Comparison of Histological Findings and Parathyroid Scintigraphy in Hemodialysis Patients with Secondary Hyperparathyroid Glands

HIDEMI NISHIDA, MASATOSHI ISHIBASHI*, YUJI HIROMATSU**, HAYATO KAIDA*, KENKICHI BABA*, IKUYO MIYAKE**, HIROFUMI IKEDO, SEIYA KATO***, KEI FUKAMI, SHUJI IIDA AND SEIYA OKUDA

Department of Nephrology and Dialysis Unit, Kurume University School of Medicine, Kurume, Fukuoka 830-0011, Japan

**Division of Nuclear Medicine and Department of Radiology, Kurume University School of Medicine, Kurume, Fukuoka 830-0011, Japan*

***Department of Endocrinology and Metabolism, Kurume University School of Medicine, Kurume, Fukuoka 830-0011, Japan*

****Department of Pathology, Kurume University School of Medicine, Kurume, Fukuoka 830-0011, Japan*

Abstract. To determine the usefulness of parathyroid scintigraphy in histological estimation for secondary hyperparathyroidism (2HPT) using Tc-99m sestamibi or Tc-99m tetrofosmin. Tc-99m sestamibi (MIBI) and Tc-99m tetrofosmin (Tetro) parathyroid imaging following double-phase study, magnetic resonance imaging (MRI), and ultrasound were performed on 14 patients with 2HPT. All patients underwent parathyroidectomy. The uptake of two tracers in parathyroid areas was compared with the histopathologic findings. Forty-nine parathyroid glands were surgically explored and histologically proven to be hyperplastic. Of these, 42 were diagnosed with nodular type (N-type) hyperplasia, and 7 with diffuse type (D-type) hyperplasia. MIBI and Tetro parathyroid imagings detected 34 and 35 parathyroid glands, respectively. The sensitivity of MIBI was determined to be 76.2% (32/42) for N-type, and 28.6% (2/7) for D-type. The sensitivity of Tetro was determined to be 78.6% (33/42) for N-type and 28.6% (2/7) for D-type. The sensitivity of both MIBI and Tetro was significantly higher for N-type than for D-type, 76.2% (32/42) vs. 28.6% (2/7) in MIBI, $P = 0.022$; 78.6% (33/42) vs. 28.6% (2/7) in Tetro, $P = 0.015$. The sensitivity of MRI was determined to be 76.2% (32/42) for N-type and 42.9% (3/7) for D-type, and the sensitivity of ultrasound was 71.4% (30/42) for N-type and 71.4% (5/7) for D-type. There was no significant difference in the sensitivity of MRI or ultrasound between N-type and D-type. The uptake ratios of MIBI and Tetro were also greater for N-type than for D-type. The detectability of both MIBI and Tetro was greater for N-type than for D-type. Tc-99m MIBI or Tc-99m Tetro parathyroid scintigraphy therefore may be used clinically to distinguish N-type from D-type parathyroid gland hyperplasia.

Key words: Parathyroid scintigraphy, Tc-99m sestamibi; Tc-99m tetrofosmin, Chronic hemodialysis, Secondary hyperparathyroidism

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METABOLIC bone disease, such as renal osteodystrophy, is one of the major complications in patient undergoing maintenance hemodialysis. One of the primary contributing factors underlying metabolic bone is secondary hyperparathyroidism, which results from a

decreased serum concentration of $1,25(\text{OH})_2\text{D}_3$ and subsequent hypocalcemia and hyperphosphatemia. The decrease in vitamin D receptors is thought to be related to the progression of 2HPT. The efficacy of high dose calcitriol pulse therapy depends on the density of vitamin D receptors in the parathyroid glands. In cases showing a poor response to vitamin D pulse therapy, parathyroid surgery may be indicated for persistent hypercalcemia, progressive extraskelatal calcification, severe progressive skeletal pain or fractures, and the appearance of calciphylaxis or intractable pruritus [1].

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Correspondence to: Hidemi NISHIDA, M.D., Department of Nephrology and Dialysis Unit, Kurume University School of Medicine, 67 Asahimachi, Kurume, Fukuoka 830-0011, Japan

Preoperative imaging techniques include ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), and Tl-201/Tc-99m pertechnetate (Tl/Tc) or Tl-201/I-123 subtraction scintigraphy [3–8]. In 1989, a new approach utilizing myocardial imaging with radiopharmaceutical Tc-99m sestamibi (MIBI) was reported for the localization of parathyroid glands of the normoxic and ectopic regions [9, 10]. Several investigators have confirmed the usefulness of this technique in identifying abnormal parathyroid glands either alone [11–14], or with subtraction imaging [15]. In 1995, we reported, for the first time, that Tc-99m tetrofosmin (Tetro) could also be used for parathyroid imaging [16]. The similarity of Tc-99m tetrofosmin to sestamibi in its myocardial behavior as well as preliminary evidence confirming its localization in abnormal parathyroid tissue, suggested that a comparison of Tc-labeled agents in patients with known parathyroid disease would be worthwhile [17, 18]. The purpose of the present study was to clarify the clinical significance of the uptake of these parathyroid tracers for distinguishing nodular type hyperplasia from diffuse type hyperplasia in hemodialysis patients. The distinction is extremely important for the selection of a suitable therapeutic scheme.

Materials and Methods

Study population

We evaluated 14 patients (8 men and 6 women, ranging in age from 37 to 61 years, mean age 47 years) with 2HPT due to chronic renal failure treated with hemodialysis. The etiology of renal failure in the uremic patients was diagnosed as chronic glomerulonephritis. The uremic patients had been on hemodialysis for 132 ± 48 months and were dialyzed three times per week. All patients failed to respond to vitamin D therapy or vitamin D pulse therapy and underwent parathyroid surgery. Their clinical characteristics at the time of parathyroidectomy are shown in Table 1. Parathyroidectomy was performed within one month after radionuclide imaging, the location, weight, and histopathologic findings were recorded. The parathyroid glands of all patients were studied through imaging with ultrasonography, MRI, and radionuclide techniques (MIBI and Tetro), and the locations, weight, and histopathologic findings of the excised glands were

Table 1. Clinical characteristics of the patients with secondary hyperparathyroidism

Case	Gender	Age (year)	Duration of HD (months)	intact PTH (pg/ml)	Ca (mg/dl)	P (mg/dl)
1	m	49	122	1100	10.2	8.7
2	f	46	74	1758	9.1	7
3	f	45	152	2399	11.1	7.5
4	f	37	150	503	11.1	8.6
5	f	49	173	608	10.9	7.6
6	m	61	147	1198	10.2	4.6
7	m	30	100	1475	9.8	4.9
8	f	53	150	1432	8.9	5.5
9	m	54	65	672	11.8	7
10	m	47	140	963	10.6	5.4
11	m	47	242	1400	9.5	5.7
12	m	45	70	1013	9.9	6.1
13	m	21	103	1421	9.3	8.2
14	m	58	171	773	10.1	4.7

HD, hemodialysis; PTH, parathyroid hormone; m, male; f, female

recorded for each patient. Informed consent was obtained from each patient as part of the protocol approved by the Institutional Clinical Subpanel on Human Studies at our university.

Tc-99m sestamibi and Tc-99m tetrofosmin parathyroid imaging

Imagings with Tc-99m MIBI and Tc-99m Tetro were performed within 3 or 4 weeks before parathyroidectomy. Each agent was administered intravenously (about 600 MBq sestamibi, Dupont, UK, and about 740 MBq tetrofosmin, Amersham International, Bucks, UK). Anterior images of the neck were recorded with a small field-of-view camera (GCA-10A, Toshiba, Tokyo, Japan) at 10 minutes and 2–3 hours after injection both in analog form on film, and digitally (256×256) on a dedicated computer system (Toshiba 550U, Tokyo, Japan) equipped with a low energy, general-purpose parallel-hole collimator. Each image was recorded for 10 minutes with a 15% window centered on the 140 keV photopeak; approximately 500,000 counts were recorded for each image. In addition, a large field-of-view gamma camera and computer system (26001 and RW 3000, Hitachi, Tokyo, Japan), equipped with a low-energy, high resolution parallel hole collimator was used to record concomitant anterior images of the mediastinum at about 1 hour after radiotracer injection. Two observers, unaware of the patients' clinical findings or of the results of MRI, evaluated the scintigrams

for the presence of abnormal increased uptake in the region of the thyroid bed or mediastinum. Early and late Tc-99m MIBI and Tc-99m Tetro images were compared, and scans were scored positive or negative for parathyroid localization and the early images were categorized as slight or intense uptake compared to thyroid uptake on the late images. The initial image, acquired at 10 minutes after radiotracer injection, was referred to as the “thyroid phase” image, and the second image at 1 hour and the third image at 3 hours were referred to as the “parathyroid phase” image following the modified imaging technique previously described by Taillefer *et al.* [11]. Tc-99m MIBI images were reviewed independently from the Tc-99m Tetro data and the results were compared. Where discrepancies occurred, the evaluators reached a consensus opinion. Areas of persistent increased uptake recorded at 1–3 hours after the injection were considered to represent parathyroid tissue. Regions of interest (ROIs) were identified and the parathyroid gland/normal thyroid tissue activity ratio (the P/T uptake ratio) in the late parathyroid images was calculated [11].

Histopathologic methods

Resected parathyroid tissues were fixed in 10% formalin for 24 hours. After dehydration with 70–100% ethanol dilutions, the tissues were embedded in paraffin wax and 4 μ m sections were stained with hematoxylin and eosin. Based on laboratory findings, all lesions were suspected to be secondary hyperplasia, and this diagnosis was later confirmed both by gross findings and through histological characterization under conventional light microscopy [19]. These lesions were variously distributed in more than one parathyroid gland and were not identified as adenoma [20]. The lesions were divided into two categories: diffuse type (D-type), which shows a predominantly diffuse sheet-like pattern of hyperplasia with normal lobular composition, and nodular type (N-type), which shows at least one nodular proliferation pattern well-encapsulated by fibrous tissue and fat cell-free accumulation of parenchymal cells [21]. Asymmetric arrangement of the tubulus, an increased number of oxyphil cells, and irregular nuclear morphology were also accounted for the N-type [19].

Table 2. Detectability of abnormal parathyroid glands by various modalities

	MIBI		Tetro		MRI		Ultrasound	
	(+)	(–)	(+)	(–)	(+)	(–)	(+)	(–)
Nodular	32	10*	33	9**	32	10	30	10
Diffuse	2	5	2	5	3	4	5	2

MIBI, Tc-99m sestamibi; Tetro, Tc-99m tetrofosmin; MRI, magnetic resonance imaging.

nodular, nodular type hyperplasia; diffuse, diffuse type hyperplasia.

* $P = 0.022$, ** $P = 0.015$ (Fisher’s exact probability test)

Statistics

All quantitative data were expressed as the mean $\pm$ standard deviation. Statistical analysis was performed using the Mann-Whitney test, the chi-square test or Fisher’s exact probability test, as appropriate. A p value of <0.05 was considered significant.

Results

Forty-nine parathyroid glands were surgically explored and histologically proven to be hyperplastic. Of these, 42 showed nodular type (N-type) hyperplasia, and 7 showed diffuse type (D-type) (Fig. 1). MIBI and Tetro parathyroid imagings detected 34 and 35 parathyroid glands, respectively (Table 2). The sensitivity of MIBI was determined to be 76.2% (32/42) for N-type and 28.6% (2/7) for D-type. The sensitivity of Tetro was determined to be 78.6% (33/42) for N-type and 28.6% (2/7) for D-type. The sensitivity of both MIBI and Tetro was significantly higher for N-type than for D-type, 76.2% (32/42) vs. 28.6% (2/7) in MIBI, $P = 0.022$; 78.6% (33/42) vs. 28.6% (2/7) in Tetro, $P = 0.015$. The sensitivity of MRI was determined to be 76.2% (32/42) for N-type and 42.9% (3/7) for D-type, and the sensitivity of ultrasound was 71.4% (30/42) for N-type and 71.4% (5/7) for D-type. There was no significant difference in the sensitivity of MRI or ultrasound between N-type and D-type. The uptake ratios of MIBI and Tetro were also greater for N-type than for D-type (Fig. 2).

Discussion

With the progression of chronic renal insufficiency,

Fig. 1. Diffuse type (A) and nodular type (B) of parathyroid hyperplasia in secondary hyperparathyroidism (Hematoxylin-Eosin staining, $\times 50$).

the total weight of the parathyroid glands may increase considerably associated with the elevation of serum PTH and abnormal set point for calcium-regulated PTH secretion. The degree of the enlargement correlates with the duration and severity of renal function impairment [22, 23]. The histopathological findings of parathyroid glands associated with chronic renal failure show that parathyroid glands change progressively throughout the development of the disease [24]. The earliest change is a decrease in the number of stromal fat cells and their partial replacement by widened cords and nests of chief cells. This type of lesion may progress into D-type hyperplasia. The advanced stages are characterized by nodular proliferation of chief cells and oncocytes [23]. Considering that all 14 patients in

Fig. 2. Tc-99mMIBI and Tc-99m tetrofosmin scintigraphy. The uptake of radiotracers in the parathyroid region was assessed as ratio to that in thyroid region. The uptake ratios of MIBI and Tetro were significantly greater for N-type than for D-type (Mann-Whitney test).

this study had a long history of hemodialysis, the majority of the parathyroidal lesions were naturally recognized as the N-type. N-type hyperplasia is usually present in patients with higher concentrations of intact PTH and the more severe bone symptoms [2]. Fukuda *et al.* [2] reported that the clinically severe N-type parathyroid hyperplasia was associated with a reduced number of vitamin D receptors per unit of gland section compared with the mild D-type gland hyperplasia. Because the density of calcium sensing receptors is lower in the N-type glands, it is apparent that vitamin D receptor abnormalities in the parathyroid glands of patients with uremia play a role in the abnormal set point for calcium-regulated PTH secretion. This may also explain the failure of vitamin D pulse therapy for N-type hyperplasia in hemodialysis patients. Indeed, the efficacy of high dose calcitriol therapy depends, to a certain degree, on the vitamin D receptor density in the parathyroid and on the size of the parathyroid. Therefore, it would be useful to be able to distinguish N-type hyperplasia from D-type hyperplasia with simple clinical techniques.

MIBI and Tetro scintigraphies have been proposed as preoperative methods of locating parathyroid ade-

noma in primary hyperparathyroidism [11, 26–28]. In patients with 2HPT, however, the efficacy of these techniques has been reported to be less [11, 26]. The relationship between the uptake of these tracers and the subtypes of hyperplasia remains unclear. The present study revealed that both MIBI and Tetro provide significantly better localization for N-type hyperplasia than for D-type hyperplasia. In many cases, since N-type parathyroid glands are resistant to vitamin D pulse therapy. MIBI and Tetro parathyroid imaging may help clinicians to determine the appropriateness of vitamin D pulse therapy. The histological significance of radionuclide uptake in MIBI or Tetro parathyroid scintigraphy following double-phase study is still unknown in the field of hemodialysis [11, 16]. We previously reported that MIBI uptake by parathyroid glands did not reflect the rate of mitochondria-rich cells [29]. Gogusev *et al.* [30] recently reported that the number of calcium sensors on the surface of N-type hyperplastic cells was lower than that found in D-type

cells. Tc-MIBI is sequestered inside the cytoplasm and mitochondria, and its degree of cellular incorporation and retention depends on the electric potential generated through the cellular and mitochondrial membrane [31]. However, the actual mechanism of radiotracer capture in the hyperplastic parathyroid tissue has yet to be completely understood [32]. Nevertheless, we demonstrated for the first time the positive association between Tc-MIBI and Tetro scintigraphy and subtypes of hyperplasia. Both MIBI and Tetro scintigraphy may be useful to distinguish N-type from D-type hyperplasia. Although the precise mechanism of the uptake or kinetics of MIBI and Tetro has not been clarified, those modalities may provide potential tools for the prediction of the therapeutic outcome in 2HPT. Future studies are necessary to investigate whether Tc-99m MIBI and Tetro parathyroid imaging using double-phase techniques are useful in planning therapy for patients with 2HPT.

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