Spectral Doppler Analysis of Parathyroid Adenoma: Correlation Between Resistive Index and Serum Parathyroid Hormone Concentration

Afshin Mohammadi[1]
Farzad Moloudi[2]
Mohammad Ghasemi-rad[3]

OBJECTIVE. The purpose of this study was to evaluate the correlation between spectral wave analyses by measuring the resistive index and serum intact parathyroid hormone (iPTH) concentration in primary hyperparathyroidism.

SUBJECTS AND METHODS. From March 2008 to April 2012, 46 consecutively registered patients underwent color and spectral Doppler ultrasonography for determination of vascularity and vascular resistance of parathyroid adenoma. The color Doppler sonographic findings were compared with methoxyisobutylisonitrile (MIBI) scintigraphic findings, serum iPTH concentration, and the volume of the gland.

RESULTS. The mean resistive index in parathyroid adenoma was 0.69 ± 0.12. The study showed a strong negative relation between resistive index and serum iPTH concentration. There was a significant negative relation between the volume of the gland and the resistive index.

CONCLUSION. There is a relation between degree of perfusion in parathyroid adenoma and serum iPTH concentration. Resistive index may be an objective alternative parameter for determining the vascularity of adenoma for monitoring of response to alcohol ablation therapy and medical management.

Keywords: color Doppler, parathyroid adenoma, ultrasound

DOI:10.2214/AJR.12.9296

Received May 19, 2012; accepted after revision September 13, 2012.

[1]Department of Radiology, Urmia University of Medical Sciences, Modaress Blvd, Ershad Ave, Urmia, West Azerbaijan, 05555 Iran. Address correspondence to A. Mohammadi (Mohamadi_afshin@yahoo.com).

[2]Student Research Committee, Urmia University of Medical Sciences, Urmia, Iran.

[3]M. D. Aryan Clinical Laboratory, Kashani Ave, Urmia, Iran.

WEB
This is a web exclusive article.

AJR 2013; 201:W318–W321

0361–803X/13/2012–W318

Primary hyperparathyroidism is the third most common endocrine disease after diabetes mellitus and thyroid disease [1], and parathyroid adenoma is the most common cause of primary hyperparathyroidism [2]. Sonography and methoxyisobutylisonitrile (MIBI) scintigraphy are the routine standard imaging modalities in the preoperative evaluation of parathyroid adenoma and hyperplasia, but both techniques have low specificity in the diagnosis of parathyroid adenoma [3]. Color Doppler sonography has been used successfully and is a valuable adjunctive technique in preoperative localization of parathyroid adenoma [4, 5]. Color Doppler sonography shows the rich capillary network of parathyroid adenoma. Different parenchymal flow patterns of parathyroid adenomas have been reported, including no flow, spot of fire, central vascularity, peripheral vascularity (ring), and combined central and peripheral vascularity [5]. To our knowledge, the relations between findings at Doppler spectral wave analysis, biochemical profiling, and MIBI scintigraphy of primary hyperparathyroidism have not been evaluated extensively [6, 7].

The main purpose of this study was to evaluate the relation between resistive index and serum intact parathyroid hormone (iPTH) concentration in primary hyperparathyroidism. The color Doppler vascular pattern of parathyroid adenoma changes with medical and alcohol ablation treatment, but it is a subjective index. Clarification and quantification of degrees of perfusion by measurement of resistive index and its relation to serum iPTH concentration may yield alternative parametric data for monitoring the response of parathyroid adenoma to alcohol injection therapy.

Subjects and Methods

From March 2008 to April 2012, 46 consecutively registered patients (10 men, 36 women) with primary hyperparathyroidism underwent color Doppler sonography and ^{99m}Tc MIBI scanning before parathyroidectomy by traditional unilateral neck dissection. Primary hyperparathyroidism was diagnosed when iPTH concentration was elevated or at the high end of the normal range and accompanied by elevated total or ionized calcium concentration.

We prospectively evaluated the sonographic data and compared them with postoperative histopathologic results as the reference standard method of de-

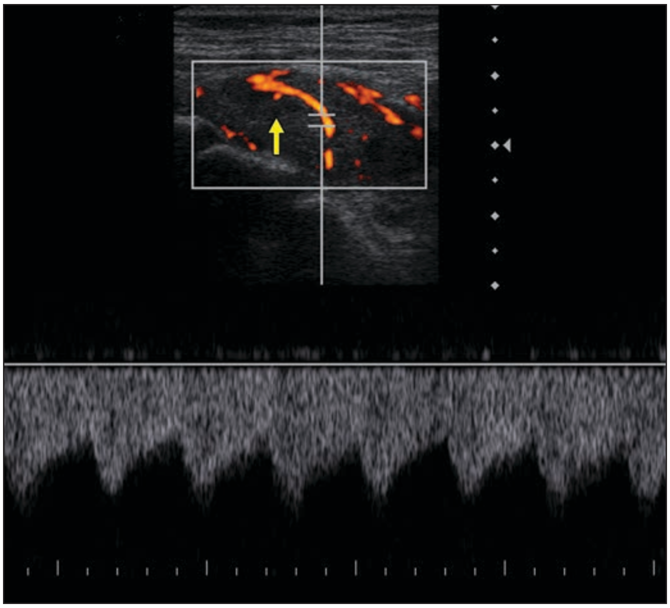

Fig. 1—39-year-old woman with primary hyperparathyroidism. Spectral Doppler sonogram shows blood flow with low resistance (resistive index, 0.6) to parathyroid adenoma (*arrow*).

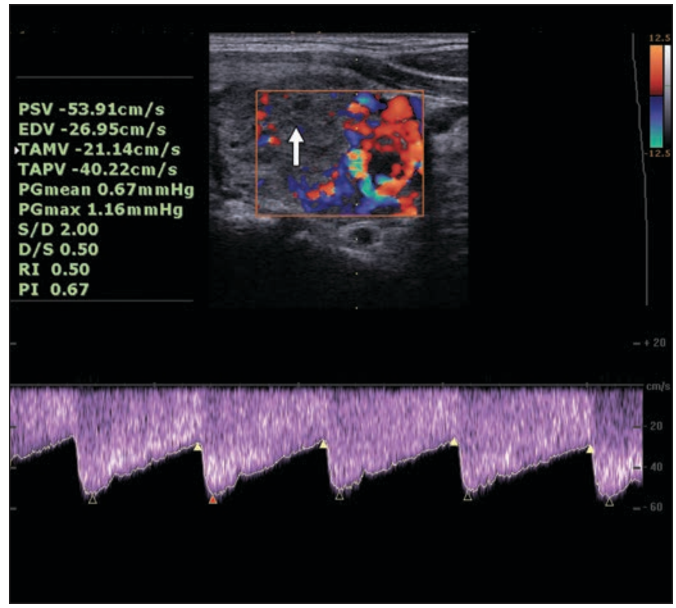

Fig. 2—34-year-old woman with primary hyperparathyroidism. Spectral Doppler sonogram shows blood flow with low resistance (resistive index, 0.5) to parathyroid adenoma (*arrow*).

termining the diagnostic accuracy of imaging modalities in the diagnosis of parathyroid adenoma. Blood calcium, phosphate, and iPTH were measured by immunoassay within 72 hours before the ultrasound examination. Ethical approval was obtained from institutional review board and our university ethics committee.

Color Doppler sonography was performed to determine the vascularity of all parathyroid adenomas. A single radiologist with 7 years' experience performed all of the ultrasound examinations (Nemio 30 system, Toshiba) with a high-frequency (11 MHz) linear array transducer. The patients were supine and the neck hyperextended for ultrasound scanning from the level of the mandibular angle to the sternal notch. All of the ultrasound examinations were performed before the ^{99m}Tc MIBI scanning results were available. The upper mediastinum was evaluated with a 4-MHz curved probe when necessary.

The parathyroid gland volume measurement was determined with the ellipsoid formula 0.52*xyz* with diameters *x, y,* and *z* in the three orthogonal planes. Both transverse and sagittal images were obtained. Postoperative histopathologic examination was considered the reference standard confirming test for the study. Color Doppler sonography was performed with the Doppler parameter set to detect the vascularity of a parathyroid adenoma. The color settings were optimized in each patient to avoid aliasing and color bleed over the vessel wall. For objective evaluation of tissue perfusion, we used spectral Doppler sonography (Figs. 1 and 2) to measure the resistive index (*RI*) of the arterial supply to each adenoma within the gland according to the formula $RI = (V_{max} - V_{min}) / V_{max}$, where *V* is velocity. The color settings were optimized to avoid aliasing and color bleed over the vessel wall.

In ^{99m}Tc MIBI scintigraphy, anteroposterior thyroid gamma camera images of the neck and upper part of the thorax were acquired for 5 minutes 20 minutes after IV administration of ^{99m}Tc pertechnetate (20 mCi). The images were obtained with patients supine. Scans were then acquired 15 minutes (thyroid phase) and 120 minutes (parathyroid phase) after IV administration of 15–20 mCi of ^{99m}Tc MIBI. The images were obtained with a single-head gamma camera (ADAK, Epic) over 10 minutes with a pinhole collimator. The MIBI scan was considered positive for parathyroid lesions when an increase in uptake was detected in the thyroid phase. Technetium 99m–labeled MIBI SPECT was performed 20–30 minutes after IV injection of the radiotracer, and the images were reconstructed to produce 3D projections. SPECT was performed in a full anterior (180°) view as 32 frames at 30 seconds per frame. Focal increased uptake in the parathyroid site was considered a positive finding.

Statistical analysis was performed with SPSS statistical analysis software (version 16, SPSS). Continuous variables were reported as mean ± SD and categoric variables as frequencies. Because the distribution of PTH and volume was not normal, a nonparametric Spearman test was used for evaluation of the correlation between patient biochemical data, gray-scale ultrasound volume measurement, and Doppler index values. One-way analysis of variance, chi-square test, and a multivariate linear model were used for the evaluation of variables.

Results

All 46 patients (female-to-male ratio, 3.6:1; mean age, 50.57 ± 12.53 years) with primary hyperparathyroidism underwent surgery at our university hospital. Skeletal involvement, especially bone pain, was the most common presenting symptom (73% of the patients). Bone pain and limb claudication due to a giant brown tumor in the iliac wing were the presenting symptoms in two patients. Renal calculi, including nephrocalcinosis, were present in 46% of the patients. Proximal muscle weakness was seen in 44%. No patient had psychiatric symptoms or obvious neurologic problems. Three patients had gastrointestinal symptoms such as nausea, vomiting, and constipation, and intractable vomiting was the major presenting symptom in one man. Parathyroid adenoma was not palpable at careful examination.

The mean preoperative serum calcium concentration was elevated (11.44 ± 1.03 mg/dL; range, 10.6–17 mg/dL), and the patients had low inorganic phosphorus concentrations (2.18 ± 0.66 mg/dL). The mean postoperative serum calcium concentration was 8.4 ± 1.16 mg/dL. The mean preoperative serum iPTH concentration was 521.46 ± 514.45 pg/mL (range, 80–2000 pg/mL), and the mean postoperative serum iPTH concentration was 57 ± 6.2 pg/mL (range, 34–64 pg/mL). The mean

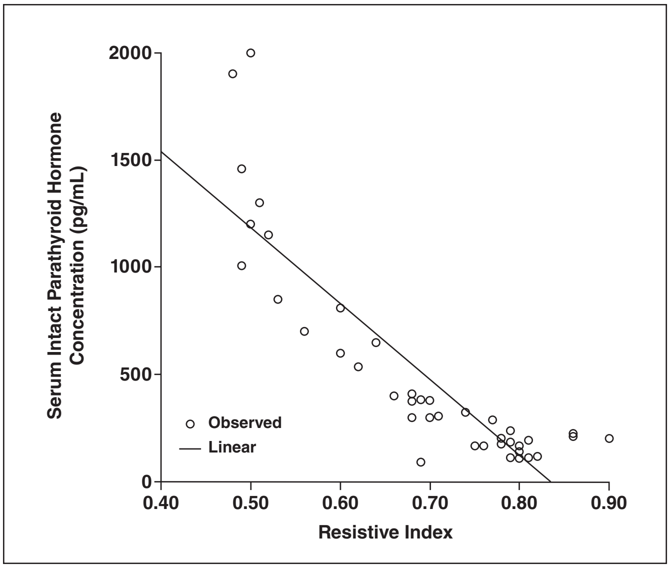

Fig. 3—Graph shows correlation between resistive index of parathyroid adenoma per patient and serum intact parathyroid hormone concentration for each patient.

volume of parathyroid adenomas was 2.01 ± 1.99 cm^3 (range, 0.2–7.5 cm^3).

The mean resistive index in parathyroid adenoma was 0.69 ± 0.12. Our study showed a strong negative correlation between resistive index and serum iPTH concentration ($r = –0.85$, $p < 0.0001$). There was a significant negative correlation between volume of the gland and resistive index ($r = –0.46$, $p = 0.002$). The correlation between serum iPTH concentration and resistive index was a linear-in-fitted regression line, and at lower resistive index values, serum iPTH increase showed linear regression (Fig. 3).

The mean resistive index value in MIBI-positive adenoma (0.66 ± 0.11) was significantly lower ($p = 0.02$) than the MIBI-negative adenoma value (0.75 ± 0.1). We also found a positive correlation between the volume of parathyroid adenoma and serum iPTH concentration ($r = 0.35$, $p < 0.035$). There was a significant difference between serum iPTH concentrations between MIBI-positive (660 ± 530 pg/mL) and MIBI-negative (222 ± 146 pg/mL) adenomas ($p = 0.025$), but the mean volume of parathyroid lesions did not exhibit significant differences between MIBI-positive (2.38 ± 2.09 cm^3) and MIBI-negative (1.7 ± 1.78 cm^3) adenomas.

Discussion

Primary hyperparathyroidism mostly occurs between the ages of 40 and 60 years [8, 9]. Yu et al. [10] found that patients with primary hyperparathyroidism are at increased risk of all-cause mortality and cardiovascular mortality even when they have mild untreated primary hyperparathyroidism. The parathyroid glands are composed of three cell types. The first is chief cells, which secrete PTH. The second is oxyphil cells, which are packed with mitochondria; their function is unknown. The third cell type is transitional oxyphil cells mixed with adipose tissue [11].

The mean age of the patients in this study agreed with that in previous studies [12–16]. According to our latest search, the mean parathyroid adenoma gland size and serum iPTH concentration in patients with primary hyperparathyroidism in our study agreed with those of studies in Asia and South America [15, 17–20] but was at least two or three times as great as that in studies conducted in the United States and Europe [21, 22]. Nichols et al. [22] found that the mean weight of all resected parathyroid adenomas was 1.14 ± 2.29 g. Tomas et al. [21] found that the mean weight of parathyroid adenomas was 840 mg. We believe that the main source of the difference was that almost all of our patients had symptomatic hyperparathyroidism.

We found a correlation between serum iPTH concentration and sonographic estimation of the volume of parathyroid adenomas. Our results contrast to those of a study [15,16] that did not show a correlation between serum iPTH concentration and weight of the parathyroid glands. Our results, however, are in agreement with those of Kakuta et al. [23], which showed a correlation between serum iPTH concentration and weight of the parathyroid glands. Those authors found that the volume of parathyroid glands at ultrasound is a good indicator of weight: Larger glands secrete more whole iPTH per gland.

Technetium 99m–labeled sestamibi molecules are distributed in the body through blood flow and cross the cell membranes by passive diffusion. Theses molecules usually are concentrated intracellularly in the region of the mitochondria [24]. This process makes the mitochondria-rich oxyphil cells of parathyroid adenoma more readily detectable. The exact mechanism of this elective uptake in abnormal parathyroid glands remains debatable, but among the various factors, hypervascularity and mitochondrial richness of the parathyroid oxyphil cells are significantly related to positive MIBI uptake [25].

The factor most commonly attributed to false-negative MIBI scan results is the size of the parathyroid gland. Smaller glands are less likely to be detected than are larger glands. The degree of radiotracer uptake in parathyroid adenomas depends on differences in perfusion and metabolic activity, oxyphil cell content, and P-glycoprotein expression [26, 27].

According to our results, there is a significant negative correlation between serum iPTH concentration and resistive index, meaning that parathyroid glands with a lower resistive index secrete more iPTH than do adenomas with highly resistive blood flow. As a result, severe hyperparathyroidism due to a hyperfunctioning adenoma may be associated with more blood flow than mild hyperparathyroidism. Our results are in agreement with those of a study by Ozcan and Oktay [7].

According to our results, the significant negative correlation between the resistive index of parathyroid adenoma and serum iPTH and MIBI results reveals that hypervascularity and degree of adenoma perfusion may play an important role in oversecretion of PTH or adenoma that is detectable on MIBI scans. In our study, there was a negative correlation between resistive index and volume of the gland, but there was not a significant difference in gland volume between MIBI-positive and MIBI-negative parathyroid adenomas. Ozcan and Oktay [7] found that Doppler indexes such as pulsatility index, resistive index, and the ratio of peak systolic velocity to end-diastolic velocity were not in good correlation with volume and iPTH concentration. Those investigators found that there was a positive correlation between iPTH concentration and total flow volume output of enlarged glands in secondary hyperparathyroidism. According to our study results, quantification of perfusion by resistive index value may yield parametric data for monitoring the response of enlarged glands to medical and ablation therapies. Medical and percutaneous ethanol injection therapies can alter the vascular color Doppler patterns of parathyroid adenoma [7]. Color and spectral Doppler sonography can be used for identification and follow-up of response to therapy of abnormal glands [7].

Our study had three limitations. First, larger series of patients are needed to verify our results in assessing resistive index in the treatment of patients with primary hyperparathyroidism. Second, volume estimation of parathyroid adenoma was performed sonographically, and small parathyroid and ectopic adenomas can be overlooked in this way. Third, color Doppler sonography is an operator-dependent procedure that requires experience for minimizing variability in results.

Conclusion

Serum iPTH concentration negatively correlates with the resistive index of parathyroid adenomas in primary hyperparathyroidism. The degree of perfusion as assessed by resistive index in parathyroid adenoma may play an important role in secretion of PTH. These data may be useful in the medical and alcohol ablation management of primary hyperparathyroidism as an adjunctive and objective method in assessment of response to treatment.

References

1. Demıralay E, Altaca G, Demırhan B. Morphological evaluation of parathyroid adenomas and immunohistochemical analysis of PCNA and Ki-67 proliferation markers. *Turk Patoloji Derg* 2011; 27:215–220
2. Mihai R, Wass JA, Sadler GP. Asymptomatic hyperparathyroidism: need for multicentre studies. *Clin Endocrinol (Oxf)* 2008; 68:155–164
3. Akbaba G, Berker D, Isik S, et al. A comparative study of pre-operative imaging methods in patients with primary hyperparathyroidism: ultrasonography, 99mTc sestamibi, single photon emission computed tomography, and magnetic resonance imaging. *J Endocrinol Invest* 2012; 35:359–364
4. Kamaya A, Quon A, Jeffrey RB. Sonography of the abnormal parathyroid gland. *Ultrasound Q* 2006; 22:253–262
5. Mohammadi A, Moloudi F, Ghasemi-rad M. Preoperative localization of parathyroid lesion: diagnostic usefulness of color Doppler ultrasonography. *Int J Clin Exp Med* 2012; 5:80–86
6. Pretolesi F, Silvestri E, Di Maio G, et al. US imaging and color Doppler in patients undergoing inhibitory therapy with calcitriol for secondary hyperparathyroidism. *Eur Radiol* 1997; 7:721–725
7. Ozcan UA, Oktay I. Assessment of parathyroid glands in hemodialysis patients by using color Doppler sonography. *Eur Radiol* 2009; 19:2750–2755
8. Yu N, Donnan PT, Murphy MJ, et al. Epidemiology of primary hyperparathyroidism in Tayside, Scotland, UK. *Clin Endocrinol (Oxf)* 2009; 71:485–493
9. Suh JM, Cronan JJ, Monchik JM. Primary hyperparathyroidism: is there an increased prevalence of renal stone disease? *AJR* 2008; 191:908–911
10. Yu N, Donnan PT, Flynn RW, et al. Increased mortality and morbidity in mild primary hyperparathyroid patients. The Parathyroid Epidemiology and Audit Research Study (PEARS). *Clin Endocrinol (Oxf)* 2010; 73:30–34
11. Eslamy HK, Ziessman HA. Parathyroid scintigraphy in patients with primary hyperparathyroidism: ^{99m}Tc sestamibi SPECT and SPECT/CT. *RadioGraphics* 2008; 28:1461–1476
12. Ambrosoni P, Heuguerot C, Olaizola I, et al. Can we use ^{99m}Tc-MIBI in functional studies of the parathyroid gland? *Nephrol Dial Transplant* 1998; 13(suppl 3):33–36
13. Stawicki SP, El Chaar M, Baillie DR, et al. Correlations between biochemical testing, pathology findings and preoperative sestamibi scans: a retrospective study of the minimally invasive radioguided parathyroidectomy (MIRP) approach. *Nucl Med Rev Cent East Eur* 2007; 10:82–86
14. Carpentier A, Jeannotte S, Verreault J, et al. Preoperative localization of parathyroid lesions in hyperparathyroidism: relationship between technetium-99m-MIBI uptake and oxyphil cell content. *J Nucl Med* 1998; 39:1441–1444
15. Sukan A, Reyhan M, Aydin M, et al. Preoperative evaluation of hyperparathyroidism: the role of dual-phase parathyroid scintigraphy and ultrasound imaging. *Ann Nucl Med* 2008; 22:123–131
16. Saxe AW, Lincenberg S, Hamburger SW. Can the volume of abnormal parathyroid tissue be predicted by preoperative biochemical measurement? *Surgery* 1987; 102:840–845
17. Alexandrides TK, Kouloubi K, Vagenakis AG, et al. The value of scintigraphy and ultrasonography in the preoperative localization of parathyroid glands in patients with primary hyperparathyroidism and concomitant thyroid disease. *Hormones (Athens)* 2006; 5:42–51
18. Gopal RA, Acharya SV, Bandgar T, et al. Clinical profile of primary hyperparathyroidism from western India: a single center experience. *J Postgrad Med* 2010; 56:79–84
19. De Feo ML, Colagrande S, Biagini C, et al. Parathyroid glands: combination of ^{99m}Tc MIBI scintigraphy and US for demonstration of parathyroid glands and nodules. *Radiology* 2000; 214:393–402
20. Erbil Y, Barbaros U, Tukenmez M, et al. Impact of adenoma weight and ectopic location of parathyroid adenoma on localization study results. *World J Surg* 2008; 32:566–571
21. Tomas MB, Pugliese PV, Tronco GG, et al. Pinhole versus parallel-hole collimators for parathyroid imaging: an intraindividual comparison. *J Nucl Med Technol* 2008; 36:189–194
22. Nichols KJ, Tomas MB, Tronco GG, et al. Preoperative parathyroid scintigraphic lesion localization: accuracy of various types of readings. *Radiology* 2008; 248:221–232
23. Kakuta T, Tanaka R, Kanai G, et al. Relationship between the weight of parathyroid glands and their secretion of parathyroid hormone in hemodialysis patients with secondary hyperparathyroidism. *Ther Apher Dial* 2008; 12:385–390
24. Arbab AS, Koizumi K, Toyama K, et al. Uptake of technetium-99m-tetrofosmin, technetium-99m-MIBI and thallium-201 in tumor cell lines. *J Nucl Med* 1996; 37:1551–1556
25. Lee VS, Spritzer CE, Coleman RE, Wilkinson RH Jr, Coogan AC, Leight GS Jr. The complementary roles of fast spin-echo MR imaging and double-phase ^{99m}Tc-sestamibi scintigraphy for localization of hyperfunctioning parathyroid glands. *AJR* 1996; 167:1555–1562
26. Piñero A, Rodríguez JM, Martínez-Barba E, Canteras M, Stiges-Serra A, Parrilla P. Tc99m-sestamibi scintigraphy and cell proliferation in primary hyperparathyroidism: a causal or casual relationship? *Surgery* 2003; 134:41–44
27. Bhatnagar A, Vezza PR, Bryan JA, et al. Technetium-99m-sestamibi parathyroid scintigraphy: effect of P-glycoprotein, histology and tumor size on detectability. *J Nucl Med* 1998; 39:1617–1620