

Secondary hyperparathyroidism status in Brazil: Brazilian Census of Parathyroidectomy

Situação do hiperparatireoidismo secundário autônomo no Brasil: dados do Censo Brasileiro de Paratireoidectomia

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Submitted on: 10/07/2011

Approved on: 11/04/2011

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This study was undertaken at the Brazilian Nephrology Society.

The authors report no conflict of interest.

ABSTRACT

Introduction: Secondary hyperparathyroidism (SHP) is a common and serious complication of chronic kidney disease (CKD), with a negative impact on morbidity and mortality. Despite advances in the clinical management of SHP, treatment failure still occurs in a significant number of patients. In such cases, parathyroidectomy (PTx) is indicated. **Objective:** To have an overview of the prevalence of severe SHP and of its surgical treatment in hemodialysis (HD) patients in Brazil. **Methods:** This was an observational and descriptive study. Data were obtained from questionnaires posted to 660 dialysis units (DU). **Results:** Results are expressed in absolute values and percentages, or means and standard deviation, as appropriate. 226 (34%) DU answered the questionnaire, providing data about 32,264 HD patients. The prevalence rate of severe SHP (PTH > 1,000 pg/mL) was 10.7% (n = 3,463). 68 hospitals countrywide perform PTx. Around 40% of them are university centers. 49 (21.7%) DU reported not to have a specialized medical center to refer their patients with severe SHP. 74 (33%) DU reported that the time interval between surgery indication and its performance was over 6 months. The main recognized obstacles to surgery performance were: difficulty to perform the preoperative exams, lack of head and neck surgeons and the long waiting time. **Conclusions:** Although severe SHP is highly prevalent in Brazil, a significant number of patients do not have access to PTx. Better public health policies and liaison between nephrologists and head and neck surgeons are urgently required to change this reality. **Keywords:** Renal Insufficiency Chronic. Hyperparathyroidism, Secondary. Parathyroidectomy.

RESUMO

Introdução: O hiperparatireoidismo secundário (HPS) é uma complicação comum e grave no curso da doença renal crônica (DRC), com impacto direto sobre a morbidade e mortalidade desses pacientes. Apesar dos avanços no tratamento clínico do HPS a falência terapêutica ocorre em parcela significativa dos pacientes. Nesses casos, a paratireoidectomia (PTx) é indicada. **Objetivo:** Este trabalho visa abordar a situação atual no Brasil de pacientes com HPS em hemodiálise com indicação de PTx. **Métodos:** Estudo observacional, descritivo, com dados obtidos de questionário enviado a 660 centros de diálise (CD). **Resultados:** Os resultados estão expressos em valores absolutos, médias e desvio padrão; 226 (34%) CD responderam ao questionário, representando 32.264 pacientes em hemodiálise (HD). A prevalência de pacientes com paratormônio (PTH) > 1.000 pg/mL foi de 3.463 (10,7%). Em 49 (21,7%) CD não é possível encaminhar os pacientes para PTx. Cerca de 40% dos serviços que realizam PTx são ligados a centros universitários. Em 74 (33%) CD o tempo de espera para que um paciente seja operado é superior a 6 meses. Foram contabilizados 68 serviços que realizam PTx. Os principais problemas relacionados para a realização de PTx foram: dificuldades com a realização dos exames pré-operatórios, escassez de cirurgiões de cabeça e pescoço, e longa fila de espera. **Conclusões:** a prevalência de HPS grave é elevada em nosso meio. Uma parcela significativa de pacientes não tem acesso ao tratamento cirúrgico. Uma melhor organização das políticas de saúde pública, além de um maior entrosamento entre nefrologistas e cirurgiões de cabeça e pescoço, em torno dessa questão, são necessários para a mudança dessa realidade. **Palavras-chave:** Insuficiência Renal Crônica. Hiperparatireoidismo Secundário. Paratireoidectomia.

INTRODUCTION

Chronic kidney disease (CKD) affects millions of people worldwide, being now considered a public health problem.¹ CKD patients have a high mortality rate,² a significant proportion of which is attributed to mineral-bone disorder (MBD), a condition encompassing biochemical alterations, vascular calcification and bone disease.^{1,3}

With CKD progression, there is reduced synthesis of calcitriol and reduced serum calcium (Ca) levels, with increased serum levels of phosphorus (P), FGF-23 and parathyroid hormone (PTH), characterizing secondary hyperparathyroidism (SHP).⁴ These alterations may also be associated with vascular calcification and bone fractures.²

SHP treatment has traditionally been based on the control of hyperphosphatemia with dietary restriction and the use of P-chelating agents, of hypocalcemia with calcium salts and calcitriol, and of the PTH levels with calcitriol and, more recently, with selective vitamin D-receptor activators (VDRA) and calcium-mimetics.^{5,6}

In spite of the advances in the treatment of SHP, therapeutic failure is frequent, with an estimated 5.5-30% of CKD patients on dialysis eventually undergoing parathyroidectomy (PTx) for inadequate response to medical therapy. These figures increase with dialysis time.⁷⁻⁹ Although another option to PTx is percutaneous ethanol or calcitriol injection, the only study undertaken in Brazil did not show satisfactory results.⁸

According to the Brazilian Nephrology Society's guidelines, PTx is indicated when PTH serum levels remain persistently over 800 pg/mL, in the following settings: (a) hypercalcemia and/or hyperphosphatemia refractory to medical treatment; (b) extraosseous calcifications (soft and/or cardiovascular tissues) or calcific uremic arteriopathy (calciphylaxis); (c) progressive, debilitating, advanced bone disease unresponsive to medical treatment and; (d) large-sized parathyroid glands (volume > 1.0 cm³) on ultrasonography.¹⁰

The high prevalence of CKD patients with SHP and PTx indication has been recognized in several countries. In Japan, 10% of the patients on hemodialysis (HD) for over 10 years and 30% of those on HD for over 20 years, need PTx.⁷ In 1982, the European Dialysis and Transplantation Association Registry reported a 5/1,000 patients/year incidence of PTx during the second or third year on dialysis, but a rate of over 40/1,000 patients/year among those on dialysis

for more than 10 years.¹¹ The *Dialysis Outcomes and Practice Pattern Study* (DOPPS), which assessed the HD status and quality from 1996 through 2001 in European countries, the United States and Japan, revealed that PTx is less frequent in Japan than in Europe (4.1% prevalence, with a 0.6/100 patients/year PTx incidence).¹²

In Brazil, the prevalence rate of SHP patients with PTx indication is unknown. It is thought that the access of SHP patients to medical and surgical treatment is limited and particularly restricted to university centers. It is noteworthy that CKD conservative treatment is offered by few centers, which hampers early control of MBD. Moreover, PTH measurement, both in patients on conservative treatment and in those on dialysis, is only allowed (RDC ordinance 154) at 6 month-intervals.¹³ There are also restrictions on the use of some medications, such as calcium mimetics and new vitamin D analogues. SHP is thus underdiagnosed and undertreated.

The purpose of this study was to assess the prevalence of HD patients with SHP and PTx indication in Brazil, as well as identify the factors that influence the availability of surgery for SHP.

METHODS

This was an observational, descriptive, cross-sectional study. During the August 2010-March 2011 period, the Brazilian Nephrology Society Committee of Mineral-Bone Disorder in Chronic Kidney Disease posted a questionnaire to the technical responsible staff of the 660 Brazilian dialysis units (DU). The questions concerned SHP, and clinical and biochemical data covering the second semester of 2010 were collected.

The questionnaire enquired about: (1) The number of HD patients in the unit; (2) the number of patients with PTH levels over 1,000 pg/mL; (3) the biochemical method used for PTH measurement; (4) the referral procedure once SHP with PTx indication was diagnosed; (5) average time on the waiting-list for PTx; (6) source of medications to treat the bone hunger syndrome in the postoperative period of PTx and; (7) the main obstacles to the performance of PTx. Each question was followed by a blank space for information recording.

A serum PTH level of 1,000 pg/mL was defined as the cut-off value above which there was a high likelihood of PTx indication.

The results were described as absolute values, percentages, means and standard deviations (SD).

RESULTS

Of the 660 questionnaires posted 226 (34%) were answered, which corresponded to a sample of 32,264 patients, an estimated 35% of the whole dialysis population of Brazil, according to the 2010 dialysis census.¹⁴

Table 1 shows the numbers of DU which responded, and of their patients with PTH > 1,000 pg/mL, according to the geographic region. São Paulo had the highest figures (60 DU and 9,240 patients) and Pará the lowest ones (1 DU and 58 patients). 10.7% of the patients (3,463 out of the total 32,264) had PTH > 1,000 pg/mL, with the highest rate in Rio de Janeiro (22.9%; n = 689) and the lowest one in Pará (1.7%, n = 1).

Chemoluminescence was the most frequent technique for PTH measurement, being used by 165 (73%) units. 43 (19%) units used another method and 17 (8%) did not inform the method used.

Table 2 shows the referral procedure used for SHP patients with PTx indication. 49 (21.7%) units could not refer these patients, which corresponds to a total of 6,440 patients, 650 (10.1%) of whom had PTH levels > 1,000pg/mL, with surgical indication, although they will not be operated on. 28 (41.2%) of the services providing PTx belong to university hospitals. Table 3 shows the distribution of the services performing PTx, according to the geographical regions. The northern region has no such service, and the center-west has only 2. These two regions have 74 DU, with a total of 7,771 patients.¹⁴ São Paulo has the largest number of services, with 18 (26.4%). Waiting-time for

Table 1 NUMBER OF DIALYSIS UNITS NUMBER AND PERCENTAGE OF THE TOTAL OF PATIENTS ON DIALYSIS AND NUMBER AND PERCENTAGE OF PATIENTS WITH PATHYROID HORMONE LEVELS > 1,000 PG/ML ACCORDING TO GEOGRAPHIC REGION.

Region	Number of dialysis units	Number of patients	Number of patients with PTH > 1.000 pg/mL
South-east	122	18,592 (57.6%)	2,279 (12.3%)
South	55	6,039 (18.7%)	456 (7.6%)
North-east	32	5,695 (17.7%)	522 (9.2%)
Center-west	14	1,810 (5.6%)	201 (11.1%)
North	3	128 (0.4%)	5 (3.9%)
Total	226	32,264 (100%)	3,463 (10.7%)

PTH: parathyroid hormone.

Table 2 REFERRAL OF PATIENTS WITH SECONDARY HYPERPARATHYROIDISM AND INDICATION OF PARATHYROIDECTOMY

Destination	Number of dialysis units
Services with CKD-MBD ambulatory facilities	132 (58.4%)
No referral arrangements	49 (21.7%)
The same unit where dialysis is performed	32 (14.2%)
Unified Health System hospitals	10 (4.4%)
Insurance-covered hospitals	2 (0.9%)
Total	226 (100%)*

MBD: mineral-bone disease; CKD: chronic kidney disease

*1 (0.4 %) dialysis unit informed that they rarely had patients with secondary hyperparathyroidism.

Table 3 SERVICES AND UNIVERSITY HOSPITALS PERFORMING PARATHYROIDECTOMY: NUMBER AND PERCENTAGE OF THE TOTAL, ACCORDING TO GEOGRAPHICAL REGION IN BRAZIL

Region	Number of services	Number of university hospitals
South-east	36 (53%)	17 (25%)
South	21 (31%)	6 (8.8%)
North-east	9 (13%)	5 (7.3%)
Center-west	2 (3%)	0 (0%)
North	0 (0%)	0 (0%)
Total	68 (100%)	28 (41.2%)

PTx is described in Table 4. In 74 (32%) units the waiting time is longer than 6 months. As for drug hunger syndrome medication (calcitriol and calcium salts) dispensation, 156 (69%) units request the drugs from the Special Medication Program of the Brazilian Unified Health System, 41 (18%) redirect the medications from patients who had the drugs withdrawn, because of hypercalcemia and hyperphosphatemia, to those in need, and 18 (8%) cover the cost of the drugs. 5% of the units did not inform about this issue.

Table 5 describes the main obstacles to the performance of PTx. 136 (60%) units reported 2 difficulties and 75 (33%) reported 3 difficulties.

Table 4 WAITING-TIME FOR PARATHYROIDECTOMY

Time (months)	Number of dialysis units
< 1	26 (12%)
> 1 and ≤ 6	56 (25%)
> 6 and ≤ 12	46 (20%)
> 12 and ≤ 24	19 (8%)
> 24	9 (4%)
No possibility of referral	52 (23%)
No information	18 (8%)
Total	226 (100%)

Table 5 MAIN OBSTACLES TO THE PERFORMANCE OF PARATHYROIDECTOMY REPORTED BY THE DIALYSIS UNITS

Obstacle reported	Number of dialysis units
Difficulty with preoperative examinations	88 (38.9%)
Lack of head and neck surgeons	64 (28.3%)
Long waiting time for PTx	60 (26.5%)
Few ambulatory services specialized in CKD-MBD	52 (23%)
Difficulty to get the unified health system authorization for PTx	31 (13.7%)
Lack of hospital beds	29 (12.8%)
Difficulty to get postoperative medications	15 (6.6%)
Patient's refusal to undergo PTx	10 (4.4%)
Lack of intensive care beds	7 (3%)

PTx: hyperparathyroidectomy; MBD: mineral-bone disorder; CKD: chronic kidney disease.

DISCUSSION

This was the first study undertaken in Brazil about the status of SHP patients and their need of PTx. The response rate (34%) was low and unevenly distributed according to geographical region, with Pará and Acre having the lowest figures.

The prevalence rate of SHP was 10.7%, taking into account PTH levels > 1,000pg/ml, a situation in which PTx indication is practically unequivocal. The prevalence rate would probably be higher if the 800pg/ml cut-off point recommended by the Clinical Practice Brazilian Guidelines were followed. It is noteworthy that a significant percentage of patients with PTH up to 500pg/ml do not respond to medical therapy either, which would further increase the number of patients requiring surgery.

As for the services performing PTx, 28 (41.1%) are linked to university hospitals. There are few such services belonging to the supplementary health network (n = 2; 0.9%). Because PTx is a middle-complexity surgical procedure, few patients requiring an intensive care environment for their recovery, secondary-care hospitals staffed with nephrologists and head and neck surgeons could implement the procedure, thus alleviating the load of university hospitals.

According to the Brazilian Dialysis Census, 13.3% of the country's dialysis patients have supplementary insurance coverage.¹⁴ However, few DU manage to refer their privately insured patients to PTx in the privately insured hospitals, thus further adding to the cost to be met by the Unified Health System.

Most patients undergoing PTx develop the bone hunger syndrome during the postoperative period, thus requiring large amounts of calcium salts and calcitriol. Although most DU obtain calcitriol from the Special Medications Program of the Unified Health System, bureaucratic constraints lead to the delayed dispensation of insufficient amounts, as reported by 15 (6.6%) DU. This forces the units to redirect medication from those who had it withdrawn due to hypercalcemia and/or hyperphosphatemia, or pay with their own or the patients' resources.

In Brazil, 68 services perform PTx, of which 36 (53%) are in the south-east. If we take into account that Brazil has approximately 92,000 patients on dialysis, and that the estimated prevalence of SHP with indication of PTx is 10.7%, about 9,800 patients should be operated on. 350 to 500 PTx are estimated to be performed every year in Brazil, which allows a projection of 20 years before all present surgical indications are met.

A study undertaken at the CKD-MBD ambulatory service of the *Hospital das Clínicas* of the São Paulo University showed a 25%/year mortality rate among those waiting for a PTx, almost twice as high as that among the general population of patients on dialysis.¹⁵

According to the Brazilian Head and Neck Society, Brazil has 529 specialists in the field. The north and center-west have 48 specialists and 74 DU, with about 7,771 patients; yet, no PTx is performed in these regions. In São Paulo, although there are 18 services performing PTx and 241 specialists, the highest density in Brazil, in the two main CKD-MBD ambulatory reference centers (São Paulo University and Federal University of São Paulo) the waiting time is over 18 months. There are technical, political, economical and organizational reasons hampering liaison of public health managers, dialysis units, nephrologists, head and neck surgeons and centers performing PTx.

One of the main obstacles to performing PTx concerns preoperative exams. Patients under 40 years of age, without diabetes mellitus, with no symptoms of coronary disease and who are no smokers are at low risk of cardiovascular complications, which obviates the need of invasive cardiovascular investigations. Specific PTx preoperative investigations include neck ultrasonography and parathyroid scintigraphy for gland localization. These exams can be omitted, however, with resource to intraoperative localization of the glands. Likewise, intensive care beds are seldom required after PTx. These considerations should reduce the waiting lists.

At the same time, the health system must be organized with the creation of reference services for PTx, increased access to SHP diagnosis and treatment, greater degree of freedom for PTH determination, addition of calcium-mimetics and vitamin D receptor agonists to the list of medications dispensed by the Unified Health System and greater patients' access to nephrologists and head and neck surgeons. Simple actions, such as medication dispensation during the bone hunger postoperative period, authorization of PTx performance in secondary care hospitals and revision of the reimbursement of the professionals involved with the surgical procedure and postoperative care could solve many problems.

Medical associations, such as the Brazilian Nephrology Society and the Brazilian Head and Neck Surgery Society should not only lead the continuing professional education and issue treatment protocols in this field, but also warn public health

managers about the situation of CKD patients with SHP in the country.

The main limitations of our study were its cross-sectional, observational design, along with the regional disparities and the 1,000 pg/mL as the cut-off point for PTx indication, which probably reduced the SHP prevalence. Furthermore, we did not obtain immediate morbidity and mortality data, such as the length of hospital admissions due to SHP complications or surgery-related complications.

ACKNOWLEDGEMENTS

The Brazilian Nephrology Society thanks the dialysis units which voluntarily responded the questionnaire, and Mrs Rosalina Soares and Mr Wellington Anselmo, from the executive secretariat, for their invaluable help with this study.

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