ULTRASOUND DETECTION OF PARATHYROID HYPERPLASIA AND CORRELATION WITH CLINICIAL AND LABORATORY FINDINGS IN PATIENTS WITH CHRONIC KIDNEY DISEASE

DETECCIÓN DE HIPERPLASIA DE PARATIROIDES POR ULTRASONOGRAFÍA Y CORRELACIÓN CON SIGNOS CLÍNICOS Y DE LABORATORIO EN PACIENTES CON ENFERMEDAD RENAL CRÓNICA

César Augusto Restrepo Valencia [1]
David Santacruz Pacheco [2]
Campo Elías Castillo Pinilla [3]
José Arnoby Chacón Cardona [4]

SUMMARY

Objective: To determine whether there is any correlation between parathyroid hyperplasia, as detected by high-resolution ultrasound, and clinical and laboratory variables in patients with hyperparathyroidism secondary to stage-5 chronic kidney disease (CKD) on hemodialysis. Design: Descriptive. Location: RTS Ltda. Renal Unit in Caldas, Santa Sofía Hospital and Children's Hospital. Patients: All patients, 18 years of age, with stage – 5 CKD who were on dialysis therapy (hemodialysis or peritoneal dialysis), and with PTH levels greater than 400 pg / ml. Methods: After giving their written consent to participate in the study, all patients underwent high-resolution thyroid and parathyroid ultrasound (Phillips Team Enviisor CHD - 12 MHz transducer) performed by a medical specialist in radiology. Variables such as etiology, duration of the CKD, time on dialysis therapy, type of dialysis, presence of symptoms related to hyperparathyroidism (bone pain, fractures, pruritus),and laboratory variables like an intact PTH, calcium, phosphorus, calcium x phosphorus, and alkaline phosphatase were analyzed in order to determine if there was a significant correlation between the variables and the detection of parathyroid hyperplasia documented by high resolution ultrasound. Results: Of 403 patients evaluated, 92 met the inclusion criteria, 86 were scanned and 6 were excluded. In these patients, the most common cause of CKD was hypertensive nephrosclerosis. Thirty-seven patients were on peritoneal dialysis and 49 on hemodialysis, with an average time on dialysis of 61.4 ± 36.6 months. The average levels of PTH in pg / mL were 829,465 ± 473,631. The most prevalent clinical symptom was bone pain, found in 52.2% of patients. Ultrasound showed enlarged parathyroid glands in 30 patients (34.88%), with single-gland hyperplasia in 23 (26.74%), two-gland hyperplasia in 4 (4.65%) and three-gland hyperplasia in 3 (3.48%). The correlation between laboratory variables and the presence of parathyroid hyperplasia showed no statistical significance when compared with the group without ultrasound documentation of enlarged parathyroid glands. Conclusion: Parathyroid hyperplasia may be present in any patient with stage-5 CKD and intact PTH levels greater than 400 pg/ml, regardless of the clinical and laboratory variables. Ultrasound should be performed in all patients with high PTH values in order to refer them to the appropriate therapy.

KEY WORDS (MeSH)
Hyperplasia
Ultrasonography
Hyperparathyroidism, secondary
Kidney failure, chronic

PALABRAS CLAVE (DeCS)
Hiperplasia
Ultrasonografía
Hiperparatiroidismo secundario
Fallo renal crónico

RESUMEN

Objetivo: Determinar la correlación entre la hiperplasia de paratiroides detectada por ecografía de alta resolución y variables clínicas y de laboratorio en pacientes con hiperparatiroidismo secundario a enfermedad renal crónica (ERC) estadio 5 en terapia dialítica en RTS Ltda, sucursal Caldas, Hospital Santa Sofía, Hospital Infantil. *Métodos:* A los pacientes detectados se les

[1]*Medical intern – nephrologist. Associate Professor, Universidad de Caldas, Manizales, Colombia.*

[2]*Resident Doctor, 3rd year of Internal Medicine, Universidad de Caldas, Manizales, Colombia.*

[3]*Radiology Doctor. Lecturer. Universidad de Caldas, Manizales, Colombia.*

[4]*Doctor MSc. Tenured Professor, Universidad de Caldas, Manizales, Colombia.*

practicó ultrasonografía de tiroides y paratiroides con un equipo de alta resolución. Se analizaron variables como etiología, duración de la ERC, tiempo en terapia dialítica, tipo de diálisis, presencia de síntomas relacionados con hiperparatiroidismo (dolor óseo, fracturas, prurito) y las variables de laboratorio PTH intacta, calcio, fósforo, producto calcio por fósforo y fosfatasa alcalina. *Resultados:* De 403 pacientes evaluados, 92 cumplieron con los criterios de inclusión y se realizó ultrasonografía en 86. En este grupo de pacientes la causa más común de ERC fue nefroesclerosis hipertensiva, con un tiempo promedio en diálisis de 61,4 ± 36,6 meses. De los pacientes, 37 se encontraron en diálisis peritoneal y 49 en hemodiálisis. La correlación entre las variables de laboratorio y la presencia de hiperplasia de paratiroides no demostró significancia estadística cuando se comparó contra el grupo sin documentación ecográfica de crecimiento glandular paratiroideo. *Conclusión:* La hiperplasia de paratiroides puede estar presente en cualquier paciente con ERC estadio 5 y valores de PTH intacta mayores a 400 pg/ml, independientemente de sus variables clínicas y de laboratorio. Es necesario practicarle ultrasonografía a todos los pacientes con cifras altas de PTH, con el fin de asignarles una terapia eficiente.

Introduction

Secondary hyperparathyroidism (HPS) is an important complication in patients with chronic kidney disease (CKD). It is associated with bone complications and an increase in cardiovascular morbimortality (1). The parathyroid hormone rises in these patients as a consequence of low concentrations of 1.25 dihydroxyvitamin D3, phosphorous retention, reduction in the quantities of serum calcium, and in the expression of Vitamin D receptors sensitive to calcium (2,3).

Typically, serum concentrations of the parathormone (PTH) have been used in patients with CKD to establish the degree of hyperparathyroidism; but the size of the parathyroid glands recently detected by ultrasound has increased given that it has therapeutic and prognostic implications.

In patients with CKD, the parathyroid glands with nodular hyperplasia grow in a diffuse and polyclonal way. If it is not adequately treated, the growth can turn nodular where there is autonomous monoclonal cell proliferation and a high potential of growth (5). The factors involved in this pattern of occurrence are not clear to date (6); there is also no knowledge of genetic mutations which can explain it (7). This suggests that the metabolic alterations that accompany CKD could play an important role in triggering these events.

The cells that form the parathyroid glands with nodular hyperplasia are characterized by a reduction in the number of Vitamin D and calcium receptors (8,9), which make them refractory to conventional medical therapy. Glands with nodular hyperplasia in patients with CKD can be detected through high resolution ultrasound, which offers the patients the best therapeutic option. This radiological study is inexpensive, non invasive, does not have collateral effects, does not contribute ionizing radiation and can be repeated as many times as needed (10,11).

Establishing the correlation between the presence of parathyroid glands that are larger than 300 mm^3, detected by ultrasound, and clinical and laboratory alterations in patients with CKD would identify the population which requires a routine practice of such radiological study. A few research studies have tried to establish this correlation, but the results are controversial (12,13). This article is an additional contribution and limits the analyzed population to those which have an intact PTH value over 400 pg / ml, with the purpose of acquiring a higher probability to detect parathyroid hyperplasia.

Materials and Methods

In the RTS Ltda. Renal Unit in Caldas (Manizales, Colombia, South America), all patients, over 18 years of age, with stage – 5 CKD were identified using dialysis therapy (hemodialysis and peritoneal dialysis), with intact PTH values over 400 pg / ml. These patients were told the importance of participating in the study, and those who accepted needed to submit their written consent. The following were considered as exclusion criteria: a background of neck surgery, the patient's refusal to participate in the study or voluntary withdrawal.

Variables such as gender, age, time of CKD diagnosis and dialysis, intact PTH concentrations, calcium, phosphorous, alkaline phosphate and calcium x phosphate product were taken into account. The patients were asked if they suffered from clinical symptoms compatible with hyperparathyroidism: bone pain, fracture and itch.

After being given the authorization of the patient, a doctor specialized in radiology took a parathyroid ultrasound with high definition equipment (Equipment Phillips Enviisor CHD - Transductor 12 MHz). Parathyroid hyperplasia was recognized by the presence of round or oval masses, hypoechogenic, homogenous, with or without blood flow, located in the rear section of the thyroid gland. The volume of the detected parathyroid gland was obtained by applying formula (a x b x c x Π) / 6 expressed in mm^3, where a, b and c correspond to the diameter of the three dimensions (14).

The PTH concentrations were determined by Radioimmunoassay (RIA), and calcium, phosphorous and alkaline phosphate concentrations were determined by spectrophotometry. Regarding the statistical analysis, patients were characterized according to the following variables: hyperparathyroidism with study group (GE) and without a control group (C); parathyroid hyperplasia; presence of hyperplasic glands with a volume between 300 and 500 mm^3 (GEa), and hyperplasic glands with a volume over 500 mm^3 (GEb). Meanwhile, the time values were classified under: dialysis lasting under 24 months, between 25 and 60 months, and over 60 months; intact PTH between 400 and 800, 800 and 1500, over 1500 pg / ml, and glandular volume under 500 and over 500 mm^3. All this data was taken with the purpose of creating groups that could result in statistically significant differences.

Time was measured in months, the categorical variables were described in terms of percentage and the numeric variables were established using the average, the standard deviation, and the minimum and maximum percentile values (25, 50 and 75). A correlation was sought between the characteristics of the patients with test x^2. Every test with $p < 0.05$ was considered significant. The analysis of variables was carried out with software Epi Info ® 6.04d and Epidat 3.1.

Results

Using a descriptive study, the clinical history of 403 dialysis patients was analyzed. Out of these, 92 people complied with the inclusion criteria. 6 patients were excluded. Lastly, 86 people were analyzed (figure 1).

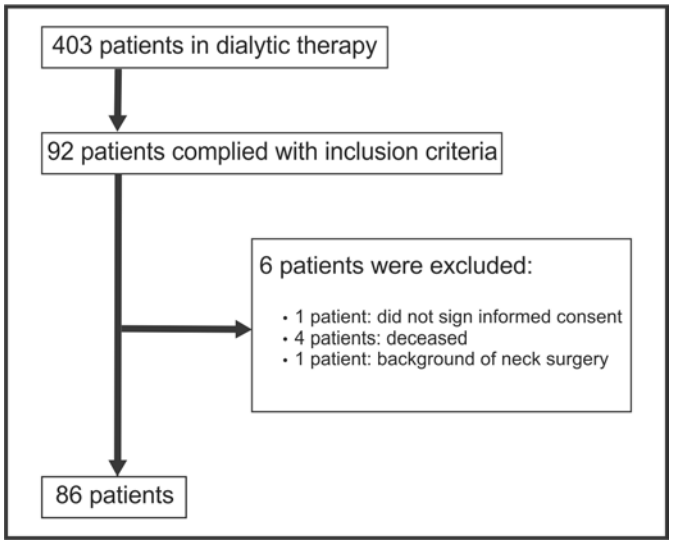

Figure 1 Profile of patients when entering the study.

The base characteristics of the tested patients are shown in table 1. Most of them were over 40, were undergoing hemodialysis and had gone through an average of sixty months in dialysis. The most prevalent symptom in patients with secondary hyperparathyroidism was bone pain (52.2%).

Out of 86 tested patients, the ultrasound showed that 30 of them (34.88%) showed an increase in the size of the parathyroid gland. Hyperplasia was identified in one single gland in 23 patients (26.74%); two glands in 4 patients (4.65%), and three glands in 3 patients (3.48%).

When comparing all the patients with hyperplasic glands (GE) with patients without documented glandular growth (GC), no statistically significant difference was observed between the analyzed clinical and laboratory variables.

When dividing patients with parathyroid hyperplasia according to the volume detected in GEa and GEb and comparing them with the group of patients without an increase of parathyroid gland volume (GC), no statistically significant differences were detected either with the analyzed clinical and laboratory variables. Equal results became evident in the subgroup analysis (table 2, figures 2 and 3)

Discussion

Hyperparathyroidism secondary to chronic kidney disease is a serious complication, as it is associated with osteitis cystic fibrosis, soft tissue vascular calcifications and high cardiovascular morbimortality.

Independently from the factors which stimulate hyperplasia of parathyroid glands, it is initially diffuse and polyclonal: It subsequently turns nodular with monoclonal proliferation and has an aggressive growth potential (5,6). A very important point is that the cells which constitute the hyperplasic parathyroid glands experience a reduction in the number of receptors to vitamin D and calcium, and this reduction is more accentuated in nodular areas (9.15)

In studies of patients who required surgical parathyroidectomy (PQx), the Tominaga group, when evaluating parathyroid glands, found that over 85% of those who weighed over 500 mg presented nodular hyperplasia, which is equivalent to an estimated value of 330 mm^3 (16), which is a range that can be detected by the ultrasound (10). Similar findings are described by Kakuta and collaborators (17) and Matsuoka and collaborators (18); however, as important data, the last group only detected a weak correlation between glandular size and intact PTH values. To date, it is widely accepted that a glandular volume larger than 500 mm^3 in an ultrasound indicates the presence of nodular hyperplasia (19). Studies have proven the superiority of ultrasound when compared to CT scan in hyperparathyroidism diagnosis (20), and an equal sensitivity to a Sestamibi scan when glands are located in the neck (11).

Table 1. Base characteristics of patients when entering the study

Demographic Data	**Average (Standard Deviation)**
Age	48.9 ± 14.2
Gender (male / female)	44 / 42
Duration of dialysis (months)	60.8 ± 36.4
Duration of CKD (months)	165 ± 39.2
Patients in peritoneal dialysis (number)	37
Patients in hemodialysis (number)	49
Laboratory Data	**Average (Standard Deviation)**
PTHi (pg / mL)	± 473,631
Minimum value of PTHi (pg / mL)	Pg / mL
Maximum value of PTHi (pg / mL)	2500 pg / mL
Ca (mg / dL)	10,321 ± 0.863
P (mg / dL)	5,127 ± 1,284
Ca x P	53,198 ± 14,835
Alkaline Phosphate (UI / L)	284,696 ± 116,293
Related symptoms to hyperparathyroidism	**Number of patients (percentage)**
Bone pain	34 (52.2%)
Fractures	2 (3%)
Itch	29 (44.8%)
Causes of kidney failure	**Number of patients**
Hypertensive nephrosclerosis	26
Unknown	15
Diabetic Nephropathy	15
Chronic Glomerulonephritis	14
Obstructive Nephropathy	5
Chronic Tubular-Interstitial Nephritis	3
Polycystic Kidney	3
Lupus Nephritis	3
Diffuse Glomerulosclerosis	1
Renal Agenesis	1

Table 2. Clinical and biochemical characteristics of patients with secondary hyperparathyroidism to chronic kidney disease

Variables		Patients without hyperplasia(GC) (n = 56)	Patients with hyperplasia (GE) (n=30)		Value p (GC vs. GE)	Value p (GC vs. GEa)	Value p (GC vs. GEb)	Value p (GEa vs. GEb)
			< 500 mm3 (GEa) (n = 19)	>500 mm3 (GEb) (n = 11)				
Age (years)	< 40	15	5	5	0.69	0.79	0.38	0.5
	40-65	30	13	5	0.73	0.38	0.87	0.39
	> 65	11	1	1	0.19	0.26	0.68	0.72
Duration of Dialysis (months)	<24	9	4	5	0.21	0.88	0.07	0.32
	25 - 60	20	6	0	0.20	0.96	Not Applicable	Not Applicable
	> 60	27	9	6	0.94	0.74	0.95	0.78
Duration of CKD (months)	< 60	27	10	5	0.94	0.94	0.87	1
	>60	29	9	6	0.94	0.94	0.87	1
Type of dialysis	Hemodialysis	35	8	6	0.23	0.19	0.87	1
	Peritoneal D.	21	11	5	0.23	0.19	0.87	0.78
Etiology	Congenital kidney agenesis	0	1	0	Not Applicable	Not Applicable	Not Applicable	Not Applicable
	Unknown	8	3	4	0.44	0.82	0.18	0.4
	N. Diabetic	9	5	1	0.87	0.51	0.89	0.5
	Diffuse Glomerular-sclerosis	0	1	0	Not Applicable	Not Applicable	Not Applicable	Not Applicable
	Glomerular - nephritis	10	0	4	0.81	Not Applicable	0.32	Not Applicable
	N. Hypertensive	19	5	2	0.43	0.74	0.5	0.95
	Tubular – Intersticial Nephritis	1	2	0	0.57	0.31	Not Applicable	Not Applicable
	Lupus Nephritis	2	1	0	0.57	0.31	Not Applicable	Not Applicable
	Obstructive Nephropathy	5	0	0	Not Applicable	Not Applicable	Not Applicable	Not Applicable
	Polycystic Kidney	1	2	0	0.57	0.31	Not Applicable	Not Applicable
Gender	Male	32	7	4	0.11	0.2	0.35	0.71
	Female	24	12	7	0.11	0.2	0.35	0,71
Symptoms	Pain	21	10	3	0.76	0.37	0.76	0.33
	Fracture	1	1	0	0.76	0.99	Not Applicable	Not Applicable
	Itch	17	9	3	0.5	0.28	0.87	0.48
Calcium (mg / dL)	< 10	23	6	1	0.15	0.64	0.09	0.33
	>10	33	13	10	0.15	0.64	0.09	0.33
Phosphorus (mg / dL)	< 3	2	0	1	0.57	Not Applicable	0.99	Not Applicable
	3 - 4.5	15	7	1	0.8	0.58	0.38	0.21
Ca x P	< 55	34	12	5	0.89	0.93	0.54	0.57
	>55	22	7	6	0.89	0.93	0.54	0.57
Alkaline Phosphate (mg / dL)	30 - 120	25	9	5	0.96	0.95	0.77	0.78
	>120	31	10	6	0.96	0.95	0.77	0.78
PTHi (pg / L)	400 - 800	36	12	5	0.64	0.85	0.40	0.57
	800 - 1500	17	5	4	0.83	0.96	0.97	0.86
	>1500	3	2	2	0.38	0.8	0.39	0.97

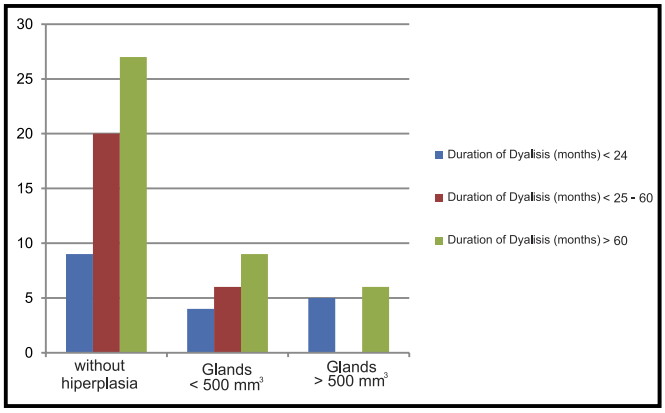

Figure 2. Correlation between dialysis time and presence of parathyroid hyperplasia

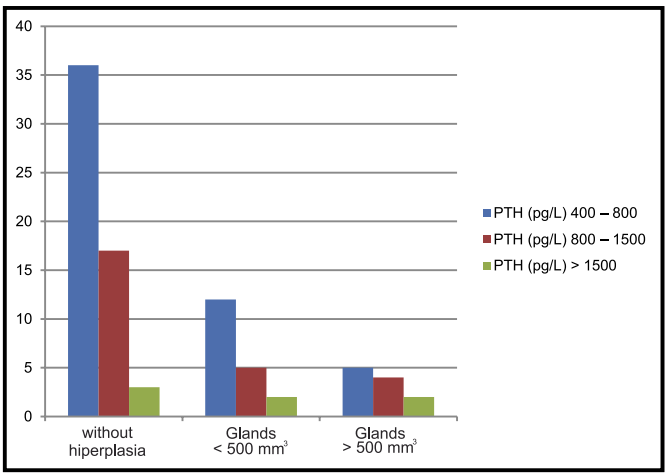

Figure 3. Correlation between intact PTH values and presence of parathyroid hyperplasia

Characteristically, glands with nodular hyperplasia show a reduction in the number of receptors to vitamin D and calcium, which cause therapeutic implications. Indridason and collaborators proved a strong correlation between the presence of gland hyperplasia detected by ultrasound and the failure in suppressing the PTH secretion before the hypercalcemic stimulus (21).

In several studies where refractoriness to calcitriol therapy or their similar non calcemics (22-OXACALCITRIOL) has been noticed, glands larger than 300 mm^3 must be detected with ultrasound, and the presence of nodular hyperplasia must be detected by and due to histopathological studies of surgically removed glands (18,22-25).

Based on the previous point, it is clear that the therapeutic focus of secondary hyperparathyroidism must be modified, ideally according to the ultrasound findings: In the absence of a response to vitamin D analogous (six months treatment) or when the former cause collateral effects (hypercalcemia or hyperphosphatemia) in patients with secondary hyperparathyroidism (intact PTH greater than 500 g/ml) and glandular hyperplasia (mainly greater than 300 mm^3), other therapeutic alternatives must be used such as oral cinalcacet, intraglandular injections of ethanol and calcitriol or surgical parathyroidectomy (26). Factors such as a cost - effectiveness analysis, the age of the patient, surgical risk, seriousness of hyperparathyroidism and gland size could tilt the balance towards on therapeutic decision or another (27, 28).

It has been suggested that cinacalcet (a modulator which increases sensitivity of the calcium receptors in the main cells to the extracellular calcium ions), would be the ideal medication to prescribe to patients with nodular hyperplasia, based on the capacity of the medication to revert it. This has been observed in in vivo studies, which suppress the proliferation of parathyroid cells (29). Controversial publications are included in clinical practice: in a case report of a patient with serious secondary hyperparathyroidism, a dosage of 50 mg per day was able to reduce the size of three hyperplasic glands, all with a volume lesser than 500 mm^3 (30). Meola and collaborators., during a 24-30 month study, followed up an ultrasound to nine patients with serious secondary hyperparathyroidism. Cinacalcet was prescribed to them. The researchers saw that the glandular volume decreased when it was lesser than 500 mm^3, but only in 54% of the glands with volumes larger than 500 mm^3(31).

Hirai and collaborators prescribed cinalcacet during six months to patients with secondary hyperparathyroidism. These reported a significant improvement in all bone metabolism markers three months in the group of patients with hyperplasic glands lesser than 500 mm^3. However, in the analysis of the volume of parathyroid glands, no important changes were detected (32).

Vulip and collaborators (33) found that if cinacalcet is prescribed during one year, at progressively larger dosages, with the purpose of obtaining optimum calcium, phosphorous and intact PTH values, this action did not modify the size of parathyroid glands, and even 27% increased in size. Tanaka and collaborators (34) diagnosed cinacalcet to 20 patients during 44 weeks, in progressive dosages of 25 mg per day up to 100 mg. They observed that the treatment not only improved the serum concentrations of calcium and phosphorous and a reduction of intact PTH to less than 250 pg / ml in patients without nodular hyperplasia, in two patients after 120 weeks had passed; but also, with nodular hyperplasia, a significant elevation of intact PTH, calcium, phosphorous and product CaxP was also detected. In this way, it was established that cinacalcet lacks long term efficiency in patients with nodular hyperplasia. Kakuta and collaborators (35) evaluated the response to cinacalcet in 37 patients treated during six months and observed that cinacalcet caused very irregular behavior in the glandular volume, without changes in 63.9%, reduction in 21%, and an increase in 14.8%.

Some authors have suggested correlations between the detection of hyperplasic parathyroid glands and clinical and laboratory variables in patients with CKD. Hamada and cols, evaluated twelve patients with CKD without taking into account their intact PTH values, before starting their dialysis and immediately after starting it. Hamada and collaborators detected glandular hyperplasia in five patients by using an ultrasound with an 8 MHz. lineal transductor. They did not find any correlation between the finding of glandular hyperplasia and the cause of CKD, age, gender, serum calcium, alkaline phosphate and seric creatinine; however, it was more frequent in patients with intact PTH greater than 350 pg / ml (12).

Takebayashi and collaborators (19), independently of the value of intact PTH, detected (through ultrasonography) glandular hyperplasia in 30% out of 207 patients in dialysis, with an average of 2.3 glands per patients. Taketayashi and collaborators described a correlation between the detection of glandular hyperplasia and the time of dialysis, but not with the values of intact PTH.

Brzac and collaborators (13) detected glandular hyperplasia in 75% out of 72 patients with CKD in chronic hemodialysis and compatible

paraclinics with hyperparathyroidism, using a 4 – 7-5 MHz lineal transductor, as well as a correlation between their findings with a longer period of dialysis and higher concentrations of intact PTH.

This study did not detect a correlation between the detection of glandular hyperplasia through ultrasonography and the examined variables. Our study is the largest one to date which has tried to establish a correlation between clinical and laboratory variables that have typically been considered relevant in stimulating growth of parathyroid glands. This proves that the development of glandular hyperplasia is unpredictable and that the factors that cause it have not been clearly identified to date.

Another important aspect is that glandular hyperplasia can occur from early stages once stage-5 chronic kidney disease has developed, and that the determination of intact PTH serum quantities and other typical indicators are not sufficient to adequately treat bone and mineral disorders that accompany CKD. That is why it is essential to perform a routine ultrasound no every patient which enters dialysis, with the purpose of offering a better therapeutic option.

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Correspondence

César A. Restrepo V.
Carrera 28B No. 71A - 56
Manizales, Colombia
caugustorv@une.net.co

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