Bone fractures among adult Nigerians with hyperthyroidism: risk factors, pattern and frequency

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Background: Hyperthyroidism is a common endocrine disorder with multi-systemic effects, the least reported of which is bone loss and fractures.
Objective: The aim was to evaluate the risk factors, pattern and frequency of bone fractures among Nigerians with hyperthyroidism.
Methodology: An analytical study was undertaken of 40 patients with hyperthyroidism aged between 21 and 50 years. They were seen at the outpatient Endocrine, Diabetic and Metabolism (EDM) clinic of Lagos State University Teaching Hospital (LASUTH). Using an interviewer-administered questionnaire, information on sociodemographics, medical history, clinical and biochemical parameters and dual-energy X-ray absorptiometry (DXA) scan was obtained. Risk of fracture was assessed using WHO and ISCD risk calculators. During statistical analysis, quantitative and qualitative data were expressed as mean (SD) and percentages.
Results: In all, 40 patients with hyperthyroidism were studied with a mean age of 36.16 (8.43) years. There were 32 females (80%, female:male ratio 4:1) and mean body mass index was 24.14 (4.3) kg/m. Hyperthyroidism was defined by Waynes' scoring index greater than 19 and confirmed by elevated thyroid hormones (FT4 39.44 (24.11) (pmol/l), FT3 12.13 (7.83) (pmol/l)) and suppressed TSH 0.26 (0.03) (u/U/ml). Increased bone turnover was documented by elevated bone formation markers (osteocalcin 45.7 (19.9) ng/ml and alkaline phosphatase 221.1 (143.46 IU/l)), bone resorption markers (24-hour calcium excretion 590.95 (506.1) mg/day). The mean BMD T- and Z-scores were reduced –2.0 (1.2). Bone loss was observed in 31 (72.5%) hyperthyroid subjects, but only three (7.5%) had fractures due to minor trauma.
Conclusion: Bone fractures may not be uncommon in hyperthyroidism. Early screening for bone diseases should be encouraged to improve treatment outcome.

Keywords: bone mineral density, fractures, hyperthyroidism

Introduction

Thyrotoxicosis is a clinical syndrome characterised by an accelerated metabolism resulting from an excessive amount of circulating thyroid hormones. It has multi-systemic manifestations with clinical features ranging from silent to florid[1] that may occur with signs of hyperactivity, including atrial fibrillation—especially in the elderly, muscle weakness and wasting, heart failure and if uncontrolled may lead to a thyroid storm.

Common causes of hyperthyroidism include Graves' disease, toxic multinodular and solitary nodular goitre.

Thyroid hormones are essential for normal skeletal growth and maintenance of bone mass.[2] Excessive circulating thyroid hormones may result in bone loss, which may manifest with bone pains, trivial and stress fractures or hip fractures from acute pressure.[3] These bone changes are characterised by enhanced bone turnover in both trabecular and cortical bone, leading to increased porosity and mobilisation of bone mineral,[4] though the cortical bone is more commonly affected than trabecular bone for which reason bone mineral density (BMD) is best measured at the distal forearm in hyperthyroidism.[5] These bone changes of hyperthyroidism may or may not be reversible with medical therapy, thereby putting patients at increased risk of fractures.[6]

Correlating the two disease conditions of fractures and hyperthyroidism may remain a dilemma and diagnostic challenge, especially among primary care physicians, since bone loss in hyperthyroidism is a rarely reported complication in sub-Saharan Africa. In addition, dual energy X-ray absorptiometry (DXA) scanning—the gold standard for the determination of bone mineral density—is not accessible or available in our environment of limited resources.

There are few reports on the prevalence, the pattern, the risk assessment of fractures and the burden of hyperthyroidism disease in Nigeria. This study therefore sought to evaluate these factors among hyperthyroid patients at EDM clinic, LASUTH.

Methodology

This was a descriptive analytical study carried out at the Endocrine, Diabetic and Metabolic unit run by the Department of Internal Medicine, Lagos State University Teaching Hospital, Ikeja (LASUTH) over a one-year period (2011).

All 40 patients who presented with clinical and biochemical features of hyperthyroidism of more than 3 months' duration were included in the study. Ethical approval for the study was obtained from HREC of LASUTH and signed informed consent was obtained from each participant. Sociodemographic and

other clinical data were collected using structured interviewer-administered questionnaires. Only patients who met the inclusion criteria were recruited. Exclusion criteria included: chronic medical disorders, other secondary causes of osteoporosis, history of childhood fractures, pregnancy, significant alcohol intake (24 gm in a day) or smoking 20 packets per year, caffeine intake, menopause, drug use (of oestrogen, thiazide diuretic, calcium, for management of osteoporosis, and vitamin D) in the last 12 months and the presence of proteinuria.

Fasting blood samples were drawn for biochemical and hormonal assay, which included serum calcium, albumin, phosphorus, creatinine, bone markers (osteocalcin and alkaline phosphatase as bone formation markers), free thyroxine (FT4), free triiodothyronine (FT3), sensitive thyroid stimulating hormone (sTSH), parathyroid hormone, 25-hydroxyvitamin D and 24-hour calcium excretion as bone resorption marker. Early morning urine was analysed for creatinine and phosphorus. BMD, T- and Z-scores were determined using DXA Lunar Pixi #50734 9 (http://www.bonedensitymachines.com).

Definition of terms

(1) Wayne's index, a diagnostic tool to facilitate objectivity and improve the accuracy of clinical assessment of hyperthyroidism, is used to define symptoms and signs of thyrotoxicosis. A score of 19 or more implies toxic hyperthyroidism, score between 11 and 19 is equivocal, while less than 11 is consistent with euthyroidism.[7] Only subjects with toxic hyperthyroidism were recruited. This was confirmed by biochemical hyperthyroidism with sTSH < 0.5 u/U/ml, fT4 > 22.0 pmol/l, fT3 > 6.5 pmol/l.[7]

(2) Increased bone turnover is defined by elevated bone formation markers represented by alkaline phosphatase > 130 U/l,[8] osteocalcin > 25.3 ng/ml[9] and/or bone resorption markers as 24-hour calcium excretion > 4 mg/kg per 24 hours.[10]

(3) The International Society of Clinical Densitometry (ISCD) criteria defined osteoporosis Z-score < −2.0.[11]

The World Health Organization (WHO) criteria are based on T-score up to −1.0 SD normal, −1.1 to −2.5 SD osteopenia, and below <−2.5 SD osteoporosis.[12]

Table 1: Characteristics of hyperthyroid patients

Variable	n = 40 Mean (SD)
Serum:	
Corrected calcium (mmol/l)	2.3 (0.19)
Phosphorus (mmol/l)	1.43 (1.28)
Alkaline phosphatase (IU/l)	221.1 (143.46)
TSH (u/U/ml)	0.26 (0.03)
Free thyroxine (pmol/l)	39.44 (24.11)
Free triiodothyronine (pmol/l)	12.13 (7.83)
Osteocalcin (ng/ml)	45.7 (19.9)
25-hydroxyvitamin D (nmol/l)	56.56 (16.63)
Parathyroid hormone (pg/dl)	51.7 (5.37)
Urine:	
24-hour Ur Ca Exc (mg/day)	590.95 (506.71)
24 -hour Ur Phos Excr (mg/day)	1471.35 (1667.56)
DXA:	
T-/Z-score	−2.0 (1.2)

(4) Fracture risk calculator tools:
  (a) FRAX calculation tool (WHO model): Assessment of fracture risk is significant when the 10-year probability of major clinical osteoporotic fracture (in spine, forearm, hip or shoulder) is greater than 20%, and for hip fracture greater than 3%.[13]
  (b) International Society of Clinical Densitometry models: Automatically calculates risk in reference to the age of the patient. The FORE Fracture Risk Calculator (FRC)[14] and Garvan Fracture Risk (GFR) calculator[15] estimate 10-year fracture risk of hip fracture and any other major osteoporotic fracture. In addition to convectional 10-year fracture risk assessment, Garvan et al. incorporated 5-year risk of both fracture types.

Statistical analysis

The data were analysed using the Statistical Package for the Social Sciences (SPSS) Version 21.0 (IBM Corp, Armonk, NY, USA) with quantitative data reported as means (+ standard deviation), and qualitative data as percentages (%).

Result

The mean age of hyperthyroid patients was 36.13 (8.43) years; 32 (80%) were females while 8 (20%) were male and body mass index (BMI) of subjects was 24.4 (4.34) kg/m².

In this study, a significant number of hyperthyroid patients (19 [47.5%]) presented with a recurrent history of bone and joint pains, cramps/spasms (62.5%) as well as proximal myopathy (47.5%).

Furthermore, subjects demonstrated increased bone turnover evidenced by elevated bone markers (osteocalcin, alkaline phosphatase and 24-hour urinary calcium excretion). The mean sera calcium and phosphorus were within normal range (Table 1). The BMD (g/cm2), T- and Z-score were reported for hyperthyroid individuals. However, there was no significant difference in correlation between T- and Z-score because the hyperthyroid subjects were near their peak adult bone mass (see Table 1). According to the BMD diagnosis, using WHO criteria showed that 9 (22.5%) were normal, 19 (47.5%) had osteopenia and 12 (30%) had osteoporosis.

The 10-year probability of hip fracture and any other large (major) osteoporotic fractures was calculated using different fracture calculation tools. Hip fracture risk was documented as follows: FRAX 16.6 (10.1), FORE 1.4 (1.2) and Garvan 17.2 (8.6) and major osteoporotic fracture risk, FRAX 18.1(10.1), FORE 2.5 (1.6) and Garvan 25 (11.3).

A fracture was observed in three (7.5%) of the study subjects, two (66.7%) of whom were females and had osteopenic fractures, while the third had a low-normal T-score fracture. The three hyperthyroid patients with fractures had hypocalcaemia, hypophosphatemia and vitamin D insufficiency (Table 2).

Discussion

A large number of these hyperthyroid patients presented with complaints of osteopenia in addition to the clinical characteristics of thyrotoxicosis in the referral centres. They were investigated and the diagnosis confirmed by biochemical parameters, in addition to dual-energy X-ray absorptiometry. It is worth mentioning that both conditions were handled as different entities by the general practitioners in the referring hospitals.

Table 2: Characteristics of hyperthyroid patients with fractures

Variables	Case 1	Case 2	Case 3	Normal range
Serum calcium corrected (mmol/l)	1.8	1.9	2.0	2.15–2.55
Serum phosphorus	0.8	0.7	0.7	0.8–2.0
Alkaline phosphatase (IU/l)	215	263	222	9.0–130
Serum creatinine (umol/l)	54	46	62	55–115
Calcium excretion (mg/kg/day) (osteoclastic activity)	752	825	957	4 mg/kg
Free thyroxine (pmol/l)	27.1	27.5	36.1	12.0–22.0
Free triiodothyronine (pmol/l)	8.4	14.6	11.7	3.0–6.5
Thyroid stimulating hrmone (u/U/ml)	0.27	0.28	0.25	0.54–3.7
Osteocalcin (ng/ml)	27.5	50	29	3.8–25.3
25-hydroxyvitaminD (nmol/l)	40	40	42	75–250
Parathyroid hormone (pg/dl)	12	12	17	10–65
DXA g/cm2 T-score/Z-score	0.385–1.7	0.456–1.2	0.467–0.4	-> −1

Population and case-control studies reported hyperthyroidism onset above age 50 years as an independent risk factor for hip and vertebral fractures,[16,17] and was also a cause of excess mortality in previous hyperthyroid patients.[18] While most of those studies were performed in the older population, our study involved patients with overt hyperthyroidism below the age of 50 years because hyperthyroidism is more commonly seen in the third to fifth decades of life in this part of the world and therefore it is pertinent also to evaluate the extent of bone loss and fracture risk in this age group within our community.

The bony skeleton is a metabolically active organ that undergoes continuous remodelling throughout life by dual and coupled activities of bone resorption and formation,[19] tightly coupled in a temporal and spatial sequence to ensure the maintenance of skeletal mass and integrity.[20] Remodelling is necessary to maintain both the structural integrity of the skeleton and also to perform metabolic functions as a storehouse of calcium and phosphorus.[20]

In hyperthyroidism, the bone remodelling cycle is shortened; the duration of resorption remains largely unaltered with the duration of bone formation reduced significantly. This leads to a failure to replace resorbed bone completely, resulting in a net loss of about 10% of mineralised bone per cycle[21] making bone loss a common feature of overt hyperthyroidism. This results from accelerated bone remodelling, and reduced bone density could lead to osteoporosis and an increase in fracture rate as evidenced by an increase in the bone markers.[22]

The mean BMD, T- and Z-scores of our subjects were reduced. This is consistent with a number of similar prospective studies[22–24] that reported low bone mass as an important risk factor for fractures. In this study, bone loss of 77.5% (osteoporosis and osteopenia) was recorded. However, none of the patients with fractures in this study fell into the ISCD osteoporosis classification. Therefore, there is a need to re-stratify our study using WHO criteria, which is consistent with a previous study[24] in which the lower the Z-score, the greater the risk of fracture.

There is a high fracture risk in hyperthyroidism. The limitations of these calculator models are that they were developed from studying population-based cohorts from Europe, North America, Asia and Australia but not in African black individuals, the age limits of these models and the specificity of BMD. These calculators should be modified with the inclusion of the distal radius because cortical tissues are predominantly affected more than trabecular bone (abundant in the spine or femora) in hyperthyroid patients and also age entry should be lower, maybe from 30 years upwards.

Though low bone mineral density (BMD) may be a major contributory factor to fracture risk, non-BMD risk factors[16] that increase the fracture risk of osteopenia in our study include low BMI, weight loss, low serum calcium and vitamin D insufficiency. These factors contributed significantly to fracture risk in our studied population.

The occurrence of fractures was observed in only a few of our subjects, though the frequency may be higher as many fractures may have passed unnoticed. There are reports of about two-thirds of fractures being asymptomatic and diagnosed as an incidental finding on X-ray.[25] Two of the three were significant fractures; two of the patients had osteopenia (−1.2 and −1.7) and the third patient had a normal T-score of −0.4, although this is at least −0.4 SD below the score expected for age and sex. This may be indicative that low bone mass is a critical factor for fractures, with values of bone mass in patients with fractures overlapping substantially with values in those with no fractures, and it has been argued that measurement of bone mass is not helpful.[26] In most studies, however, a decrease of 1 SD in bone mass has been associated with an increase of 50–100% incidence of fractures.[26]

The pattern of fractures in our hyperthyroid subjects involved bones predominantly made up of cortical bone tissue confirmed by pattern and sites of fractures. These are in the left lower third of the tibia, left lower third of the radius (left forearm)/Colles fracture, left distal phalanx of the fourth toe or left index finger following minor trauma. This is in conformity with the finding in a previous study of cortical involvement more than trabecular bone.[5]

Neither age or sex was protective against fractures among the study subjects, though there are reports of fractures being common in older age groups, and post-menopausal females when the protective effect of oestrogen is quite reduced.[27,28]

There are studies suggesting that skeletal changes of hyperthyroidism could result from elevated T3 or TSH levels through action on either osteoblastic or osteoclastic activities.[21,29,30] Other contributory factors are increased serum interleukin –6

levels, B-adrenergic receptor-mediated acceleration of bone activation frequency and bone loss due to the increased sympathetic tone that inhibits osteoblastic proliferation and bone formation.[31] Though these patients are on anti-thyroid therapy and the beneficiary effect of anti-thyroid medications cannot be overemphasised, patients' thyrotoxic state was still uncontrolled. Longitudinal studies of patients successfully treated for thyrotoxicosis had reported conflicting results, with the suggestion that thyrotoxic bone loss may be potentially reversible.[32,33] The mainstay of treating hyperthyroidism is medical therapy with thiourea, i.e carbimazole, radio-iodine ablation and surgical management by partial or total thyroidectomy.

A previous study in Nigerians among hyperthyroid patients has documented an osteoporosis rate of 45%.[34] Hyperthyroidism is an established risk factor of secondary osteoporosis, and an increased fracture risk as documented by this study.

For a better management outcome, fractures must be managed in association with the thyrotoxic state to improve quality of life, and to reduce the physical disability associated with the burden of the disease and the financial consequences. Therefore, patients with spontaneous or mild fractures should be screened for thyroid diseases or vice versa. Early diagnosis and prompt management of the thyrotoxic state is essential with early screening for bone-related complications.

Conclusion

Fractures may not be uncommon in hyperthyroidism in this age group. Patients who have fractures should undergo screening for thyroid disease. Risk factors contributory to fractures in hyperthyroidism include low BMI, weight loss and vitamin D insufficiency in addition to reduced bone mineral density.

Recommendation

Early diagnosis and prompt management of a thyrotoxic state are imperative with early screening for bone-related complications to be incorporated into evaluation to reduce morbidity and improve patient outcome.

Disclosure statement

No potential conflict of interest was reported by the authors.

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