



TIKUR ANBESSA SPECIALIZED HOSPITAL (TASH)

OSTEOPORESIS IN HYPERTHYROIDPATIENTS WITHOUT TRADITIONAL RISK FACTORS: A HOSPITAL-BASED CROSS-SECTIONAL STUDY AT TIKUR ANBESSA SPECIALIZED HOSPITAL ENDOCRINOLOGY CLINIC, ADDIS ABABA, ETHIOPIA

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OSTEOPORESIS IN HYPERTHYROIDPATIENTS WITHOUT TRADITIONAL RISK FACTORS

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Abstract

Background: Hyperthyroidism is associated with adverse skeletal outcomes, including low bone mineral density (BMD) and secondary osteoporosis. However, evidence on the magnitude and predictors of osteoporosis among hyperthyroid patients in Ethiopia is lacking.

Objective: To assess the prevalence of osteoporosis and associated factors among hyperthyroid patients attending the Endocrinology Clinic at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia.

Methods: An institution-based cross-sectional study was conducted on 51 hyperthyroid patients selected through census sampling. Data were collected using interviewer-administered questionnaires and clinical records. BMD was measured by DXA scan and fracture risk assessed using the FRAX tool. Binary logistic regression was performed to identify associated factors, with $p<0.05$ considered statistically significant.

Results: Of the 51 patients, 37.3% had BMD below the expected range for age, consistent with secondary osteoporosis. The mean Z-score was –1.4. Low BMD was not significantly associated with age, sex, BMI, disease etiology, or treatment regimen. Osteoporosis prevalence was higher among patients with uncontrolled hyperthyroidism (66.7%) than among euthyroid (30.6%) or hypothyroid patients (33.3%). Wayne's score showed significant correlation with osteoporosis ($p=0.035$). Vitamin D deficiency and poor dietary diversity were common among osteoporotic patients, but not statistically significant. Multivariable regression did not identify independent predictors. The FRAX tool failed to identify patients within the osteoporotic range.

Conclusion: More than one-third of hyperthyroid patients had osteoporosis, independent of traditional risk factors. Routine BMD assessment should be considered in hyperthyroid patients, as the FRAX tool may underestimate fracture risk in this population.

Keywords: Osteoporosis, Hyperthyroidism, Overt Hyperthyroidism, Sub clinical Hyperthyroidism, DXA Scan.

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Acronyms and Abbreviation

ALP	Alkaline Phosphatase
AOR	Adjusted Odds Ratio
BMD	Bone Mineral Density
COR	Crude Odds Ratio
DXA	Dual X-ray Absorptiometry
FRAX	Fracture Risk Assessment Tool
FT3	Free Triiodothyronine
FT4	Free Thyroxine
SPSS	Statistical Package for Social Science
TASH	Tikur Anbessa Specialized Hospital
TSH	Thyroid Stimulating Hormone

1. Introduction

Background

Hyperthyroidism defined as excessive production of thyroid hormones, is classified as overt hyperthyroidism and sub clinical hyperthyroidism based on the level of thyroid stimulating hormone (TSH) and thyroid hormone levels (1,2). Thyroid hormones are essential for normal skeletal growth and maintenance of bone mass. Excessive circulating thyroid hormones may result in bone loss (3,4). Hyperthyroidism, characterized by excess thyroid hormone synthesis and secretion from the thyroid gland has several causes , but Graves' disease and multinodular goitre are the most common causes of hyperthyroidism in young/middle-aged people(5,6).

Hyperthyroidism causes high bone turnover with an increased frequency of initiation of bone remodeling sites together with increased bone resorption and formation rates. The remodeling time is shortened with imbalance between resorption and formation that results in a net loss of approximately 10% of bone per remodeling cycle (2). Osteoporosis is by far the most common metabolic bone disease and is characterized by low bone mass with microarchitectural alteration of bone structure and leading to reduced bone strength (7–9).

Osteoporosis is increasingly recognized as a major global public health problem (10). Based on a systematic review and meta- analysis performed on 17 relevant studies, the reported prevalence of hyperthyroidism in Europe was 0.75% and in large Iranian population-based cohorts, hyperthyroidism was reported 0.8-2.2% of the participants (11). Hyperthyroidism affects approximately 0.7-1.4% of people worldwide. The global prevalence of hyperthyroidism in iodine-sufficient countries is estimated at 0.2-2.5% (12). Nigerian study indicates that osteoporosis is a common occurrence among hyperthyroid patients (13). In Ethiopia, it is predicted that there are approximately 7.3 million cases of osteoporosis (14). Institution based report showed the prevalence of Hyperthyroidism in 376 patients at TASH was 61.7%, it was more common in women than men (5,15).

According to the researcher's knowledge, this area has not been fully explored or comprehended in Ethiopia. Early identification and treatment of osteoporosis in hyperthyroid patients are crucial, for lowering death and disability rates.

Statement of the problem

Untreated hyperthyroidism has well-documented skeletal consequences including low bone mineral density (BMD), secondary osteoporosis (16,17). Thyroid diseases are among the commonest endocrine disorders worldwide (11).The global prevalence of hyperthyroidism is approximately 0.2% to 1.3% in iodine-abundant areas. Graves' disease , accounts for 70%–80% of hyperthyroidism in iodine-sufficient areas and 50% in iodine insufficient areas (11).

Osteoporosis is a significant public health concern characterized by decreased bone mass (11). Among various risk factors contributing to the development of osteoporosis, hyperthyroidism has emerged as a critical and recognized contributor (11,18). Many patients may remain undiagnosed or inadequately managed, leading to a higher incidence of osteoporosis-related fractures, which can severely impact quality of life, functional status, and healthcare costs (19).

Osteoporosis is becoming an urgent and serious global epidemic (20). Osteoporosis is reported as a complication of hyperthyroidism in Korean study with the prevalence of osteopenia or osteoporosis being 5.59% in men and 18.18% in women (21). Few studies have reported the prevalence of hyperthyroidism. In Africa, 2% and 1.6% prevalence rates were reported in South Africa and Nigeria, respectively (22). Other Nigerian studies indicates that osteoporosis is a common occurrence among hyperthyroid patients (23).

Osteoporosis in thyroid disorder has the lowest report especially in sub-Saharan Africa. Ethiopian studies on endocrinology primarily focus on diabetes mellitus, while osteoporosis studies only consider lifestyle factors. As such, magnitude of osteoporosis and associated factors among hyperthyroid patients have not been fully investigated or understood.

This study seeks to identify the magnitude and associated factors that allow for early detection and therapy of hyperthyroidism, to reduce the chance of developing osteoporosis, to lessen the risk of fracture and improve the quality of life.

Significance of the study

Health care officials will be able to direct the necessary efforts to lower the disease burden by using epidemiological data and its defined characteristics on osteoporosis caused by hyperthyroidism. The results of this study will be used by clinicians who provide patient care to raise awareness among patients and the community about the need for screening of high-risk groups. The results can also be utilized to identify contributing causes and improve client health conditions, which may help hyperthyroidism patients and lower the disease's complications and mortality rate. Furthermore, it will aid in the strengthening and implementation of adequate hyperthyroidism treatment, as well as inspire other researchers to conduct more comprehensive research in similar settings. Finally, the findings of this study can be used as a baseline source for future research.

2. Literature review

Introduction

Hyperthyroidism is defined by elevated circulating free thyroid hormones, and overt hyperthyroidism is recognized as a low bone density or osteoporosis risk factor (24). Hyperthyroidism is a well-known trigger of high bone turnover that can lead to the development of secondary osteoporosis (25). Multiple observational studies from around the world have shown the relationship between overt hyperthyroidism and bone disease, by documenting an association of TSH levels with bone turnover markers, bone mineral density (BMD), fracture risk, and more recently, bone quality (26).

Magnitude of Hyperthyroidism and osteoporosis

Hyperthyroidism is defined by elevated circulating free thyroid hormones. It is increased synthesis and secretion of thyroid hormones in thyroid follicular cells resulting in thyrotoxicosis, and overt hyperthyroidism is recognized as a low bone density or osteoporosis risk factor (23,27) It is a well-known trigger of high bone turnover that can lead to the development of secondary osteoporosis (28). Globally, hyperthyroidism affects about 0.2% to 1.3% of the general population, and 5- to 10-fold higher in women as compared to men. It is classified as overt or subclinical based on thyroid function tests values (29,30)

According to World Health Organization (WHO), osteoporosis is as a progressive systemic skeletal disease characterized by low bone mass and micro architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture (31).

Thyroid hormones, are an essential factor in maintaining bone structure and strength. When patients develop hyperthyroidism, they are at increased risk for fractures (32). The literature shows that the normal bone remodeling cycle of approximately 200 days is reduced to almost 100 days in the case of hyperthyroidism (33), which supports the idea that hyperthyroidism reduces bone mineral density by almost 10% for every bone remodeling cycle. Although Bone densitometry studies revealed that bone mineral density (BMD) is decreased in all skeletal sites(34), hyperthyroidism differentially influences trabecular and cortical bone metabolism, with the latter being more predominantly affected (35).

According to a study in Korea, the prevalence of osteopenia or osteoporosis was 5.59% in men and 18.18% in women (25). The prevalence of fracture was 9.11% in men and 11.81% in women respectively (25).Fractures were generally frequent in hyperthyroid patients and were specifically more common in men aged <50 years, and in women aged >50 years (25).

A cross-sectional study in Thailand evaluating BMD in premenopausal women, as analyzed by DXA, revealed significantly lower BMD in hyperthyroid women compared to controls at the lumbar spine (0.928 versus 0.991), the total hip (0.838 versus 0.917), and the femoral neck (0.774 versus 0.832) (36).

A study in Nigerian adults with hyperthyroidism, 19 (47.5%) had osteopenia and 12 (30%) had osteoporosis, and also The mean BMD and Z-scores were reduced (1,2). Bone loss was observed in 31 (72.5%) hyperthyroid subjects, but only three (7.5%) had fractures due to minor trauma (4).

Factors associated with Osteoporosis among hyperthyroid patients

Socio-demographic factors

A study of Argentina euthyroid postmenopausal patients with a history of hyperthyroidism due to Graves' disease showed lower whole-body BMD than matched controls (37). The BMD expressed as Z-score was less in whole body and lumbar spine in postmenopausal in comparison to premenopausal women with previous overt hyperthyroidism due to Graves' disease (37). In the postmenopausal patients, the Z-score of lumbar spine BMD correlated negatively with TRAb(37) (38).

A study in Denmark showed that patients with untreated hyperthyroidism had significantly decreased BMD which was associated with an increased risk of hip fracture, which increases significantly with age. This aspect is more evident in postmenopausal women with a three-to-fourfold increase in fracture. In united states, BMD was also evaluated in geriatric patients with toxic nodular goiter in women with a low TSH level (0.1 mU/L) resulting in a threefold increment risk for hip fracture (relative hazard, 3.6 [95% CI, 1.0 to 12.9]) and a fourfold increased risk for vertebral fracture (odds ratio, 4.5 [CI, 1.3 to 15.6]) compared with women who had normal TSH levels (0.5 to 5.5 mU/L (39,40) .

In a study from Korea, complications of hyperthyroidism such as osteoporosis and fractures, occurred more often in younger patients, similar finding were seen in Portugal study in young hyperthyroid patients with reported result of, total lean body mass and the mean BMD at lumbar spine, hip, and whole body were significantly decreased in the hyperthyroidism group (40,25). In this group, there was also a trend for an increased prevalence of reduced BMD/osteoporosis and osteoporotic vertebral fractures (15,25) .Hyperthyroid women were more frequently affected with osteoporosis, with the highest incidence in their 50s; men showed the highest incidence in their 70s (15). In contrast, in the general population, osteopenia or osteoporosis showed high prevalence in women in their 70s and men in their 80s (15). Similarly age and postmenopausal status affected BMD in women (40).

The prevalence of osteoporosis was significantly associated with age ($p<0.001$) in the study done in Nepal (41).

A meta-analysis study indicated that subclinical hyperthyroidism did not affect lumbar spine bone Mineral Density (BMD) in females or males (42). However, a significant reduction in femoral neck BMD was observed in females, but not in males(42). Further, there was a significant increase in hip fractures events in both females and males with subclinical hyperthyroidism (42).

In US During 39 952 person-years (median follow-up, 13 years), hip fracture incidence (per 1000 men-years) was 13.65 in men with subclinical hyperthyroidism (n = 29) and men with subclinical hyperthyroidism had a multivariable-adjusted HR of 3.27. After excluding those with baseline use of thyroid-altering medications, men with endogenous subclinical hyperthyroidism had a higher HR of 4.91, however no clear association between subclinical dysfunction and fracture was observed in women (35). In a study from Iran, males with hyperthyroidism (TSH<0.10 mIU/L) and subclinical hyperthyroidism were found to be at increased risk for hip fracture (43). Education is another significant factor associated with Osteoporosis (36). A retrospective cohort study done in Taiwan has shown that participants who had higher educational years (OR = 0.43 [0.41, 0.46]) were significantly associated with a lower risk of low BMD (36).

Biomedical evidence

In a study from India, serum T3 had strongest inverse correlation with BMD at spine, hip and femur (1). According to this study, T3 is the best predictor of reduced BMD at spine, hip and

forearm, followed by phosphate (1). Corrected serum calcium and alkaline phosphate (ALP) levels were also significantly elevated in GD patients compared with controls (P<0.001)(1).

The level of TSH was also associated with osteoporosis in previous study done in Korea (40). A high risk of osteoporosis was reported in patients with low TSH levels or subclinical hyperthyroidism (40). In USA study, low serum TSH levels (0.1 mU/L) as an indicator of hyperthyroidism in women older than 65 were correlated with higher new hip fractures (39). According to a cross-sectional study in Europe there is a stronger association between low TSH and low BMD in distal (cortical) bone in comparison to the ultra-distal (trabecular) bone of the radius (37).

In Egypt, Serum ALP, a bone formation marker from osteoblasts, was significantly elevated in GD patients compared to normal controls confirming the increased bone turnover observed in patients with hyperthyroidism (30). Serum phosphate was an important predictor of BMD at forearm in GD patients (44).

In studies done in Korea and Iraq, both elevated bone formation and bone resorption markers are seen in hyperthyroidism suggesting increased bone turnover and osteoclastic bone resorption activity(40,43). This increased mobilization of bone mineral, often leads to hypercalcemia and hyperphosphatemia (45,46). In the United States, lower BMD and FRAX scores for hip and osteoporotic fractures were associated with TPO-Ab in euthyroid postmenopausal women (47).

In Nigeria, the bone markers such as TSH, osteocalcin, total alkaline phosphatase, and urinary calcium/creatinine ratio were significantly elevated in thyrotoxic subjects compared with controls (4). In Egypt, Bone Mineral Density (BMD) was significantly lower in toxic multinodular goiter compared to controls (30). There was a significant positive correlation between free T3 and free T4 with biochemical markers of bone turnover, but a negative correlation between TSH and those biochemical markers of bone turnover (30). The duration of the thyrotoxic state positively correlated with the assessed bone turnover markers, but it is negatively correlated with the Z-score of BMD in the studied hyperthyroid patients (30).

Hyperthyroidism disease and treatment related characteristics

Hyperthyroidism induced by thyroid-stimulating hormone-suppressive therapy in patients with differentiated thyroid cancer has been shown to be a cause of secondary osteoporosis in Korea (6). The main causes of exogenous subclinical hyperthyroidism are inappropriate replacement dose

of thyroxine and TSH suppressive L-thyroxine doses in the therapy of benign thyroid nodules and thyroid carcinoma (8). Available data in Italy similarly suggest that a long-term TSH suppressive dose of thyroxine may decrease BMD and may induce an increased risk of fracture (8).

An Indian patients study showed, the pattern of recovery of bone loss after one year of ant-thyroid therapy suggesting early recovery at hip and lumbar spine and deterioration at forearm (48). However, bone density remained below aged-matched controls (48).

Suppressive doses of L-T4 are used in patients with differentiated thyroid carcinoma as a complementary treatment after thyroidectomy and radioactive iodine therapy (49). Although an endogenous hyperthyroidism is a risk factor of secondary osteoporosis, the effects of supra physiological doses of levothyroxine on bone are still under discussion (49). In a study from India, baseline I^{131} uptake was inversely associated with BMD and was found to be a predictor of increased bone mineral loss (1).

In England, the relative risk of any fractures for patients with thyroidectomy versus their controls was increased 1.5-fold (95% CI, 0.7–3.2) (50). In USA, there is a little but statistically significant rise in the risk of hip fractures among thyroidectomized patients (51).

A study done in Egypt has showed the severity and the duration of the thyrotoxicosis state are directly related to the derangement of biochemical markers of bone turnover and bone loss (30).

Lifestyle characteristics

Body Mass Index (BMI) has also been found to be another factor for Osteoporosis fracture in previous different studies (35,52,44,53). In the Korean study, BMI affected BMD in both women and men (40). In the study from Portugal, the total lean body mass and the mean BMD at lumbar spine, hip, and whole body were significantly decreased in the hyperthyroidism group (25). In this group, there was also a trend for an increased prevalence of reduced BMD/osteoporosis and osteoporotic vertebral fractures (25). Participants who were underweight consumed a vegetarian diet or who had higher triglyceride levels were significantly associated with a higher risk of low BMD in Taiwan (36). Physical exercise is a factor significantly associated with Osteoporosis in the study done Southwest China and Tigrai region, Ethiopia (54,55).which showed limited physical exercise increase risk of osteoporosis, due to loss induction of bone mass growth that is stimulated by exercise especially the weight bearing type (56).

Previous study conducted from the different part of the world also show Alcohol consumption and smoking were the predictors variables for Osteoporosis in previous studies in US (57,58), Korea (59) Serbia (60) and Tigrai region, Ethiopia (35,52,61,53,55).

Various studies conducted across different parts of the world have shown that smoking and alcohol consumption significantly contribute to the development of osteoporosis (35,52,61,53,55). Research findings from the United States, Korea, Serbia, and the Tigray region of Ethiopia consistently indicate that these lifestyle factors are strong predictors of reduced bone density and increased risk of osteoporosis (35,52,61,53,55). These studies highlight the global impact of smoking and alcohol use on bone health, emphasizing their role as major risk factors in different populations and settings.

Conceptual frame work

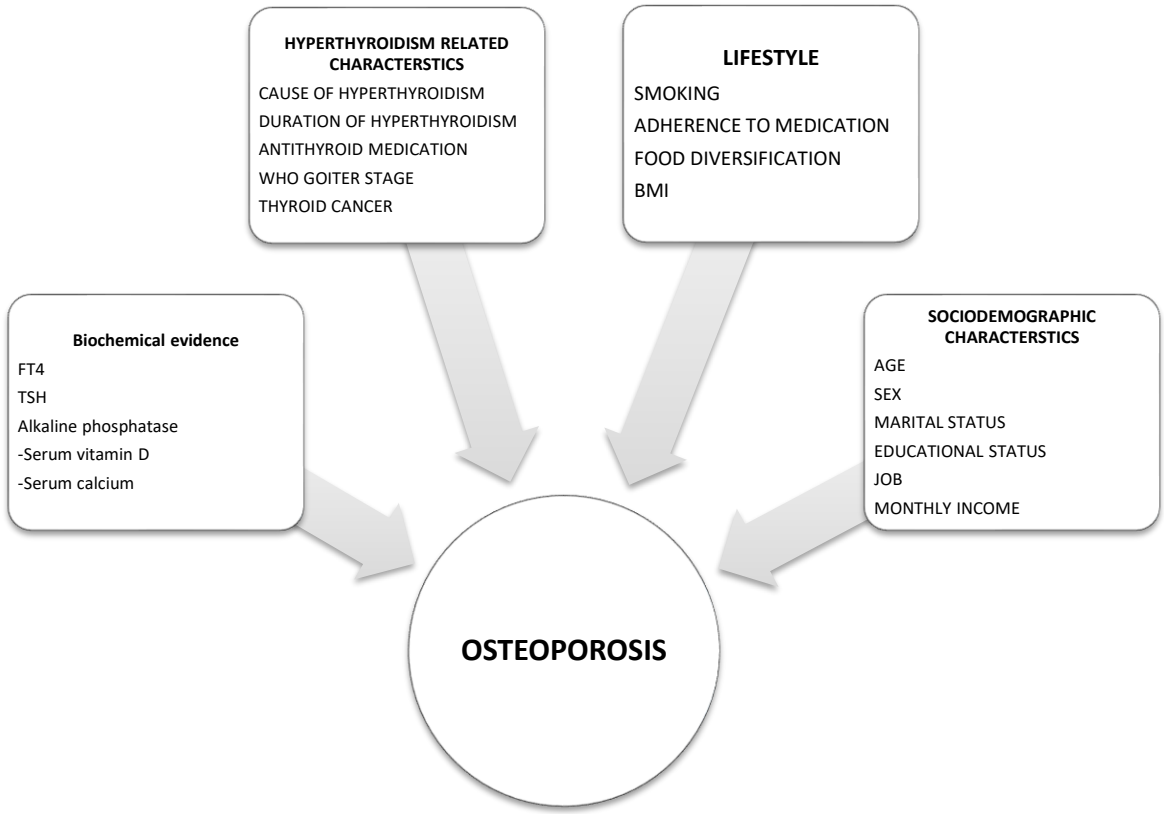


Figure 1 Conceptual framework

The conceptual framework of this study illustrates the factors associated with osteoporosis among hypothyroid patients. It has been developed based on a comprehensive review of relevant literature, integrating existing evidence and theoretical perspectives to identify potential determinants influencing the occurrence of osteoporosis in this population (9,55,26,27,36,56,54).

3. Objective of the study

General objective

- To assess the magnitude of osteoporosis and associated factors among hyperthyroid patient at Tikur Anbessa Specialized Hospital Endocrinology clinic, Addis Ababa Ethiopia from April 1 to July 31 2025.

Specific objective

- To assess the magnitude of osteoporosis among hyperthyroid patients at Tiku Anbessa Specialized Hospital Endocrinology clinic, Addis Ababa Ethiopia from April 1 to July 31 2025.
- To determine associated factors for osteoporosis among hyperthyroidism patients at Tikur Anbessa Specialized Hospital Endocrinology clinic, Addis Ababa Ethiopia from April 1 to July 31 2025.

4. Methodology

Study area and period

The study was conducted in Tikur Anbessa Specialized Hospital, which is located in Addis Ababa, the capital city of Ethiopia.

Opening of the Tikur Anbessa Specialized Hospital (TASH) in 1972, the hospital became the only site for training medical doctors. In 1998, the TASH, the largest referral hospital in the country, with 700 beds, was transferred to the school of medicine by the Federal Ministry of Health, and it has since become a University teaching hospital. The TASH is now the main teaching hospital for both clinical and preclinical training of most disciplines. It is also an institution where specialized clinical services that are not available in other public or private institutions are rendered to the whole nation.

The TASH has 234 doctors, 379 nurses and 115 other health professionals dedicated to providing health care services. The various departments, faculties and residents under specialty training in the school of medicine provide patient care in the hospital. In addition, almost all regional and federal hospitals in Addis Ababa are affiliated to the School of Medicine as clinical services and training sites. The hospital provides national endocrine referral clinic which provides specialized and comprehensive clinic services (62,63).

The study was conducted from April 1 to July 31 2025.

Study design

Institution based Cross sectional study design was implemented.

Study Population

Source population: All hyperthyroidism patients who had follow up at endocrine follow up clinic in Tikur Anbessa Hospital Addis Ababa, Ethiopia.

Study population: Hyperthyroidism patients who had follow up at endocrine follow up clinic during the study period from April 1 to July 31 2025, and who satisfied the study eligibility criteria.

Inclusion criteria

Hyperthyroid patients followed in endocrine follow-up clinic during the study period were included in this study.

Participant's age ranged from 18 to 50 years old.

Exclusion criteria

Hyperthyroid patients who have follow up for less than 6 months, patients who had previous documented pathologic fracture, patients on treatment for previously diagnosed osteoporosis, post-menopausal or premature ovarian failure women , patients on Glucocorticoid use were excluded.

Sample size and sampling procedures

Sample size determination

The overall computed sample size for this hospital-based analytical cross-sectional study was 424, which exceeds the total population (260). The overall population is small and falls below the projected sample size for presenting a complete and credible picture of the population. A census was conducted, and all hyperthyroidism cases were part of the study.

Sampling methods

First, all hyperthyroidism patients were selected then study participants who fulfilled inclusion criteria were selected and be part of the study.

Data collection Instrument and Procedure

Primary data was taken via trained individuals with structured questionnaire, which was adopted by reviewing other studies (1,7,8,21,64). The questionnaire included questions about Socio demographic characteristics, lifestyle, hyperthyroidism related characteristics and biochemical evidence. Osteoporosis was assessed clinically with FRAX score and biochemically using serum calcium and alkaline phosphatase and radio graphically using DXA scan of the spine. We used

Kobo Toolbox software to collect data and the DXA scan result was directly collected from Pioneer diagnostic center.

Study variable

Dependent variable

Osteoporosis among hyperthyroidism patients (Yes/no)

Independent variable

Socio demographic characteristics: - Age, sex, marital status, educational status, job, and income per month

Lifestyle: - Cigarette Smoking, food diversification, BMI and adherence to medication **Hyperthyroidism related characteristics:** - Causes of hyperthyroidism, duration of hyperthyroidism and anti-thyroid medication

Biochemical evidence: - TSH, FT4, ALP, and Ca

Operational definition

Osteoporosis - with radiological evidence of osteoporosis either using the International Society of Clinical Densitometry (ISCD) criteria (established (severe) osteoporosis *z*-score < −2.0 with one or two osteoporotic fractures or osteoporosis by *z*-score < −2.0). The present study utilized the International Society of Clinical Densitometry criteria as the patients fall within the young age group (21).

Hyperthyroidism - is defined by clinical and/or biochemical evidence of hyperthyroidism: FT4 > 22.0 pmol/L, FT3 > 6.5 pmol/L, and TSH < 0.3 μ/U/ml. Overt hyperthyroidism is defined as Wayne score > 19 in addition to the biochemical pointers of thyrotoxicosis (65).

Increased bone turnover is present if: total alkaline phosphatase > 130 U/L (bone formation marker) (21).

Serum TSH, FT3 and FT4 concentrations will be measured in the clinical laboratory of TASH.

The normal reference range of TSH is 0.3 ~ 4.5 mU/L, and the normal reference ranges of FT3 and FT4 are 3.5 ~ 6.5 pmol/L and 11.5 ~ 22.7 pmol/ L, will be measured using standard laboratory methods (7,43).

Overt hyperthyroidism: - is a condition where the body has high levels of thyroid hormones. It's characterized by low levels of thyroid-stimulating hormone (TSH) and high levels of triiodothyronine (T3) and/or free thyroxine (fT4).

Subclinical hyperthyroidism: -defined as TSH outside the reference range of values and FT3 and FT4 within the normal range (8,18).

Secondary osteoporosis- is defined osteoporosis that occurs as a result of a medical condition or medication (18).

FRAX score - a Fracture Risk Assessment Tool that estimates the 10-year probability of hip fracture and major osteoporotic fracture (hip, clinical spine, proximal humerus, or forearm) for **untreated** patients from age 40 to 90 years (66–68).

DXA scan - DXA measures bone mineral content (BMC, in grams) and bone area (BA, in square centimeters), then calculates "areal" BMD (aBMD) in g/cm^2 by dividing BMC by BA (7,36,69).

Adherent: respondents who scored ≥ 6 points of the Morisky medication adherence scale (70).

Participants were classified as current smokers if they smoked at least one cigarette per day, as occasional smokers if they smoked usually less than one cigarette per day, as former smokers if they had smoked regularly or occasionally in the past and as never smokers if they had never smoked (71).

Body mass index: - was calculated from measured height and weight as weight in kilograms divided by height in meters squared (64).

Data quality control

Before data collection, training was given for the data collectors to integrate the objective of the study, the method used and contents of the questionnaire by the principal investigators. The questionnaire was first prepared in English language, then translated to Amharic, and back translated to English to maintain consistency. Pretesting was done on 5% (10) of the total sample size in TASH to identify potential problems that will arise during the actual data collection period and the identified problems were revised accordingly. Pretest Participants did not participate in the actual data collection period. Completeness, accuracy and consistency of the collected data were checked during data collection by the principal investigator. Data was coded before data entry. Double entry was done at least 10% of the collected data to minimize data entry errors.

Data processing and analysis

All questionnaires were coded, entered to in Epi-Data version 4.7.0 software and exported to SPSS version 27.1 software for data cleaning and analysis. Descriptive statistics were used to describe the magnitude of Osteoporosis among hyperthyroidism patients and result of descriptive statistics was expressed as percentages and frequencies.

Bi variable and multivariable binary logistic regression was done to identify associated factors of Osteoporosis among hyperthyroidism patients. Variables with a p-value ≤ 0.25 in the Bi variable analysis was considered as candidate variables for multivariable logistic regression

model and variables with a p-value <0.05 was considered as statistically significant. Adjusted odds ratio (AOR) with 95% confidence interval (CI) was presented to identify the presence and strength of association of dependent and independent variables in the model.

Ethical consideration

Ethical clearance was obtained from Addis Ababa University, College of health sciences ethical institutional review board. A copy of this letter was sent to the TASH research department for approval to perform this study at TASH endocrine clinic.

Each study participant was informed by the data collectors about the goal, anticipated advantages, and potential risks or discomforts of the research during the data collection procedure. Participants in the study was given the assurance by the data collectors that their names will not be used, that their information will be kept private, and that their participation will be based solely on their free will.

They were also given the freedom to decline participation at any time, skip any questions, and ultimately be asked if they voluntarily want to participate. Their desire to participate was then confirmed verbally. All information gathered was kept private and secret, and only the study team members has access to it.

Dissemination of study finding

The result of the study will be submitted to the Tikur Anbesa specialized hospital research department and Library. It will be presented to TASH heath care professionals and higher management bodies for the possible intervention plan and activities of the study findings. It will be sent to Addis Ababa public health research and Emergency Management bureau, and the paper also be sent for publication in scientific peer reviewed journal.

5. Results

Out of 260 patients attending the clinic during the study period, 51 met the inclusion criteria and were included in the analysis. The mean age was 38.5 years, with 58.8% aged between 40 and 49 years. The majority were female (88%), while 12% were male.

The mean body mass index (BMI) was 26 kg/m², with 33% classified as overweight, 21.6% as having class I obesity, and 8% as underweight. Thirty-four participants (66%) were married. Regarding education, 3 patients had not attended formal schooling, while 15 had completed primary school, 18 had completed secondary school, and 15 had attended college.

Occupationally, 14 participants were housewives, 14 were unemployed, 9 were employed in private organizations, and 8 were government employees. The majority (98%) resided in urban areas. The average monthly income was slightly above 6,000 birr. Twenty-nine patients had a food diversity score of fewer than three food groups within the previous 24 hours. More than 80% of participants reported eating three or more meals per day. Tea and coffee consumption were reported by 59% and 70% of patients, respectively. Additionally, 63% of patients did not engage in regular physical exercise.

Regarding diagnosis, 32 patients (62.7%) were presumed to have Graves' disease, 17 (33.3%) had toxic multinodular goiter, and two (3.9%) had toxic adenoma. The average duration of hyperthyroidism was 6.8 years, with 60% having less than five years of follow-up. Based on Wayne's score, 70.6% of patients were clinically euthyroid. Thyroid function tests conducted within three months of the study showed similar findings: 54.9% were euthyroid, 17 patients (33.3%) were hyperthyroid, and 11.8% were hypothyroid. Comparison of clinical Wayne's score with thyroid function test has shown 56% sensitivity, 76.2% specificity and 33.3% PPV and 88% NPV.

At the time of the study, 43 patients were receiving treatment, six were in remission, and 2 had discontinued treatment due to agranulocytosis. The mean daily dose of propylthiouracil (PTU) was 223 mg, with 60% receiving between 100 and 300 mg. Nine patients were on carbimazole, with a mean daily dose of 23 mg. Only 39% of patients were on beta-blocker therapy.

Among the 43 patients for whom alkaline phosphatase was measured, the mean level was 60 mg/dL, with half in the low-normal range and half in the high-normal range. Serum calcium measurements, available for 32 patients, revealed a mean value of 9.5 mg/dL; 84.5% were normocalcemic, 12% were hypercalcemic, and 3.5% were hypocalcemic. Vitamin D levels were measured in 10 patients: five were deficient, three had insufficient levels, and two had normal levels.

Comorbidities were present in 22 patients. These included hypertension (n=11), retroviral infection (n=6), type 1 diabetes mellitus (n=1), type 2 diabetes mellitus (n=6), chronic kidney disease (n=1), dyslipidemia (n=1), hematologic malignancy (n=3), and heart failure (n=2).

Table 1: Socio-demographic and behavioral characteristics of the study population

Variable	Categories	Number	Percent
Age (mean) in years		39.5 ±7.4	
Age categories (in years)	18-29	6	11.8
	30-39	15	29.4
	40-49	30	58.8
Sex	Male	6	11.8
	Female	45	88.2
BMI (mean) in Kg/m²		26.1 ± 5.4	
BMI categories in Kg/m²	Underweight	5	9.8
	Normal	16	31.4
	Overweight	17	33.3
	Obesity	13	25.5
Marital status	Single	10	19.6
	Married	34	66.7
	Divorced or widowed	7	13.7
Educational status	No formal education	3	5.3
	Primary school	15	29.4
	Secondary school	18	35.3
	College level	15	29.4
Occupational status	Unemployed	28	54.9
	Private organization employee	9	17.6
	Government employee	8	15.7
	Others*	6	11.8
Income in ETB- median (IQR)		4000 (0, 10,000)	
Income categories in ETB	=<2000 ETB	5	9.8
	2001-5000 ETB	6	11.8
	5001-1000 ETB	15	29.4
	>10000 ETB	25	49.0
Alcohol intake	Yes	6	11.8
	No	45	88.2
Dietary diversity score	0-3 food items	29	56.9
	4-6 food items	22	43.1
Tea consumption	Yes	30	58.8
	No	21	41.2
Coffee consumption	Yes	36	70.6
	No	15	29.4

Physical Exercise	Yes	19	37.3
	No	32	62.7

* Merchant 1, Daily laborer 5

Table 2: Disease related characteristics of the study population

Variable	Categories	Frequency	Percent
Duration of hyperthyroidism (years)	Median (IQR)	5 (3, 11)	
	< 5 years	29	56.9
	≥ 5 years	22	43.1
Cause of hyperthyroidism	TMNG or TA	19	37.3
	Grave's Disease	32	62.7
Treatment status	On ATDs	43	84.3
	Off ATDs*	8	15.7
Type of treatment (n=43)	PTU	34	79.1
	Carbimazole	9	20.9
Current thyroid status (biochemical, TFT)	Euthyroid	28	54.9
	Hyperthyroid	17	33.3
	Hypothyroid	6	11.8
Current thyroid status (clinical, Wayne's)	Hyperthyroid	7	13.7
	Euthyroid	36	70.6
	Equivocal	8	15.7

ATD- Anti-thyroid drugs; TMNG- toxic multinodular goiter; TA- toxic adenoma

* Remission- 6, ATD discontinued for adverse effects- 2

Prevalence of secondary osteoporosis due to hyperthyroidism

More than a third 19 (37%) of the participants had osteoporosis (Z scores < -2.0) (Figure 1). For the total study population, the median (IQR) Z-score for lumbar, left total hip and left femoral neck are -1.5 (-2.3, -0.4), -0.7 (-1.2, 0), and -0.5 (-1, 0.2), respectively. Similarly, the median (IQR) BMD for lumbar, left total hip, and left femoral neck are 0.94 (0.83, 1.03), 0.99 (0.89, 1.13), and 0.91 (0.83, 1.03), respectively (Figure 2).

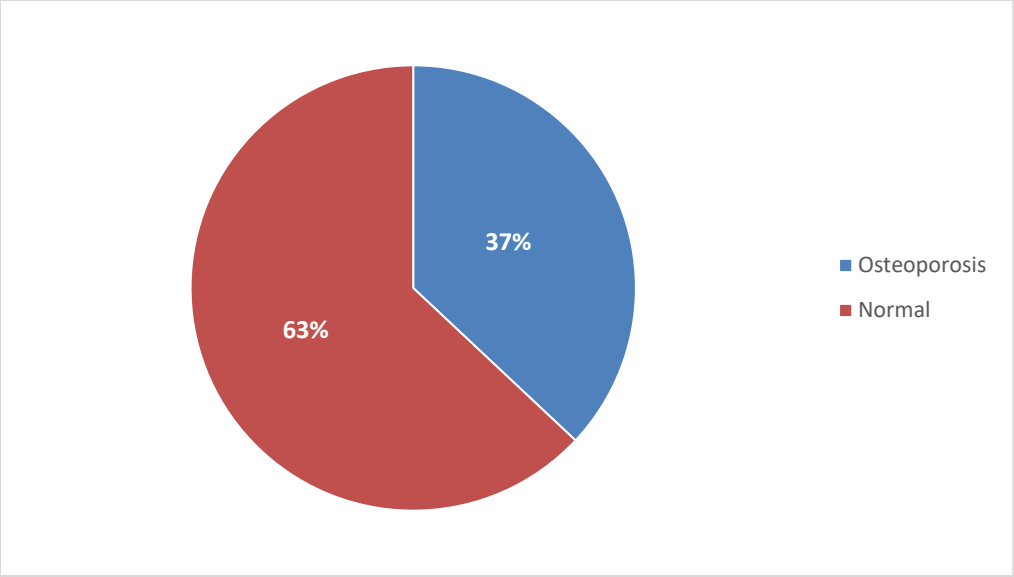


Figure 2: Prevalence of Osteoporosis among the study participants (n=51)

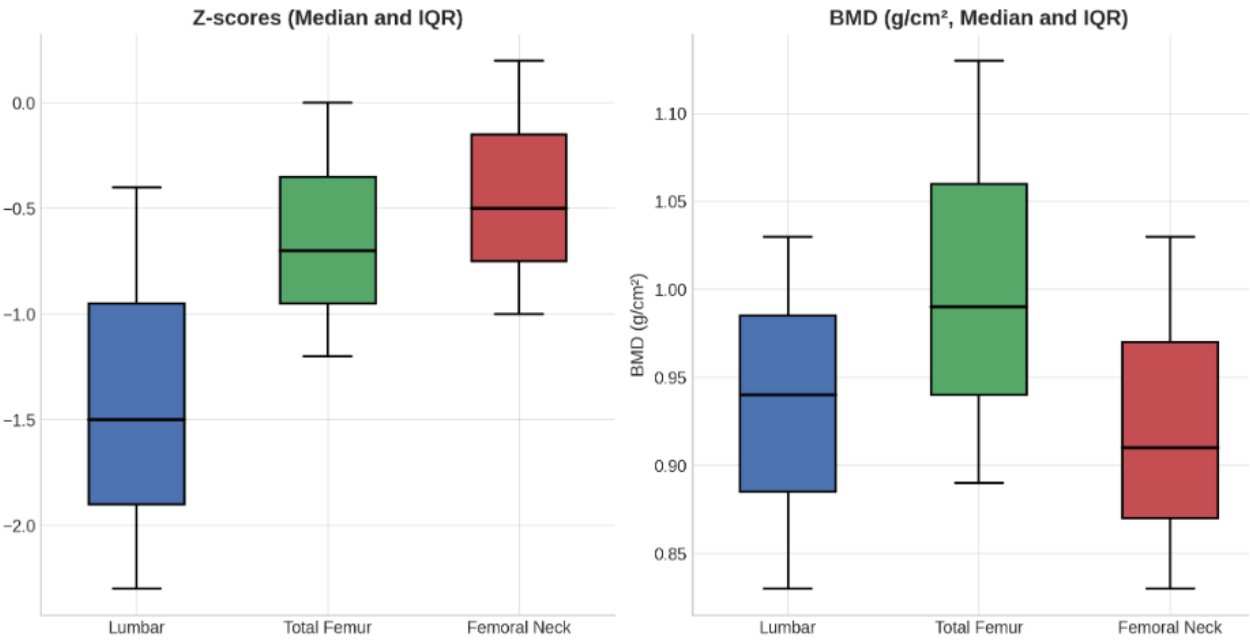


Figure 3: Median Z-scores and Bone Mineral Density (BMD) with Interquartile Ranges at the Lumbar Spine, Total hip, and Femoral Neck in Study Participants (n=51)

Factors associated with secondary osteoporosis due to hyperthyroidism

Among the 19 patients with low BMD, 11 were aged 40–49 years, 6 were aged 30–39 years, and 2 were aged 18–29 years (p = 0.955). Of the 45 females, 17 (37.8%) had osteoporotic-range BMD, while 2 of the 6 males (33.3%) had BMD below the expected range (Fisher's exact p = 0.6). Nearly half (47.6%) of the osteoporotic patients had a BMI < 25 kg/m² (p = 0.2).

Regarding physical activity, 12 patients (37.5%) with osteoporosis reported no regular exercise, while 7 patients (36.8%) engaged in regular exercise. The majority of osteoporosis cases (n = 11) were among patients diagnosed with hyperthyroidism within the past 5 years, followed by 5 patients diagnosed between 6–10 years prior, and 3 patients diagnosed more than 10 years prior (p = 0.3).

By etiology, osteoporosis was found in 6 of 17 patients with toxic multinodular goiter, 12 of 32 with presumed Graves' disease, and 1 of 2 with toxic adenoma (p = 0.9).

Regarding treatment, 9 of the 19 osteoporotic patients were on propylthiouracil (PTU) 100–300 mg/day, 3 were on < 100 mg/day, 2 were on > 600 mg/day, and 3 were taking carbimazole.

Among patients thyroid function test done, those with uncontrolled hyperthyroidism, 6 of 9 (66.7%) had osteoporosis, compared with 11 of 36 (30.6%) euthyroid patients and 2 of 6 (33.3%) hypothyroid patients (p = 0.113). In sub group analysis of individuals with subclinical hyperthyroidism osteoporosis was not observed.

Using Wayne's score, 12 clinically euthyroid patients, 6 patients with equivocal status, and 1 hyperthyroid patient had low BMD (p = 0.035).

Vitamin D deficiency was present in 3 osteoporotic patients. All osteoporotic patients had alkaline phosphatase levels < 130 mg/dL. Additionally, 41.4% of the osteoporotic patients scored < 3 food items on the dietary diversity score (p = 0.3). Thirteen osteoporotic patients were normocalcemic, and 1 was hypercalcemic.

Multiple regression analysis of TFT, BMI and Wayne's score showed AOR ,3.8(95% CI :[0.95-0.7, 19] p= 0.07, 1.9 (95%CI:[0.57, 6.7] p=0.29, 1.3(95%CI [0.3,4.6] p=0.3 respectively

Clinical FRAX score assessment revealed that none of the patients were in the osteoporotic range even after age and thyroid status adjustment.

Table 3: Factors associated with secondary osteoporosis due to hyperthyroidism in study population

Variable		Osteoporosis n (%)		COR (95%CI)	AOR (95% C.I)	P
		No	Yes			
BMI (Kg/m^2)	<25	11(34.3)	10(52.6)	2.1(0.6-6.7)	0.33 (0.07, 1.49)	0.15
	≥25	21(65.7)	9(47.4)	1		
Wayne Score	Euthyroid	24(75)	12(63.2)	1.75(0.5,5.98)	0.4(0.59,2.8)	0.36
	Hyperthyroid	8(25)	7(36.8)	1		
TFT	Hyperthyroid	3(10)	6(31.6)	1.8(0.9-3.6)	0.2(0.014, 3.3)	0.27
	Euthyroid	25(78)	11(57.9)	1		
	Hypothyroid	4(12)	2(10.5)	1		
PTU dose	<300	16(80)	12(85.7)	1.5(0.24,9.6)	0.6(0.073,4.7)	0.6

	>300	4(20)	2(14.3)	1		
Duration of hyperthyroidism	<5 years	18(56.25)	11(57.9)	1.07(0.34,3.4)	0.7(0.14,4)	0.7
	≥5 years	14(43.75)	8(42.1)	1		

6. Discussion

Thyroid hormones play an essential role in maintaining bone structure and strength. In hyperthyroidism, patients are at increased risk of fractures (22). Evidence from the literature indicates that the normal bone remodeling cycle of approximately 200 days is shortened to around 100 days in hyperthyroidism (29). Supporting the observation that bone mineral density (BMD) may be reduced by nearly 10% with each accelerated remodeling cycle (29).

Although bone densitometry studies have demonstrated reduced BMD at all skeletal sites (30). hyperthyroidism appears to differentially affect trabecular and cortical bone, with cortical bone being more predominantly impacted (31). In the present study, DXA scans were performed on the lumbar spine, left femur, and femoral neck.

The prevalence of osteoporosis in our study population was 37.3%, which is lower than the 45% reported in Nigeria. The mean Z-score in our study was −1.4, compared to −2 in the Nigerian study. This difference may be explained by the variation in the DXA assessment site, as the Nigerian study used the distal radius (1).

No significant difference in osteoporosis prevalence was observed between males and females, unlike a Korean study that reported a prevalence of 5.4% in males and 18% in females (15). This variation may be due to differences in the study populations, particularly the inclusion of older participants (above 50 years) in the Korean study (15).

In our cohort, age was not independently associated with osteoporosis in younger patients with hyperthyroidism, consistent with findings from Nigeria and Portugal (1,25). These results

highlight that hyperthyroid patients are at increased risk of osteoporosis regardless of age or gender(1,25). This may explain why the clinical FRAX score failed to predict osteoporosis risk in our sample, even when age adjustments of up to 10 years were applied—reinforcing that age becomes a more significant determinant of osteoporosis risk after the age of 60.

No statistically significant association was found between osteoporosis and disease duration or the underlying cause of hyperthyroidism, similar to findings from Egypt (30) . Thyroid function tests, Wayne's clinical score, and BMI were also included in multivariable regression analysis, but none showed independent associations with osteoporosis. However, thyroid function tests demonstrated a trend toward correlation between uncontrolled hyperthyroidism and osteoporosis (AOR 3.8, 95% CI [0.95–19], p = 0.07).

In agreement with studies from Nigeria and Egypt, no significant correlation was found between alkaline phosphatase levels and osteoporosis, despite other bone turnover markers being elevated in those studies (1,30).

7. Conclusion and recommendation

This study adds to the limited data on osteoporosis in younger hyperthyroid populations, demonstrating that bone loss occurs independently of age, sex, and common clinical predictors. By showing that the FRAX score underestimates fracture risk in this group and that routine biochemical markers offer limited predictive value, our findings support the use of direct bone density assessment in all hyperthyroid patients. These results suggest that earlier screening and intervention strategies may be warranted, even in patients traditionally considered low risk by

age-based criteria. Given our limited resource set up it might be prudent to further study less expensive screening modalities like vertebral fracture assessment with XRAY. As this is a cross-sectional study, we recommend further longitudinal studies to elucidate causality.

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2. Annexes

Information sheet

Title of the Research Project: Magnitude of osteoporosis and associated factors among hyperthyroid patient at Tikur Anbessa Specialized Hospital Endocrinology clinic, Addis Ababa Ethiopia. Analytical cross sectional study

Name of Investigators: Dr Mahlet

Name of the Organization: Tikur Anbessa specialize hospital.

Introduction

You are invited to participate as study subject in this research because you have been selected by chance. Your participation is voluntarily. Please take as much time as you need to read the information sheet.

Purpose of the Research Project

We are asking you to take part in this study because we are trying to assess the level of Magnitude of osteoporosis and associated factors among hyperthyroid patient at Tkiur Anbessa Specialized Hospital. This helps us to design effective prevention and control measure.

Procedure

If you are willing to participate, you need to understand the purpose of the study and give your verbal consent. Data will be collected by structured questioner, laboratory and x ray findings.

Potential Risks and Discomforts

There are no anticipated risks to your participation, but you may spend some minutes for filling the questioner.

Benefits to subjects and/or to the society

Based on the screening result you will be treated accordingly. Additionally, the result of the study will be beneficial to design effective prevention and control measure against Osteoporosis among Hyperthyroidism patients. Hence, you are indirectly benefiting other patients and the society in this respect.

Compensation for participation

You will not receive any payment for your participation in this research study.

Confidentiality and privacy

There is no sensitive issue that you will be asked related with your personal privacy, any information that is obtained in connection with this study and that can be identified with you will remain confidential. The information collected about you will be coded using numbers.

Participation and withdrawal

You can choose whether to be a part of this study or not. You can jump questions and withdrawal at any time without consequences of any kind.

Questionnaire

Data collection sheet

Participant Code # _____ Reference#_____ Date ___/___/__

Table 4 Socio-demographic characteristics respondent

SN	Socio-demographic Questions	Response	Remark
1.	Sex	1. Male 2. Female	
2.	Age	----------	
3.	Marital status?	1. Married 2. Single 3. Widowed 4. Divorced 5. Separated	
4.	Educational status?	1. Illiterate 2. Primary School 3. Secondary school 4. Diploma 5. Degree 6. MSc/MPH 7. Other (specify)__	
5.	Occupation	1. Housewife 2. Daily laborer 3. Merchant 4. Governmental employee 5. Private/NGO employee 6. Unemployed 7. Pensioner 8. Others----------	
6.	Monthly income in ETB?	----------ETB.	

Table 5 Lifestyle, Hyperthyroidism related characteristics and Biochemical evidence of participants.

Sn	Hyperthyroidism related characteristics	Response	Remark
1.	Causes of hyperthyroidism		
2.	Duration of hyperthyroidism	_____	
3.	Type of anti-thyroid medications	_____	
4.	WHO Goiter stage	1. Stage 1 2. Stage 2 3. Stage 3 4. Stage 4	
5.	Thyroid cancer	1. Yes 2. No	
	Life style	**Response**	**Remark**
6.	Do you ever forget to take your medicine?	1. Yes 2. No	
7.	Do you take your medicine on time?	1. Yes 2. No	
8.	Do you sometimes stop taking your medicine, when you feel better?	_____	
9.	Do you stop taking it sometimes if you feel worse when you take the medicine?	1. Yes 2. No	
10.	Have you ever smoke cigarette?	1. Yes 2. No	
11.	If yes for question number 10. Have you had smoked in the past?	1. Yes 2. No	
12.	If you smoke cigarette currently, how many cigarettes per day	----------	

	Nutrition food diversification related characteristics	Response	Remark
13.	Group of food items consumed in the last 24 hours	1.Bread and other cereals 2. Green leafy Vegetables 3. Fruits 4. Roots and tubers (like potatoes) 5. Meat, poultry& fish 6. Legumes (Bean, pea, lentils or nuts 7. Egg 8. Milk and milk products 9. Fats and oils 10. Foods containing fat and sugar	
14.	Dietary diversity score	1. 0-3 food items 2. 4- 6 food items 3. > 6 food items	
15.	Meal frequency per day	1. Once 2. Twice 3. Three times 4. Four times and more	
16.	Post meal consumption of Tea (within 30 min)	1. No 2. Yes	
17.	Post meal consumption of Tea (within 30 min)?	1. Always 2. Sometimes	
18.	Post meal consumption of Coffee (within 30 min)?	1. yes 2. No	
19.	Post meal consumption of Coffee (within 30 min)?	1. Always 2. Sometimes	
20.	Height	----------	
21.	Wight	----------	
22.	BMI	----------	
23.	Do you do physical exercise	1. No	

		2. Yes	
24.	Have you ever drink alcohol? days _____	1. No 2. Yes	
25.	If yes for question number 24 How many times you drink alcohol in the past 15 days	----------	
26.			
	Biochemical evidence	**Results**	**Remark**
27.	TSH	----------	
28.	FT3	----------	
29.	FT4	----------	
30.	ALP	----------	
31.	CA	----------	
32.	Serum Vitamin D	----------	
	Imaging results	**Results**	**Remark**
33.	DXA scan	----------	
34.	FRAX score	----------	