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Is There a Gender Difference in Clinical Presentation of Renal Hyperparathyroidism and Outcome after Parathyroidectomy?

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Keywords

Secondary hyperparathyroidism · Chronic kidney disease · Parathyroidectomy · Gender medicine · Cerebrovascular complication

Abstract

Introduction: Gender has been proven to influence the pathophysiology and treatment of numerous diseases, including kidney diseases and hormonal dysfunction like hyperparathyroidism. Thus, higher parathormone levels have been demonstrated in women with end-stage kidney disease, when compared to men. ***Objectives:*** We questioned whether female gender is associated with an increased risk for parathyroid nodular hyperplasia and necessary parathyroidectomy in dialysis patients and assessed demographics as well as outcome data for women and men undergoing parathyroidectomy for renal hyperparathyroidism. ***Patients and Methods:*** One hundred and thirty patients (men = 75, female = 55) with end-stage renal disease on chronic dialysis and advanced secondary hyperparathyroidism who underwent parathyroidectomy between 2008 and 2014 at our center were analyzed retrospectively. Perioperative characteristics and short-term outcome were evaluated with respect to biological gender. ***Results:*** No differences could be demonstrated for patient demography, comorbidities and the perioperative course between males and females. Only preoperative calcium levels were lower in female than in male patients (2.3 ± 0.19 vs. 2.3 ± 0.26, $p = 0.04$). There were more women, however, with cerebrovascular complications during follow-up ($p = 0.04$). There was no postoperative mortality, and all complications and comorbidities with exception of cerebrovascular diseases were equally distributed between female and male patients. ***Conclusion:*** Overall, we could not demonstrate many significant differences between male and female patients with end-stage renal diseases, chronic dialysis and operated secondary hyperparathyroidism. Only preoperative electrolyte levels were higher in male than in female patients, and cerebrovascular complications developed more often in females than in males during long-term follow-up.

Introduction

Secondary hyperparathyroidism (sHPT) is highly prevalent among patients with end-stage renal disease (ESRD) [1–3] and is associated with progressive bone disease, susceptibility to bone fractures, and vascular calcification as well as myocardial infarction and reduced life expectancy [4–7]. Since gender differences have been found in patients with chronic kidney disease (CKD) we questioned whether men and women with renal sHPT may also present with different symptoms, variable pathophysiology and disease tolerance, as well as different response to therapy.

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Physiological differences in the kidneys of men and women include both morphological and physiological aspects [8–10]. Studies have shown that men have larger and wider kidneys compared to women [9], although the overall kidney volume seems to be equivalent [10]. Women have a higher renovascular resistance, a lower absolute glomerular filtration rate and lower renal plasma flow compared to men [11]. At a molecular level, men and women exhibit significant differences. Kidneys of men exhibit larger mitochondria, more lysosomes and more abundant ribosomes in the proximal tubular cells than the kidneys of women [12]. At a functional level, sex differences have been reported in the renin-angiotensin system and in the regulation of blood pressure [13, 14]. Additionally, it has been shown that sex hormones play a significant role: estrogen increases synthesis of angiotensinogen and decreases the synthesis of renin and angiotensin-converting enzyme. Testosterone, on the other hand, is associated with an increased renin release in small animal models [15, 16]. As such, sex has been interpreted as an important factor influencing both kidney function and the progression of kidney disease [17]: female gender is at risk for developing CKD [18–20] and is more prevalent in women than in men [21]. Additionally, Indridason et al. [22] described gender-specific differences in primary CKD and with patients on chronic dialysis: thus, females exhibited a higher rate of diabetes mellitus, and their dialysis dose was higher than that of men.

Interestingly, female gender favors parathyroid cell proliferation, and parathyroid glands of uremic women are more prone to develop nodular hyperplasia compared to their male counterparts [23–25]. This effect of gender-specific parathyroid growth and parathyroid function could be explained by different factors, including the different serum estrogen levels in men and women, since estrogen receptors have been shown to be expressed on parathyroid cells [26]. Even though estradiol levels are normal in the majority of women undergoing dialysis [27, 28], amenorrhea or anovulatory periods are common in these patients and long periods of unopposed estrogen exposure may lead to parathyroid stimulation [26, 29, 30]. Additionally, it was shown that women do suffer from a larger phosphate burden than men [24, 25] and women undergoing dialysis presented with higher parathormone (PTH) serum levels than men [31–33].

Altogether women inherit a higher risk for developing primary hyperparathyroidism [34, 35], and in uremic women an increased severity of sHPT has been found in comparison to men [22, 24, 31, 33, 36, 37]. Therefore, more female patients undergo parathyroidectomy (PTX) [32, 33, 37, 38], when compared to men.

Female patients in general exhibit a higher susceptibility to bone fractures and a higher risk for ESRD [39]. Additional to this, the overall incidence of hip fractures in patients with chronic renal dialysis is about fourfold to the normal population [39] and increases with age [40–44]. When compared to men, women with sHPT further demonstrate more profound downregulation of bone mineral metabolism before PTX [19, 45]. The abnormal ovarian function, frequently observed in uremic women [27, 28], may additionally predispose for increased bone mineral and total bone resorption. These factors may explain, why Isaksson et al. [46] could demonstrate that sPTX reduces the risk of hip fractures especially in female patients with sHPT. In contrast to this, Rudser et al. [47] found no sex differences in bone fracture risk after PTX. Ishani et al. [48] even reported that PTX had no effect on bone fracture rate in patients on chronic dialysis, after PTX. They did not compare gender effects, however.

In this study we analyze whether gender plays an important role in patients with renal sHPT because of terminal kidney insufficiency and chronic dialysis and we compared patient history, operative procedures and results of early as well as long-term postoperative follow-up.

Materials and Methods

All patients undergoing PTX due to sHPT at our center, between 2008 and 2014, have been included into our database prospectively and were analyzed retrospectively. All patients of our cohort had renal HPT due to ESRD with dialysis and were listed for renal transplantation. Patients were analyzed for demographic parameters like age, body mass index and sex as well as disease-specific information, comorbidities and beginning of dialysis. Prospective data collection and retrospective analysis were performed in accordance with the Declaration of Helsinki and approved by the local Ethics Committee.

Perioperative laboratory values were recorded including creatinine, calcium, intact PTH and hemoglobin levels. Operation-specific data such as procedure and operation time were also included.

Intra- and early postoperative procedures, morbidity and mortality were registered, including complications like bleeding, vocal cord palsy, length of hospital stay and persistence of hyperparathyroidism. In long-term follow-up, overall survival and cardiovascular as well as cerebrovascular events were assessed.

The existing data and the added information were extracted into an Excel datasheet (Microsoft Office Excel 2019, Microsoft Corporation, Redmond, WA, USA). The statistical analyses and the created diagrams were made with Statistical Package for Social Sciences software (SPSS® 25.0, Chicago, IL, USA). Patients were analyzed with respect to biological gender. Descriptive values are given as median or mean, SD and range. If parameters for both groups were normally distributed, a Student *t* test could be performed for probable significance. Quantitative variables with non-parametric distribution were checked by the Mann-Whitney U test for significant differences. Further correlations or relations between categorical data were calculated by the χ^2 test and Fisher's exact test. The significance level was set at $p < 0.05$.

Table 1. Demographic parameters of patients (*n*, %) undergoing parathyroidectomy for secondary hyperparathyroidism (*n* = 130)

Sex[1]	
Male	75 (58)
Female	55 (42)
Age, years[1]	
Mean	50±14
Range	12–82
ASA >III	110 (85)
aHT yes	128 (98)
Diabetes yes	31 (24)
Adipositas yes	15 (12)
CHD yes	35 (27)
Dialysis dependency yes	130 (100)
Age at beginning of dialysis, years	
Mean	46±14.8
Range	12–78
Duration of time between dialysis and PTX, years	
Mean	4.7±3.9
Range	0–27
Dialysis intervals 3 times/week	130 (100)
Kidney disease	
Glomerulonephritis	35 (27)
Tubulointerstitial	19 (15)
Hypertensive	20 (15)
Diabetic	18 (14)
Polycystic	15 (12)
Atrophic	4 (3)
Alport syndrome	2 (2)
Amyloidosis	1 (1)
Other	13 (10)
Unknown	3 (2)
Operative procedure	
Total PTX	29 (22)
Subtotal PTX	88 (68)
Selective PTX	13 (10)
Duration of surgery, min	
Mean	131±39
Range	61–237
Postoperative complication yes	28 (22)
Myocardial infarction	17 (13)
Apoplexy	8 (6)
Bleeding	3 (2)
Hospital stay, days	
Mean	6±5
Range	1–39

[1] Matched parameters. Values as numbers and percentages or means ± SD. ASA, American Society of Anesthesiologists; aHT, arterial hypertension; CHD, coronary heart diseases; PTX, parathyroidectomy.

Results

In total 130 patients with PTX for sHPT could be included retrospectively. All patients had ESRD and had been on dialysis for approximately 4.7 years (±3.9, range 0–27), while being listed for renal transplantation. There was a slight majority of male patients (58%, *n* = 75). For all patients in this cohort, the age distribution ranged from 12 to 82 years with a mean of 50 ± 14 years. Nearly all patients were classified according to the American Society of Anesthesiologists in group III or higher when the patient's specific risk factors were considered before surgery. Comorbidities such as arterial hypertension occurred in nearly all patients (98%, *n* = 128). Diabetes mellitus has been verified in 31 patients (24%), and almost 15 (12%) patients were classified as obese according to body mass index ≥30. Thirty-five (27%) patients were recorded with coronary heart disease. All patients were on dialysis due to ESRD, and dialysis was performed 3 times per week. The mean age at the beginning of dialyses for this cohort was 46 ± 15 years. The majority of patients was on dialysis due to glomerulonephritis (*n* = 35, 27%), tubulointerstitial kidney damage (*n* = 19, 15%), hypertensive kidney disease (*n* = 20, 15%), diabetic nephropathy (*n* = 18, 14%) or polycystic renal disease (*n* = 15, 12%; Table 1).

Most patients underwent subtotal PTX (*n* = 88, 68%). Total PTX was performed in 29 cases (22%) including 5 patients with autotransplantation of parathyroid tissue into the sternocleidomastoid or forearm muscle. Selective PTX was performed in 13 cases (10%) only, and mainly for re-operation of persisting hyperparathyroidism. The mean duration of surgery was 131 ± 39 min and ranged from 61 to 237 min. The mean hospital stay was 6 ± 5 days (1–39 days), and postoperative complications occurred in 28 patients (22%). The majority of severe complications in our patients were myocardial infarction in 16 patients (13%), developing mainly during long-term follow-up. One patient demonstrated paroxysmal atrial fibrillation immediately postoperatively, and 8 (6%) patients were recorded with cerebrovascular events during long-term follow-up. Postoperative bleeding with need for surgical revision was seen in 3 cases (2%). None of the patients died during hospital stay, nor up to 30 days postoperatively. There was no statistically significant difference in patient history or perioperative complications between female and male patients (Table 2).

Also, comorbidities like arterial hypertension, diabetes mellitus, obesity and coronary heart disease were distributed similarly between the groups. Male patients showed a slight tendency to be younger at the onset of dialysis dependence with no statistical difference (44 ± 14 vs. 49 ± 16 years, $p = 0.08$; Fig. 1). The time between onset of dialysis and PTX was similar with 4.5 ± 3.5 for male and 4.9 ± 4.4 years for female patients ($p = 0.58$; Fig. 2).

Distribution of kidney diseases showed a tendency for more glomerulonephritis in male patients (31% vs. female 22%), while polycystic kidney disease seems to occur twice as often in female patients (8% male vs. 16% female) without significant differences overall.

Operative procedures were not statistically different for patients in both groups (Table 2), nor was length of

Table 2. Demographic parameters for male and female patients undergoing parathyroidectomy for secondary hyperparathyroidism (n = 130)

	Male (n = 75)	Female (n = 55)	p value
Age, years[1]			
Mean	49±13	53±15	0.11
Range	26–75	12–82	
ASA >III	63 (85)	47 (90)	0.61
aHT yes	74 (99)	54 (98)	0.39
Diabetes yes	17 (23)	14 (26)	0.66
Adipositas yes	8 (11)	7 (13)	0.68
CHD yes	19 (25)	16 (30)	0.58
Age at dialysis dependency, years			0.08
Mean	44±14	48.8±15.6	
Range	18–73	12–78	
Dialysis-depending time till operation, years			
Mean	4.5±3.5	4.9±4.4	0.58
Range	0–18	0–27	
Kidney disease			
Glomerulonephritis	23 (31)	12 (22)	0.38
Tubulointerstitial	12 (16)	7 (13)	
Hypertensive	10 (13)	10 (18)	
Diabetic	9 (12)	9 (16)	
Polycystic	6 (8)	9 (16)	
Atrophic	3 (4)	1 (2)	
Alport syndrome	2 (3)	0	
Amyloidosis	0	1 (2)	
Other	7 (9)	6 (11)	
Unknown	3 (4)	0	
Treatment with cinacalcet yes	33 (44)	19 (35)	0.27
Operative procedure			
Total PTX	14 (19)	15 (27)	0.44
Subtotal PTX	54 (72)	34 (62)	
Selective PTX	7 (9)	6 (11)	
Duration of surgery, min			
Mean	131±37	131±42	
Range	61–237	67–236	0.98
Postoperative complication yes	14 (19)	14 (25)	0.35
Myocardial infarction	9 (12)	7 (13)	0.83
Apoplexy	2 (3)	6 (12)	0.04
Bleeding	0	0	
Hospital stay, days			
Mean	7±5	6±5	0.91
Range	1–28	1–39	
Potassium level preoperative, mmol/L			
Mean	5.0±0.7	4.7±0.85	0.05
Range	3.4–7.0	3.1–7.3	
Parathyroid hormone level preoperative, ng/L			
Mean	800±489	653±425	0.79
Range	3–2,085	112–2,164	
Calcium level preoperative, mmol/L			
Mean	2.3±0.19	2.3±0.26	0.04
Range	1.7–2.7	1.21–2.91	
Hemoglobin level preoperative, mg/dL			
Mean	11.9±1.9	11.6±1.95	0.29
Range	6.3–16.5	5.7–16.1	
Potassium level postoperative, mmol/L			
Mean	4.7±0.63	4.7±0.64	0.66
Range	3.6–6.1	3.1–6.2	
Parathyroid hormone level postoperative, ng/L			
Mean	44±83	41±94	0.09
Range	3–440	3–416	
Hemoglobin level postoperative, g/dL			
Mean	11.1±1.4	11.2±1.65	0.82
Range	8.5–14.5	8.3–15.9	
Hyperkalemia postoperative yes	11 (15)	7 (14)	0.82

[1] Matched parameters. Values as numbers and percentages or means ± SD. ASA, American Society of Anesthesiologists; aHT, arterial hypertension; CHD, coronary heart diseases; PTX, parathyroidectomy.

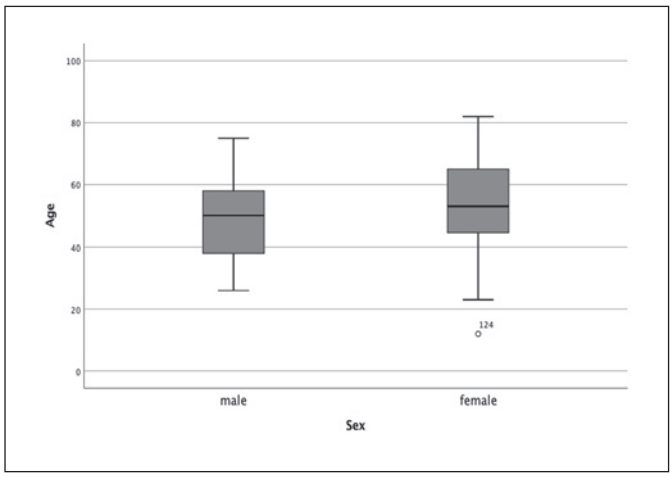

Fig. 1. Boxplot showing distribution of age at beginning of dialysis for female and male patients with no significant difference (male patients 44 ± 14 years vs. female patients 49 ± 16 years, p = 0.08).

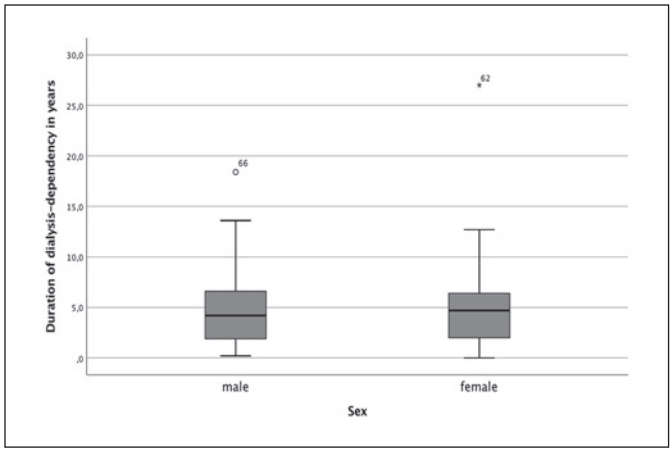

Fig. 2. Boxplot displaying duration of dialysis until parathyroidectomy for female and male patients without any significant difference (4.5 ± 3.5 years for male vs. 4.9 ± 4.4 years for female patients, p = 0.58).

hospital stay (p = 0.91). Postoperative complications were different between the groups, however. Female patients were more likely to develop cerebrovascular complications like central strokes during long-term follow-up. Six of 8 events occurred in female patients (p = 0.04). All patients have been monitored after PTX for detection of cardiac arrhythmias with no significant differences (1 male patient). Myocardial infarction was detected equally in both groups (male 9 [12%] vs. female 7 [13%], p = 0.83).

Male patients displayed higher serum potassium levels (5.0 ± 0.7 mmol/L vs. female 4.7 ± 0.85 mmol/L, p = 0.05), preoperatively. After surgery, serum potassium levels did not show any differences for both sexes (4.7 ± 0.6 mmol/L vs. female 4.7 ± 0.6 mmol/L, p = 0.05). Hyperkalemia was equally distributed in both genders (11 [15%] vs. female 7 [14%], p = 0.82). PTH decreased or normalized in both

groups without any statistically significant differences between sexes ($p = 0.09$). Preoperative serum calcium levels of female patients were significantly higher (2.3 ± 0.19 mmol/L vs. female 2.3 ± 0.26 mmol/L, $p = 0.04$). There was no difference in hemoglobin levels, neither pre- nor postoperatively, between both groups (Table 2).

Discussion/Conclusion

Gender has been suggested to be an important factor, when kidney function and progression of kidney disease are investigated [17, 21]. Although the causes of renal failure were different between the 2 groups in our cohort, there were no gender differences in age, comorbidities and time of dialysis before PTX. Our results differ from international studies: Indridason et al. [22] showed that among dialysis patients more women were diagnosed with sHPT than men. Our group may be biased for listing to transplantation. Biological sex influences the pathogenesis of numerous diseases, including metabolic disorders such as diabetes [49]. Diabetes is the most common cause of ESRD in industrialized countries [50, 51], and its prevalence tends to increase over time. In our cohort, no significant difference could be observed concerning the number of patients with diabetes mellitus. Furthermore, review of the recent literature [18–20, 45] shows that women tend to have shorter time on dialysis before PTX than men. This is not reflected in our patients, where we could not see any difference between male and female patients concerning time on dialysis before PTX. This may be explained by the fact that our patients were generally operated on early: the mean time of dialysis before surgery was 4.7 ±3.9 years, which is half the time stated in the literature [45]. But early surgical intervention for renal hyperparathyroidism in CKD patients may prevent metabolic and bone-related complications. Comparing perioperative laboratory parameters, only calcium values showed a significant difference between sexes. 40% of our patients, however, had been treated with cinacalcet preoperatively, which lowers calcium levels. Overall, it is well known that women have lower hemoglobin and hematocrit levels than men [21]. Anemia is a common problem in patients with ESRD, particularly when they are on chronic dialysis. Factors that may be responsible for anemia in CKD are blood loss, shortened red cell life span, vitamin deficiencies, erythropoietin deficiency, iron deficiency, infection and inflammation. Among these, erythropoietin deficiency is considered as the most important cause [52]. Additionally, sHPT leads to reduced response to the erythropoietin-stimulating agent [53] and both can be attributed to decreased red blood cell production. Furthermore, calcitriol deficiency and parathyroid overproduction in patients with sHPT may inhibit erythropoiogenesis because of secondary bone marrow fibrosis and may reduce red blood cell survival, both aggravating renal anemia [54]. Previous studies in hemodialysis patients revealed a significant relationship between erythropoietin-stimulating agent hyporesponsiveness and higher intact PTH level and the inverse relationship between PTH and hemoglobin level [55–57]. In our center most patients were treated with erythropoietin to treat anemia, and we could not calculate any difference in hemoglobin levels between both sexes.

While overall postoperative complications were low, we saw significantly more cerebrovascular events in female patients during follow-up. This result has not yet been documented in the literature for sHPT and needs to be confirmed in further trials. Interestingly, although some studies do report a higher incidence of stroke in females compared to male patients, in general [58], it was attributed to differences in age, medical history and other relevant risk factors, but not to gender differences, as it occurred in our patients [59].

This study has several limitations. It is a retrospective and monocentric study with a limited number of patients. Furthermore, we do not have any information about bone mineral density in our patients and also no information on sex-specific hormones or information about menstruation or menopause of our female patients.

In conclusion, we assessed the impact of gender on history and peri- as well as postoperative outcome in patients with renal sHPT. Clinical and biochemical history only showed minor differences between both sexes with higher preoperative calcium levels in men. Operative procedures and early postoperative complications were not different. But in long-term follow-up women suffered from significantly more cerebrovascular complications than men. This latter finding is new and unexpected but has to be confirmed in further studies.

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Statement of Ethics

This is a retrospective noninterventional study. All procedures performed were in accordance with the ethical standards of the Institutional Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. An ethical approval for processing and publication of the data has been obtained by the institutional Ethics Committee (EA4/086/19); no written informed consent was necessary.

Disclosure Statement

The authors declare that they have no conflict of interest.

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Author Contributions

C.B., D.U. and M.T.M. contributed to the study conception and design, analysis, interpretation of data and writing of the manuscript. D.U., T.S., E.M.D. and M.T.M. participated in the acquisition and analysis of data. J.P. contributed to the analysis and interpretation of data, the study conception and critical review of the manuscript.

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