Addis Ababa University

College of Health Sciences School of Medicine

Department of Internal Medicine

Clinical risk assessment of osteoporosis in patients with overt hyperthyroidism in Tikur Anbessa Specialized Hospital, Endocrinology unit, April 2025

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Declaration

I, Zerubabel Getahun, do hereby declare that this research thesis is a result of the works of my own making except where due is made in a review of previous literature in the content and by my knowledge, has never been submitted for any prior academic award or qualification in this Institution.

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Approval of thesis submission

I hereby certify that I have read this thesis prepared under my direction and recommend that it can be accepted as fulfilling the thesis requirement.

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Research summary

Name of investigator	Dr. Zerubabel Getahun Kiflu
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List of abbreviations

TASH – Tikur Anbessa Specialized Hospital

FRAX – Fracture Risk Assessment Tool

TSH – Thyroid stimulating hormone

T3 – Triiodothyronine

FT4 – Free thyroxine

TFT – Thyroid function test

CKD – Chronic kidney disease

IRB – Institutional Review Board

QoL – Quality of life

AAU – Addis Ababa University

CHS – College of health science

Abstract

Background

Osteoporosis is a significant public health concern characterized by low bone mineral density and an increased fracture risk, particularly in patients with overt hyperthyroidism. However, data on the magnitude of osteoporosis risk in this population, particularly in Ethiopia, remain limited.

Objective

To assess the 10-year osteoporotic fracture risk and its determinants among patients with overt hyperthyroidism at Tikur Anbessa Specialized Hospital in Addis Ababa, Ethiopia.

Methods

An institution-based prospective cross-sectional study was conducted among adult patients diagnosed with hyperthyroidism receiving follow-up care at the Endocrine Clinic of Tikur Anbessa Specialized Hospital. The FRAX score was used to assess the 10-year osteoporotic fracture risk. Data were collected using a standardized, pre-tested questionnaire. Statistical analysis was performed using SPSS, with descriptive statistics used to summarize patient characteristics. Logistic regression analysis was planned to identify factors associated with intermediate to high osteoporotic fracture risk, with a significance level of 95%. However, regression analysis could not be conducted due to the small number of patients in these categories.

Results

Overall, a total of 134 patients with hyperthyroidism were included in this study, with a mean age of 56.3 ± 10.9 years; the majority (88.1%) was female. The most common cause of hyperthyroidism was toxic multinodular goiter (49.3%), followed by Graves' disease (15.7%). All patients except four were taking antithyroid medication at the time of testing, and over half of the patients had normal or elevated TSH levels. The 10-year fracture risk calculated using the FRAX tool showed a low mean risk for major osteoporotic fractures (2.72%) and hip fractures (0.71%). Only 3.7% (5/134) of patients were classified as being at high risk for hip fractures (≥3%). The risk factors for intermediate to high osteoporotic fracture risk could not be determined because there were not enough patients in these categories to conduct regression analysis.

Conclusion and Recommendations

The results provide evidence of low 10-year osteoporotic fracture risk for patients with hyperthyroidism, with only a small percentage of patients at high risk for hip fractures. Future studies would benefit from larger sample sizes and longer follow-up periods to better establish this information, particularly in limited-resource environments, as fracture risk may be unrecognized, particularly due to limitations in diagnostics.

Keywords: Osteoporosis, Hyperthyroidism, FRAX, Bone Mineral Density

1. Introduction

1.1 Background

Osteoporosis is defined as low bone mineral density caused by altered bone microstructure, ultimately predisposing patients to low-impact, fragility fractures (1). It is caused by an imbalance of bone resorption and bone remodeling, leading to decreased skeletal mass (1). Osteoporosis can be Primary osteoporosis is related to the aging process in conjunction with decreasing sex hormones, whereas secondary osteoporosis can be multifactorial, and one of the common causes is related to endocrinopathies like hyperthyroidism, hyperparathyroidism, or overtreatment of hypothyroidism (2). Osteoporotic fractures lead to a significant decrease in quality of life, increasing morbidity, mortality, and disability (3).

Thyroid hormones are necessary for normal skeletal growth and development. The bone effect of hyperthyroidism is therefore characterized by accelerated bone turnover caused by direct stimulation of bone cells from high thyroid hormone concentrations, and subsequently, this may result in loss of bone mass (4).

Hyperthyroidism increases bone turnover, with increases in both osteoclast and osteoblast activities. As a result, the bone remodeling cycle is shortened, although all phases of the cycle are not affected equally. The duration of the resorption phase is largely unaltered, while the duration of the formation phase is reduced significantly. This leads to a failure to replace resorbed bone completely, resulting in a net loss of about 10% of mineralized bone per cycle (5).

Hyperthyroidism is associated with an increased lifetime risk for fractures, even after achieving euthyroid. This fact may play an important role in the higher mortality rate among previously hyperthyroid patients later in life. Subclinical hyperthyroidism may also affect bone density; however, its effect on fracture rate remains to be established (6).

1.2 Statement of the problem

Osteoporosis is a global public health problem, affecting populations that are already at risk for osteoporosis because of underlying medical conditions (7). Osteoporosis causes a decline in bone mineral density and the structure of bone that increases fracture risk and geriatric morbidity and mortality. In many cases, osteoporosis is a complication of other chronic health conditions such as hyperthyroidism, which is associated with increased bone degradation (8).

Hyperthyroidism is a condition that generates excess thyroid hormones, resulting in effects on multiple body systems, including bone metabolism (9). The association between hyperthyroidism and osteoporosis is well established, as multiple studies show the chronic exposure to excess thyroid hormones leads to increased bone resorption and reduced bone formation and that it is a causative factor in osteoporosis and at risk when prolonged time in hyperthyroid states (10).

Osteoporosis and its risk factors are poorly documented in Ethiopia, where healthcare practitioners are generally confronted with multiple challenges, such as poor access to specialized care and the absence of robust epidemiological studies. Thus, the burden of this disease on populations yet to be established, for example, individuals with overt hyperthyroidism, is unknown and severely hampers the capacity to accurately diagnose and manage osteoporosis in Ethiopia.

Tikur Anbessa Specialized Hospital in Addis Ababa is an important medical facility for many patients with chronic diseases such as hyperthyroidism. The hospital has become one of the few places in the country capable of managing complex endocrine disorders, and as an obvious consequence, has seen an increase in patients presenting with hyperthyroid symptoms. There is, however, a need to explore the complications of the disease, in particular, the risk for the development of osteoporosis.

There is a scarcity of local research outlining the prevalence of osteoporosis in hyperthyroid patients, which has potential implications for how healthcare providers carry out screening and management of hyperthyroidism. To design interventions that could minimize morbidity by risk of fractures, it is important to know the prevalence of osteoporosis in patients with hyperthyroidism. This study aims to address the gap in the literature and to provide relevant data pertaining to local Ethiopian studies.

1.3 Significance of the study

The present study investigates the extent, clinical presentation, and risk for osteoporosis in patients with overt hyperthyroidism. The study's importance will be exhibited in five ways. First, the study allows healthcare providers to form medications and management plans that address both hyperthyroidism and osteoporosis, which enhances patient care. Second, understanding the population that is at risk allows the healthcare system to identify patients who require the greatest resources and focus on those needing increased assessment and management. Third, the study findings can allow health systems to better develop evidence-based guidelines for the management of osteoporosis in hyperthyroid patients. Fourth, the study not only increases education and awareness of the risk of osteoporosis in hyperthyroid patients in health professionals but may also promote a proactive approach for patients. Lastly, the study aims to reduce the risk of morbidity and mortality related to osteoporosis; they want to enhance the quality of life in hyperthyroid patients through effective management of their bone health, and the impact of decreasing fractures will reduce the burden of treatment and rehabilitation costs.

2. Literature review

2.1. Global burden of osteoporosis in overt hyperthyroidism

Osteoporosis is a systemic skeletal disorder characterized by decreased bone mass and density, predisposing to an increased risk of fracture. (11) Osteoporosis is asymptomatic until a fracture occurs, mostly in the hip, spine, and wrist. Osteoporosis can be caused by various factors (idiopathic), such as hormonal changes, nutrient deficiencies, genetic factors, and lifestyle factors. (6)

Hyperthyroidism is a condition that results from the oversecretion of thyroid hormones (thyroxine [T4] and triiodothyronine [T3]) by the thyroid gland. Hyperthyroidism is a state of increased metabolic activity, which subsequently affects many organ systems (6). Causes of hyperthyroidism are varied, with underlying Graves' disease and toxic nodular goiter being the most common, and then also exogenous excess of thyroid hormone. Symptoms of hyperthyroidism include weight loss, increased resting heart rate, anxiety, and high body temperature intolerance. With regard to skeletal health, hyperthyroidism is alarming due to increased bone turnover, which can cause diminished skeletal density (10).

Epidemiological data indicates that the prevalence of osteoporosis and fragility fractures in individuals with hyperthyroidism is higher than in the general population. This relationship is of considerable public health importance, since individuals with hyperthyroidism are at risk of secondary osteoporosis and the debilitating fracture risk that goes with it, and subsequently significant compromise in quality of life (8, 9).

There are studies that demonstrate a positive correlation between osteoporosis severity (BMD loss) and the duration and severity of hyperthyroidism. Specifically, one observational cohort study showed a statistically significant reduction in bone mineral density (BMD) when individuals with serum thyroid-stimulating hormone (TSH) levels were 0.50 mU/L or less (12). The correlation was even stronger when TSH was less than 0.10 mU/L, indicating that the level of hyperthyroidism itself may have a large influence on the morbidity associated with secondary osteoporosis. Clinically, this must stress the importance of monitoring TSH levels promptly and accurately in individuals with hyperthyroidism, as this information could affect the osteoporosis/fracture risk of this population (10).

A study in sub-Saharan Africa also provides insight into the characteristics of a hyperthyroid population at risk for osteoporosis (13). A study conducted on April 5, 2018 (13), included 40 hyperthyroid subjects, with a sample that was predominantly female (32 females vs. 8 males), yielding a female-to-male ratio of approximately 4:1.

The mean age in these subjects was 36.16 years of age, suggesting that many affected individuals are young adults, which is concerning in the context of untreated hyperthyroidism and the long-term effects on bone health (13).

Of the studied subjects, 27.5% were treatment-naive, while 72.5% were receiving antithyroid treatment. The mean duration of thyroid disease in the study population was 27.40 months, with the subjects on treatment averaging 13.07 months of antithyroid treatment. Bone markers osteocalcin, total alkaline phosphatase, and the urinary calcium/creatinine ratio were significantly elevated in hyperthyroid subjects as compared to controls, indicating increased bone turnover and a higher risk of osteoporosis. However, circulating biomarkers, including 25-hydroxyvitamin D, calcium, parathyroid hormone (PTH), and phosphate, were similar, which suggests some similarity with regards, to vitamin D and other minerals in this population (13, 14).

Globally, the effects of thyrotoxicosis as a fracture risk factor have been established. A prospective cohort study from the International Journal of Endocrinology of women over 65 years of age was observed over a four-year period, monitoring fracture incidence and risk. The study (n = 686) found that women with TSH less than 0.1 mU/L had 4.5 times the risk of vertebral fractures and 3.6 times the hip fracture risk. Women who had TSH of 0.1 - 0.5 mU/L, which was within the normal range of TSH (0.5 - 5.5 mU/L), presented with minimal fracture risk. This supports the hypothesis that controlling thyroid function is important for not only the metabolic health of patients but also for their bone health (15, 16).

Hyperthyroidism and possible complications such as osteoporosis in Ethiopia require specific attention. At the facility level, healthcare workers are instrumental in identifying these problems; for example, Tikur Anbessa Specialized Hospital represents a key tertiary referral hospital. Most patients with hyperthyroidism may be considered to be at risk for osteoporosis, and Tikur Anbessa Specialized Hospital is likely to see a good number of patients who have hyperthyroidism and may be at risk for osteoporosis. Therefore, it will be very important to institute patient-specific screening and management protocols at the facility level to address the specific needs of patients.

The area of investigation research between hyperthyroidism and osteoporosis is complex yet important. The literature on a global and regional level indicates that in hyperthyroid patients with osteoporosis, the knowledge and management of bone health are essential.

As healthcare providers, and certainly within the context of Tikur Anbessa and Specialized Hospital, we should have methods and interventions in place that can implement screening for osteoporosis and improve the health status of such people. If the links between thyroid function and bone density become understood, there would be more options available to assist those at risk and help them have a healthier and longer life.

2.2. Associated risk factors for osteoporosis in overt hyperthyroidism patients

2.2.1 Biological and socio-demographic factors

Osteoporosis is an area of significant concern for the overtly hyperthyroid patient population, and multiple biological factors contribute to its development in this group of patients. One main biological factor is the effect of sustained exposure to elevated thyroid hormone levels. Hyperthyroidism increases bone turnover, resulting in increased bone resorption that exceeds bone formation. As a result, a sustained hyperthyroid state can lead to significant decreases in bone mineral density (BMD). Studies show that patients with consistently subnormal levels of thyroid-stimulating hormone (TSH) experience elevated rates of bone loss and fragility fractures. This is compounded by age, especially in post-menopausal women, where hyperthyroid effects increase the risk of decreased BMD and osteoporosis. The biological interaction between thyroid hormones and bone metabolism underscores the importance of rigorous monitoring and management of thyroid function in hyperthyroid patients with a history of osteoporosis or at high risk of developing osteoporosis (16).

Genetic factors can clearly influence the risk for developing osteoporosis, in addition to hormonal influences. A family history of osteoporosis can increase risk factors significantly since genetic dispositions affect how much bone mineral density a person has, as well as how well a person's bones even work in terms of structural composition. Certain genetic markers related to bone metabolism can be co-occurring conditions with lower BMD that lead to a more fragile makeup when combined with other conditions such as hyperthyroidism, but the genetic makeup has implications that could make patients with thyroid issues a higher risk population, particularly in regions with higher rates of thyroid conditions. Factors that influence biological risk factors of osteoporosis in patients with overt hyperthyroidism are important to also dictate biological risk factors and ensure the proper preventive steps are taken (5, 12).

In conjunction with biological risk factors, sociodemographic factors also contribute to osteoporosis. Age is a sociodemographic factor that can impact risk of osteoporosis as well, particularly for women going through menopause. The risk factors for osteoporosis increase with age, as do the risks for health conditions following a change in hormone composition that comes with menopause and hyperthyroidism. Furthermore, the demographics of certain regions will also impact the occurrence of hyperthyroidism and osteoporosis (13, 17).

Lastly, socioeconomic status (SES) has a direct effect on the prevention and management of osteoporosis in patients with overt hyperthyroidism. For example, lower SES individuals are confronted with multiple barriers to healthcare access, such as limited access to diagnostic services, nutrition deficits, and a lack of education regarding the importance of bone health. Socioeconomic barriers also limit finances and purchasing a balanced diet with sufficient calcium and vitamin D for bone mineral density (5, 12, 13). Additionally, lower SES is often correlated to increased stress and mental health issues that impede lifestyle choices and compliance with treatment plans. Addressing the sociodemographic and socioeconomic barriers is an important step in developing community health programs and educational interventions to improve outcomes for patients with overt hyperthyroidism and osteoporosis risk. While allocating time to think about the complex relationships between biological and sociodemographic factors will apply to better approaches to prevention and management, improving the quality of care for patients with overt hyperthyroidism and the risk of osteoporosis is critical for health-care providers (7, 13, 16-18).

2.2.2 Clinical Factors

Clinical variables are important determinants of the risk and progression of osteoporosis in patients presenting with overt hyperthyroidism. One of the main clinical determinants includes the duration and severity of hyperthyroidism (12), where chronicity and higher thyroid function activate bone turnover, producing an increase in net bone resorption relative to formation. Individuals with poorly treated or untreated hyperthyroidism are consequently at increased risk of developing osteoporosis. The level of thyroid function is key, usually measured via TSH (serum thyroid-stimulating hormone) levels, whereby individuals with TSH levels below the normal range (0.5-5.5 mU/L), displayed greater loss of bone density. As a result of this, once risk is determined, management of hyperthyroidism and TSH should be monitored in individuals at risk of osteoporosis.

The presence of comorbidities is another clinical factor that affects the risk of osteoporosis in overt hyperthyroid patients. Many hyperthyroid patients have comorbid conditions, such as diabetes, cardiovascular problems, or autoimmune conditions that can affect the general state of their health and result in further bone loss. For example, rheumatoid arthritis can induce chronic inflammation, which can affect the density of the bones. Furthermore, some drugs used to manage certain comorbidities, especially corticosteroids, are established as a means of increasing bone loss. Consequently, to facilitate successful management, an overall view of all health conditions and their treatments must be taken to construct the best management plan for the patient's specific conditions.

Medication adherence and management are also important clinical considerations with osteoporosis in the context of patients with unequivocal hyperthyroidism. Some of the antithyroid medications that are required to manage hyperthyroidism have different effects on bone health. Some treatment drugs can improve thyroid function variables and stabilize bone density, while others, particularly if they are unmonitored, may create additional problems. When patients are identified as high risk for fractures, considering specific osteoporosis drugs for treatment should also be introduced, as in the case with bisphosphonates and hormone replacement. Healthcare providers must educate patients about the importance of adherence to their prescribed medications and follow up with regular management of their bone health, including screening in the form of dual-energy x-ray absorptiometry (DEXA).

In summary, lifestyle factors, such as nutrition and physical activity, can also impact the clinical management of osteoporosis in patients with overt hyperthyroidism. Adhering to daily calcium and vitamin D intake is essential for bone health, but patients with hyperthyroidism may struggle to meet these nutritional needs due to different dietary restrictions or poverty. Although physical activity is an important factor to help improve bone density, patients with hyperthyroidism may lack the energy or motivation to exercise. By encouraging a healthy diet high in nutrients that help support bone, along with promoting a safe, individualized exercise program, healthcare professionals can perhaps help lower the risk of osteoporosis. Together, when all of the clinically approaches are integrated, healthcare professionals would be able to intervene on multiple levels for the management of osteoporosis in patients with overt hyperthyroidism; this would undoubtedly be a positive influence on these patients' quality of life while also reducing the risks of hip fracture (12, 17).

2.2.3 Environmental and Socioeconomic Factors

Environmental and socioeconomic factors can influence the occurrence and management of osteoporosis, particularly in patients with overt hyperthyroidism. Firstly, the environment plays a large part in whether people have access to health care. In many ways, and particularly in low-resource situations, people may have substantial barriers to appropriately accessing healthcare in a timely manner. For patients with overt hyperthyroidism, timely medical attention is important to help avoid complications like osteoporosis. There are a number of ways an inadequate healthcare system, e.g., insufficient specialists and diagnostic capabilities, can impact the ability of patients to seek evaluation/intervention, mostly through delays in evaluation/intervention. Prolonged exposure to high levels of thyroid hormone will increase bone resorption and decrease bone mineral density, thus increasing fracture risk (7).

Socioeconomic status (SES) is an important risk factor for osteoporosis in people with overt hyperthyroidism. People from lower SES backgrounds may have financial limitations about being able to purchase healthy foods, especially those high in calcium and vitamin D, which are important for healthy bones. Malnutrition and deficiencies further exacerbate the effects of hyperthyroidism on bone density (12, 13, 19).

Cultural beliefs and practices grow out of environmental and socioeconomic factors, which in turn shape how individuals make sense of their health and well-being. Sometimes, individuals in certain cultures prioritize traditional medicine and therapies over conventional medicine, which may lead to delays in treating hyperthyroidism appropriately. Such delays may lead to patients being untreated longer, increasing their risk for osteoporosis (5, 7, 12, 13, 16, 17). Cultural beliefs about aging and health may also hinder patients' degree of engagement with their health care, both in treatment and adherence to health recommendations such as exercise and dietary habits. Education and outreach designed around the cultural context of the patients is critical in getting patients with overt hyperthyroidism to engage in proactive behaviors concerning their health.

2.2.4. Lifestyle Factors

Lifestyle factors have a major impact on the development and management of osteoporosis, especially in patients with overt hyperthyroidism. One of the biggest lifestyle factors is physical activity. Weight-bearing exercise and resistance exercise are an important part of living and maintaining or increasing bone density. Some individuals with hyperthyroidism have symptoms including fatigue, muscle weakness, and increased heart rate, which can be discouraging toward continued physical activity. This lack of exercise can worsen bone loss because bones need mechanical loading to grow and maintain. Prescribing forms of activity that are suited to each patient, while also considering their own capabilities and limitations, can keep someone active and protect their bone health (5, 12, 19).

Nutrition is another lifestyle factor to consider when thinking about osteoporosis risk in patients with overt hyperthyroidism. Inadequate calcium and vitamin D intake is paramount for bone health, but many people will have trouble getting the required nutrition due to their diets, finances, or lack of knowledge. When individuals are on a diet that provides less than adequate calcium intake, there is an increased risk of bone resorption and osteoporosis. Furthermore, lactose intolerance or other dietary needs may discourage some individuals to deny dairy products as viable sources of calcium. Providers should encourage patients about

diet and that a healthy diet has all the nutrients supportive of bone health and equate that to supplementing when there are not enough dietary needs met (5, 12, 13, 19).

Substance use, especially smoking and excessive consumption of alcohol, significantly impacts patients' bone health who present with overt hyperthyroidism. Smoking is associated with decreased bone density and an increased risk of fracture due to the impact on calcium absorption and hormone regulation, which ultimately play an important role in the maintenance of bone health (12, 13, 19). Likewise, excessive alcohol utilization can interfere with calcium balance in the body and inhibit bone formation. Patients with hyperthyroidism might be at an even higher risk factor for these lifestyle issues, as stress and anxiety associated with their illness may lead to unhealthy coping mechanisms. Counseling and community support programs that address these behaviors are an important part of reducing patients' risk of developing osteoporosis and improving their overall health (5, 12, 13).

2.2.5 Conceptual framework

The framework tries to figure out and support the study entitled *'Magnitude and associated risk factors of osteoporosis in patients with overt hyperthyroidism in Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2024: A Cross-Sectional Study*. It is developed specifically for this study by the principal investigator after reviewing related literature (1, 5, 7, 13, 16-20)

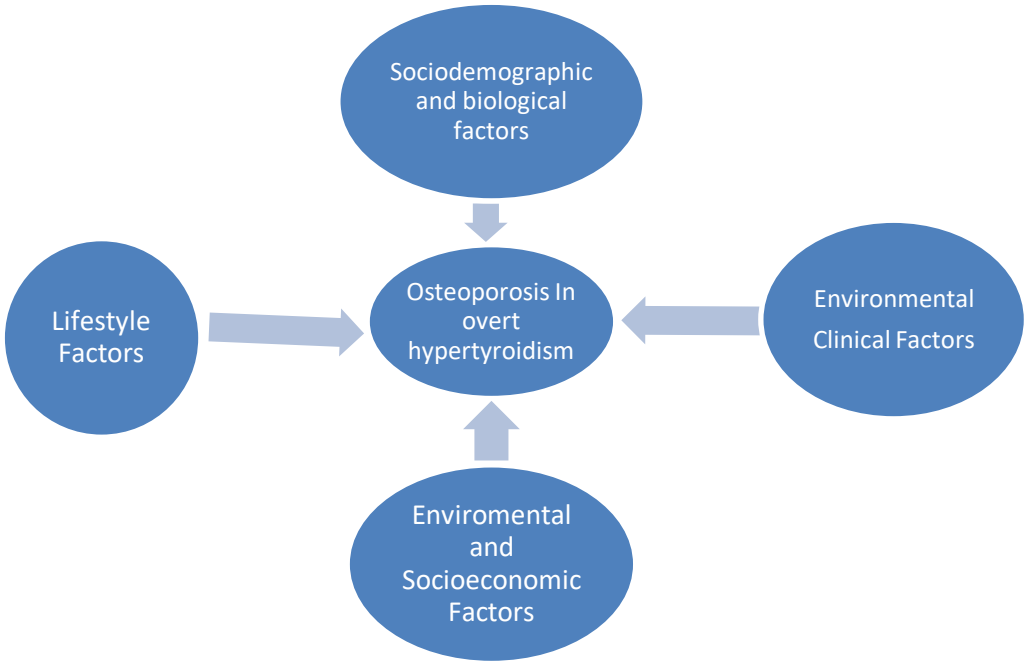


Figure 1 depicts factors that affect osteoporosis in overt hyperthyroidism

3. Objective

3.1 General objective

- To assess the ten-year osteoporotic fracture risk and its determinants among patients with overt hyperthyroidism at Tikur Anbessa Specialized Hospital in Addis Ababa, Ethiopia.

3.2 Specific objective

- To determine the ten-year osteoporotic fracture risk using the FRAX score among patients with overt hyperthyroidism.
- To identify the ten-year risk factors associated with intermediate to high osteoporotic fracture risk in patients with overt hyperthyroidism

4. Methodology

4.1 Study area

This study will be conducted among adult medical patients who had follow-ups at the endocrine clinic in Tikur Anbessa Specialized Hospital (TASH), one of the tertiary referral hospitals in Addis Ababa, Ethiopia. It is one of the biggest and pioneer teaching centers under the administration of Addis Ababa University. The study area is located at the center of the capital city of Ethiopia, Addis Ababa. TASH is the country's largest teaching and tertiary hospital, with more than 400,000 patients seen at an outpatient follow-up clinic annually. TASH is a referral center for many referral hospitals as well as a hospital under which very vast clinical service is given, including some specialty services only found in TASH. The overall number of endocrine patients in the follow-up clinic is 1532 per month.

4.2 Study design and period

An institution-based prospective study that was conducted from January 2025 to February 2025 G.C.

4.3 Population

4.3.1 Source population

All adult patients with hyperthyroidism who had follow-up at TASH endocrine clinic, Addis Ababa, Ethiopia

4.3.2 Study population

All adult patients with hyperthyroidism who fulfill the inclusion criteria and who had a follow-up at Tikur Anbessa Specialized Hospital

4.4 Selection criteria

4.4.1 Inclusion Criteria:

- Patients with overt hyperthyroidism

4.4.2 Exclusion Criteria:

- Pregnant or lactating women
- Patients currently undergoing treatment for active cancer

4.5 Sample size, sampling technique, and sampling procedures

4.5.1 Sample size

The last sample size (n) required for the study was calculated using the formula to estimate a single population proportion.

$$n = \frac{Z_{\frac{\alpha}{2}}^{2} P (1 - P)}{d^{2}}$$

Where;

n = required sample size

$Z_{\alpha/2}$ = critical value for normal distribution at 95% confidence interval= 1.96 ($\alpha = 0.05$).

P = Proportion = 50%

d = margin of error= 9%

$$n = \frac{(1.96)^2*(0.5)(1-0.5)}{(0.1)^2} = 119$$

Taking a 15% non-response rate, the total sample size will be 137.

4.5.2 Sampling technique and procedure

First, all adult hyperthyroidism patients who have followed up at the TASH endocrine clinic were selected from the registration book. From this list, the study participants were selected through systematic random sampling techniques till the sample size was achieved. The interval (K-value) was calculated by dividing the number of patients by the sample size. The first patients were selected by lottery methods.

4.5.3 Data collection tools and procedure

We will use a pre-tested data retrieval (abstraction) checklist, developed after reviewing different works of literature. The checklist was prepared in English for ease of the data abstraction process; it contains socio-demographics, clinical variables, imaging variables, and laboratory results. The data was extracted from the electronic record and patient medical record chart. The questionnaires were prepared in the Kobo Collect tool and collected in the Android tools (mobile and tablet). The trained general practitioners were collecting the data.

4.6 Data quality control

The pre-test was done on 10% of the similar study population but not on the actual data (on patients from Zewuditu Memorial Hospital). The principal investigator was instructing the data collectors on data extraction procedures, data sources, and inclusion and exclusion criteria. The investigator will conduct a daily supervision and follow-up check for the completeness and consistency of the data.

4.7 Operational definition

- **Hyperthyroidism**: A condition characterized by overproduction of thyroid hormone by the thyroid gland
- **Overt hyperthyroidism**: Defined as suppressed TSH & high T3 or FT4
- **Osteoporosis**: WHO definition, BMD T-score is -2.5 SD or less than the young adult mean.
- **Long-standing hyperthyroidism:** Refers to a condition where the thyroid gland produces excess amounts of thyroid hormone (T3 and T4) over an extended period, usually more than one year.
- **FRAX score:** Estimates the 10-year fracture risk based on factors like age, gender, BMI, smoking, and family history. It categorizes major osteoporotic fracture risk as low (<10%), intermediate (10%-19%), or high (≥20%), and hip fracture risk as low (<3%) or high (≥3%).

4.8 Data processing and analysis

The data in Excel format (downloaded from Kobo Collect) will be uploaded to SPSS version 27.1 for cleaning and analysis. We will use proportions (percentages) to describe categorical data. For continuous variables, the normal distribution variables' mean (±standard deviation) will be utilized, while the non-normal distribution variables' median (interquartile range) will be employed. To compare categorical variables, the chi-square test or Fisher's exact test will be employed. A logistic regression analysis will be used to identify the variables associated with osteoporosis. All variables with a p-value <0.20 in the univariate analysis will be selected for the multivariate analysis model. A p-value of <0.05 and a 95% confidence interval will be considered statistically significant.

4.9 Ethical consideration

Ethical clearance and approval will be obtained from the AAU CHS TASH Research Ethical Review Committee. The data will be fully anonymized and will not be accessible by any third party other than the study team. Informed consent will not be applicable for the secondary data and will be waived by the ethical review committee.

4.10 Results dissemination

The findings of the study will be submitted to the TASH Department of Internal Medicine and the college library. The findings will be presented at national conferences. The result will be published in open-access and peer-reviewed journals for international readers.

5. Result

5.1 Sociodemographic characteristics

A total of 134 patients volunteered to participate out of 137 estimated, with a response rate of 97.8%. The mean age of the participants was 56.3 ± 10.9 years, and the majority was female, comprising 88.1% (118/134) of the sample. Most participants were aged between 40 and 55 years (53% (71/134)), lived in urban areas (80.6% (108/134)), and were married (70.1% (94/134)). Regarding education, 34.3% (46/134) had completed primary school, while 17.2% (23/134) had no formal education. The most common occupation was housewife, 56.7% (76/134). Regarding BMI, 56.7% (16/134) had a normal BMI, while 9% (12/134) were overweight or obese (table 1).

Figure 1: Sociodemographic and Clinical Characteristics of the Study Participants in TASH, 2025

Variables		**Frequency**	**Percentage**
Sex	Female	118	88.1
	Male	16	11.9
	40-55	71	53.0
	56-65	34	25.4
	≥66	29	21.6
Education	No formal education	23	17.2
	Primary school	46	34.3
	Secondary school	36	26.9
	Higher education	35	21.6
Residence	Rural	26	19.4
	Urban	108	80.6
Marital status	Single	8	6.0
	Married	94	70.1
	Widowed	22	16.4
	Divorced	10	7.5
Occupation	Unemployment	12	9.0
	Housewife	76	56.7
	Pensioner	14	10.4
	Self employed	23	17.2
	Government employee	9	6.7
BMI(n=137)	<18.5	9	6.7
	18.5-24.49	76	56.7
	25-29	37	27.6
	≥30	12	9.0

5.2 Comorbidities and medications used

In the analysis of comorbidities by system, hypertension was the most common comorbidity, affecting 33.58% (54/134) of participants, followed by diabetes mellitus, 23.8% (33/134); RVI, 10.34% (14/134); and rheumatoid arthritis (RA), 5.08% (8/134) (table 2).

Regarding medications, antihypertensives were the most frequently used, 40.3% (54/134), followed by antidiabetic medications and lipid-lowering agents. Diuretics and bone health medications accounted for smaller proportions, with "Others" representing 7.54% (table 2).

Figure 2: Distribution of Comorbidities and Medication Use Among the Study Participants at TASH, 2025

Comorbidities disease category	**Frequency**	**Percentage**
Cardiovascular	82	61.2
Endocrine/Metabolic**	45	33.6
Gynecologic/Obstetric	21	15.7
Musculoskeletal	19	14.2
Neurological	11	8.2
Infectious Disease	13	9.7
Respiratory	5	3.7
Others diagnosis+	12	9.0
Medications		
Antihypertensives	54	40.3
Antidiabetic Medications	15	11.2
Lipid-Lowering Agents (Statins)	15	11.2
Anticoagulants/Antiplatelets	13	9.7
Diuretics	10	7.5
Bone Health Medications	6	4.5
Others medications *	8	6.0

Note: Diagnoses included under "Others+" are as follows: hematologic (2 cases), hepatic (2 cases), cancer (5 cases), and psychiatric (3 cases). The "Others*" category consists of Analgesics and Anti-inflammatories (3), Gastrointestinal Medications (3), and Corticosteroids (2).**others than Hyperthyroidism

5.3 Cause of hyperthyroidism, duration, and medication

The major causes of hyperthyroidism were toxic MNG, 49.3% (66/134), and Graves' disease, 15.7%, (21/134). Most participants were diagnosed at ages 36 to 45 years, 32.8% (44/134). The majority had <5 years duration of hyperthyroidism, 42.9% (57/134) and were on PTU, 85.8% (115/134), as the primary medication.

Figure 3: Causes, Diagnosis, Duration, and Medication in Hyperthyroidism among Study Participants in TASH 2025

Cause of hyperthyroidism		Frequency	Percentage
	Graves' disease	21	15.7
	Toxic adenoma	17	12.7
	Toxic MNG	66	49.3
	Not known	30	22.4
Age at diagnosis(years)	<35	27	20.1
	36-45	44	32.8
	46-55	32	23.9
	≥56	31	23.1
Duration on Hyperthyroidism	<5	57	42.5
	6-10	41	30.6
	≥11	36	26.9
Duration on medication	< 5	61	47.7
	6-10	36	28.1
	≥11	31	24.2
Type of medication	Methimazole	5	3.7
	PTU	125	92.5
	Not on Medication	4	2.9

5.4 Laboratory and Imaging Findings

Within a subsample of patients, abnormal thyroid function was exhibited, with 48% (47/98) of patients with low TSH, 29.3% (29/75) with elevated Free T4, and 20.4% (10/48) with elevated Free T3 indicating possible hyperthyroidism. In addition, 12.5% (4/32) of patients had elevated creatinine levels, indicating possible kidney dysfunction.

Only a few participants had determinations for serum calcium, phosphate, and vitamin D levels. Serum calcium was measured in 7 individuals, with levels ranging from 1.1 to 8.39 mg/dL. Phosphate levels were determined in 3 participants, ranging from 3.43 to 3.8 mg/dL, all within the normal range of 2.5–4.5 mg/dL. Vitamin D levels were available for 7 individuals, with values ranging from 8.7 to 39.1 ng/mL, and 48.2% (3/7) had levels within the normal range of 20–50 ng/mL.

Of the four patients who underwent imaging, two had abnormal findings. One had a left-hand X-ray showing non-uniform joint space narrowing, subchondral sclerosis, and DIP and PIP joint involvement, while another had a lumbosacral MRI revealing moderate degenerative disc disease with multi-level involvement, a small posterior central broad-based disc protrusion at L4-L5, facet degeneration, and ligamentum flavum buckling, causing moderate spinal canal and bilateral neural foramen stenosis.

Figure 4: Distribution of Hormone and Creatinine Levels Among the Study Participants in TASH, 2025

Hormone		Frequency	Percentage
TSH (n=98)	Low (<0.4 ÂµU/mL)	47	48.0
	Normal (0.4 - 4.0 ÂµU/mL)	43	43.9
	High (>4.0 ÂµU/mL)	8	8.2
Free T4 (n=75)	Low (<0.8 ng/dL)	6	6.1
	Normal (0.8 - 1.8 ng/dL)	64	64.6
	High (>1.8 ng/dL)	29	29.3
Free T3 (n=49)	Low (<2.3 pg/mL)	23	46.9
	Normal (2.3 - 4.2 pg/mL)	16	32.7
	High (>4.2 pg/mL)	10	20.4
Creatinine (n=32)	Normal (<1.2)	28	87.5
	Elevated (≥1.2)	4	12.5

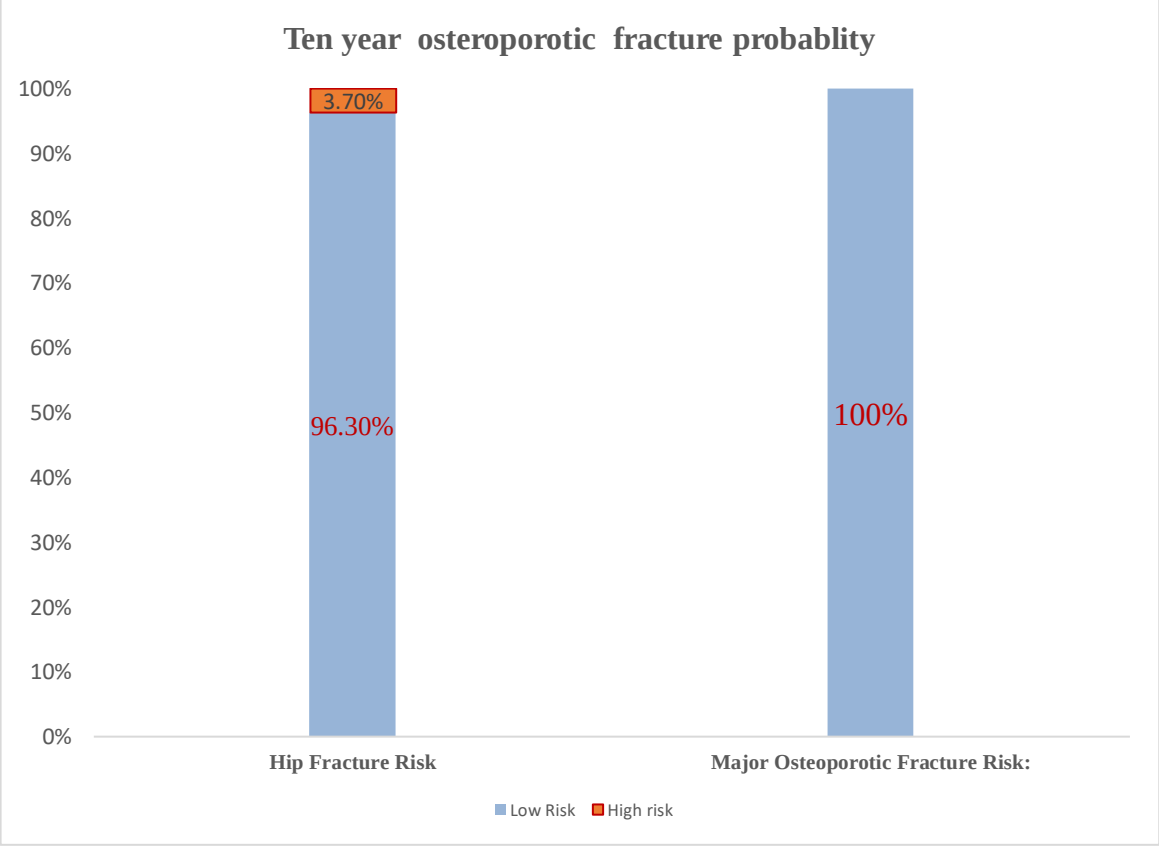
5.5: Ten-Year Osteoporotic Fracture Risk Among Patients with Overt Hyperthyroidism

The ten-year osteoporotic fracture risk was evaluated using the FRAX (Fracture Risk Assessment Tool) for both major osteoporotic fractures and hip fractures. The mean (±SD) ten-year probability of major osteoporotic fractures was 2.72 ± 1.95%, with a range from 0.5% to 8.9%. All study participants had a ten-year major osteoporotic fracture risk of less than 10% (figure 1).

For hip fractures, the mean (±SD) ten-year probability was 0.71 ± 0.85%, with a range from 0.0% to 4.1%. Among the study participants, 3.7% (5 out of 135) were classified as high risk (≥3%), while the remaining 96.3% (130 out of 135) were categorized as low risk (<3%) (Figure 1).

Due to the small number of patients with intermediate to high major osteoporotic fracture risk and high hip fracture risk (only five patients), regression analysis could not be conducted for the second specific objective.

***Figure** 5: Ten-Year Osteoporotic Fracture Risk Distribution Based on FRAX Tool Assessment for Major Osteoporotic and Hip Fractures.*



5.6 Hyperthyroid state versus euthyroid state

Among the study participants, a total of 86 individuals had documented thyroid function test (TFT) results that indicated either hyperthyroid or euthyroid status. Of these, 28/86 participants (32.5%) were found to have hyperthyroidism, while the remaining 58/86 (67.4%) were euthyroid. Among the five participants identified as high-risk for hip fracture, 5 were found to be hyperthyroid.

Figure 6: Hyperthyroid state versus euthyroid state

		Hip fracture 10 year risk		Total
		Low risk	High risk	
Thyroid function	**Hyperthyroidism**	23	5	28
	Euthyroidism	58	0	58
Total		81	5	86

5.7 Biochemical characteristics in patients with hyperthyroidism

From a total of 86 individuals who had a documented TFT, results showed that 6/86 (6.9%) were hyperthyroid, 61/86 (70.9%) were euthyroid, and out of these, 32/61 (52.4%) had a normal FT4 with slightly low TSH.

Figure 7: Biochemical characteristics in patients with hyperthyroidism

		FT4		Total
		Normal	High	
TSH	**Low**	32	6	38
	Normal	29	19	48
Total		61	25	86

6. Discussions

The study evaluated the ten-year risk of osteoporotic fractures and its associated determinants in patients with overt hyperthyroidism at TASH, Addis Ababa. The mean age of the participants was 56.3 years, with 88.1% of them being female. Toxic multinodular goiter (49.3%) was identified as the most prevalent underlying cause. Almost all participants were on antithyroid medication, and more than half had normal or above TSH levels. The most common comorbidities observed were hypertension (33.57%) and diabetes mellitus (23.8%). The findings indicated that almost all patients had a low risk for both major osteoporotic fractures and hip fractures. However, a small proportion (3.7%) was classified as being at high risk for hip fractures.

Our study participants' mean age (56.3 years) and female predominance (88.1%) were aligned with global epidemiological patterns where hyperthyroidism disproportionately affects women, particularly in perimenopausal age groups (6, 12). The demographic overlap of age-related bone loss and direct fracture risk, when combined with the populations vulnerable to estrogen-deficient bone loss, makes it a priority to monitor bone health proactively. However, the cohort's relatively younger age likely reduced fracture risk, as a decline in bone density is much higher after the age of 65 (12). Toxic multinodular goiter (49.3%) is the most common cause of hyperthyroidism in our study and is consistent with a regional pattern in sub-Saharan Africa linked to chronic iodine deficiency and nodular thyroid disorders (13). This diverges from Western countries like the United States and Japan, where Graves' disease accounts for 60–80% of hyperthyroidism cases (6, 10). The high rate of antithyroid medication (>50% achieving normal TSH levels) highlights effective disease management at TASH, a finding consistent with specialized centers in South Africa and India (13, 17).

Hypertension (33.57%) and diabetes (23.87%) were the most common co-morbid conditions in overt hyperthyroid individuals in our study. Though they are known to increase fracture risk through chronic inflammation, vascular dysfunction, and the potential for falls from neuropathy (17, 19), we expect that these comorbid conditions, with appropriately managed hyperthyroidism, may have lessened their individual effects. For example, adequate glycemic control in diabetes reduces levels of advanced glycation end-products that impair bone quality, whereas hypertension managed with non-diuretics avoids the calcium-wasting effects of diuretics (17, 19). The relationship between comorbidity management and the control of hyperthyroidism may also help explain the low overall risk of future fracture seen in our cohort as compared to studies in India and Pakistan, whose fragmented models of care lead to excessive skeletal fragility in hyperthyroid patients (17).

The study showed that all patients (100%) had a low risk of major osteoporotic fractures over the next ten years, and almost all (96.3%) had a low risk of hip fractures. This contrasts with global studies linking overt hyperthyroidism to elevated fracture risk (12, 15). This lower score in our findings might be related to the following reasons. First, the majority of participants (>50%) achieved normal TSH levels through antithyroid medication, a critical factor in mitigating bone resorption. Prolonged TSH suppression accelerates bone turnover by directly stimulating osteoclast activity and indirectly increasing thyroid hormone-driven calcium excretion (10, 12). Second, the majority of our patients were on antithyroid medication and regular follow-up, which contrasts with underserved regions where untreated hyperthyroidism remains a silent driver of osteoporosis. Third, the reliance on clinical risk scores (e.g., FRAX)—rather than direct bone mineral density (BMD) measurements in our study may underestimate fracture risk in younger patients with subclinical bone loss. For example, a Brazilian study using DEXA scans found that 20% of hyperthyroid patients with "low" clinical risk scores had osteopenia undetected by FRAX (12). Similarly, in Egypt, researchers identified trabecular bone microarchitectural damage in euthyroid patients with a history of hyperthyroidism, suggesting that clinical tools alone inadequately capture residual skeletal vulnerability (15). While Ethiopia's reliance on these tools reflects resource constraints, it may obscure nuanced risks in younger individuals. Regional Advantages: Diet and sunlight exposure Ethiopia's traditional diet, rich in calcium-containing legumes (e.g., lentils, chickpeas) and leafy greens, may offset deficiencies common in hyperthyroidism. Additionally, high-altitude geography enhances ultraviolet B exposure, promoting vitamin D synthesis—a stark contrast to countries like Norway or the United Kingdom, where limited sunlight necessitates widespread supplementation (5). However, without direct dietary or vitamin D data, this remains speculative. Lastly, almost all of our study participants do not engage in risky behaviors such as alcohol use and tobacco smoking. However, most also participated in physical activities for about 150 minutes per week, which likely contributed to the lower osteoporosis risk observed in them.

7. Strength and limitation

This study had several strengths. It offers critical context-specific insights into osteoporotic fracture risk among hyperthyroid patients in Ethiopia, a region historically underrepresented in osteoporosis research, particularly in sub-Saharan Africa, where iodine deficiency and toxic multinodular goiter are prevalent. While the study utilized standardized clinical risk assessment tools such as FRAX, offering a means of comparison with available data on osteoporosis from high-income countries, it offered a broader perspective of fracture risk by including sociodemographic, clinical, and laboratory data, including comorbid conditions. There were also limitations to the study. Firstly, the lack of bone mineral density measurements relied solely on clinical risk scores and may likely underestimate the prevalence of significantly low bone density in younger demographic patients with subclinical bone loss. Secondly, the study reflects a referral hospital cohort of hyperthyroid patients and may not represent the rural populations or untreated populations in the rest of Ethiopia, where timely diagnosis may be delayed and access to health care poses an even greater risk. Thirdly, this study was managed at a tertiary referral center with specialists from multiple disciplines, where effective management may have reduced osteoporosis risk through optimized medication when appropriate, thus affecting the study accuracy and results presented. Fourthly, dietary calcium and vitamin D intake data were not included and likely affect bone health in patients with hyperthyroidism. Despite being prospective in design to reduce missing data, ten-year fracture risk could not be calculated for 15.4% of participants with missing data. Finally, while we aimed to assess risk factors for an intermediate-to-high ten-year osteoporosis risk, we were unable to conduct this extra analysis because only five patients had high hip fracture risk and none had high major fracture risk.

8. Conclusion and recommendation

This study demonstrated that all patients had a low ten-year risk of major osteoporotic fractures, and nearly all (96.3%) had a low risk of hip fractures. Therefore, we forward the following recommendations. Continue prioritizing timely diagnosis and antithyroid therapy to maintain TSH normalization, a key factor in preserving bone health. Advocate for increased availability of DEXA scans in Ethiopia to detect subclinical bone loss, particularly in high-risk patients, despite the overall low fracture risk. Conduct larger-scale or multinational studies to investigate predictors of intermediate-to-high fracture risk. Test the impact of calcium/vitamin D supplementation, exercise programs, or prophylactic bisphosphonates in high-risk patients. Validate alternatives to DEXA (e.g., quantitative ultrasound) in resource-limited settings like ours rather than depending only on clinical risk scores.

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Annex I: Questionnaire on the clinical risk assessment in patients with overt hyperthyroidism mellitus

Code _____

I-care number _____ Date of interview _____/2024

Section 1: **Demographics**

1. Age? _____years
2. Gender?
   a. Male b. Female
3. Residence?
   a. Urban b. Rural
4. Current marital status?
   a. Single b. Married c. Divorced d. Widowed
5. What is your level of education?
   a. No formal education
   b. Primary school
   c. Secondary school
   d. Higher education
6. What is the occupation you practiced over the past 12 months?
   a. Government employee
   b. Self-employed
   c. Housewife
   d. Farmer
   e. Pensioner
   f. Unemployed

Section 2: **Thyroid History**

7. How long have you had hyperthyroidism? ____ years
8. How old were you when you were diagnosed with hyperthyroidism? _____ years
9. Type of hyperthyroidism (if available)
   a. Graves' disease
   b. Hashimoto thyroiditis
   c. Toxic adenoma
   d. Others, specify _____
10. What type of treatment are you currently taking for your hyperthyroidism? Choose all that apply.
    a. PTU (_____ years)
    b. Methimazole (_____ years)
    c. Other, specify _____

Section 3: **Physical Examination & Laboratory Results**

11. Weight _____ Kg
12. Height _____ cm
13. TSH _____
14. Free T4 _____
15. Total T3 _____
16. Serum calcium levels (mg/dl) _____
17. Serum Phosphate level (mg/dl) _____
18. Serum Vitamin D level _____
19. Serum parathyroid hormone level _____
20. Serum creatinine _____ mg/dl
21. Bone imaging (X-ray or CT scan...) result

_____

Section 4: **Osteoporosis Risk Factors**

22. Physical activity level
    a. Vigorous (75 minutes a week, e.g., running)
    b. Moderate (150 minutes a week, e.g., Walking at a fast pace)
    c. How much time do you spend sitting on a usual day? (home, work, transportation) _____ hours
23. Smoking status?
    d. Never
    e. Ex-smoker. Smoked _____ cigarettes daily for _____ years
    f. Current smoker. Smoke _____ cigarettes daily for _____ years
24. Do you consume more than 3 units of alcohol a day?
    g. Yes
    h. No
25. History of chronic medical conditions. Choose all that apply.
    a. Untreated long-standing hyperthyroidism
    b. Hypogonadism
    c. Diabetes mellitus
    d. Chronic liver disease
    e. Chronic kidney disease
    f. Rheumatoid arthritis
    g. Hypertension
    h. Dyslipidemia
    i. Epilepsy
    j. Menopause, if yes, age at menopause _____ years

26. Current medications (use of medication within the past year): Choose all that apply.
    a. Osteoporosis prevention or treatment
        - Vitamin D or calcium supplementation
        - Treatment with bisphosphonates, denosumab or teriparatide
    b. Oral contraceptives
    c. Hormone replacement therapy
    d. Oral glucocorticoids: currently taking or exposed for 3 months at a dose of prednisolone 5 mg PO/day
    e. Thyroid replacement
    f. None of the above

FRAX - Fracture Risk Assessment Tool

No.	Risk Factors	Response	
1	Age ***see above**		
2	Sex ***see above**	Male ☐	Female ☐
3	Weight (in Kg) ***see above**		
4	Height (in cm) ***see above**		
5	*Previous fragility fracture (arising from trivial trauma)*	Yes ☐	No ☐
6	*Parent fractured hip*	Yes ☐	No ☐
7	Current smoking ***see above**	Yes ☐	No ☐
8	Glucocorticoids (currently taking or exposed for 3 months at a dose of prednisolone 5 mg PO/day) ***see above**	Yes ☐	No ☐
9	Rheumatoid Arthritis ***see above**	Yes ☐	No ☐
10	Secondary Osteoporosis **(Yes for all- Hyperthyroidism)**	**Yes** √	No ☐
11	Alcohol 3 or more units/day ***see above**	Yes ☐	No ☐
12	*BMD femoral neck (g/cm^2)* **#if available**		

The 10-year probability of **(calculated)**
Major osteoporosis-related fracture _____ %
Hip fracture_____ %