **(6)**.

Other findings in the current study included that both groups had insignificant differences with regard to baseline laboratory data and electrolytes, while the cases group had significantly lower vitamin D in comparison to the control group (14.98 ± 6.62 vs. 34.68 ± 13.92 (ng/ml); $p < 0.001$). In agreement with this study, **Sudha et al.** found low vitamin D levels among patients with SCH.

The results of the present research indicated that subclinical hypothyroidism patients deal with vitamin D deficiency (< 20 ng/mL) more than healthy people. In the study of **Evliyaoğlu et al.**, patients with < 20 ng/mL were considered as vitamin D deficient, and they showed that the prevalence of vitamin D deficiency is more common in people with SCH than in normal

people **(7)**. Previous studies stated the same findings **(8, 9)**.

The current study stated that patients SCH had significantly higher TC (184.89 ± 25.91 vs. 165.78 ± 23.67 (mg/dl); *p*= 0.02) and LDL (114.8 ± 29 vs. 94.78 ± 17.54 (mg/dl); *p*= 0.012) in comparison to the control group but both groups had insignificant differences as regard TG and HDL. Many reported studies revealed significantly higher cholesterol levels and low-density lipoproteins among patients with SCH **(10-14)**.

The current study found that patients with SCH had significantly higher TSH in comparison to the control group (10.05 ± 1.64 vs. 1.85 ± 0.46 (mU/L); $P < 0.001$), but both groups had insignificant differences with regard to free T3 and free T4. In agreement with this study, **Akter et al.** stated that patients with SCH had significantly higher levels of TSH in comparison to the control group (7.77 ±1.61 vs. 3.03 ±0.98; $p < 0.001$) **(15)**.

Another finding in the current study was that patients with SCH had significantly lower BMD. It was found that 12 (60%) patients had no osteopenia or osteoporosis, while 2 (10%) patients had osteopenia and 6 (30%) patients had osteoporosis. These results were similar to previous reports **(6, 16)**.

Different hypotheses have been proposed about the mechanisms of the association between thyroid function and bone metabolism. Thyroid hormones have been shown to affect osteoclasts directly. However, one cross-sectional study suggests that longstanding suppressive therapy with LT4 may have no significant adverse effects on BMD in differentiated thyroid carcinoma patients with subclinical hypothyroidism **(17)**.

Another study showed that thigh muscle strength decreases in subjects with subclinical hyperthyroidism and possibly leads to an increased risk for fall-related fractures. The low BMD that characterizes osteoporosis is one of the most significant risk factors for fracture. Subclinical hyperthyroidism has been associated with decreased BMD and may contribute to osteoporosis, which increases vulnerability to fractures **(18)**.

In contrast to these findings, a previous study reported that there was no association between subclinical hypothyroidism and increased risk of hip fracture or lower BMD at the spine or hip in elderly men or women in a large, population-based cohort. This may be attributed to a different study population, where their study was concerned with only elderly patients **(6)**.

Also, our study found a significant positive correlation between BMD and FT4 and FT3, while a significant negative correlation exists between BMD and TSH. A similar study performed in Korean individuals reported that variations in TSH levels within the euthyroid and subclinical range are positively correlated with BMD at the lumbar spine, FN, and total hip, and a negative relationship between TSH and fT4, whereas total T3 and TSH correlated positively with BMD **(19)**.

To our knowledge, this is the first study that evaluated the diagnostic accuracy of TSH in patients with SCH to predict osteoporosis. At the cutoff point, TSH > 9.45 had 95% accuracy in predicting bone mineral disorders in patients with SCH, with an area under the curve of 0.939.

The main limitations of the current study included a relatively small sample size, being conducted in a single center, no long-term follow-up, and we didn't assess the effect of therapeutic options in such patients on BMD. Yet, our study discussed a very important issue in our locality: a lack of data about its prevalence. Also, we created a cutoff point for TSH to predict osteoporosis in patients with SCH.

Conclusion

Subclinical hypothyroidism is associated with reduced BMD at the forearm. Patients with SCH are vulnerable to developing osteopenia and osteoporosis with subsequent pathological fracture. At the cutoff point, TSH > 9.45, had 95% accuracy for predicting bone mineral disorders in patients with SCH, with an area under the curve of 0.939. It's recommended that such a study be performed on many patients in multiple centers.

References:

1. Tuchendler D, Bolanowski M. The influence of thyroid dysfunction on bone metabolism. Thyroid Res. 2014;7:12.
2. Cojić M, Cvejanov-Kezunović L. Subclinical hypothyroidism - whether and when to start treatment? Open Access Maced J Med Sci. 2017;5(7):1042-6.
3. Kim MK, Lee WY, Kang JH, et al. 2014 clinical practice guidelines for overweight and obesity in Korea. Endocrinol Metab (Seoul). 2014;29(4):405-9.
4. Lee K, Lim S, Park H, et al. Subclinical thyroid dysfunction, bone mineral density, and osteoporosis in a middle-aged Korean population. Osteoporos Int. 2020;31(3):547-55.
5. Lee WY, Oh KW, Rhee EJ, et al. Relationship between subclinical thyroid dysfunction and femoral neck bone mineral density in women. Arch Med Res. 2006;37(4):511-6.
6. Garin MC, Arnold AM, Lee JS, Robbins J, Cappola AR. Subclinical thyroid dysfunction and hip fracture and bone mineral density in older adults: the Cardiovascular Health Study. J Clin Endocrinol Metab. 2014;99(8):2657-64.
7. Evliyaoğlu O, Acar M, Özcabı B, et al. Vitamin D deficiency and Hashimoto's thyroiditis in children and adolescents: a critical vitamin D level for this association? J Clin Res Pediatr Endocrinol. 2015;7(2):128-33.
8. Tamer G, Arik S, Tamer I, Coksert D. Relative vitamin D insufficiency in Hashimoto's thyroiditis. Thyroid. 2011;21(8):891-6.
9. Bozkurt NC, Karbek B, Ucan B, et al. The association between severity of vitamin D deficiency and Hashimoto's thyroiditis. Endocr Pract. 2013;19(3):479-84.
10. Kapila RS, Harharpreet Kaur JS. Lipid profile in patients with subclinical hypothyroidism. Eur J Mol Clin Med. 2022;9(3):781-8.
11. Caraccio N, Ferrannini E, Monzani F. Lipoprotein profile in subclinical hypothyroidism: response to levothyroxine replacement, a randomized placebo-controlled study. J Clin Endocrinol Metab. 2002;87(4):1533-8.
12. Turhan S, Sezer S, Erden G, et al. Plasma homocysteine concentrations and serum lipid profile as atherosclerotic risk factors in subclinical hypothyroidism. Ann Saudi Med. 2008;28(2):96-101.
13. Karthick N, Dillara K, Poornima K, Subhasini A. Dyslipidaemic changes in women with subclinical hypothyroidism. J Clin Diagn Res. 2013;7(10):2122-5.
14. Laway BA, War FA, Shah S, Misgar RA, Kotwal SK. Alteration of lipid parameters in patients with subclinical hypothyroidism. Int J Endocrinol Metab. 2014;12(3):e17496.
15. Akter N, Akter T. Pattern of dyslipidemia among patients with subclinical hypothyroidism and its relation with thyroid-stimulating hormone. BIRDEM Med J. 2021;11(3):172-8.

16. Bertoli A, Fusco A, Andreoli A, et al. Effect of subclinical hypothyroidism and obesity on whole-body and regional bone mineral content. Horm Res Paediatr. 2002;57(3-4):79-84.
17. Cooper DS, Biondi B. Subclinical thyroid disease. Lancet. 2012;379(9821):1142-54.
18. Brennan MD, Powell C, Kaufman KR, et al. The impact of overt and subclinical hyperthyroidism on skeletal muscle. Thyroid. 2006;16(4):375-80.
19. Kim TH, Joung JY, Kang M, et al. A modest protective effect of thyrotropin against bone loss is associated with plasma triiodothyronine levels. PLoS One. 2015;10(12):e0145292.