

## Sestamibi Positive Vs Negative Scan In Primary Hyperparathyroidism; A Clinical Dilemma

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### ABSTRACT

**Objectives:** In primary hyperthyroidism Tc-99m Sestamibi (MIBI) scanning is commonly used for localization of abnormal parathyroid gland and the reported sensitivity is very high. However, false negative scan remain a problem. We examined whether serum calcium and parathormone (PTH) level have any impact in the sensitivity of MIBI scan.

**Study design:** A retrospective review of 55 patients with primary hyperparathyroidism who underwent MIBI scan from January 2012 to December 2014 were included in this study. All patients underwent parathyroid surgery followed by histopathological confirmation.

**Results:** In total, 55 patients were studied. Mean age was  $41.3 \pm 19.8$  years (range 21-63 years). MIBI scan was true positive in 37 cases and false negative in 18 cases. The sensitivity of MIBI scan was 67.2 %. Mean serum calcium level was 12.3 mg/ dL. More than 62.2 % of patients with calcium level greater than 12.3 mg/dL had a positive scan as compared with 37.8% of those with lesser value ( $P < 0.05$ ). Similarly a serum PTH level greater than  $316 \pm 139$  pg/mL correlated with positive scans in 78.4 % as opposed to 21.6 % in those with lower levels ( $P < 0.01$ ).

**Conclusion:** Lower calcium and PTH level significantly correlate with reduced sensitivity of MIBI scan. Although we did not find the best cut-off level of serum calcium and PTH level that can predict a positive scan.

**Key words:** Primary hyperparathyroidism, Sestamibi scan, Hypercalcemia, Parathormone (PTH).

### INTRODUCTION

In recent years primary hyperparathyroidism has been diagnosed with increasing frequency due to increase awareness and advances in laboratory techniques. With the increase of biochemical screening even asymptomatic primary hyperparathyroidism is diagnosed. Of all available imaging modalities Tc-99m sestamibi scanning has become the modality of choice as compared to other modalities such as ultrasonography, CT and MRI.

The reported sensitivity of MIBI scan ranges from 70-85%, which increases to 90-95% especially when imaging, is optimized with SPECT and SPECT/CT (1). In spite of that a substantial number of patients with elevated PTH level may have false negative sestamibi scan. In these cases, no adenoma/hyperplasia is visualized on the scan although the patient may have parathyroid pathology leading to diagnostic dilemma. The aim of this review study is to see whether serum calcium and PTH level have any impact in the sensitivity of MIBI scan.

### MATERIALS AND METHODS

A retrospective review of 55 patients with primary hyperparathyroidism referred to our department for Tc-99m sestamibi parathyroid scanning between January 2012 to December 2014 were included in this study. Diagnostic criteria for primary hyperparathyroidism were based on high PTH level associated with hypercalcemia. In this study normal reference range for serum PTH was 9-80 pg/mL and serum calcium was 8.3-10.1 mg/dL. The dual - phase method of parathyroid imaging was conducted using standard protocol. All patients received 20 mCi Tc-99m sestamibi intravenously. Early phase (20-minutes post injection) and delayed phase (2-hour post injection) SPECT images were acquired on a dual head SPECT/CT system (Symbia, Siemens). The images were acquired into a 128 x128 matrix with 30 sec per step having 60 steps over a full 360° orbit. In delayed view a low dose CT was also performed covering the area of SPECT acquisition.

Transverse images were reconstructed in coronal and sagittal views. Sestamibi scan were designated as either 'positive' or 'negative'. A positive scan was defined when an area of relatively increased radiotracer uptake in early phase persisted and became more prominent in delayed phase because of slower washout of radiotracer from parathyroid than from thyroid gland. Conversely negative scan was considered when delayed images show no unusual activity in the neck region. The results were correlated with serum calcium and PTH level. All patients underwent surgery followed by histopathological confirmation.

Statistical analysis was performed using SPSS software version 15. Effects of variable on the result of MIBI scan were studied using chi-square and regression analysis.

P value < 0.05 was considered statistically significant.

## RESULTS

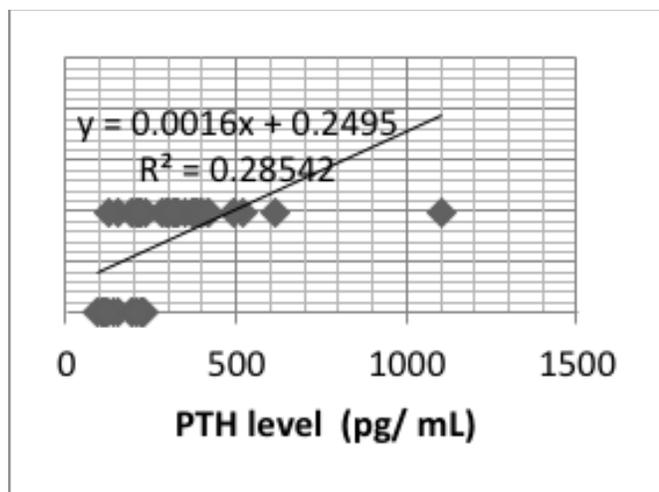
A total 55 patients with hypercalcaemia and high serum PTH level were studied. Mean age was  $41.3 \pm 19.8$  years (range 21-63 years). Female were predominant than male which was 31 (56.4 %) and 24 (43.6%) respectively. MIBI scan was true positive in 67.2 % (n=37) cases and false negative in 32.8 % (n=18) cases. The overall sensitivity of MIBI scan was 67.2 %. Mean PTH level was  $316 \pm 139$  pg/mL. Among the 37 patients with positive scan 29 (78.3%) had serum PTH level above the mean value whereas, rest eight (21.7%) had below the mean value. Meanwhile among 18 patients with negative scan 7 (38.8%) had a PTH level above the mean value and 11 (61.2 %) had below the mean level (P<0.01). Mean PTH level in true positive and in false negative scan group was  $412 \pm 259$  pg/mL and  $215 \pm 137$  pg/mL respectively. Similarly, among the patients having positive scan 62.2% (n=23) had serum calcium level greater than 12.3 mg/dL as opposed to 37.8 % (n=14) in those with lower level. Among 18 false negative cases, five (27.7 %) had

below and 13 (72.3 %) had above the mean value of calcium (p<0.05).

## DISCUSSION

MIBI scan is the current imaging modality of choice for localization of abnormal parathyroid gland. A normal parathyroid gland does not take up sestamibi. The exact mechanism of its selective uptake in abnormal parathyroid gland remains debatable (1). High mitochondrial activity is considered to be the major component of tracer uptake by parathyroid tissue in-patient with high PTH level. Moreover, several factors that have been reported to be associated with sestamibi imaging are size of gland, multiglandular disease, histopathological variants, serum calcium level, PTH level, vitamin D level and use of calcium channel blockers (2). The overall sensitivity of MIBI scan documented in several studies ranges from 70 to 85%. In this study the sensitivity is 67.2%, which is lower than the reported value. According to the study result, higher level of PTH is significantly related with a true positive scan (P<0.01). Mean PTH level in patients with true positive scan is  $412 \pm 259$  pg/mL and  $215 \pm 137$  pg/mL in patients with false negative scan which gives an impression of correlation between sensitivity of MIBI scan and PTH level. Our findings are consistent with Siegel *et al.* who reported a correlation between the sensitivity of parathyroid scintigraphy and PTH level. In their retrospective review mean PTH level were 367 pg/mL in true positive scan group and 148 pg/mL in false negative scan group (3). Similarly Parikhshak *et al.* showed the same finding where low PTH level and sensitivity of the MIBI scan are inversely related. Comparing the parathormone level their mean PTH level was 158 pg/ mL whereas in our study it is higher (4).

Regarding the calcium level, a review of literature focused on technical and biological factors affecting MIBI scan showed that the plasma calcium greater than 11.3 mg/dL had a positive scan compared to those with lesser value.



**Figure 1:** Scatter plot showing the degree of correlation between the serum PTH level (x-axis) and MIBI scan finding (y-axis).

The degree of hypercalcaemia in primary hyperparathyroidism seems to be closely related to defective regulation of PTH secretion, metabolic rate and elevated membrane potential rather than increased mass of parathyroid tissue (5). Indeed, in some patient hypercalcaemia may be surprisingly increased despite only modest glandular enlargement. Therefore, serum calcium level in primary hyperparathyroidism may play a key role in modifying MIBI kinetics by influencing the membrane potential. In this study mean serum calcium level is 12.3 mg/dL. 37.8 % of true positive scan had a calcium level below the mean value whereas, 62.2 % had above the mean value. On the other hand in false negative cases 72.3 % had a calcium level below the mean value and 27.7 % had above the mean value. These findings have similarities with Saanislaw *et al.* study where serum calcium level was significantly higher in positive scan cases ( $p < 0.04$ ) (6).

Hypercalcaemia accompanied by elevated PTH level is diagnostic of hyperparathyroidism. However, a cautionary note is that during the review we found a minority of scans positive patients who had serum calcium levels in upper

limit of normal reference range. This is called normocalcemic hyperparathyroidism.

**Table 1:** Correlation of sestamibi scans result (true positive Vs false negative) with mean calcium and PTH level.

Scan designation <sup>⊠</sup>	Mean calcium (mg/dL) <sup>⊠</sup>	Mean PTH (pg/mL) <sup>⊠</sup>
True positive (n=37)	13.2 ± 1.9	412 ± 259
False negative (n=18)	10.9 ± 0.91	215 ± 137
Significance <sup>⊠</sup>	$p < 0.05$ <sup>⊠</sup>	$p < 0.01$ <sup>⊠</sup>

We did not include these cases in our review but, it should be kept in mind that the condition is an indication of early diagnosis of the disease. According to Westerdahl and Bergenflez study high glandular weight and high PTH level were important factors for delectability of adenoma (7). In contrary there are literatures where the investigators showed no significant correlation between MIBI uptake and serum calcium and PTH level (8).

This study also showed that some other biochemical profile like serum albumin, magnesium and inorganic phosphate were low in patients with a positive scan though the relation was not so significant. Among other influencing factors size of the gland is thought to be an important one to affect the positivity of the scan. In a report by Richard *et al.*, an adenoma weight >600 mg and oxyphil content > 20 % increased the rate of obtaining a positive scan by 10 and 4 fold respectively (9). In this study neither weight of the gland nor the cellular type of the gland were included.

The limitation of the study was small study population and ignoring other influencing factors. We only emphasized on the importance of PTH and calcium level in predicting the result of the MIBI scan. In our small-scale study we were unable to identify a figure at which we can fully predict that any given abnormal parathyroid gland will yield a positive result.

Further large cohorts are needed for a definite consensus to find out the best cut-off level of biochemical parameter that can predict a positive scan.

## CONCLUSION

It was important to note that, diagnosis of primary hyperparathyroidism was made on clinical and biochemical data. There was no definite lower limit of serum PTH and calcium level which can predict a positive scan. So, by understanding the limitations in each modality clinician should take the therapeutic decision.

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