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Original Article

The Value Of ^{99m}Tc Methoxyisobutyl Isonitrile (MIBI) In The Detection Of Functionally Suppressed Thyroid Tissue In Autonomously Functioning Thyroid Nodules And The Relation Of Its Uptake With The Different Hormonal States

Shahenda Salem*, Amr Amin * and May Fawzy **.

* Radiation Oncology And Nuclear Medicine Center (nemrok), Kasr El-aini Hospital, Cairo University And ** Internal Medicine Departement, Kasr El-aini Hospital, Cairo University.

Abstract

Introduction: autonomously functioning thyroid nodules (AFTNs) result in suppression of the extranodular normal thyroid tissue through the pituitary-thyroid axis feedback mechanism. Assessment of this tissue by sonography does not give a clue about its functional status to help in the management decision. Rescanning after TSH stimulation test is helpful but hazardous especially in elderly patients with cardiovascular disorders.

Aim of the work: To visualize and assess the suppressed extranodular thyroid tissue with ^{99m}Tc MIBI both visually and semi quantitatively and relate its uptake to the hormonal status of the patients.

Patients and methods: the study included 98 patients with AFTNs. All patients were subjected to full history and clinical examination, thyroid hormonal assay, and thyroid scanning using ^{99m}Tc pertechnetate* ($^{99m}TcO_4$) and ^{99m}Tc MIBI 48 hours later. Nodular/extranodular uptake (N/EN) was calculated after background subtraction for both $^{99m}TcO_4$ and ^{99m}Tc MIBI scans.

Results: The study included 98 patients (85 females and 13 males). Their age ranged from 16 to 66 years (mean 45 years). According to the results of hormonal assay the patients were classified into 3 groups: group I with elevated T3, T4 and low TSH (68 patients), group II with elevated T3, normal T4 and low TSH (12 patients), group III with normal T3, T4 and low TSH (18 patients). N/EN uptakes of ^{99m}Tc pertechnetate and ^{99m}Tc MIBI were 12.8± 5.3 and 4.8± 1.6 for group I, 10.2± 4.4 and 2.7± 0.8 for group II and 4.2± 1.3 and 1.7± 0.3 for group III, respectively. A statistically significant difference was found between the 3 groups in ^{99m}Tc MIBI uptake ($P<0.01$). For ^{99m}Tc pertechnetate uptake; no statistically significant difference was found between the groups I & II ($P>0.05$), however a statistically significant difference was found between group I & III and group II & III ($P<0.05$). Conclusion: ^{99m}Tc MIBI is a valid tracer for visualization of suppressed but functioning extranodular thyroid tissue in patients with AFTNs. ^{99m}Tc MIBI uptake is correlated with different hormonal states of the patients.

Key words: *Autonomous functioning thyroid nodules, ^{99m}Tc MIBI, suppressed extranodular thyroid tissue.*

Introduction:

AFTNs are subtype of functioning thyroid nodules that are independent of TSH stimulation, forming a 'hot' nodule (1). The incidence of hot nodules varies from 6-25% (2). They are clinically discrete, usually single and can occur at any age. The underlying mechanism of autonomy depends on the mutation in the Thyrotropin receptors, which activates adenyl cyclase enzyme (3). Cyclic adenosine monophosphate stimulates the growth and function of the thyroid nodule (4). However the extranodular thyroid tissue does not have thyrotropin receptors and remains stable in growth and function (5).

Biochemical assessment of patients with AFTNs showed that most of the patients are euthyroid (6). Another group of patients has subclinical hyperthyroidism. The production of T4 in those patients is adequate to maintain the euthyroid state but is not under the control of pituitary TSH and therefore the serum TSH concentration falls (7). Hyperthyroidism may be the first presentation in some patients. In other patients with euthyroid hot nodule, as the nodule enlarges in size hyperthyroidism becomes a definite clinical presentation (8). If hyperthyroidism occurs, TSH will be suppressed causing suppression of the extranodular thyroid tissue through the pituitary-thyroid feed back inhibition mechanism. Failure of visualization of the extranodular thyroid tissue using conventional thyroid imaging with ^{131}I, ^{123}I or $^{99m}TcO_4$ scanning has been noticed (9). The presence of normal but suppressed thyroid tissue should be confirmed prior to treatment either by surgery or radioactive iodine to avoid subsequent hypothyroidism. Sonography is a simple convenient method that can be used to visualize the suppressed thyroid tissue but it does not give any physiological information. The lobe may be present but not functioning. Re-scanning following TSH stimulation test proved to be potentially hazardous especially in elderly patients or in patients with cardiac diseases because of the potential release of thyroid hormones into the circulation (10). While bovine proteins can cause allergic reactions, Human TSH is not commercially available in many countries (11).

Imaging of patients with autonomous functioning thyroid nodules by Thallium 201 and ^{99m}Tc MIBI have been previously reported (9, 12). Recently, fluorine-18 fluorodeoxyglucose have been used in those cases (13).

Uptake of ^{99m}Tc MIBI by the thyroid tissue is not affected by the pituitary-thyroid axis feedback mechanism (12). So we tried to image patients with AFTNs using ^{99m}Tc MIBI in order to visualize both nodular and extranodular thyroid tissue.

Aim of the work:

To visualize and assess the suppressed extranodular thyroid tissue in patients with AFTNs using ^{99m}Tc MIBI both visually and semiquantitavily and relate its uptake to the different hormonal states of the patients.

Materials and Methods:

The study included 98 patients. They were selected from patients who presented to the Internal Medicine department and Nuclear Medicine department (NEMROCK) at Kasr El-Aini hospital with solitary thyroid nodules during the period from January 2001 to January 2003.

Detailed history, full general and local clinical examination of the neck was done taking into consideration the symptoms and signs of hyperthyroidism.

Blood samples were withdrawn from all patients and complete thyroid hormonal profiles were assessed. ^{125}I radioimmunoassay (RIA) used for quantitative assessment of free T3, T4 and TSH. Normal range of these hormones was 1.5-7 Pmol/L, 7-25 Pmol/L and 0.2-5mIu/L, respectively.

Conventional thyroid scans were done in all patients using I.V. injection of 5 mCi $^{99m}TcO_4$ and revealed 'hot' nodule with faint to non-visualization of the extranodular thyroid tissue. Two days later repeated scanning using I.V. injection of 15 mCi of ^{99m}Tc MIBI was performed.

Camera setup was the same in both studies. Imaging started 15 min after radiopharmaceutical injection. The patients were imaged in a supine position with the neck extended. A dual head ADAC gamma camera fitted with a low energy high-resolution collimator and a dedicated computer system was used. Five hundreds kilo counts images were taken in a 128x128 matrix. Both scans were assessed both visually and semiquantitatively. Visual assessment of the extranodular thyroid tissue in both studies was classified into non-, faint and good visualization (in relation to other lobe). Regarding semiquantitative analysis, regions of interest (ROIs) were created over the AFTNs, over the extranodular thyroid tissue and 3 pixels below the right lobe of the thyroid gland (background). Mean count (count per pixel) in the ROIs were determined. N/EN uptake ratios were calculated according to this formula in both $^{99m}TcO_4$ and ^{99m}Tc MIBI scans: AFTNs uptake-background (N)/ extranodular uptake-background (EN).

Statistical analysis: t-student's test was used to compare the mean values between each two groups. P value is considered significant when it is < 0.05.

Results:

The study included 85 females (83.3 %) and 13 (12.7 %) males. The age of the patients ranged from 16 to 66 years (mean 45 years).

The patients were classified according to their thyroid hormonal profile into 3 groups:

1. *Group (I):* 68 patients (69.4 %) with high T3, T4 & low TSH [definite hyperthyroid] (figure 1).
2. *Group (II):* 12 patients (12.2 %) with high T3, normal T4 & low TSH [isolated hyperthyroid] (figure 2).
3. *Group (III)*: 18 patients (18.4 %) with normal T3, T4 & low TSH. [subclinical hyperthyroid] (figure 3).

Hormonal levels of the 3 group of the patients were found to be:

Group I [definite hyperthyroid]: T3 level ranged from 9.1-27.6 Pmol/L (16.02 ± 4.9), T4 level ranged from 25.7-66.1 Pmol/L (40.8 ± 10.01) and TSH level ranged from 0.001-0.1 mIu/L (0.02± 0.3).

Group II [isolated hyperthyroid]: T3 level ranged from 10.8-21.3 Pmol/L (16.7± 3.99), T4 level ranged from 7.5-25 Pmol/L (18.8± 4.5) and TSH level ranged from 0.01-0.1 mIu/L (0.05± 0.05).

Group III [borderline hyperthyroid]: T3 level ranged from 2.2-7 Pmol/L (4.5± 1.5), T4 level ranged from 7.0-24.4 Pmol/L (16.9± 5.1) and TSH level ranged from 0.01-0.1 mIu/L (0.05± 0.05) (table 1).

All Cases were assessed both visually and semiquantitatively.

Visual assessment: The visual assessment of the extranodular tissue in ^{99m}Tc pertechnetate and ^{99m}Tc MIBI scans in the 3 groups is presented in table 2.

In *group I:* non visualization of the extranodular thyroid tissue was observed in 46 out of 68 patients (67.6%), while faint visualization of the extranodular thyroid tissue was noticed in 22/68 patients (32.4%) in ^{99m}Tc pertechnetate scans.

In *group II:* non visualization of the extranodular thyroid tissue was observed in 6 out of 12 patients (50%), while faint visualization of the extranodular thyroid tissue was noticed in the other 50 % of patients (6/12) in ^{99m}Tc pertechnetate scans.

In *group III:* All the 18 patients (100%) included in this group showed faint visualization of the extranodular thyroid tissue in ^{99m}Tc pertechnetate scans.

All 98 patients in the previous 3 groups portrayed well visualization of their extranodular thyroid tissue using ^{99m}Tc MIBI scans (100%).

Semi quantitative assessment: The N/EN uptake ratios of ^{99m}Tc MIBI and ^{99m}Tc pertechnetate scans in the 3 groups are presented in table 3.

The N/EN uptake ratio of 99mTc MIBI was found to be 4.8 ±1.6, 2.7± 0.8 and 1.7± 0.3 for group I, II and III, respectively. While The N/EN uptake ratio of 99mTc pertechnetate was found to be 12.8± 5.3, 10.2 ±4.4 and 4.2± 1.3 for group I, II and III, respectively. Statistical analysis of the 3 patient groups revealed a statistically significant difference between the mean values of the N/EN ^{99m}Tc MIBI uptake ratios in the 3 groups, which correlates also to the different levels of thyroid hormones ($p<0.01$). However, regarding the N/EN uptake ratios of ^{99m}Tc pertechnetate scan we did not find a statistically significant difference between groups I and II [the hyperthyroid patients] ($P> 0.05$), but we found a significant difference between the groups I & III and group II & III [hyperthyroid patients I &II and borderline thyroid patients III] ($P < 0.05$).

Discussion:

^{99m}Tc MIBI was able to visualize the extranodular tissue, which could not be clearly defined by ^{99m}Tc pertechnetate scan in all patients. The same results were obtained previously by ^{99m}Tc - t- butyl isonitrile (99mTc - TBI) (14) and 201Tl (15). The uptake was higher in hyperfunctioning nodules than in suppressed normal thyroid tissue.

^{99m}Tc MIBI is a monovalent cation with a central Tc (I) core that is surrounded by six lipophilic ligands coordinated through the isonitrile carbon (16)

^{99m}Tc MIBI has been used as a myocardial imaging agent (17). The fundamental cellular membrane transport of 99mTc MIBI is affected by the potential gradient across the cell membrane, blood flow and probably the metabolic activity of the cell itself. Inside the cell, 99mTc MIBI becomes sequestered largely within the inner matrix of the mitochondria by the negative transmembrane potentials. When plasma membrane potentials and mitochondrial membrane potentials are depolarized, there is inhibition of the net uptake and retention of ^{99m}Tc MIBI (18).

^{99m}Tc MIBI thyroid uptake is not clearly understood. Based on microscopic findings, more abundant mitochondria and blood flow are often described in the AFTNs (19). The cationic charge and lipophilicity of ^{99m}Tc MIBI, mitochondrial and plasma membrane potentials of the follicular cells as well as cellular mitochondrial content can play a significant role in the thyroid uptake of this agent. However, uptake may be caused by indirect phenomena such as increased thyroid blood flow and capillary permeability (20, 21).

Its uptake is not dependent on TSH stimulation, so the extranodular tissue was visualized in all 98 cases in our series. This finding was also previously reported by Alonso et al., 1998 (22).

The patients were divided into 3 groups: definite hyperthyroid patients (*group I*), isolated hyperthyroid (*Group II*) and subclinical hyperthyroid (*Group III*). Unlike the study by Erdil et al. (15), which included only the first 2 groups, we included also the cases of normal T3, T4 and low TSH (subclinical hyperthyroid) as many older persons with this condition go on to overt hyperthyroidism (8, 23, 24). This number of old persons included in the current study was 11 with a percentage of 11.2%. The scans of the patients included in group III gave the same scintigraphic criteria as the first 2 groups (a hot nodule with suppressed extranodular thyroid tissue). But what is worth mentioning is that visual assessment ^{99m}Tc pertechnetate scan of this group of patients revealed faint visualization of the extranodular thyroid tissue in all cases (18/18). Unlike the other 2 hyperthyroid groups, where faint visualization was noticed in only 22/68 in group I and in 6/12 in group II. Non-visualization was noticed in 46/68 in group I and in 6/12 in group II. This finding can be explained by the fact that suppression of the extranodular normal thyroid tissue is affected by the higher levels of T3 and T4 which suppresses the level of TSH and increases more in group I than group II and more in group II than group III.

N/EN uptake of ^{99m}Tc MIBI was 4.8± 1.6 for group I, 2.7± 0.8 for group II and 1.7± 0.3 for group III. The N/EN uptake of ^{99m}Tc MIBI was significantly higher in definite hyperthyroid group of patients (high T3 and T4) than isolated T3 hyperthyroid patients than subclinical hyperthyroid patients (P values as shown in table 3). Crane et al., 1993, mentioned that there is increase in the metabolic activity and mitochondria content in the follicular cells of the AFTNs resulting in consequent increase in ^{99m}Tc MIBI localization within the mitochondria, as > 90% of ^{99m}Tc MIBI is localized within the mitochondria (25).

N/EN uptake of ^{99m}Tc pertechnetate was 12.8± 5.3, 10.2± 4.4 and 4.2 ± 1.3 for group I, II and III respectively. No statistically significant difference was found between groups I & II (P>0.05), however a statistically significant difference was found between group I & group II and group II & group III (P values as shown in table 3). This means that there is no significant difference in the ^{99m}Tc pertechnetate uptake between the clinically hyperthyroid groups but the difference between each hyperthyroid group and the subclinical hyperthyroid group is significant and could be attributed to the increase in the blood flow.

The same values have been reported by Erdil et al.,(2000), in a study done on 32 patients. The authors published N/E uptakes for pertechnetate, and ^{99m}Tc MIBI of 11.37 ± 4.53 and 4.76 ± 1.38, respectively, in T3 + T4 hyperthyroid patients and 9.46 ± 3.64 and 2.73 ± 0.63, respectively, in T3 hyperthyroid patients. The N/E uptake of ^{99m}Tc MIBI in T3 + T4 hyperthyroid patients was significantly higher than that in T3 hyperthyroid patients. However, there was no significant difference for ^{99m}Tc pertechnetate uptake (P > 0.05) when the N/E uptakes of both groups of patients were compared (15).

Cases that show good visualization of the extranodular thyroid tissue by ^{99m}Tc MIBI scan after having been partially or completely suppressed on ^{99m}Tc pertechnetate scan with a high uptake ratio can be candidates for treatment by either, radioactive iodine or surgically with minimal risk of developing hypothyroidism.

Conclusion:

^{99m}Tc MIBI is a valid tracer for visualization of normally functioning but suppressed extranodular thyroid tissue in patients with AFTNs prior to surgery or radioactive iodine treatment in order to avoid subsequent hypothyroidism. In our study, ^{99m}Tc MIBI uptake was used as an index to predict thyroid function and to differentiate between euthyroid and hyperthyroid hormonal states.

Table (1): Results of hormonal assay in 3 different patients groups

	Group I	Group II	Group III
T3:range	9.1-27.6	10.8-21.3	2.2-7
M*±SD**	16±4.9	16.7±3.99	4.5+1.5
T4:range	25.7-66.1	7.5-25	7-24.4
M±SD	40.8±10.01	18.8±4.5	16.9+5.1
TSH:range	0.001-0.1	0.01-0.1	0.01-0.1
M±SD	0.02±0.3	0.05±0.05	0.05+0.05

*M: mean, **SD: standard deviation.

Table (2): Visual assessment of the extranodular tissue in ^{99m}Tc pertechnetate and ^{99m}Tc MIBI scans in the 3 patientsgroups

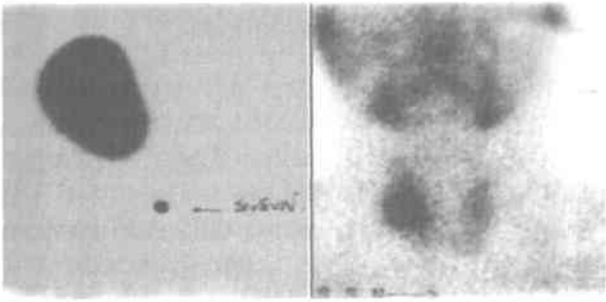
	99mTc pertechnetate scan			99mTc MIBI scan		
	Non visualized	Faintly visualized	Well visualized	Non visualized	Faintly visualized	Well visualized
Group I (68)	46(68%)	22(32%)	0(0%)	0(0%)	0(0%)	68(100%)
Group II (12)	6(50%)	6(50%)	0(0%)	0(0%)	0(0%)	12(100%)
Group III (18)	0(0%)	18(100%)	0(0%)	0(0%)	0(0%)	18(100%)

Table (3): The N/EN uptake ratio in the 3 patients groups for ^{99m}TcMIBI and ^{99m}Tcpertechnetate scans

	Group I	Group II	Group III
N/EN uptake ratio in MIBI scan	4.8 1.6*	2.7 0.8*	1.7 0.3**
N/EN uptake ratio in pertechnetate scan	12.8 5.3†	10.2 4.4‡	4.2 1.3‡

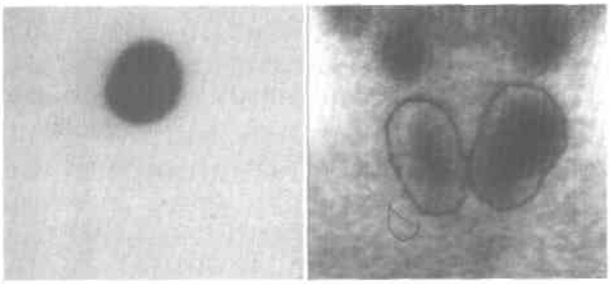
* *P value* between group I & group II and between group II and III <0.001
** *P value* between group I & III<0.00001.
† *P value* between group I & group II >0.05.
‡ *P value* between group I & group III and between group II and III <0.0001.

Figure (1)



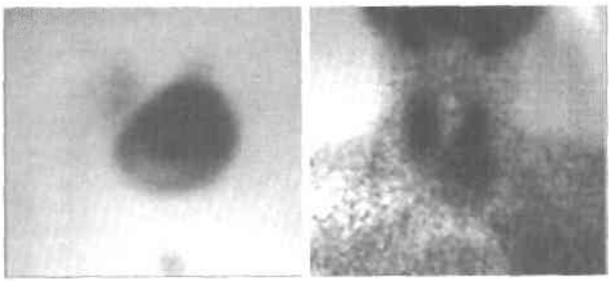
$^{99m}TcO_4$ ^{99m}Tc MIBI

Figure (2)



$^{99m}TcO_4$ ^{99m}Tc MIBI

Figure (3)



$^{99m}TcO_4$ ^{99m}Tc MIBI

Figure (1)

A male patient, 50 years old, presented with clinically palpable thyroid nodule. Thyroid hormonal profile: high level of T3, T4 and low TSH. 99mTc pertechnetate scan revealed AFTN at the right lobe of thyroid gland with non visualization of the rest of the gland. 99mTc MIBI scan revealed good visualization of both lobes.

Figure (2):

A female patient, 19 years old, presented with clinically palpable thyroid nodule. Thyroid hormonal profile: high level of T3, normal T4 and low TSH. 99mTc pertechnetate scan revealed AFTN at the left lobe of thyroid gland with non visualization of the rest of the gland. 99mTc MIBI scan revealed good visualization of both lobes.

Figure (3):

A female patient, 48 years old, presented with clinically palpable thyroid nodule. Thyroid hormonal profile: normal level of T3, T4 and low TSH. 99mTc pertechnetate scan revealed AFTN at the left lobe of thyroid gland with faint visualization of the rest of the gland. 99mTc MIBI scan revealed good visualization of both lobes.

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