Positive ^{99m}Tc-MIBI and the subtraction parathyroid scan are related to intact parathyroid hormone but not to total plasma calcium in primary hyperparathyroidism

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Abstract

Objective: Primary hyperparathyroidism (pHPT) is characterised by increased parathyroid hormone (PTH) secretion and consequently increased plasma calcium. During the last few decades parathyroid scintigraphy (PS), is applied in almost all patients with pPHT before surgery and specifically before minimally invasive parathyroidectomy. The aim of this study was to find the best cut-off levels of total plasma calcium and intact PTH (iPTH) that correlate with positive technetium-99m-methoxy isobutyl isonitrile (^{99m}Tc-MIBI) PS and with positive subtraction PS (SPS) in patients with pHPT and thus the positive diagnostic value of these PS. **Subjects and Methods:** We studied 50 patients, operated for pHPT, aged from 22-78 years, (median age 60 years), 45 female and 5 male, with a total number of 57 parathyroid glands (PG), (46 adenomas and 11 hyperplasias). All patients underwent SPS before surgery. Static scintigrams of the head, neck and chest were performed 15min after the intravenous (i.v.) injection of 740MBq of ^{99m}Tc-MIBI. Late scintigrams of the head, neck and chest were performed 2h and 3h after the injection of ^{99m}Tc-MIBI. Four to 24h after the washout of ^{99m}Tc-MIBI from the parathyroid and the thyroid glands, we injected i.v. 185MBq of ^{99m}Tc-pertechnetate (^{99m}TcP) and after 15min we performed the PS. Normalization and motion correction of the early ^{99m}Tc-MIBI scan and the ^{99m}TcP followed. We then subtracted the ^{99m}TcP from the ^{99mT}c-MIBI scan. The areas of increased uptake on the ^{99m}Tc-MIBI scan visible at the early and late or at the subtraction images represented the hyperfunctioning tissue of the enlarged and hyperfunctioning parathyroid glands. Scintigraphic findings were graded subjectively, from 1 to 5 depending on the degree of the uptake of the radiopharmaceutical. Normal iPTH levels were between 10.0-65.0pg/mL and normal total plasma calcium between 2.13-2.65mmoL/L. **Results:** Of all patients 12/50 and 38/50 had both PS positive grade 4 and very positive grade 5 findings respectively. In all patients iPTH levels ranged from 54 to 837pg/mL, median value 187.0±133.8pg/mL, and total plasma calcium ranged from 2.40 to 3.83mmoL/L, median value, 2.87±0.237mmoL/L. In 43 patients, both calcium and the iPTH levels were elevated. Strong positive correlation was found between scintigraphic findings and levels of iPTH: P=0.003. A significant relation between plasma calcium levels and different grades of scintigraphic findings was not found, although significant correlation was found between iPTH and plasma calcium levels (P=0.021). **Conclusion:** In patients with pHPT, the ^{99m}Tc-MIBI PS and the subtraction PS showed a strong correlation to iPTH (P=0.003) but not to total plasma calcium levels indicating the importance of both the ^{99m}Tc-MIBI and the subtraction parathyroid scans to indicate pHPT.

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Introduction

Primary hyperparathyroidism (pHPT) has the third highest incidence of all endocrinopathies after diabetes mellitus and hyperthyroidism and is caused by the increased secretion of parathyroid hormone (PTH) by one or more enlarged parathyroid glands (PG). Primary hyperparathyroidism is typically caused by a solitary parathyroid adenoma, less frequently in about 15% of cases by multiple parathyroid glands (MGD) and rarely in about 1% by parathyroid carcinoma [1-4]. Patients with MGD have either double adenomas or hyperplasia of three or of all four PG [5].

Increased PTH secreted from one or more PG, results in increased total plasma calcium concentration, which may lead, to formation of renal calculi, osteopenia, chondrocalcinosis and muscle weakness, most often asymptomatic detected by routine laboratory tests. Diagnosis of pHPT is primarely achieved by positive biochemical parameters, i.e. elevated levels of PTH and of plasma calcium.

Surgical exploration of the neck is the usual treatment for HPT. Reoperation (Figure 1) is often uneffective and followed by many side-effects. Scintigraphic imaging is mandatory as well as ultrasonography because surgeons would like to know where abnormal parathyroid tissue lies before any operation [6-10].

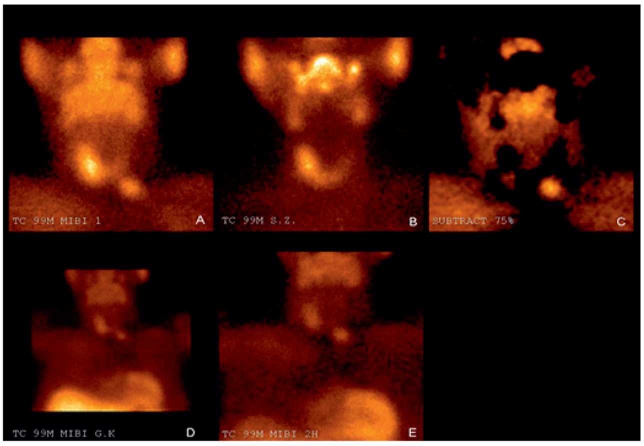

Figure 1. A- Early ^{99m}Tc-MIBI scintigram of the neck, **B-** ^{99m}TcP scintigram, **C-** Subtraction image, **D-** early ^{99m}Tc-MIBI scintigram of the chest, **E-** Delayed ^{99m}Tc-MIBI scintigram of the neck and chest. Male, 55 years of age, pHPT recidivans, Parathyroidectomia subtotalis aa XV, total-Ca-2.85, iPTH-250.38pg/mL, SCT grade 5: enlarged lower left parathyroid gland (A,C,D,E), and suspicion of enlargement of PG on the right side (C).

In the last few decades parathyroid scintigraphy (PS) is a routine procedure before surgery [11-14] and specifically before minimally invasive parathyroidectomy [15-18]. There is much discussion about the role of serum calcium and the increased levels of PTH in pHPT and also about their relation to positive PS [19-25]. So the aim of this study was to find the possible relation of total plasma calcium and intact PTH with positive technetium-99m-methoxy isobutyl isonitrile (^{99m}Tc-MIBI) PS in patients with pHPT. We used the combined dual phase and subtraction ^{99m}Tc-MIBI, ^{99m}Tc-pertechnetat, ^{99m}TcP (PS).

Subjects and Methods

This study included 50 patients, operated and historically diagnosed with pHPT, aged from 22-78 years, (median, 60 years), 45 female and 5 male, with a total of 57 hyper functioning parathyroid glands, (46 adenomas and 11 hyperplasiae), who underwent two PS before surgery.

Static scintigrams of the head, neck and chest were performed 15min after the i.v. injection of 740MBq of ^{99m}Tc-MIBI. Anterior projection images were obtained using an ADAC gamma camera with a low energy, high resolution collimator in zoom mode, in 256×256 matrix size with a 20% energy window, gathering 2×106 impulses per position. Late scintigrams of the head, neck and chest were performed 2h and 3h after the i.v. injection of ^{99m}Tc-MIBI. Four to 24h after washout of ^{99m}Tc-MIBI from the PG and from the thyroid gland, another i.v. injection of 185MBq ^{99m}TcP was administered, and 15min later, static scintigrams of the head and neck in the anterior projection were performed, gathering 2×106 impulses per position. After normalization and motion correction of both PS, subtraction of the ^{99m}TcP, PS from the ^{99m}Tc-MIBI PS was performed. The areas of increased uptake of ^{99m}Tc-MIBI visible on the early and late or on the subtracted images represented the hyperfunctioning tissue of the enlarged PG (Figure 2). Scintigraphic findings were graded from 1 to 5 according to the degree of the radiopharmaceutical (RF) uptake subjectively as follows: grade 1-negative findings, grade 2-probably negative findings, grade 3-suspected positive findings, grade 4-positive findings and grade 5-very positive findings. Normal iPTH levels were 10.0-65.0pg/mL and normal total plasma calcium levels were 2.13-2.65mmoL/L.

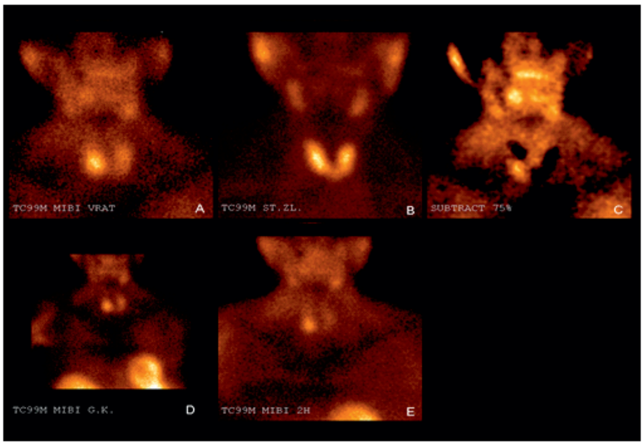

Figure 2. A- Early ^{99m}Tc-MIBI scintigram of the neck, **B-** ^{99m}TcP scintigram, **C-** Subtraction image, **D-** early ^{99m}Tc-MIBI scintigram of the chest, **E-** Delayed ^{99m}Tc-MIBI scintigram of the neck and chest. Male, 68 years of age, pHPT, Calculosis renis bill, total-Ca-2.84moL/L, iPTH-71.3pg/mL, SCT grade 5: enlarged lower right parathyroid gland clearly seen on subtraction image (C), rapid wash-out seen on delayed image (E).

Statistics

Descriptive and analytical statistics (SPSS version 20.0) were used. Analytical statistics implied the non-parametric Mann-Whitney test for the statistics of plasmatic calcium levels and levels of iPTH in different groups of scintigraphic findings and the Spearman's correlation between iPTH and plasmatic calcium levels. The default level of significance was $P<0.05$.

Results

All 50 patients had positive both scintigraphic findings. Twelve had grade 4 and 38 grade 5. In all patients iPTH levels ranged from 54 to 837pg/mL, median value, 187.0±133.8pg/mL, and plasma calcium levels ranged from 2.40 to 3.83 mmoL/L, median value, 2.87±0.237mmoL/L. Fourty three patients had elevated both calcium and iPTH levels. In the remaining 7/50 patients the PTH and plasma Ca values did not match. Four more patients had elevated iPTH and normal plasma Ca levels (Figure 3). The remaining three (3/50) patients had normal iPTH levels and elevated plasma Ca levels.

Median plasma calcium levels in patients with scintigraphic findings grade 4 were 2.92mmol/L±0.115mmol/L, whi-

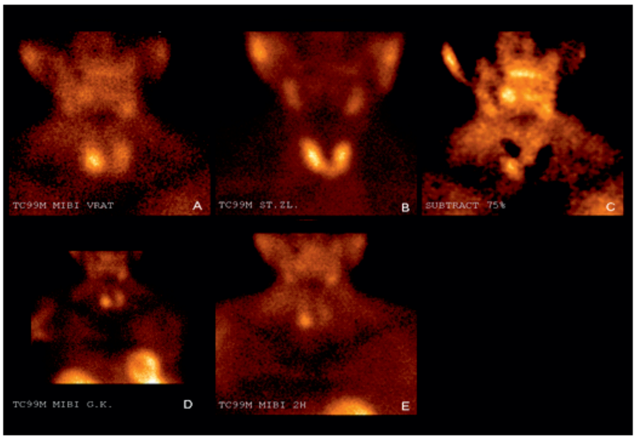

Figure 3. A- Early ^{99m}Tc-MIBI scintigram of the neck, **B-** ^{99m}TcP scintigram, **C-** Subtraction image, **D-** early ^{99m}Tc-MIBI scintigram of the chest, **E-** Delayed ^{99m}Tc-MIBI scintigram of the neck and chest. Female, 73 years of age, *normocalcemic* pHPT, total-Ca-2.6mmoL/L, iPTH-210.2pg/mL , SCT grade 5: enlarged lower right parathyroid gland.

le in patients with scintigraphy findings grade 5 were 2.825 mmol/L±0.2658mmol/L. According to Mann-Whitney test, we did not find a statistically significant difference between plasma calcium levels and scintigraphic findings.

Strong positive correlation was found between scintigraphic findings and levels of iPTH: iPTH was significantly higher in patients with higher grade of scintigraphic findings, P=0.003 (Figure 4). The minimal iPTH level for PS grade 4 findings was 54pg/L, while for grade 5 findings was 57pg/L. For PS findings grade 4, median iPTH was 151pg/L, and for grade 5 median iPTH was 228.50pg/L.

Correlation was found between iPTH and plasma calcium levels (Figure 5). There was an average (P=0.021) strength of this correlation, based on the Spirman's correlation coefficient.

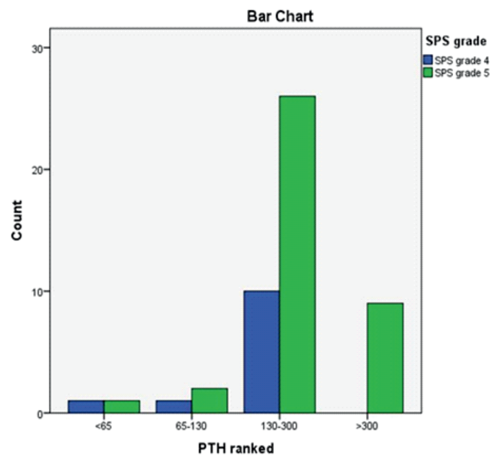

Figure 4. Relationship between iPTH levels and scintigraphic grade.

Discussion

The RF ^{99m}Tc-MIBI, was primarily introduced for myocardial perfusion imaging. This RF is liposoluble, intracellular, and ac-

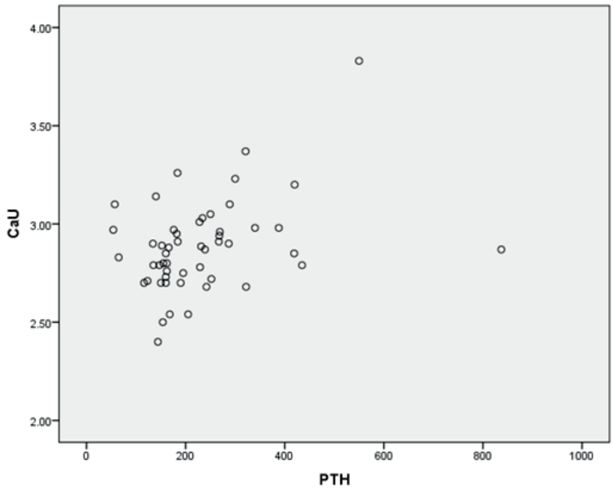

Figure 5. Correlation between iPTH and plasma calcium levels - dispersion diagram

cumulates in certain malignant tumors, the abnormal PG and in the functional thyroid tissue. It is usually eliminating faster from normal thyroid gland as compared to the hyperfunctional PG. The site of its accumulation is mitochondria, but the complete binding mechanisms are insufficiently known [20, 26-28]. Correlation of positive scintigraphic findings with biochemical parameters of pHPT, as well as the size and histopathology of hyperfunctional PG, are subject of analysis of a great number of past and current research papers. A positive correlation was found between the scintigraphic findings and the size of the hyperfunctional PG [18, 28-33]. It was also found that the intensity of ^{99m}Tc-MIBI accumulation was positively correlated with nodular hyperplasia and the oxyphilic cells content of the PG [30-32]. Kinetics of this RF can be changed according to different levels of total plasma calcium, which influences membrane potential. The non-recognition of some hyperfunctional PG, by scintigraphy, suggests the predominance of bright cells in the PG [21, 29-33]. Research on this subject is on- going.

Hypercalcemia is a common metabolic disorder caused by various pathological conditions. It is usually the result of pHPT, malignancy, and vitamin D-induced hypercalcemia. Less common causes of hypercalcemia are drug-induced states (eg. lithium, thiazide diuretics), immobilization, tuberculosis, sarcoidosis, and rhabdomyolysis [34, 35]. Pons et al (2003) [20], analysing many biological factors that influence ^{99m}Tc-MIBI uptake in hyperfunctional parathyroid tissue found that serum calcium levels may modify radiotracer kinetics by influencing the membrane potential of parathyroid cells, thus influencing ^{99m}Tc-MIBI uptake. So far no direct positive correlation between plasma levels of calcium and positivity of scintigraphic findings was found [22, 23]. We also did not find a correlation between plasma calcium levels and positive scintigraphic findings.

Mshelia DS et al (2012) [22] suggested that with serum calcium less than 2.51mmoL/L, a ^{99m}Tc-MIBI PS was not recommended. Others concluded that in patients with suspected pHPT and calcium levels above 2.75mmol/L, PS performed before surgery is often positive, while if calcium was below

2.475mmol/L PS was rarely positive [23]. Both studies, estimated the value of PS, taking into account both levels of total calcium and PTH.

Four of our patients had normal calcium levels, with elevated iPTH. The entity of normocalcemic pHPT is well described in many studies. Normocalcemic total and ionized calcium in pHPT is characterized by increased levels of iPTH, total and ionized calcium in generally asymptomatic individuals. The differential diagnosis should be considered in all secondary HPT cases. Others emphasized the importance of related laboratory tests in cases of suspected nephrolithiasis, osteoporosis etc [36]. Recognition of the normocalcemic phenotype of pHPT supports a biphasic time course in which PTH levels are first elevated followed by frank hypercalcemia [37].

A large number of papers suggest a positive correlation between the scintigraphic detection of hyperfunctioning PG and elevated serum iPTH levels [24]. The most significant factors in detecting pHPT are increased gland volume, increased serum iPTH and a positive ^{99m}Tc-MIBI uptake and retention of the RF [38] as in our study.

Others found that serum PTH levels higher than 160pg/mL correlated with positive PS in 93% of the cases as opposed to 57% with lower PTH levels [25]. More than 95% of patients with calcium more than 2.825mmol/L had a positive scan as compared with 60% of those with lower values. In a group of patients operated for adenoma and pHPT, others found that PTH levels were significantly higher in patients with true positive scans than in patients with false positive and false negative scans, and concluded that there is a correlation between the sensitivity of PS and presurgical PTH [39].

Duarte PS et al (2005) [23] concluded that in patients with calcium levels between 2.475mmol/L and 2.75mmol/L the pertinence of performing the PS will depend on PTH levels, and will be high for patients with PTH serum levels above 120pg/mL and very low for patients with PTH level below 65pg/mL.

In our study, PTH levels were higher than 130pg/mL in 90% of our patients. Others found 120pg/mL as the discriminating level for PTH for positive PS [23], while for others only a levels greater than 160pg/mL correlated with positive scans in 93% [25]. On the other hand, others conclude that there is no lower limit of PTH which can predict a negative study, and that ^{99m}Tc-MIBI PS is most likely to identify and localize parathyroid adenomas when both PTH and calcium are elevated [39].

Three of our 50 patients had normal iPTH levels, but elevated plasma calcium levels. In all of them a PG adenoma was removed. As in our study, in another study, a case of a young patient with severe hypercalcemia and low levels of PTH was reported. In this case, pPHT due to an adenoma in the lower left of the neck was confirmed [34]. Consideration should be given to repeat if necessary, measurements of PTH and serum calcium because dynamic metabolic changes may occur in the presence of secondary contributing factors. It has been reported a case of pHPT with cyclical secretion of PTH which may have caused repeated hypercalcemic crises followed by a spontaneous drop in PTH and temporary remission [35].

Patients who for treatment do not meet surgical indications should be monitored [40].

In conclusion: We suggest that in patients with pHPT, having elevated iPTH and total plasma calcium levels, the ^{99m}Tc-MIBI and the subtraction parathyroid scans were always positive indicating pHPT. While iPTH levels were in strong correlation with PS, calcium levels were not per se correlated to positive ^{99mT}c-MIBI or to subtraction parathyroid scans. This paper indicates the importance of both the ^{99m}Tc-MIBI and the subtraction parathyroid scans to suggest pHPT diagnosis.

The authors declare that they have no conflicts of interest

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