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Clinical significance of metabolic superscan in patients with hyperthyroidism

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Abstract

BACKGROUND: Hyperthyroid patients commonly complain of generalized bony aches, which are frequently overlooked due to the more prominent symptoms of cardiovascular and nervous disturbances. Hyperthyroid patients are expected to have abnormal bone metabolism as part of the generalized hypermetabolic status.

The aim of this study is to verify the presence of metabolic bone superscan in association with the hypermetabolic stats in various groups of hyperthyroidism. Secondly, to correlate these superscan features with the various laboratory results in hyperthyroid patients.

MATERIAL AND METHODS: Forty-five hyperthyroid patients confirmed by clinical and laboratory results were enrolled in this work. In all patients, a ^{99m}Tc-pertechnetate thyroid uptake scan was acquired. On a different day, total body bone scan was acquired three hours post IV injection of 555–925 MBq of ^{99m}Tc-MDP. Serum FT3, FT4, TSH, Ca++, alkaline phosphatase (AP) and parathyroid hormone (PTH) were monitored in all patients as markers of thyroid and bone metabolism. Ten cases with no thyroid diseases were included as a control group. Patients with thyroiditis or long history of antithyroid drugs for more than one year were excluded from the study.

RESULTS: The patients were subdivided into three groups: Graves' disease (GD) (n = 30), toxic nodular goiter (TNG) (n = = 10) and autonomous toxic adenoma (AT) (n = 5). The TSH for the whole group was significantly suppressed compared to the control group with higher suppression in the Graves' disease group than in the TNG or AT groups. ^{99m}Tc-pertechnetate uptake values in the Graves' disease group were significantly higher than the TNG and AT groups (p < 0.05).

Metabolic superscan (MSS) was noted in 90 % of the Graves' cases, 20% in TNG and in none of the AT group. There were no significant differences regarding Ca+, AP and PTH between the Graves' and non-Graves' groups (p > 0.05).

CONCLUSIONS: Disturbances in bone metabolism are more prevalent in Graves' disease than in other types of hyperthyroidism. The addition of the bone scan to the diagnostic work up of patients with Graves' disease is a sensitive indicator for metabolic bone changes and could help in the future management and follow up for this group of patients.

Keywords: hyperthyroidism, Graves' disease, superscan, bone scan, metabolic bone changes

Introduction

Hyperthyroidism is an autoimmune disease with a hypermetabolic state characterized by overproduction of thyroid hormones due to hyper-functioning thyroid tissue. The main leading thyroid pathologies are diffuse toxic hyperplasia (Graves' disease — GD), toxic multinodular goiter (TNG) and autonomous toxic adenoma (AT). The pathophysiology of hyperthyroidism includes accelerated bone turnover in favour of bone resorption related to direct stimulation of bone cells by the high levels of circulating thyroid hormones. Thyroid hormones exert their effect on osteoblasts via nuclear receptors to stimulate osteoclastic bone resorption. On the other hand, correction of hyperthyroid status may result in normalization of bone turnover [1–3].

Biomarkers for bone metabolism include bone formation (osteoblastic activity) or bone resorption (osteoclastic activity) and are usually used to monitor metabolic changes in metabolic bone diseases including hyperthyroidism. They have many limitations including availability, cost, technical demand and multiplicity (no single test is specific enough to give a definite answer for the metabolic status of bone). In addition, these laboratory assays suffer from a lack of standardization, cross reactivity, and difference in immunoassays and are influenced by gender, age, diurnal variation, and renal and liver diseases [4–8].

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Skeletal uptake of 99mTc-labelled diphosphonate depends primarily upon osteoblastic activity and skeletal vascularity. As there is direct coupling between bone resorption and formation; an osteoblastic response follows osteoclastic activity in a coordinated pattern leading to new bone formation. It is recognized that bone-seeking radiopharmaceuticals are subject to rapid and increased ionic exchange with the bone mineral at sites of new bone formation, with particular affinity for areas where active mineralization is occurring. The bone scan image therefore represents a functional display of the total skeletal metabolism and has a potentially valuable role to play in the assessment of patients with metabolic bone disorders, including hyperthyroidism [8, 9]. Accelerated bone turnover in patients with hyperthyroidism is expected to produce metabolic superscan (MSS) features in the bone scan images. These features may include increased tracer uptake in the axial skeleton, long bones and peri-articular areas with prominent calvaria. Other features are faint visualization of kidneys, beading of costochondral junctions and neck tie sternum. The frequency and severity of these features in bone scans is directly proportional to the degree of accelerated bone turnover [10–13].

These considerations, besides the limited literature about studies on the use of bone scanning to evaluate patients with hyperthyroidism, encouraged us to perform the current prospective study. The objectives are, firstly, to verify the presence of metabolic superscan features in various groups of hyperthyroidism and, secondly, to correlate the superscan features with the available laboratory results in hyperthyroid patients.

Material and methods

Patients

The current prospective study involved fifty-five subjects who were enrolled into two separate groups. The first group comprised forty-five patients diagnosed with hyperthyroidism by both clinical and laboratory results. The second group comprised ten subjects with no thyroid illness who were considered as a control group. All subjects were seen at the nuclear medicine department of the National Cancer Institute during the period from December 2003 to November 2005. The study was discussed and approved by the ethical committee of the National Cancer Institute in Cairo University. Informed consent with a complete description of the procedures was signed by all patients and/or their relatives. The median age for the hyperthyroid patients was 37 years (range 22–52 years) compared to 35 years (range 30––40 years) for control cases. The prevalence of hyperthyroidism was greater in females, with a female:male ratio of 3:1. This gender ratio was the same in the control cases as well. The exclusion criteria were patients with a history of thyroiditis or long history of anti-thyroid medication (more than one year). In addition, patients taking oral contraceptives, calcium supplements, vitamin D or other medication that might affect bone metabolism were excluded. No cases were post-menopausal or had evidence of hepatic or renal disorders.

Methods

The laboratory assessment of thyroid functional status was based on chemo-luminescence assay of FT3, FT4 and TSH, in addition to the biochemical markers for bone metabolism that included serum calcium ($Ca++$), alkaline phosphatase (ALP) and parathyroid hormone (PTH) levels.

The scintigraphic part of the study incorporated the performance of 99mTc thyroid scans with uptake and 99mTc-99m MDP whole body bone scanning in two separate settings for all 55 subjects. The gamma camera used for scintigraphic imaging was a dual-head Siemens e-cam equipped with a parallel hole all-purpose collimator. The first study invloved the thyroid scan with uptake performed 20 minutes following IV administration of 185 MBq of 99mTc-Pertechnetate. The subjects were positioned supinely with hyper-extended neck, and the acquisition was carried out in the anterior view using a matrix size of 128 × 128 for two minutes. Thyroid uptake was quantified automatically after correction for background activity according to the provided software program. Additional detailed anterior view using a matrix size of 256 × 256 with 1.5 zooming was taken for 1500 k counts per image. 57Cobalt point-source marker was used to identify the suprasternal notch.

On a different day 99mTc-MDP whole body bone scanning was performed 2–4 hours following IV administration of 555–925 MBq of 99mTc-MDP. The acquisition was carried out in the anterior and posterior views simultaneously with the aid of 180 configuration of the two heads of the Gamma camera. The matrix used was 256 × × 1028 with a table speed at 10–12 cm/minute.

Statistical analysis

Results for laboratory tests and thyroid uptake were expressed as means ± SD unless otherwise indicated. Differences between groups were analyzed using Mann-Whitney U test for assessment of differences between mean values. $p < 0.05$ was considered significant.

Results

According to hormonal profile and thyroid scan findings, the studied patients were subdivided into Graves' disease (GD) (n = = 30), toxic nodular goiter (TNG) (n = 10) and autonomous toxic adenoma (AT) (n = 5). The basic clinical demographic data for these groups and the control subjects are presented in Table 1.

Table 1. Patient characteristics

	GD	TNG	AT	Controls
Number	30	10	5	10
Age: range (Median)	22–42 (32)	42–52 (47)	30–40 (35)	30–40 (35)
Female: male ratio	3:1	2.8:1	1.5 :1	3:1

GD — Graves' disease; TNG — toxic nodular goiter; AT — autonomous toxic adenoma

Table 2. Thyroid hormonal profile and metabolic biomarkers in hyperthyroid groups and control subjects

	GD	TNG	AT	Controls	p*
Ft3 (n. 1.8–4.2 pg/ml)	8.7 ± 1.5%	8.2 ± 1	8 ± 0.5	2.2 ± 0.2	0.001
Ft4 (n. 0.8–1.2 pg/ml)	6.5 ± 1.2	5.5 ± 0.9	5 ± 0.8	1 ± 0.2	0.001
TSH (n. 0.4–4 Mu/ml)	0.003 ± 0.001	0.005 ± 0.002	0.007 ± 0.002	1.7 ± 0.3	0.001
Calcium (n. 8.4–10.4 U/L)	8.7 ± 0.6	8.4 ± 0.4	8.2 ± 0.2	8.5 ± 0.5	NS
ALP (n. 53–128 U/L)	100 ± 20	85 ± 25	80 ± 20	88 ± 40	NS
PTH (n. 7–70 pg/ml)	22 ± 10	20 ± 8	20 ± 5	20 ± 4	NS

p* — is for the difference between the hyperthyroid groups and the control group; GD — Graves' disease; TNG — toxic nodular goiter; AT — autonomous toxic adenoma; N — normal value; NS — non-significant; ALP — alkaline phosphatase; PTH — parathormone

Table 3. Thyroid uptake and metabolic superscan in hyperthyroid groups and control subjects

	GD	TNG	AT	Controls	p*
Thyroid uptake (N.0.4–4%)	24 ± 4%	15 ± 5%	10 ± 2%	2.5 ± 1%	0.001
MSS	27/30 (90%)	2/10 (20%)	0/5 (0%)	0/10 (0%)	0.001

p* — is for the difference between the hyperthyroid groups and the control group; GD — Graves' disease; TNG — toxic nodular goiter; AT — autonomous toxic adenoma; MSS — metabolic superscan

Laboratory findings

The TSH for the whole group was 0.005 IU ± 0.003 IU which was significantly suppressed compared to the control group with 1.7 IU ± 0.5 IU ($p < 0.001$). The TSH values for the Graves' disease group were 0.003 IU ± 0.001 IU, TNG group 0.005 IU ± ± 0.002 and the AT group 0.007 IU ± 0.002 IU with no significant differences between the groups ($p > 0.05$). The FT3 and FT4 values for the GD group were higher than those for the TNG and AT groups, as shown in Table 2. However, the difference was not statistically significant ($p > 0.05$). On the other hand, there were clear differences between the control group FT3 and FT4 levels compared to all the hyperthyroid groups (Table 2).

Analysis of the metabolic biomarkers showed normal results for all subjects studied (Table 2). The ALP was slightly elevated in the GD group compared to the rest of the groups but the difference was not statistically significant. Ca++ and PTH levels were comparable in all the studied hyperthyroid and control groups.

Scintigraphic findings

99mTc-thyroid scan with uptake

The qualitative interpretation for the 99mTc-Pertechnetate thyroid scan was essential in defining the different subgroups. Features suggestive of Graves' disease included dense homogenous diffuse uptake in both lobes, while those for TNG included multiple nodules with more than one prominently hot nodule. AT is characterized by a single large toxic nodule with suppression of the rest of the gland in most cases. The uptake values for all of the hyperthyroid groups were 18% ± 8%, which was significantly higher than the control group at 2.5% ± 1% ($p < 0.001$). Quantitatively, the thyroid uptake value made it possible to differentiate between the various hyperthyroid groups, especially in defining the Graves' group. Table 3 illustrates that the uptake for the Graves' group (24% ± 4 %) was significantly higher than the TNG and AT groups (15% ±5% and 10% ± 2% respectively) ($p < 0.05$ for both).

99mTc-MDP bone scintigraphy

Interpretation of the bone scans was done by two experienced nuclear medicine physicians. Six criteria were set for the diagnosis of MSS, namely:
— prominent uptake in calvarium;
— prominent uptake in sternum;
— increased bone/soft tissue ratio;
— faint visualization of kidneys;
— prominent uptake in appendicular skeleton;
— beaded costal ends.

The presence of more than three of these criteria was considered diagnostic for metabolic superscan.

Metabolic superscan features were present in 27 out of the 30 patients with GD (90%). This was higher than the rest of the hyperthyroid groups as only two patients (20%) of the TNG group exhibited MSS features ($p < 0.01$) and none from the AT group had any significant MSS features ($p < 0.001$). The bone scan features in the control group were normal with no pathological findings (Table 3).

A correlation between the high level of thyroid uptake and MSS was found only in GD but not in the rest of the hyperthyroid patients. Figures 1A, 1B, 2A and 2B show MSS patterns in patients with GD while Figures 3A and 3B show bone scans lacking MSS in the other groups of hyperthyroidism.

Discussion

Hyperthyroidism, a clinical syndrome characterized by manifestations of excess thyroid hormone, is a commonly recognized condition of the thyroid gland. It affects bone metabolism and is thought to be an under-recognized but important cause of osteoporosis [14]. Hyperthyroidism accelerates bone turnover and shortens the normal bone remodelling cycle [15, 16].

Osteoporosis is a major public health problem in which there is a disturbance in the osteoblastic and osteoclastic activities with a predominance of bone resorption resulting in accelerated bone turnover. Thyroid hormones are known to exert direct effects on
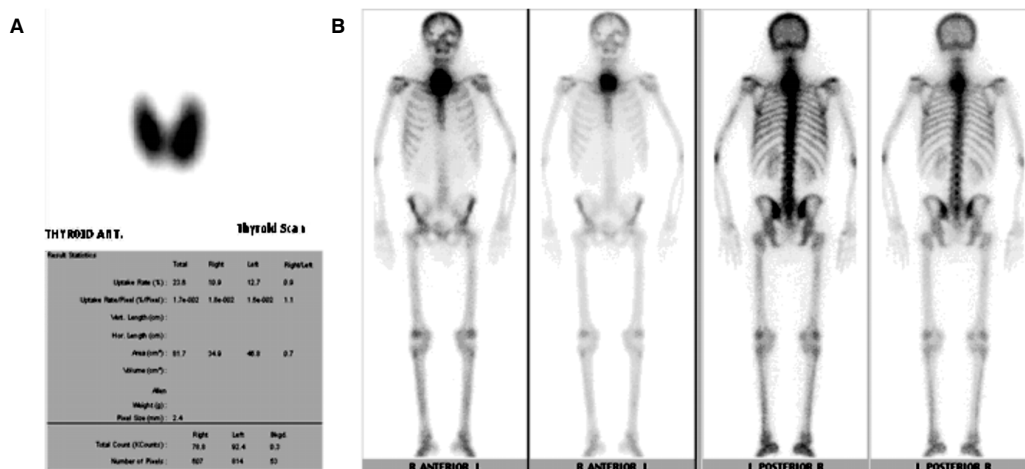
Figure 1. 40-year-old male patient has severe hyperthyroidism attributed to Graves' disease. **A.** ^{99m}Tc- thyroid scan and uptake shows diffuse intense thyroid uptake [thyroid uptake = 22.8 (normal: 0.5–4%)]. **B.** ^{99m}Tc-MDP bone scan performed 2 weeks post I-131 therapy shows MSS features with residual intense intra-thyroidal I-131 activity.
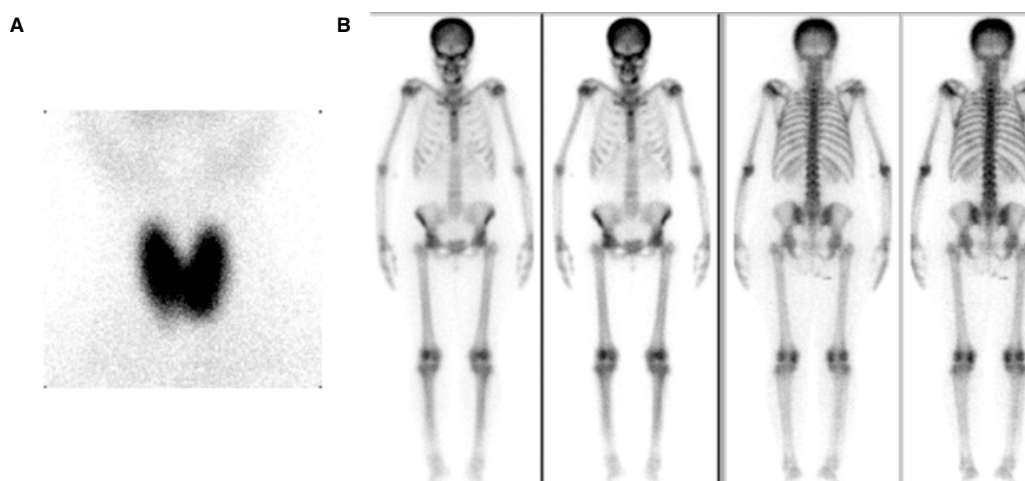

Figure 2. 35-year-old female patient has active GD. **A.** ^{99m}Tc-thyroid scan shows diffuse intense thyroid uptake with suppressed back-ground activity. The uptake was 21% (normal: 05-4%). **B.** ^{99m}Tc-MDP bone scan showing MSS.

bone formation and resorption, and the excess thyroid hormones leads to a net loss of bone and hence reduction in bone mineral density (BMD) [17].

On the other hand, it is reported that correction of hyperthyroid status may result in normalization of bone turnover [1–3]. Recently, the effects of anti-thyroid therapy on hyperthyroid patients' skeletons have been addressed due to the increasing worldwide interest in the prevention of osteoporosis [1, 18].

Our prospective study has shown that accelerated bone turnover, as explored by MSS features on bone scans, were significantly higher in the GD group (90%) compared to the TNG group (20%) and AT (0%) hyperthyroid patients. In addition, we found that no correlation existing between FT3, FT4 & TSH levels and the superscan features as there were no significant differences in the levels of these hormones among the variable groups of hyperthyroid patients. In contrast, reasonable correlation was found between the thyroid uptake level by scintigraphy and the superscan features in GD patients that were significantly high compared to TNG & AT. There is also agreement between our data and se-

veral other studies which have shown reduced bone mineral measurements in hyperthyroid patients [19, 20]. Auwerx et al. showed a 13% reduction in lumbar spine bone mineral using dual-photon absorptiometry [20]. Similarly, Kung et al. showed significantly lower BMDs in lumbar spine and femoral neck (0.75 ± 0.15 vs. 0.92 ± 0.16 g/cm², p < 0.005; 0.62 ± 0.12 vs. 0.70 ± 0.12 g/cm², p < 0.01) in TSH suppressed patients after Iodine-131 ablation for thyroid cancer when compared with an age and sex matched control group [21].

Hyperthyroidism causes acceleration of bone remodelling, and even though it is one of the known risk factors for osteoporosis, the metabolic effects of thyroid hormones on bone is a little-discussed subject [15].

On the basis of the previous studies showing that hyperthyroidism has a detrimental effect on bone mass or is associated with fractures [19, 22], we hypothesize that accelerated bone turnover that results in MSS features may occur at an earlier stage as part of generalized hypermetabolic status of hyperthyroidism.
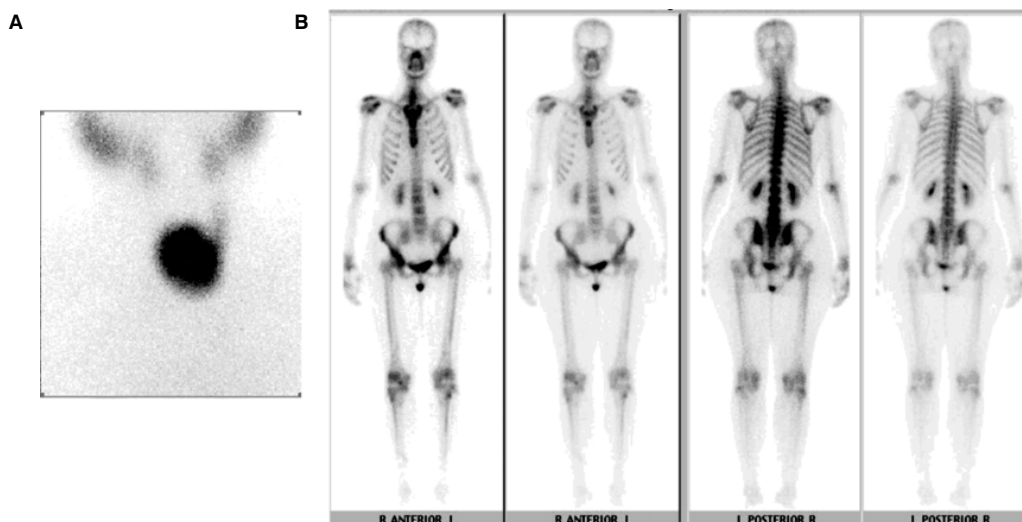
A   **B**

Figure 3. Autonomous nodule causing hyperthyroidism in a 40-year-old female patient. Thyroid uptake is 11% (normal 0.5–4%). **A.** ^{99m}Tc-thyroid scan showing autonomous nodule in right lobe of thyroid gland with uptake = 10%. **B.** ^{99m}Tc-MDP bone scan with normal configuration and no evidence of MSS features.

To our knowledge, there is limited data in the literature that focuses on the assessment of bone turnover using MSS features in various groups of hyperthyroidism or that correlates these MSS features with various laboratory results in hyperthyroid patients. Our demonstration of higher bone turnover denoted by superscan features in GD compared to TNG and AT patients, despite similar levels of thyroid hormone profiles, can be explained by mechanisms other than the effect of thyroid hormones on bone turnover, particularly in GD. This opinion is enforced by the fact that high bone turnover may continue despite normalization of FT3 and FT4 in TSH suppressed GD patients. Serum thyrotropin releasing autoantibody (TRAb), which is a triggering factor in the pathogenesis of GD, might directly affect bone metabolism independently of thyroid function. Recent reports which demonstrate that osteoblasts possess functional TSH receptors strongly support this opinion about TRAb [2, 23, 24]. Therefore, it is possible that abnormal bone metabolism in GD is partially explained by the interaction of TRAb with TSH receptors in the osteoblasts.

In contrast to other results, this work could not demonstrate a correlation between laboratory bone biomarkers including serum calcium, thyroid and parathyroid hormones. This finding can be explained by the differences in patient populations. In the current work the patients had newly diagnosed hyperthyroidism with severe symptoms. Moreover, the differences in the types and duration of the given anti-thyroid medications may account for the differences between the present study results and other investigations, as hyperthyroidism may increase the degradation rate of these biomarkers, shortening their half-life [3, 25–27].

The limitations of this study include the inability to assess other biomarkers such as bone-specific alkaline phosphatase and C-terminal propeptide of type I procollagen for bone formation and serum C-telopeptide and urinary N-telopeptide cross links for bone resorption as well as TRAb, which are not done routinely in our institute. Secondly, this study was carried out on a short-term basis without follow-up. However, the strengths of this study include its novel prospective nature in addressing the clinical usefulness of bone scans, especially MSS features, in patients with hyperthyroidism. Secondly, the study is conducted in various groups of hyperthyroidism patients who have comparable sex ratio and age range compared to control subjects.

Conclusion

The disturbance of bone metabolism in hyperthyroid patients is strongly evident in GD but not in TNG or AT. Metabolic superscan features were significantly better than biomarkers in the exploration of high bone turnover in hyperthyroid patients and particularly in GD. Importantly, the integration of bone scanning in the diagnostic work up for GD patients can be a sensitive indicator for metabolic bone changes that should be of real help in future patient management and follow up to identify Graves' patients who are at high-risk of osteoporosis and pathological fractures. Further studies are recommended to compare bone scan findings and particularly MSS features, with more specific biomarkers of bone metabolism as well as assaying TRAb in Graves' patients before therapy and during follow up.

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