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PREVALENCE AND RISK FACTORS OF POST-KIDNEY TRANSPLANT HYPERPARATHYROIDISM: A SINGLE-CENTER STUDY

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Objective: to assess the prevalence of hyperparathyroidism (HPT) and the factors affecting its development in kidney transplant recipients. **Materials and methods.** The single-center observational cohort study included 97 kidney transplant recipients – 40 men, 57 women, age 50 ± 9 years. Inclusion criteria: more than 12 months of post-transplant period, 3 months of stable renal transplant function. Non-inclusion criterion: therapy with vitamin D, with its alternatives or with cinacalcet. Dialysis ranged from 0 to 132 months (median 18); 46% of patients had pre-operative secondary HPT. A comprehensive laboratory study included evaluation of serum concentrations of parathyroid hormone (PTH), 25-OH vitamin D, calcium, phosphorus, magnesium, total alkaline phosphatase (ALP) activity, albumin, creatinine and daily proteinuria. At the dialysis stage, the target PTH range of 130–585 pg/ml was used, in the post-transplant period – ≤130 pg/ml. Glomerular filtration rate (eGFR) was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula. **Results.** Patients were divided into two groups based on PTH threshold level (130 pg/ml): the first with HPT (PTH >130 pg/ml, median 203), the second without HPT (PTH ≤130 pg/ml, median 101). Both groups were comparable in terms of gender, age, primary renal disease, dialysis modality, post-transplant follow-up, and immunosuppressive therapy regimen. In group 1 and group 2 recipients, dialysis therapy, pre-transplant median PTH level, incidence of reoperation and incidence of immediate renal graft function were 30 (14; 50) and 14 (6; 28) months ($p = 0.004$), 681 (538; 858) and 310 (182; 556) pg/ml ($p < 0.001$), 17% and 2% ($p = 0.028$), 51% and 80% ($p = 0.005$), respectively. At the time of the study, 72% of group 1 recipients had eGFR <60 ml/min, versus 36% of group 2 ($p < 0.001$). Among HPT biochemical parameters, there were differences for ionized serum calcium (1.32 ± 0.07 versus 1.29 ± 0.04 mmol/l, $p = 0.017$) and ALP activity (113 ± 61 versus 75 ± 19 u/l, $p = 0.021$). Serum vitamin D in both groups reduced in equal measures – 14 ± 4 and 15 ± 6 ng/ml. **Conclusion.** Persistent HPT in the long-term post-transplant period reaches 48.5%. Risk factors for its development included dialysis for more than 18 months, pre-operative secondary HPT, repeated kidney transplantation, delayed graft function, and eGFR <60 ml/min.

Keywords: kidney transplantation, hyperparathyroidism, kidney graft function.

INTRODUCTION

Kidney transplantation is the best modality of renal replacement therapy for patients with stage 5 chronic kidney disease (CKD). It provides a high level of medical and social rehabilitation for such patients. According to recent domestic and foreign publications, there is a steady increase in the number of kidney transplants and a high one-year and five-year survival rate for kidney transplants and recipients [1–3].

Successful kidney transplantation eliminates complicated endocrine and metabolic disorders, particularly secondary hyperparathyroidism (HPT), a characteristic and common complication of CKD. Secondary HPT, an endocrinopathy manifested by excessive secretion of parathyroid hormone (PTH), is closely associated with changes in hormonal homeostasis, calcium and phosphate metabolism, and bone metabolism caused by decreased renal function [4, 5]. Spontaneous resolution of HPT occurs in over half of kidney transplant recipients. However, this process is slow, especially with the initial suboptimal function of the graft, and it does not occur in all recipients. In the first months of the postoperative period, decreased functional mass of the parathyroid glands (PTG) leads to rapid decrease (about half) in blood levels of PTH, followed by slower process, since paratyrocytes have a longer lifespan, and only about 5% of cells are renewed annually [6, 7].

Post-transplant HPT has a significant impact on recipient and graft survival and quality. Elevated PTH levels (more than 140 pg/mL in 2.5–3 months after surgery) were found to be associated with cardiovascular complications, bone fractures, graft loss, and increased risk of overall mortality [8–12]. According to several sources, HPT prevalence among kidney transplant recipients varies widely: it is higher in the first year after surgery and lesser afterwards. Some authors have reported about 40–50% of recipients with blood PTH above 130 pg/mL in the first postoperative year, others – only about 18%; a few years after kidney transplantation, from 17% to one third of recipients had HPT [8, 13–15]. Various risk fac-

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tors for post-transplant HPT are analyzed – convincing data has already been obtained for some, while studies are still ongoing for others [13, 15–18]. One should take note of the scarcity of information on post-kidney transplant HPT, which is presented exclusively by foreign publications. Russian studies aimed at analyzing the frequency, possible risk factors of post-kidney transplant HPT, and approaches to its prevention and correction, have almost never been carried out, despite the fact that the number of such operations is increasing annually.

The aim of this study was to assess the prevalence of HPT among kidney transplant recipients and to identify the risk factors of post-kidney transplant HPT.

MATERIALS AND METHODS

The cohort, observational study was carried out at the kidney transplantation surgical department of Vladimirsky Moscow Regional Research Clinical Institute. The study included 97 cadaver kidney recipients. Their characteristics are presented in Table 1.

The inclusion criteria for the study were: 12 months post-transplant period and above, and at least a 3-month stable kidney graft function. The non-inclusion criterion was therapy with vitamin D, its substitutes or cinacalcet. All patients received cadaver kidneys. Induction immunosuppressive therapy included basiliximab administration (40 mg total dose) and methylprednisolone (1.5 g total dose), base dose prednisolone (30 mg/day, followed by a dose reduction to a maintenance dose of 5–10 mg/day), calcineurin inhibitor (cyclosporin A, tacrolimus under control of plasma concentration of the drug), and mycophenolate.

A comprehensive laboratory study included determination of blood levels of PTH (two consecutive measurements) and vitamin D (25-OH vitamin D) (in the autumn-winter period) by chemiluminescent immunoassay using the ARCHITECT system (USA), serum electrolyte concentrations, total ALP activity, albumin, nitrogen metabolism parameters and protein concentration in urine using standard methods. The target ran-

Table 1

Demographic and clinical characteristics of patients at the time of kidney transplantation

Parameter	All patients(n = 97)
Age, years	50 ± 9
Male / Female, n (%)	40/57 (41/59)
Body mass index, kg/cm^2	25.8 ± 4.3
Primary renal disease, n (%)	
Chronic glomerulonephritis, incl. at systemic lupus erythematosis and widespread vasculitis	56 (58)
Congenital hereditary nephropathy (incl. polycystic kidney)	28 (29)
Chronic interstitial nephritis	5 (5)
Other/unknown nephropathy	8 (8)
Dialysis mode, n (%)	
Hemodialysis	60 (62)
Peritoneal dialysis	22 (23)
Hemodialysis + Peritoneal dialysis	8 (8)
No dialysis	7 (7)
Duration of dialysis therapy, months	18 (6; 35)
Renal regrafting, n (%)	9 (9)
Hyperparathyroidism before kidney transplant, n (%)	45 (46)
– mild (PTH 595–800 pg/ml)	26 (27)
– moderate (PTH 801–1000 pg/ml)	5 (5)
– severe (PTH >1000 pg/ml)	14 (14)
Posttransplant period at the moment of examination, months	21 (12; 37)
Renal graft function, n (%)	
Immediate	64 (66)
Delayed	33 (34)
Min. blood creatinine level after operation, μmol/l	114 ± 35
eGFR in 1 month (at discharge from the hospital), ml/min	66 ± 22
Maintenance immunosuppression, n (%)	
Steroids	94 (97)
Cyclosporin A	15 (16)
Tacrolimus	82 (85)
Mycophenolate group drugs	97 (100)

Note. PTH – parathyroid hormone; eGFR – estimated glomerular filtration rate (according to the formula CKD-EPI).

ge of blood PTH levels at the stage of dialysis therapy was chosen to be 130–585 pg/mL [19], and in the post-transplant period – not exceeding the upper limit of the reference range (11–65 pg/mL) twice (≤130 pg/mL) [8, 15]. Serum calcium concentration was adjusted for changes in plasma albumin concentration [20]. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration [19]) formula.

The material was statistically analyzed using the SPSS Statistics 17.0 software package (SPSS Inc, USA). Distribution of features was assessed by the Kolmogorov–Smirnov test. Description of quantitative features was presented as arithmetic mean and standard deviation (M ± SD) in normal distribution, and as median, 25% and 75% quartiles [Me (Q25–Q75)] in asymmetric distribution. Qualitative features were presented as fractions (%) and absolute numbers (n). For quantitative data comparison, we used the Mann–Whitney U test (to compare differences between independent variables) and the chi-square test for classification of qualitative characteristics. The strength of the relationship between quantitative attributes was estimated using the Spearman's rank correlation coefficient. In comparing the probability, depending on the presence or absence of a risk factor, the relative risk was calculated with determination of the confidence interval boundaries (95% CI). The critical values for statistical hypotheses testing in this study was assumed to be 0.05 significance level.

RESULTS

Plasma PTH levels in the observed patients ranged from 57 to 520 pg/mL; it was within the reference range (11–65 pg/mL) only in four patients. All patients were divided into two groups based on PTH levels. The first group included 47 (48.5%) recipients with >130 pg/mL PTH level, while the second group included 50 (51.5%) recipients with PTH level ≤130 pg/mL. Thus, the HPT rate in this cohort of kidney recipients was 48.5%. It turned out to be the same with different lengths of post-transplant period – from one year to six years (Fig. 1). Comparative characteristics of patient groups are presented in Table 2.

Both groups of patients were comparable by gender, age, body mass index, primary kidney disease, and dialysis therapy modality. Both groups had the same length of post-transplant follow-up until inclusion in the study and a comparable supportive immunosuppressive therapy regimen. Recipients diagnosed with HPT had a longer period of dialysis therapy and a repeated kidney transplantation in their history. A large proportion of patients from this group had secondary HPT while on the kidney transplant waiting list, as well as a higher average PTH levels in the blood; there was direct association between the pre- and post-transplant PTH levels ($r = 0.551$, $p < 0.001$). The groups were also found to have differences

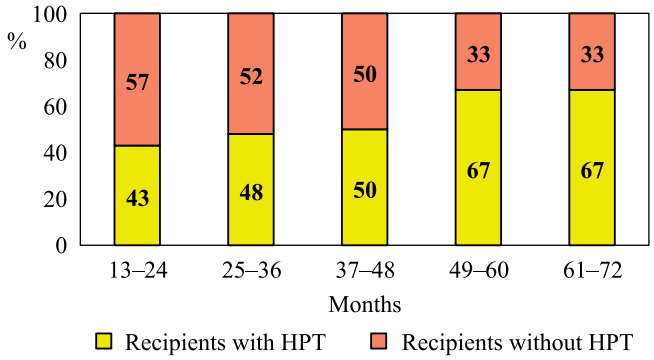

Fig. 1. The frequency of HPT at various times after kidney transplantation

in initial renal graft function. By the time the patients were examined, essential differences in graft function between both groups persisted: the median serum creatinine level in kidney recipients with HPT was 135 (110; 173) μmol/L, in recipients without HPT – 110 (80; 124) μmol/L ($p = 0.0002$), median eGFR was 50 mL/min (34; 63) and 62 mL/min (49; 84) respectively ($p = 0.0007$), daily proteinuria was 0.3 g (0.2; 0.5) and 0.2 g (0.1; 0.2) respectively, ($p = 0.04$) (Fig. 2). There was a positive

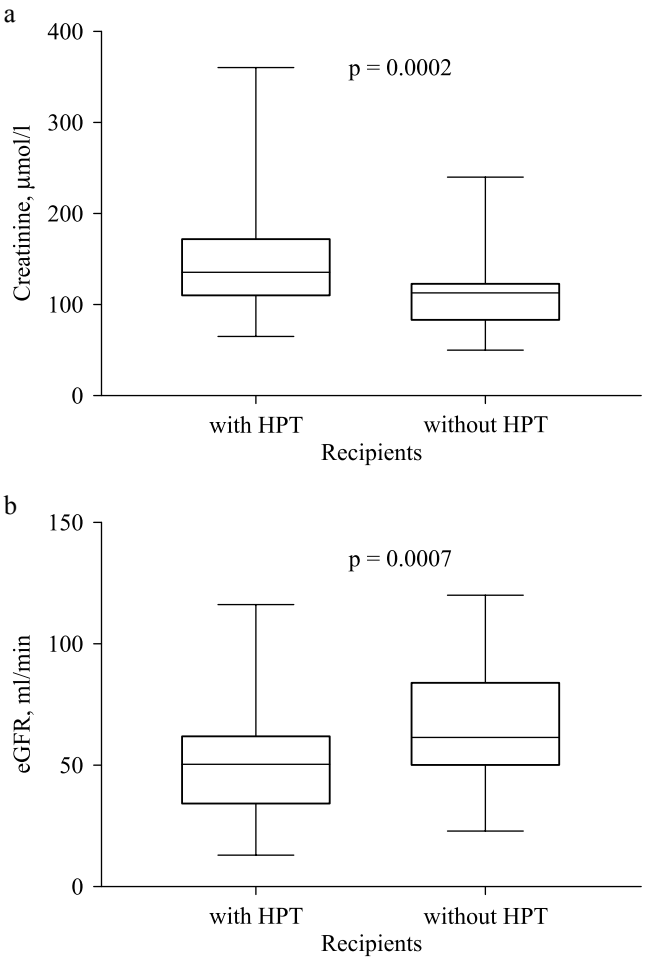

Fig. 2. Renal transplant function in recipients with and without HPT: a – blood creatinine concentration; b – estimated glomerular filtration rate

Table 2

Clinical characteristics in renal transplant recipients with and without hyperparathyroidism

Parameter	Renal transplant recipients		p
	PTH >130 pg/ml (n = 47)	PTH ≤130 pg/ml (n = 50)	
PTH, pg/ml	203 (164; 302)	101 (83; 114)	<0.001
Age, years	44 ± 9	45 ± 9	n/a
Male / Female, n	22/25	18/32	n/a
Body mass index, kg/cm^2	24.2 ± 4.6	25.3 ± 4.1	n/a
Primary renal disease, n (%)			
Chronic glomerulonephritis, incl. at systemic lupus erythematosis and widespread vasculitis	30 (64)	26 (52)	
Congenital hereditary nephropathy (incl. polycystic kidney)	10 (21)	18 (36)	n/a
Chronic interstitial nephritis	4 (9)	1 (2)	
Other/unknown nephropathy	3 (6)	5 (10)	
Dialysis mode, n (%)			
Hemodialysis	31 (66)	29 (58)	
Peritoneal dialysis	8 (17)	14 (28)	n/a
Hemodialysis + Peritoneal dialysis	5 (11)	3 (6)	
No dialysis	3 (6)	4 (8)	
Duration of dialysis therapy, months	30 (14; 50)	14 (6; 28)	0.004
Renal regrafting, n (%)	8 (17)	1 (2)	0.028
Patients with PTH >585 pg/ml, n (%)	33 (70)	12 (24)	<0.001
Blood PTH, pg/ml	681 (538; 858)	310 (182; 556)	<0.001
Posttransplant period at the moment of examination, months (min–max)	26 (14; 44)	19 (15; 35)	n/a
Patients, n (%) with duration:			
13–24 months	22 (47)	29 (58)	n/a
25–36 months	10 (21)	11 (22)	
37–48 months	5 (11)	5 (10)	
49–60 months	8 (17)	4 (8)	
61–72 months	2 (4)	1 (2)	
Renal graft function, n (%)			
Immediate	24 (51)	40 (80)	0.005
Delayed	23 (49)	10 (20)	
Min. blood creatinine level after operation, μmol/l	133 ± 42	97 ± 22	0.002
eGFR in 1 month (at discharge from the hospital), ml/min	57 ± 21	74 ± 20	<0.001
Maintenance immunosuppression, n (%)			
Steroids	46 (98)	48 (96)	
Cyclosporin A	4 (9)	11 (22)	n/a
Tacrolimus	43 (91)	39 (78)	
Mycophenolate group drugs	47 (100)	50 (100)	

Note. PTH – parathyroid hormone; eGFR – estimated glomerular filtration rate (according to the formula CKD-EPI); n/a – unreliable differences.

correlation between serum PTH and minimum (after kidney transplantation) serum creatinine ($p < 0.001$), serum creatinine at the time of examination ($p < 0.001$), and daily proteinuria ($p = 0.003$). Serum PTH was found to be negatively correlated with eGFR one month after transplantation ($p = 0.001$) and at the time of patient examination ($p < 0.001$).

Separation of patients into stages of CKD showed the following (Fig. 3). Prevalence of stage 1 CKD was an order of magnitude lower among recipients with HPT than among recipients without HPT ($p = 0.014$). In total, 34 (72%) patients with HPT had eGFR <60 mL/min versus 18 (36%) patients in the non-HPT group ($p < 0.001$).

Risk factors for post-transplant HPT were dialysis therapy lasting for more than 18 months and presence of secondary HPT at this stage, repeated kidney transplantation, delayed graft function, eGFR (transplanted kidney) <60 mL/min in the long term (Table 3).

During laboratory examination, recipients from the first group more often showed changes in calcium and phosphate metabolism resulting in hypercalcemia and hypophosphatemia, as well as elevated serum activity

of total ALP (Table 4). Serum PTH levels positively correlated with serum ionized calcium ($p < 0.001$) and ALP activity ($p = 0.003$), but did not correlate with the total serum calcium, phosphorus and magnesium concentrations. Serum vitamin D levels in both groups reduced in equal measure – half of the patients had moderate (insufficient), while the other half had significant (deficiency) reduction.

DISCUSSION

Discussing the prevalence of post-transplant HPT is quite complicated. Available information on this issue is scarce and quite contradictory. This is partly due, firstly, to restoration of hormonal-metabolic balance during the first year after successful kidney transplantation, and secondly, to lack of a clear definition of the target range of PTH in contrast to predialysis and dialysis patient populations. Data were obtained indicating a higher target blood PTH levels in kidney transplant recipients than in patients with CKD with similar GFR values. Therefore, a reliable assessment of the PTG function is carried out no earlier than 12 months after kidney transplantation. Blood PTH level >130 pg/mL is used as a diagnostic threshold for sustained HPT [8, 10, 13]. Our study, under

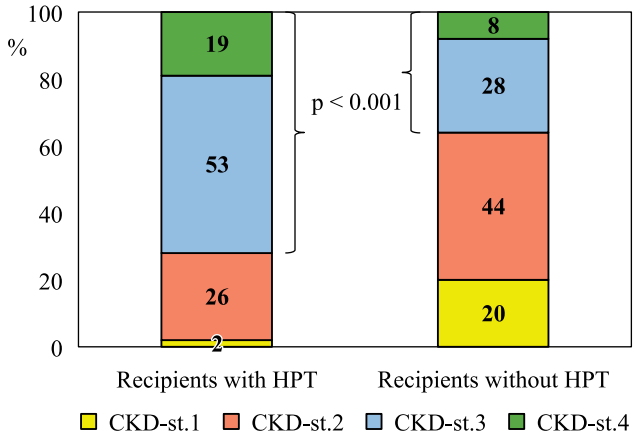

Fig. 3. CKD stages in recipients with and without HPT

Table 3

Impact of various factors on the development of hyperparathyroidism in patients after kidney transplantation

Factor	Rate in group with HPT (n = 47)	Rate in group without HPT (n = 50)	Relative risk [CI 95%]	p
Duration of dialysis therapy >18 months	31 (66%)	19 (38%)	1.736 [1.169; 2.659]	0.0082
PTH >585 pg/ml	33 (70%)	12 (24%)	2.926 [1.785; 5.046]	<0.0001
Kidney regrafting, n (%)	8 (17%)	1 (2%)	8.511 [1.467; 51.52]	0.0137
Renal graft function, n (%)	23 (49%)	10 (20%)	1.567 [1.584; 9.868]	0.0049
eGFR <60 ml/min, n (%)	34 (72%)	18 (36%)	2.009 [1.362; 3.089]	0.0005

Table 4

Biochemical parameters of hyperparathyroidism in renal transplant recipients

Parameter	Renal transplant recipients		p
	PTH >130 pg/ml (n = 47)	PTH ≤130 pg/ml (n = 50)	
PTH, pg/ml	203 (164; 302)	101 (83; 114)	<0.001
Ionized calcium, mmol/l	1.32 ± 0.07	1.29 ± 0.04	0.017
Hypercalcemia (Ca^{++} >1.31 mmol/l), n (%)	18 (38)	4 (8)	<0.001
Total Ca, mmol/l	2.4 ± 0.1	2.4 ± 0.1	n/a
Hypercalcemia (Ca >2.6 mmol/l), n (%)	8 (17)	1 (2)	0.03
Phosphorus, mmol/l	1.02 ± 0.20	1.01 ± 0.11	n/a
Hypophosphatemia (P <0.81 mmol/l), n (%)	11 (23)	3 (6)	0.032
Alkaline phosphatase (total), U/l (ref. 31–120 U/l)	113 ± 61	75 ± 19	0.021
Hyperenzymemia, n (%)	8 (17)	1 (2)	0.028
Magnesium, mmol/l	0.79 ± 0.08	0.76 ± 0.07	n/a
Hypomagnesemia(Mg <0.70 mmol/l), n (%)	8 (17)	7 (14)	n/a
Uric acid, µmol/l (ref. 150–420 µmol/l)	404 ± 62	375 ± 63	0.068
Hyperuricemia, n (%)	18 (38)	10 (20)	0.078
Vitamin D (calcidiol), ng/ml	14 ± 4	15 ± 6	n/a
Reference value (vitamin D >30 ng/ml), n (%)	1 (2)	1 (2)	
Deficiency (vitamin D 15–30 ng/ml), n (%)	21 (45)	21 (42)	
Hypovitaminosis D (vitamin D <15 ng/ml), n (%)	25 (53)	28 (56)	

Note. PTH – parathyroid hormone; n/a – unreliable differences.

the indicated conditions, established that HPT prevalence in kidney transplant recipients in the long-term period (1–6 years after surgery) was 48.5%. Similar data have also been given by other authors [8, 15]. This suggests that HPT is a problem not only for dialysis patients, but also for kidney transplant recipients. High prevalence of HPT at kidney transplant centers emphasizes the importance of dynamic monitoring of PTG function and related parameters of mineral and bone metabolism. The need for regular laboratory testing is also driven by the fact that HPT has no early clinical manifestations.

The leading risk factor associated with post-kidney transplant HPT is the existence of secondary HPT at the preoperative period [8, 13, 17]. The result of our study is fully consistent with this conclusion. Patients with pre-kidney transplant moderate/severe HPT have a high probability of disease persistence even with optimal graft function. Postoperative HPT is due to formation of parathyroid nodular hyperplasia formed at the stage of dialysis therapy, which is accompanied by reduced expression of calcium-sensing receptors and vitamin D receptors and is not capable of complete involution after successful kidney transplantation. Tertiary HPT attracts the most attention from nephrologists that are observing kidney transplant recipients. Its distinguishing feature is hypercalcemia, whose clinical manifestations vary from complete absence to severe damage to the cardiovascular, musculoskeletal, nervous systems and graft. Occurring in 5–10–15% of cases in the first year after kidney transplantation, hypercalcemia is associated with elevated levels of blood PTH preoperatively and postoperatively [21–24]. We also observed patients with increased serum calcium, who were more in the first group than in the second group. However, a positive correlation was established only between PTH and ionized calcium, which emphasizes the need to determine this fraction, since measuring total calcium can underestimate hypercalcemia diagnosis [6].

Another major factor in development/progression of post-transplant HPT, established in the course of our study, is the suboptimal function of the transplanted kidney in the early postoperative period or formed in subsequent years. Obviously, in both cases it leads to the same complex of hormonal-metabolic disorders and HPT formation by the same mechanisms as in CKD progression [4, 5]. There are publications supporting the interdependence of kidney transplant function and PTG function; there are as well contrary opinions on the absence of such a relationship [23, 25, 26]. This situation is possible in recipients with tertiary HPT, which can occur with a well-functioning graft.

PTH secretion is closely related to vitamin D and magnesium content in the body – their low serum concentrations stimulate the PTG function [27]. Decreased serum magnesium after kidney transplantation due to inhibition of its tubular reabsorption is initiated by calcineurin inhibitors and is more characteristic of the early postoperative period [28]. Our study, which was carried out in the long-term after kidney transplantation, revealed no relationship between PTH and magnesium levels in the blood. At the same time, it is known that serum magnesium levels may not accurately reflect the level of total body magnesium and that a normal serum magnesium level does not rule out magnesium deficiency [27]. There was also no relationship between plasma concentrations of PTH and vitamin D, in contrast to the study by Timalsina S. et al. [18]. Moreover, vitamin D levels in all recipients with both normal and hyperfunctional PTG were lower than the target range accepted in the general population [29]. However, serum vitamin D (calcidiol) levels may not accurately reflect the level of its active form, D-hormone (calcitriol), in the blood, but is only an optimal indicator of its availability in the body.

The possible role of high body mass index in recipients in post-transplant HPT is being considered. The basis for this was the data on the action of leptin stimulating PTH secretion [30]. In their study, Perrin P. et al. [8] found a significant difference in body mass index in patients with normal and increased PTG function three months after kidney transplantation. However, we did not find such a difference, which is probably due to the small sample and/or long-term follow-up.

CONCLUSION

Persistent hyperparathyroidism (secondary/tertiary) is a common disease in the long-term post-kidney transplant period. Its risk factors include prolonged dialysis therapy, preoperative secondary HPT, repeated kidney transplantation, delayed graft function, and eGFR <60 ml/min. Dynamic outpatient monitoring of renal transplant recipients requires regular monitoring of PTG function and biochemical parameters of HPT. Implementation of rational preventive and therapeutic measures for post-transplant HPT includes proper management of secondary HPT in the preoperative period and maintenance of serum PTH level, corresponding to the kidney graft function. Actual clinical practice confirms that the recommended tactics are valid [31].

The authors declare no conflict of interest.

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