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Relation between Tc-99m sestamibi uptake and biological factors in hyperparathyroidism

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Purpose: The aim of this study was to evaluate the relation between uptake ratios of Tc-99m sestamibi (MIBI) and tumor volume, serum biochemical values (i-PTH, Ca, P) and oxyphil cell content. ***Materials and Methods:*** The study population consisted of 19 patients (2 M, 17 F; mean ± SD: 47 ± 12 y). Anterior planar images of the neck and chest were acquired early (15 min) and triple late phase (1, 2 and 3–4 h) after intravenous injections of 740 MBq MIBI. Each of the surgical materials was reviewed retrospectively. The percentage of cell type (chief, oxyphil and clear cells) in the tumors was calculated by light microscopy. ***Results:*** The uptake ratio obtained from L1 (1 hour) phase was found to be higher than the uptake ratio obtained from early phase, and the difference was statistically significant (1.57 ± 0.34 and 1.43 ± 0.29, $p = 0.004$, respectively). There was no significant correlation between uptake ratios that were obtained from 4 different imaging phases and lesion volumes, i-PTH levels and calcium levels ($p > 0.05$). However, there was a significant adverse correlation between L2 and L3 uptake ratios and serum phosphorus values ($r = –0.44$, $p = 0.04$ and $r = –0.46$, $p = 0.04$, respectively). Additionally, no significant correlation between MIBI uptake ratios of each imaging phase and the laboratory data, volume of lesion or oxyphil percentage volume was found after the multiple regression analysis (E: $p = 0.46$, $r = 0.49$; L1: $p = 0.24$, $r = 0.58$; L2: $p = 0.27$, $r = 0.57$; L3: $p = 0.32$, $r = 0.55$, respectively. There was no correlation between gland oxyphil percentage volume and MIBI uptake ratios ($p > 0.05$). ***Conclusion:*** The results of our study show that the optimal imaging times after intravenous injection of MIBI are 15 minutes and 1 hour because of the shorter examination time without loss of diagnostic ability. In the present study, there was no significant correlation between MIBI uptake ratios and increased gland volume, or serum Ca and i-PTH levels. Besides, we think that oxyphil cell content may not have a main effect on MIBI uptake and retention. The fact of an adverse relation between phosphorus and MIBI retention in our study suggests that phosphorus level should be considered prior to MIBI imaging.

Key words: MIBI, hyperparathyroidism, oxyphil cell, calcium, phosphorus

INTRODUCTION

Tc-99m sestamibi (MIBI) parathyroid scintigraphy is a widely used method for the preoperative localization of hyperfunctional glands in hyperparathyroidic patients for more than ten years. There are two imaging modalities: 1) The subtraction procedure that is used together with Tc-99m pertechnetate, and 2) Dual phase imaging procedure. Both procedures are reported in many studies to have high sensitivity and specificity and are used for imaging hyperparathyroidism recently.[1,2]

MIBI is a lipophylic cationic complex. Blood flow and capillary permeability, plasma and mitochondrion membrane potentials, and cellular mitochondrial contents play important roles in its uptake by tumor cells.[4–6] In the studies that researched the parameters which influenced

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the uptake of MIBI at hyperfunctional parathyroid gland, the role of the dimensions of the gland, biochemical and metabolic condition, PTH being foremost, and finally oxyphil cell content which has a high mitochondrial content were determined. There is a consensus on the role of increase of dimension or volume and high i-PTH level; however, there are serious differences between the results of the studies that researched the contents of oxyphil cell and other biochemical parameters.[7]

The aim of this study was to evaluate the relation between uptake ratios of semi-quantitative MIBI that are obtained from early + triple late phase imaging which we believe to provide more information more than classic dual-phase imaging, with tumor volume, serum biochemical results (i-PTH, Ca, P) and oxyphil cell content.

MATERIALS AND METHODS

Patients: This study is a retrospective analysis of only positive MIBI parathyroid scintigraphy studies between January 2000 and July 2004 at our university hospial. All patients had clinical and biological evidence of hyperparathyroidism, and the diagnosis was confirmed by surgical resection and histopathology after scintigraphy studies. The study population consisted of 19 patients (2 M, 17 F) whose age at the time of study ranged from 27 to 71 years (mean ± SD: 47 ± 12 y). But, our analysis included a total of 21 lesions detected in our patient group.

Imaging: Anterior planar images of the neck and chest were acquired 15 minutes for early phase (E) and for triple late phase 1 hour (late 1 phase: L1), 2 hours (late 2 phase: L2), 3–4 hours (late 3 phase: L3) after intravenous injections of 740 MBq Tc-99m sestamibi using a large field-of-view gamma camera equipped with a parallel-hole, low energy, high resolution collimator. 5 minutes ×5 zoom images of the neck were taken with the thyroid bed in the center of the field of view. In addition, in all patients 5 minute images of the neck and chest were obtained after the neck images.

Semi-quantitative Analysis: The early and late phases of images were used to set identical circular regions of interest over the normal isthmus of thyroid parenchyma

Table 1 Preoperative biochemical, scintigraphic and postoperative histopathological data

N	Age	Laboratory			Tc-99m MIBI scintigraphy				Dimensions	Volume	Histopathology (%)			V Ox%
	y	i-PTH	Ca	P	15 min	L1	L2	L3	mm	m*l*	Chief	Clear	Oxyphil	m*l*
1	62	1840	12.8	2.8	1.60	1.69	1.85	1.97	30×22×15	5.15	40	0	60	3.09
2	53	306	11.1	2.8	1.51	1.57	1.81	1.89	20×10×5	0.52	85	10	5	0.03
3	57	810	11.2	2.7	1.15	1.32	1.41	1.59	15×12×7	0.66	95	0	5	0.03
4	56	230	11.3	2.9	1.04	1.22	1.35	1.32	15×10×3	0.23	30	60	10	0.02
5	46	175	10.3	3.8	1.91	2.02	2.03	2.11	23×10×7	0.84	95	3	2	0.02
6	36	1700	15.2	1.7	1.76	2.29	2.21	2.15	30×15×12	2.81	40	60	0	0.00
7	71	280	9.6	5.4	1.74	1.79	1.86	1.82	30×20×15	4.68	70	10	20	0.94
8	46	1260	12.3	2	1.52	1.72	1.65	1.56	40×25×20	10.40	17	3	80	8.32
9	33	2943	16.2	2.5	1.24	1.37	1.32	1.38	30×25×5	1.95	65	20	25	0.49
10	29	1174	11.1	5.3	1.15	1.70	1.22	1.16	35×30×23	12.56	70	30	0	0.00
11a					1.21	1.34	1.20	1.19	35×20×12	4.37	35	35	30	1.31
11b					1.10	1.13	1.14	1.05	30×17×8	2.12	35	30	35	0.74
	27	3175	9.2	8.1										
11c					N	N	N	N	4×4×4	0.02	90	10	10	0.002
11d					N	N	N	N	6×4×4	0.05	30	20	50	0.03
12	54	390	12.3	2.6	1.24	1.27	1.26	1.27	25×15×7	1.37	90	5	5	0.07
13	49	330	12.7	1.9	2.11	2.31	1.84	1.76	25×22×12	3.43	69	30	1	0.03
14a					1.20	1.33	1.24	1.19	10×6×6	0.19	65	5	30	0.06
14b					1.48	1.57	1.37	1.29	15×6×6	0.28	60	10	30	0.08
	50	1231	9.5	5.1										
14c					N	N	N	N	6×5×5	0.08	45	30	25	0.02
14d					N	N	N	N	6×4×4	0.05	50	35	15	0.01
15	34	923	10.2	2.8	1.25	1.30	1.34	1.27	25×20×12	3.12	9	90	1	0.03
16	42	1684	11.2	2.3	1.59	1.82	1.94	2.20	35×20×14	5.10	40	0	60	3.06
17	61	165	10.5	2.7	1.76	1.82	1.70	1.65	18×12×10	1.12	10	0	90	1.01
18	56	206	10	2.5	1.30	1.41	1.42	1.47	17×12×9	0.95	90	0	10	0.10
19	49	388	8.9	2.6	1.29	1.15	1.08	1.02	20×18×15	2.81	90	0	10	0.28
Mean	47	1124	11.1	3.6	1.43	1.57	1.54	1.54	—	3.07	—	—	—	0.93
± SD	± 12	± 990	± 1.9	± 1.9	± 0.29	± 0.34	± 0.33	± 0.37		± 3.25				± 1.92

N: Negative, V Ox%: Volume of oxyphil percentage

and the areas of increased uptake corresponding to the parathyroid glands. Average counts per pixel in the parathyroid were divided by average counts per pixel in the thyroid to calculate the parathyroid/thyroid tissue (P/T) activity ratio.

Histological Interpretation: Each of the surgical materials was reviewed retrospectively by one pathologist without any knowledge of the semi-quantitative scintigraphic results. Each lesion was classified as adenoma or hyperplasia according to the criteria suggested by Ghandur-Mnayöneh and Kimura.[7] All formalin-fixed tissues were sectioned (10-μ thickness) and stained with hematoxylin-eosin. Specimens were evaluated by light microscopy. The following observations were recorded in five randomly selected areas, each 100 × 100 μ: (1) Specific cell counts in the tumors, i.e. chief, oxyphil and clear cells [semi-quantitative assessment of the percentage of cell types on the each section]; (2) composition of fat, and (3) presence or absence of necrosis. The volume of each gland was calculated by measuring the three maximum diameters according to the ellipsoid volume formula: V = 1/6 width × length × thickness. Additionally, volume of oxyphil percentage (V Ox%) was obtained by multiplication of oxyphil percentage rate of gland with gland volume.

Laboratory: Serum calcium (Ca) and phosphorus (P) levels were determined and compared with normal values by standard methods (normal values: 8.9–10.3 mg/d*l* and 2.4–4.7 mg/d*l*, respectively). Intact parathyroid hormone (i-PTH) was measured by immunochemiluminescent assay (normal values: 14–72 pg/m*l*). Baseline values of all laboratory parameters were determined about 1–2 weeks before scintigraphy.

Statistics: The mean and standard deviation (SD) were calculated on scintigraphic ratios and biochemical values by using descriptive statistics. The results of early and triple late MIBI ratios were compared with paired Wilcoxon test. Multiple Regressions and Pearson's test were used to calculate the correlation between results of scintigraphic, biochemical and histopathological assessment. Comparison of scintigraphic ratios according to serum calcium levels were calculated with the Mann Whitney-U test. Comparisons of scintigraphic ratios according to serum phosphorus levels were evaluated with Kruskal-Wallis ANOVA test. P values less than 0.05 were considered statistically significant.

RESULTS

The results of the image interpretation and histopathological analysis are shown in Table 1. All patients had increased serum i-PTH levels. However, only twelve to 19 patients had increased serum calcium levels, and 7 patients had normal serum Ca levels. Four patients had decreased, 11 patients had normal, and 4 patients had increased serum P levels. Seventeen patients had primary hyperparathyroidism, and 2 patients had tertiary hyperparathyroidism secondary to chronic renal failure. All of the 21 scintigraphically positive lesions are confirmed with surgery. Besides, in the two tertiary hyperparathyroidism patients, 4 more MIBI negative nodes, the largest being measuring 6 × 5 mm were extirpated.

In 11 of 21 lesions, the highest MIBI uptake and retention ratios were obtained at L1 phase. While five of 21 lesions had the highest ratios in L2 phase, remaining 5 lesions had the highest ratio at L3 phase (Table 1). In our study, the imaging phase in which the highest MIBI uptake was observed, was L1 phase. The uptake ratio obtained from this phase was found to be higher at a statistically significant level than the uptake ratio obtained from early phase images (1.57 ± 0.34 and 1.43 ± 0.29, p = 0.004, respectively).

Although there was a slight decrease at uptake ratios in L2 and L3 phases compared to L1, these differences were statistically not significant (Table 1). However, some

Table 2 Comparison of scintigraphic ratios according to serum calcium levels

	Ca between normal levels n = 9	Ca upper normal levels n = 13	P values
E ratios	1.39 ± 0.27	1.47 ± 0.32	0.71 (NS)
L1 ratios	1.45 ± 0.30	1.68 ± 0.36	0.32 (NS)
L2 ratios	1.41 ± 0.33	1.63 ± 0.32	0.21 (NS)
L3 ratios	1.38 ± 0.36	1.66 ± 0.34	0.11 (NS)

N: number of positive Tc-99m MIBI glands, NS: not significant

Table 3 Comparison of scintigraphic ratios according to serum phosphorus levels

	P below normal levels n = 4	P between normal levels n = 11	P upper normal levels n = 6	P values
E ratios	1.75 ± 0.26	1.39 ± 0.27	1.31 ± 0.25	0.06 (NS)
L1 ratios	2.04 ± 0.31	1.47 ± 0.27	1.48 ± 0.25	0.036
L2 ratios	1.91 ± 0.23	1.51 ± 0.29	1.34 ± 0.27	0.034
L3 ratios	1.92 ± 0.31	1.54 ± 0.34	1.28 ± 0.27	0.034

N: number of positive Tc-99m MIBI glands, NS: not significant

Table 4 Comparison of scintigraphic ratios according to oxyphil cell content by histopathological assessment

	Oxyphil cell < 50% n = 17	Oxyphil cell > 50% n = 4	P values
E ratios	1.39 ± 0.31	1.62 ± 0.10	0.08 (NS)
L1 ratios	1.53 ± 0.37	1.76 ± 0.07	0.09 (NS)
L2 ratios	1.47 ± 0.34	1.79 ± 0.13	0.09 (NS)
L3 ratios	1.47 ± 0.36	1.85 ± 0.30	0.06 (NS)

N: number of positive Tc-99m MIBI glands, NS: not significant

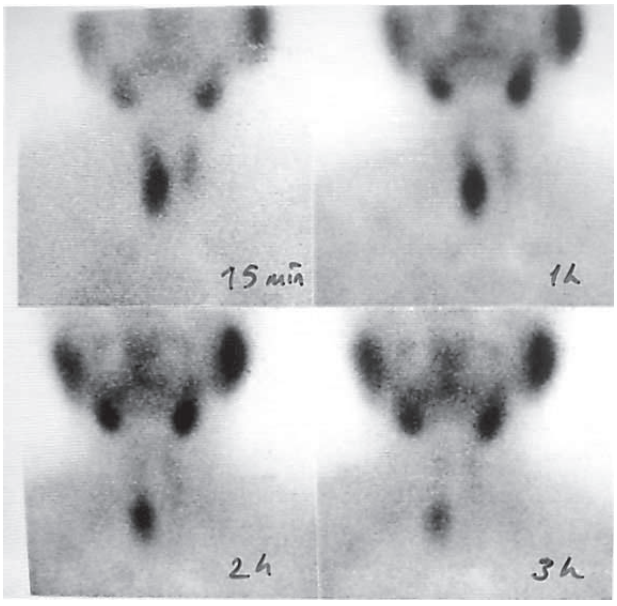

Fig. 1 The early and triple late images of MIBI parathyroid scintigraphy in a patient with left lower oxyphil cell-predominant parathyroid adenoma (patient 16 in Table 1).

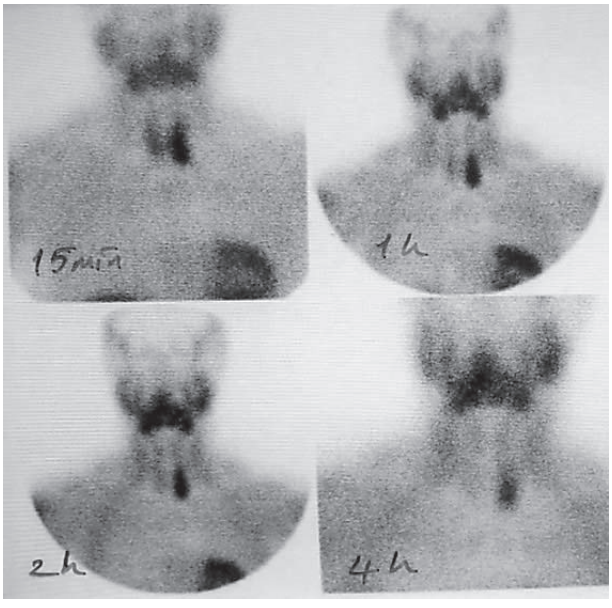

Fig. 2 The early and triple late images of MIBI parathyroid scintigraphy in a patient with right lower chief cell-predominant parathyroid adenoma (patient 13 in Table 1).

glands (Pts 10 and 13, Table 1) showed a fast washout rate between L1 and L2 phases.

All of the glands were larger than normal, and serum i-PTH levels of all patients were significantly higher than normal as well. However, there was not a significant correlation between uptake ratios obtained from 4 different imaging phases and lesion volumes and i-PTH levels ($p > 0.05$). There was not a significant correlation between serum calcium level and MIBI uptake and retention ratios either. But there was an association between uptake ratios of L1, L2 and L3 phases and calcium values ($p = 0.07$, $p = 0.08$, $p = 0.08$, respectively). In contrast, there was not a statistically significant uptake difference between patients with normal calcium and with high calcium levels ($p > 0.05$). As for evaluation of the relation between serum phosphorus level and MIBI uptake ratios, there was significant negative correlation between L2 and L3 uptake ratios and serum phosphorus values ($r = -0.44$, $p = 0.04$ and $r = -0.46$, $p = 0.04$, respectively). However, no significant correlation between MIBI uptake ratios of each imaging phase and the laboratory data, volume of lesion or V Ox% was found after the multiple regression analysis (E: $p = 0.46$, $r = 0.49$; L1: $p = 0.24$, $r = 0.58$; L2: 0.27, $r = 0.57$; L3: $p = 0.32$, $r = 0.55$, respectively). In the evaluation which with serum phosphorus levels being low, normal and higher than normal, the triple late MIBI uptake ratios between these three groups were different from each other at statistically significant levels (L1; $p = 0.036$, L2; $p = 0.034$, L3; $p = 0.034$, respectively) (Table 3). There was a significant negative correlation between serum calcium levels and phosphorus levels ($r = -0.57$, $p = 0.006$).

No large necrosis area or diffuse fat composition was observed at any of the glands that were undertaken into histopathological examination. The percentages of chief, oxyphil and clear cells that are obtained from each gland are listed in Table 1. There was no correlation between gland oxyphil percentage volume and MIBI uptake ratios ($p > 0.05$). With 50% accepted as the cut-off point, oxyphil cell content was higher than 50% in only 4 of 21 glands. The MIBI uptake ratios of these of four cases were higher compared to cases which were lower than 50%. However, the difference between these two groups was not at statistically significant (Table 4). In contrast, even though there was no oxyphil cells in 2 glands (patients 6 and 10), high level of MIBI uptake values were obtained. Representative histological appearances and scintigraphic images are shown in Figures 1 and 2.

DISCUSSION

Dual phase MIBI is a widely used method due to the high detection sensitivity of parathyroid lesions.[1,2] Even though the imaging time that was suggested for late imaging is 1.5 to 2.5 hours in the studies it was reported to be done at 1 to 4 hours intervals.[9] Moreover, there is a high variability for late imaging timing. In our study, even though there were no significant differences between mean values obtained from late images at 3 different time intervals, significant uptake differences between the images of these cases were observed (Table 1). A similar comparison was done by Arbab et al. and individual differences between 1st and 2nd hour images are re-

ported.[10] Taking late images over 1 hour can cause false negativity because of a fast washout rate. In our opinion, performing one late imaging at 1st hour is a more useful procedure for the correct diagnosis because of the shorter examination time without loss of diagnostic ability.

Recently, it was reported that the most significant two factors in detecting parathyroid lesions are increase in gland volume[11–14] and increase of serum i-PTH [7,15–18] and the major effects of these two factors on MIBI uptake and retention were accepted without debate. Although, in our study all of the glands were larger than normal and serum i-PTH levels of all patients were evaluated, and we could not find any significant correlation between early and late MIBI uptake values and gland volume and increased i-PTH level either. This finding requires the roles of other factors to be examined other than these two factors that play a role at the uptake and accumulation of MIBI in parathyroid lesions as well. One of these factors is the changes in serum calcium levels. In studies performed by two different groups, it was reported that there was not a significant difference in serum calcium levels between a MIBI positive group and MIBI negative group.[11,17] However, in other studies, it was reported that MIBI uptake is increased in the cases with high serum calcium.[14,18–20] In two of these studies it was reported that there was a statistically significant positive correlation between MIBI uptake and calcium level.[14,20] As for our study, even though there was not a significant correlation between MIBI uptake values and calcium level of the cases, an evident tendency was observed. Because of this, we think that an increase in the serum calcium level can be a factor that increases the retention of MIBI. On the other hand, the relation between the changes in serum phosphorus levels that is secondary to increased i-PTH level and MIBI uptake has not been thoroughly researched in studies conducted up to day. The main possible reason for not researching this subject is that phosphorus does not play a role in cellular uptake and wash out mechanisms of MIBI. However, in our study, we found an adverse correlation between triple late phase MIBI uptake values and phosphorus, and statistically significant MIBI uptake and retention differences in the grouping that is done according to phosphorus level. In our opinion, the main reason that underlies this adverse relation between serum phosphorus level and MIBI uptake values is due to the adverse relation between calcium and phosphorus. In fact, these changes in levels of i-PTH, calcium and phosphorus that are observed in hyperparathyroidism are indications of increased metabolism of pathologic parathyroid gland(s). It was reported that the gland hypermetabolism that was observed in hyperparathyroidism causes increased tissue perfusion.[21] The increase in uptake and retention of MIBI was an expected result of the increase in gland purfusion.

Another factor which is considered to have a role in the uptake of MIBI in hyperparathyroidism is the oxyphil cell content of the gland. The oxyphil cells in parathyroid gland can produce i-PTH in a similar way to that of chief cells.[22] The considerable main characteristics of these cells are that they have numerous and large mitochondria and the neoplasms which contain this kind of cell may show high MIBI uptake.[23–25] The relation between the existence of oxyphil cells and MIBI uptake was first researched by Thompson et al. and was reported not to have a significant relation.[26] The correlation between the existence of oxyphil cells and semi quantitative MIBI uptake ratios was first examined by Staudenherz et al. and no correlation between these two parameters could be found.[27] In contrast to this, Carpentier et al. were the first to report that in parathyroid lesions, an increase in oxyphil cell content increases the sensitivity of MIBI.[19] However, very few studies have reported results that support this study up to this time.[14,27] Among these studies, only that of Melloul et al. focused on the correlation between semi quantitative MIBI uptake ratio and oxyphil cell percentage and reported a positive correlation. In our study, differing from other studies, the correlation between semi quantitative MIBI uptake ratio and gland oxyphil percentage volume was studied. A statistically significant correlation between these two parameters is not found. In spite of this, the fact of increase in uptake ratios of glands which contain oxyphil cells more than 50% shows that there may be a partial relation between oxyphil cell content and MIBI uptake and retention. However, when MIBI positive cases are examined in all of the studies, in a similar way to our study, it is seen that the glands that have high oxyphil cell content are not common. So, we think that oxyphil cell content can not be a major factor influencing the MIBI uptake in hyperparathyroidism.

CONCLUSION

The results of our study show that the optimal imaging times after intravenous injection of MIBI are 15 minutes and 1 hour because of the shorter examination time without loss of diagnostic ability. In the present study, there was no significant correlation between MIBI uptake ratios and increased gland volume, or serum Ca and i-PTH levels. Besides, we think that oxyphil cell content may not have a main effect on MIBI uptake and retention. The fact of an adverse relation between phosphorus and MIBI retention in our study may show that phosphorus level should be considered prior to MIBI imaging. The role of phosphorus in MIBI retention and whether it increases the negativity of MIBI or not, should be researched in further studies that include a comparison of especially MIBI negative cases, in point of phosphorus.

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