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Kidney transplantation and hyperparathyroidism

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Successful kidney transplantation eliminates endocrine and metabolic disorders that predispose to the development of hyperparathyroidism, the complication typical for the chronic kidney disease; but the process of recovery from mineral and bone disorders is slowed down. The highest incidence of post-transplant hyperparathyroidism is recorded in the first postoperative year. The risk factors for its development or persistence include the high blood levels of parathyroid hormone, calcium, phosphorus, and/or alkaline phosphatase, a prolonged dialysis therapy, severe hyperparathyroidism in the preoperative period, vitamin D deficiency, a suboptimal transplanted kidney function, and also the recipient's previous history of subtotal or incomplete parathyroidectomy. The characteristic clinical and laboratory signs of post-transplant hyperparathyroidism are bone lesions, kidney graft abnormalities, hypercalcemia, and hypophosphatemia. The diagnostic algorithm includes monitoring the markers of mineral and bone metabolism, determining the bone mineral density, and imaging of thyroid glands. Correction of post-transplant hyperparathyroidism is performed surgically or pharmacologically. The

article specifies the indications to, the extent and timing of parathyroidectomy, discusses the use of native vitamin D formulations, its analogues, and calcimimetics.

Keywords: kidney transplantation, hyperparathyroidism, topical diagnosis, parathyroidectomy, vitamin D

Definition. Risk factors of disease development

Hyperparathyroidism (HPT), a parathyroid gland (PTG) disease manifested by excessive secretion of parathyroid hormone (PTH), often accompanies the chronic kidney disease (CKD) of Stage III-V. The HPT development is closely related to the decrease in renal functions leading to severe impairments of calcium-phosphorus metabolism, bone metabolism, and to PTH hypersecretion. Classical mechanisms of the HPT development include a decreased synthesis of the vitamin D active form (calcitriol), hypocalcemia, the inorganic phosphate retention in the body, an abnormal calciemic bone response to PTH. The latter has several target organs: in the kidneys, it reduces the calcium excretion with urine, produces a phosphaturic effect, and increases the calcitriol production; it participates in the skeletal system renewal by releasing the necessary amounts of calcium and phosphorus; in the small intestine, it promotes the assimilation of dietary calcium supporting its homeostasis. In the latest 1.5-2 decades, there appeared the information on a new factor initiating the development of renal HPT. It is fibroblast growth factor 23 (FGF23) that is a hormonal peptide mainly synthesized and secreted by osteoblasts. Its effects, mainly a phosphaturic one, are produced through its binding to the alternative Klotho co-receptor expressed in various organs, including the kidneys and the PTG. The FGF23 production starts increasing at early stages of CKD in response

to a positive balance of phosphorus in the body. This increase triggers the cascade of complex reactions leading to HPT formation [1, 2].

Successful kidney transplantation smoothes down the endocrine metabolism disorders, including mineral-bone disorders; but the recovery process is slow and happens not in every patient. HPT takes the leading place among post-transplant mineral-bone disorders. In the postoperative period, the PTH level in blood shows a two-phase decrease: a rapid one, approximately by half during the first half year, associated with a decreased functional PTG mass, and a gradual one in the subsequent period: the parathyroid cells have a longer lifespan, approximately 5% of these cells are renewed annually [3] .

Post-transplant HPT may be of various origin [2]. In some recipients, it is associated with the secondary HPT present in the pre-transplant period; other recipients develop HPT de novo. In the recipients with a satisfactory kidney graft function (glomerular filtration rate [GFR] over 60 mL/min), the post-transplant HPT can be of a functional type, i.e. the increased synthesis and secretion of PTH represent the PTG adaptive "response" to a kind of stimuli. Such stimuli may include the vitamin D deficiency, hypomagnesemia, possibly, some drug effects. As we observed, 96.6% of recipients had a reduced blood level of vitamin D [25(OH)D] (less than 30 ng/mL), but it had no correlation to the PTH level. Meanwhile, a sufficiently stable inverse relationship was established between the blood levels of PTH and magnesium [4].

Secondary and tertiary (post-transplant) HPT reflect already the inadequate adaptation process manifested in the cellular proliferation and PTG hyperplasia, the latter being diffused initially, and then becoming diffuse-nodular, and adenomatous later. The secondary (post-transplant)

HPT development is associated with the progressing chronic transplant nephropathy that eventually develops in all recipients, and occurs by the same mechanisms as the secondary HPT in CKD. In such cases, the recipients could have had a mild or moderately severe HPT course in the pre-transplant period, then experienced an improvement after successful kidney transplantation, and they could even avoid secondary HPT. With a prolonged reduction of the renal graft function without its correction, the HPT progresses to a severe course with the development of PTG nodular hyperplasia, i.e. the tertiary HPT [2].

With a reduced kidney graft function immediately after the transplant surgery, the secondary HPT existing before kidney transplantation does not completely regress, but continues to persist. As in the above case, an inadequate correction entails the risk of further progression to tertiary HPT with PTG nodular hyperplasia development (2, 3).

Post-transplant (tertiary) HPT can be diagnosed as early as in the first year after kidney transplantation, regardless of the kidney graft function. In this case, the HPT existence can be explained by a varied autonomy of PTG diffused-nodular/nodular hyperplasia that was formed before the kidney transplantation, i.e. by the severe HPT resulted from an inadequate treatment [2, 3]

The identified risk factors for HPT persisting after kidney transplantation include: the high blood levels of PTH, calcium, phosphorus and(or) alkaline phosphatase, a long-term dialysis therapy, and the pre-transplant therapy with cinacalcet reflecting a severe pre-transplant course of HPT, a vitamin D [25(OH)D] deficiency, and a suboptimal function of the transplanted kidney [3, 5-7]. The risk group of post-transplant HPT development also includes the recipients who previously underwent a

subtotal or incomplete parathyroidectomy (PTE). There was interesting information about the possible role of the recipient high body mass index in the post-transplant HPT development that is explained by the effect of leptin stimulating the PTH secretion [8].

The morphological substrate of post-transplant HPT may also be diverse corresponding to the complexity of genesis. More often it is represented by asymmetric hyperplasia of all four, (or less frequently of one or two) PTGs, most likely due to an uneven gland involution after successful kidney transplantation. Single or double adenoma of PTG is also be found in the kidney transplant recipients and can be of a dual origin: sporadic primary HPT or the adenomatous transformation of the hyperplasia-affected gland in secondary HPT [2].

Epidemiology

The information on the prevalence of post-transplant HPT is scanty and reported in foreign publications. Noteworthy are the significant variations in the HPT incidence rates between renal transplant recipients. This is mainly due to the fact that, in contrast to dialysis patients, the targeted PTH blood levels in transplant patients have not been clearly defined. The Russian national and some foreign clinical recommendations state the same values as those indicated for the corresponding stage of CKD, however, the studies demonstrated a higher blood level of PTH in the kidney transplant recipients than that in CKD patients with similar GFR [3, 9, 10]. Therefore, analyzing the prevalence of post-transplant HPT, some authors diagnosed it at PTH level 2 times higher than the upper limit of reference values (i.e. exceeding 130 pg/mL), and others did at the level of 2.5 times higher [5, 11]. It is even more difficult to evaluate the incidence of HPT in

kidney transplantation centers of Russia, since the monitoring of PTH and other mineral and bone metabolism markers is not a routine in every recipient. Our study showed that only some recipients, including those in the group with an optimal kidney function and the post-transplant period duration of 1 to 5 years, had the plasma PTH concentrations within the target ranges as indicated in the national clinical recommendations [4, 9].

Data from the literature indicate different HPT incidence rates at different times of the post-transplant period: it is the highest in the first post-transplant year and significantly lower in subsequent years. Thus, specifically, a recently completed American prospective multicenter observational study involving 246 recipients demonstrated that the PTH levels observed in the first postoperative year were beyond the reference values in more than 80% of recipients, and over 130 pg/mL in 40% [6]. The similar data were also reported in another small study where 50%, and 41% among 143 kidney transplant recipients, had HPT (the PTH level over 130 pg/mL) at 3 months, and at 1 year after transplantation, respectively [5]. Meanwhile, a large retrospective observational study showed that in the first year after successful kidney transplantation, only 18% of recipients (108 of 607) had elevated PTH levels; and in 8% (n=47), the elevated PTH levels were coincided with hypercalcemia [10]. The analysis of the natural course of PTG function and the calcium-phosphorus metabolism for several years also yielded a considerable scatter of values. Thus, P. Evenepoel et al. [11] who followed-up 861 renal transplant recipients for 4 years indicated only 17% of those who had either an elevated PTH level (2.5 times higher of upper limit of normal) or underwent a PTE. E.R. Perrin et al. [5] followed-up the patients after kidney transplantation for 5 years and diagnosed HPT in a third of recipients at the end of the study period.

Post-transplantation HPT has a significant effect on the survival quality and length of recipients and renal transplants. A correlation was found between the elevated PTH levels (> 140 pg/mL at 2.5-3 months after surgery) and the development of cardiovascular complications, graft loss, and an increased risk of all-cause mortality [10].

Clinical and laboratory manifestations

Clinical manifestations of pre- and post-transplant (secondary) HPT are of uniform nature, and the post-transplant (tertiary) HPT symptoms are diverse and resemble those of primary HPT, meanwhile, they are associated both with the excessive blood content of PTH, and with persistent hypercalcemia. They include the bone pathology development, the damage to the kidney graft and other organ systems.

Bone pathology is usually represented by a hypermetabolic bone disease, fibrotic osteitis, and osteopenic syndrome. Post-transplant HPT is the leading cause of mineral bone mass loss in the bones of the cortical structure (femoral neck, radial bone) predisposing them to fractures. The correlation of HPT with the susceptibility to bone fractures is known in dialysis patient population, and in primary HPT. Recently, the same relationship has been established for renal transplant recipients. A retrospective study that included 143 patients who underwent kidney transplantation from August 2004 to April 2006 showed that the PTH level over 130 pg/mL persisting for 3 months was an independent risk factor for the occurrence of bone fractures in the post-transplant period, the greatest risk being in the first year after surgery when the incidence of fractures is the highest [5].

Another serious consequence of post-transplant (tertiary) HPT is the damage to the kidney graft and its decreased function which occurrence is closely related to hypercalcemia; the latter initiates the vasoconstriction and leads to hypercalciuria followed by the development of tubulointerstitial lesions, the kidney calcinosis or lithiasis. The kidney transplant calcification (calcium phosphate deposits in the lumen of tubules) was confirmed by the protocol biopsy performed in the first year after surgery. Such patients had significantly higher serum levels of PTH and calcium, and a lower kidney function by the end of the first year [3].

Hypercalcemia and associated hypercalciuria explain the syndrome of polyuria and polydipsia. Excessive calcium in the urine causes the activation of calcium-sensitive receptors expressed in many sites of the nephron and, primarily, in the distal part of the Henle loop, which leads to an increased intratubular fluid amount and the polyuria development [12, 13]. In addition, hypercalcemia contributes to the kidney resistance to vasopressin, i.e. the development of a nephrogenic diabetes insipidus.

The most important systemic effect of post-transplant HPT is the vascular calcification that has an unfavorable prognosis for the cardiovascular system and is associated with a high risk of coronary heart disease and more frequent indications to coronary artery bypass grafting, a high risk of myocardial infarction, acute cerebrovascular accident or transient cerebral ischemic attack, peripheral arterial disease (revascularization, limb amputation), cardiovascular death, and all-cause death [14].

Serious gastrointestinal tract diseases (gastric ulcers, pancreatitis), focal extraskeletal calcification, shifts in the psychoemotional state, carbohydrate and lipid metabolism disorders, etc. can also develop. [3, 15].

The laboratory manifestations of post-transplant (tertiary) HPT include hypercalcemia and hypophosphatemia. It is the PTH hypersecretion that is associated with the development of these two syndromes. The multivariate analysis conducted by the Japanese investigators who studied 34 live kidney transplant recipients at a monthly follow-up visits for the first year showed that the only statistically significant factor responsible for post-transplant hypercalcemia was the blood level of PTH (<0.001) [16].

A similar situation has been observed with post-transplant hypophosphatemia syndrome that is quite common in the recipients of donor kidneys [4, 16, 17]. Many investigators believe that a high level of FGF23 persistent in the first 3 pot-transplant months (the so-called phenomenon of tertiary hyperphosphatonism) is of great importance: the direct relationships have been found between the fractional phosphorus excretion in urine and the blood level of FGF23, and between the degree of hypophosphatemia and the pre-transplantation level of FGF23. In addition to direct phosphaturation effect, FGF23 also inhibits the activity of 1α-hydroxylase enzyme, suppressing the calcitriol production and enhancing hypophosphatemia. Hypophosphatemia is a consequence of phosphaturia, as a rule, in the long-term post-transplant period, the same as and in the early postoperative period, but not due to the phosphaturic effect of FGF23 which level is lower than in patients with CKD at the corresponding stage, but due to the phosphaturic action of PTH, which level, on the contrary, is higher than at the same stage of CKD. The above has been confirmed by the direct relationship between the fractional urinary excretion of phosphorus and the blood level of PTH [18]. Hypercalcemia in combination with hypophosphatemia is associated with a decreased renal transplant function in the first postoperative year [19].

Diagnosis

The strategy to diagnose HPT in renal transplant recipients includes primarily the monitoring of serum concentrations of PTH, phosphorus, and calcium, the alkaline phosphatase activity (bone-specific and(or) total) in blood, the kidney transplant function, and, advisably, the vitamin D (25(OH)D) level. The frequency and scope of the examination depend on the transplanted kidney function, the degree of various abnormalities in mineral and bone metabolism and the rate of their development, as well as on the tactics of therapy [2, 9, 10, 20].

There are two aspects to be discussed separately: the first one is the reason to determine the ionized calcium level, since measuring only the total calcium concentration in blood strongly underestimates the hypercalcemia diagnosis; and the second aspect is the necessity and periodicity of studying the serum magnesium concentration, given the high incidence of hypomagnesemia in the post-transplant period [3, 21].

Measuring the blood level of PTH (normal vs. elevated) is not an easy task for a clinician. The PTH concentration ranges recommended for renal transplant recipients are the same as those for the patients at the corresponding stage of CKD. However, some studies indicate that most patients in the post-transplant period have a higher PTH level with respect to the recommended one [3, 4].

At present, there is no consensus on the clinical significance, indications, frequency and timing of bone mineral density measuring in patients with post-transplant HPT [21, 22]. The experience of Canada's kidney transplant centers demonstrated a significant variability in the practice of bone densitometry and its more frequent performance in the kidney transplants recipients compared to general population [23]. This is

due to the fact that the recommendation to test the bone mineral density in the central and peripheral skeleton dual energy X-ray absorptiometry (DEXA) in patients both in an early and late post-transplant period has a low evidence base for several reasons. The results of bone densitometry are questionable in predicting bone fractures, give no information on the bone tissue architecture and bone metabolism activity, may be confounding due to the presence of extraskeletal calcification foci, osteosclerosis or osteomalacia, and also due to a recently performed study showing that the average bone mineral density in patients after kidney transplantation corresponds to their age and gender [24]. Meanwhile, this recommendation is already under revision, as there has been the evidence that bone mineral density may be a predictor of bone fractures in patients with CKD [22].

A high-resolution peripheral quantitative computed tomography (HR-pQCT) is a significantly more informative tool, compared to DEXA, for studying the skeleton (the bone microarchitecture) that permits a separate assessment of bulk density in cortical and trabecular regions, a quantitative estimation of bone mineral mass in renal transplant recipients with HPT, but HR-pQCT has not yet been widely introduced into routine clinical practice [25].

A clearly performed imaging of abnormally altered one or several PTGs, i.e. the so-called topical diagnosis, is an important link in diagnosing the post-transplant (tertiary) HPT [2, 9]. First, it is necessary for dynamic monitoring of the PTG size in case the medical therapy is conducted, to determine the exact location of glands in case of planning a surgical treatment. Various imaging techniques are currently being used to clarify the location of pathologically altered PTGs, from available ultrasonography (ultrasound) to high-cost, high-tech versions of computed tomography

(multislice, single photon emission, positron emission), scintigraphy with radioactive technetium (^{99m}Tc-MIBI). Specialists draw the attention to the difficulties with preoperative imaging of pathologically altered PTGs, the difficulties being associated with the individual anatomic position and number of glands, the frequent presence of the thyroid gland concomitant pathology, and the enlargement of cervical lymph nodes [26].

Modern ultrasonography of the anterior surface of the neck is an available, reliable, and sufficiently informative imaging technique to diagnose an abnormally altered PTG. Its informative value is increasing if the examination is performed by an expert, when the anatomy and the number of PTGs are typical, the gland mass exceeds 500 mg (should it be lower than 500 mg, the sensitivity of the method would significantly reduce, to 30%), and when there is neither thyroid gland pathology nor enlargement of cervical lymph nodes [26]. The proliferative process in the PTG can be verified by a fine needle aspiration biopsy from the nodular mass followed by a cytological examination of the obtained tissue. The diagnostic investigations convincingly demonstrate the typical cytology of the PTG tissue and its cytomorphological differences from the thyroid tissue, on the one hand, and the distinctive cytological signs of the PTG tissue typical for post-transplant HPT, namely, a significant predominance of the parathyroid light chief cells located in the strands, small clusters, and the groups with poorly expressed intercellular contacts; small collections of parathyroid dark chief cells containing no more than 10 cells with weakened intercellular contacts; the present groups of oxyphilic (oncocyte) parathyroid cells; the presence of large basophilic secretory granules in the cytoplasm of parathyroid cells, and in the extracellular space, in a colloidal substance [27, 28]. The described cytological pattern is the evidence of both the high

functional activity of parathyroid cells (larger numbers of mature light parathyroid cells than the dark chief cells, and the presence of large secretory granules), and the predominance of destructive processes over the proliferative ones (a significant number of dystrophy-altered epithelial cells in the form of "bare" nuclei, a loose arrangement of parathyroid cells in groups with weakened intercellular contacts, absent multicellular clusters and microfollicles) [28].

The contrast-enhanced multislice spiral computed tomography (MSCT) of the neck and mediastinum increases the resolution power of the method, however, some experts believe that the sensitivity and specificity of this imaging technique are comparable to those of the ultrasound examination of the neck anterior surface. An exception may be an atypical location of pathologically altered PTGs where the diagnostic value of the MSCT increases [26].

The radioisotope scintigraphy (^{99m}Tc-technetryl) and a single-photon emission computed tomography are the most sensitive techniques to diagnose the PTG abnormalities, especially in case of a single adenoma. In cases of non-homogeneous diffused and(or) diffuse-nodular hyperplasia of several PTGs, not all of them, but only the most functionally active gland can be visualized [26].

Treatment

Approaches to the treatment of post-transplant HPT continue to be discussed. The choice of therapeutic tactics brings considerable difficulties, since the PTH hypersecretion is an important adaptive response to a reduced renal function, and this response aims at maintaining a balanced mineral and bone metabolism. An inadequately chosen extent of therapy entails the risk

of adverse consequences towards both the HPT progression, and the hypoparathyroidism development [3, 20, 21].

Surgical treatment. Until recently, the PTE surgery was the main treatment of tertiary HPT in renal transplant recipients, both the adults and children. A many-year experience demonstrates the requirement in PTE among the recipients of donor kidneys varying from 0.5% to several per cent [11, 29-32]. In the near future, the need for PTE may increase due to the widespread use of calcimimetics for the secondary HPT correction in the candidates for kidney transplantation (these drugs have not been yet approved for use in the post-transplant period, and therefore, are withdrawn at the time of surgery). According to the Swedish Renal Registry based on a survey of more than 20,000 patients on renal replacement therapy, including 417 renal transplant recipients, the duration of the post-transplant period appeared the risk factor for PTE: the highest relative risk, 1.6, was documented in the first year after surgery [33].

Planning the recipient for the surgical treatment for HPT, the following issues shall be considered [30, 31, 34, 35]:

- Indications to PTE;

- Timing for surgery: whether a long wait for the regression of the severe HPT is justified;

- The scope of surgical intervention on the PTG;

- The effect of PTE on the transplanted kidney function.

Unlike the patient population on dialysis, there are no well-developed recommendations for surgical treatment of HPT in the donor kidney recipients. While considering the indications for PTE, one should take into account the routine clinical practice established in each transplantation center and the existing laboratory abnormalities in a patient as follows:

- Severe hypercalcemia (serum calcium concentration exceeding 11.5-12.0 mg/dL) and(or) hypercalcemic crisis;

- Persistent hypercalcemia (serum calcium concentration above 10.2 mg/dL for more than 3 months after expiry of 1 year from kidney transplantation);

- High PTH level, inconsistent with the function of the renal transplant;

- A progressive reduction of mineral bone mass; bone fractures;

- Nephrolithiasis of the graft [9, 20, 21, 31, 35, 36].

However, as mentioned above, it remains unclear which PTH level in kidney transplant recipients should be considered elevated, especially in persistent normocalcemia.

At present there is no strictly established timing for performing PTE in the post-transplant period [34-36]. PTE is not recommended in the early postoperative period, a pharmacological correction of post-transplant HPT is desirable for a possibly longer period (during several post-transplant years, if possible). This is attributed to a slow restoration of the PTH, calcium, phosphorus and vitamin D homeostasis, taking place for months after surgery in donor kidney recipients, especially in those with sub-optimal function of the kidney graft [16]. Another argument in favor of not performing PTE in the early post-transplant period is the high doses of glucocorticosteroids used at this time which enhance bone resorption, while PTH, playing an important role in maintaining bone metabolism and acting as an osteoanabolic agent, to some extent resists to the proapoptotic effect of glucocorticosteroids on osteoblasts [38]. Along with this, the question on the timing of expectant management for severe HPT in kidney transplant

recipients does not have an unambiguous answer, it requires scrupulous "weighing all the pros and cons".

As for the extent of surgical intervention, PTE can be subtotal or total; the latter, respectively, being performed either with the autotransplantation of a PTG fragment subcutaneously/into the muscle, or without it. The choice of surgery remains to the surgeon's discretion and is determined in each case individually. So, T.M. Hsieh et al. [39] studied 14 (of 488) renal transplant recipients who underwent surgery for tertiary HPT: either a total PTE (n=7), or a subtotal PTE (n=7). The authors found no differences between the two groups in surgery duration, in-hospital length of stay, laboratory parameters except for blood levels of calcium and phosphorus. The patients who underwent the total PTE had a lower serum calcium concentration and a higher serum phosphorus concentration than the patients who underwent the subtotal PTE. Based on that, the authors concluded that subtotal PTE is preferable, since it reduces the risk of postoperative hypocalcemia. Probably, subtotal PTE is preferable also from the point of keeping the protective effect of PTH on bone tissue [40].

Another study presented the results of a total PTE without PTG fragment autotransplantation in 26 kidney recipients who postoperatively received 1-α-kalcidiol; all patients were alive after 5 years, 20 patients survived over 9 years. The serum calcium concentrations and blood PTH levels remained normal both after 5 years, and after 9 years; on that basis, the authors concluded that the total PTE without PTG fragment autotransplantation prevents both the persistence and the recurrence of HPT [41].

Previously, the development of recurrent HPT after PTE in recipients with a satisfactory renal transplant function was believed unlikely. However,

K. Schlosser et al. [42] identified 24 such patients (of 69) who underwent PTE in the post-transplant period; in 8 of them, the HPT was related to the PTG autograft. After the latter was removed and examined, the alterations consistent to nodular hyperplasia and the adenomatous transformation of the PTG were found, most likely, originally taking place in the transplanted fragment of the gland, despite a careful preliminary selection of the fragments. Therefore, in the authors' opinion, the total PTE without PTG fragment autotransplantation seemed to be the best surgical strategy for tertiary HPT treatment. In order to avoid the persistence and recurrence of tertiary HPT after the PTE, some authors consider it reasonable to perform the intraoperative monitoring of PTH, the same way as in primary HPT [43]. However, in contrast to primary HPT, in some patients with tertiary HPT, a more than 50% PTH decrease is recorded at 25 minutes rather than at 10 minutes after the adequate resection of the PTG.

The PTE outcomes in renal transplant recipients are generally optimistic. L.K. Dewberry et al. [33] evaluated the surgery outcomes in the period 1994-2013 and showed that hypercalcemia resolved in 97% of patients, the transient hypocalcemia was identified in 27%. The blood level of PTH after surgery decreased from 745 (285-1594) pg/mL to 97 pg/mL; in the long-term period, the median PTH was below 259 pg/mL in 78% of patients, and was 535 pg/mL in 22%. No deaths were recorded in the early postoperative period. A year after PTE, the GFR was 53 ± 28 ml/min vs. the preoperative GFR equal to 58 ± 28 ml/min.

In case the persistent postoperative hypoparathyroidism and hypocalcemia develop, the daily injections of teriparatide can be used, as well as the autotransplantation of the cryopreserved PTG tissue obtained during surgery, or the transplantation of donor PTG tissue (44).

The data on the PTE effect on the kidney graft function are contradictory. Several previously published studies based on a small sample size of patients with transplanted PTG demonstrated a GFR decline and even the development of the kidney transplant rejection crisis, although K.Schlosser et al. [42] performed reoperations in 8 patients for the PTG-autograft-derived recurrent HPT and reliably emphasized the stable function of the kidney graft for 6 months postoperatively. In the long-term period (38 ± 6 months), they recorded the increase in the serum creatinine level, which, in their opinion, was already the result of progressing chronic transplant nephropathy.

One of recent studies reviewed a 31-year experience of the surgical treatment for tertiary HPT: PTE was performed in 15 of 2981 (0.5%) renal transplant recipients [30]. The authors indicated that over a long follow-up period (23-142 months, the median of 54 months), none of the patients who underwent PTE experienced a deterioration of the transplanted kidney function. The authors believe that such result was attributed to the fact that all patients had an optimal transplant function preoperatively. However, the same authors have found a possible relationship between the renal transplant function and the PTE technique. The patients who underwent the total PTE with the PTG fragment autotransplantation had significantly lower blood levels of PTH and calcium but also a decrease in GFR. In contrast, the patients who underwent the subtotal (or incomplete) PTE, had the blood levels of PTH and calcium decreased to a lesser extent, and the GFR increased at 3 months after surgery; although there was no significant difference in GFRs regarding the surgical techniques used. Based on the obtained data, the authors suggest that the subtotal (or incomplete) PTE

chosen can reduce the risk of the kidney transplant damage; and when planning the surgical intervention, it should be performed in such extent.

The analysis of the short-term and long-term effects of PTE on the renal transplant function was made in a retrospective study by G. Fereira et al. [32]. The study group consisted of 28 renal transplant recipients who underwent PTE; the control group included 28 recipients operated on for the urinary tract and digestive system diseases. Both groups were comparable by gender, age, immunosuppressive therapy, the follow-up duration after kidney transplantation, and renal transplant function. In the early postoperative period, the deteriorated graft function was recorded in both groups, being reported as extremely severe in the study group. The peak increase in the serum creatinine concentration was recorded after 5 days as statistically significant from 1.58 to 2.29 mg/dL ($p < 0.05$) in the PTE group vs. from 1.49 to 1.65 mg/dL ($P > 0.05$) in the control group. The kidney graft function stabilized after 24 ± 10 months in the PTE group (the blood level of creatinine was 1.91 mg/dL), and after 31 ± 24 months in the control group (the blood level of creatinine was 1.72 mg/dL). The long-term follow-up (for more than 5 years) demonstrated similar renal transplant and recipient survival rates in both groups. I. Lou et al. [31] recorded no cases of worsened kidney transplant function and no kidney graft rejection crisis development, either.

Currently, the pathophysiology mechanism of reduced renal graft function after PTE remains still unclear. The suggested potential causes of the kidney function worsening may be the following: a post-surgery change in the blood PTH concentration, the surgical intervention and anesthesia per se, and, possibly, an immunological conflict [45, 46]. There is a reason to believe that PTH has a hemodynamic property that enhances its effect on the

kidney graft function. Its N-terminal fragment is homologous to a parathyroid-like protein that was identified first as a tumor-producing peptide, which does not exclude the similar effects of these two substances. Data from experimental studies show that the parathyroid-like protein can act as an endogenous vasodilator, modulating renal responses to vasoactive stimuli. This concept suggests that after PTE, in conditions of decreased circulating PTH, the glomerular vasoconstriction induced by calcineurin inhibitors may increase and the serum creatinine level is increased as well. At the same time, there is no evidence that the elevated PTH level would have a beneficial effect on the kidney transplant and recipient survival rates. Conversely, post-transplant HPT is a risk factor of worsening the transplanted kidney function, thus enhancing, as mentioned above, nephrocalcinosis [3, 21, 36].

There is another aspect of the surgical treatment for HPT in renal transplant recipients that is under discussion: whether PTE should be performed in patients awaiting for kidney transplantation who have severe HPT responding to a drug therapy. It is suggested that PTE should be performed in the pre-transplant period in order to prevent the tertiary HPT occurrence and to minimize the risk of renal graft function impairment during the surgical treatment; and here the subtotal PTG removal is the optimal technique. This will avoid the need for PTE after kidney transplantation and at the same time retain the PTG function, preventing the development of adynamic bone disease [39].

Conservative treatment. For the prevention and conservative treatment of post-transplant HPT with hypo-/normocalcemia, the vitamin D-based drugs (native vitamin D preparations, non-selective/selective vitamin D receptor activators) are used with regular dynamic monitoring of serum

calcium, phosphorus and PTH levels, and daily monitoring of calciuria [3, 20, 21].

No specific recommendations have been developed yet for the use of native vitamin D preparations in the prevention and treatment of (non-hypercalcemic) HPT in renal transplant recipients. Nevertheless, KDIGO (Kidney Disease: Improving Global Outcomes) recommends, as the first line of therapy, that the level of calcidiol be restored to the optimum when it drops below 30 ng/mL [20]. Although several previous studies reported a decrease in PTH levels and an increase in bone mineral mass when taking colecalciferol in the first post-transplant year, the overall therapeutic efficacy of the native vitamin D preparation remains controversial [3, 20, 46]. A safe and favorable effect of a large dose 100,000 IU of vitamin D_3 (colecalciferol) every 2 weeks for the first 2 months, then monthly for 22 months in recipients with vitamin D deficiency was confirmed in a randomized clinical trial VITALE: the serum concentration of 25(OH)D was maintained in the range of over 30, but no more than 80 ng/mL [48]. Vitamin D shall be prescribed with calcium supplements, since the kidney transplant recipients are prone to a negative calcium balance [3, 20, 21].

Active metabolites of vitamin D and their analogues are preferable for the recipients with a reduced renal transplant function (GFR less than 60 ml/min). As with the native vitamin D preparation, several recently published studies have shown that oral administration of calcitriol after kidney transplantation reduces the blood PTH concentration, improves the bone mineral content, and is associated with an increased renal graft survival [3, 20, 47].

In recent years, the several studies have been published on the use of a new generation of vitamin D analogues, a selective vitamin D receptor

activator. The drugs of this class effectively suppress PTH secretion, have minimal hypercalcemic and hyperphosphatemic effects, possess favorable pleiotropic properties and have been successfully used for the prevention and treatment of secondary HPT at pre-dialysis and dialysis stages of CKD [49-53].

One of the studies, a prospective, randomized, controlled trial evaluating the effect of oral paricalcitol (administered on the 3rd day after the surgery) on the HPT incidence by the end of the first year after kidney transplantation showed a 29% HPT rate in the paricalcitol-treated group and 63% in the control group. Significant differences between the groups in blood levels of PTH were recorded at one month after the initiation of paricalcitol use, remained the same trend throughout the year; and at the end of the study period, the blood PTH levels made 42 pg/mL in the paricalcitol group versus 85 pg/mL in the control group ($p = 0.0004$). Similar dynamic changes were observed in daily calciuria, but it did not exceed 250 mg/day. The authors did not find differences between the groups in bone-specific alkaline phosphatase activity, serum calcium, phosphorus and vitamin D, in densitometry parameters, and the renal transplant function, although in latter case, the incidence of moderate to severe interstitial fibrosis, and the inflammation signs were more frequently recorded in the control group. Based on the data obtained, the authors concluded that the oral paricalcitol effectively prevents the development of post-transplant HPT in the first year after surgery [48].

The study by E. Gonzalez et al. [50] confirmed the efficacy and safety of the oral form of the selective vitamin D receptor activator in a relatively low dose for a long-term control of secondary HPT in recipients with a long-functioning renal transplant and a vitamin D deficiency. A reliable control of

secondary HPT with paricalcitol administration to patients after kidney transplantation and good drug tolerability were demonstrated in other studies: an observational study, a retrospective multicenter study, and a single-center prospective randomized controlled cross-over study [51-53].

Cinacalcet, a drug from the class of calcimimetics, has been used for a temporary correction of hypercalcemia in tertiary HPT. Cinacalcet has not been approved yet for HPT treatment in patients after kidney transplantation, but is has been recommended for the hypercalcemia correction in primary HPT. Apparently, the similarity of the morphofunctional and clinical characteristics of the tertiary and primary HPT, as well as the fact that at present cinacalcet is the only available drug for correcting hypercalcemia and hypophosphataemia in patients with post-transplant HPT, appeared to be the starting point for its clinical (off-label) use. For the recent decade (since the first publications in 2004), a great experience has been gained in observational studies, including the own clinical experience of the author [54-55], and the experience of long-term treatment with cinacalcet, which demonstrated a high efficacy and safety of the drug in the treatment of hypercalcemia, hypophosphatemia, and HPT in renal transplant recipients [3, 20, 47, 54-56]. Clinicians unanimously stressed that hypercalcemia and hypophosphatemia improvement, as well as the reduction of PTH blood levels were achieved in almost all patients while on cinacalcet therapy, although the extent of such improvement can vary greatly, possibly, because of the specific pharmacokinetics/pharmacodynamics of the drug and/or the grade of PTG hyperplasia and nodular transformation [57]. The hypocalcemic effect of cinacalcet is associated, first, with the suppression of PTH-mediated calcium release from bone tissue and, second, with an

increased urinary calcium excretion by the stimulation of calcium-sensitive receptors located in the kidney tubular system [55, 56].

The systematic review and meta-analysis, as well as the randomized controlled trial published several years ago confirmed the results of earlier research on this subject [58, 59]. The systematic review and meta-analysis included 21 non-randomized prospective and retrospective studies performed from 2004 to January 2012 where the dynamic changes of blood calcium, phosphorus, PTH, and creatinine levels were assessed in 411 patients who were investigated within 3 to 24 months. The studies demonstrated that the serum calcium concentration decreased by 0.29 mmol/L, the serum phosphorus concentration increased by 0.15 mmol/L, the blood PTH level decreased by 102 pg/ml, and the blood creatinine did not change. A randomized clinical trial had a relatively small number of patients enrolled (n=114), and a short follow-up period (1 year), but it also confirmed the efficacy and safety of cinacalcet in the renal transplant recipients with hypercalcemic HPT. The primary endpoint of the study, the achievement of serum calcium level below 2.55 mmol/L, was recorded in 78.9% of patients in the cinacalcet group, and in 3.5% in the placebo group. The secondary endpoints: the changes in bone mineral density (BMD) at the femoral neck and in bone turnover markers were similar in two groups, and the dynamics changes of phosphatemia were positive in the cinacalcet group. The plasma PTH level in the study group decreased by 128 ± 34 pg/mL, the calculated GFR remained stable in both groups. Based on the data obtained, the authors concluded that cinacalcet provides an effective correction of hypercalcemia, hypophosphatemia, and PTG hyperfucntion in the patients after kidney transplantation [59].

Some researchers express their concern about ambiguous data on the effect of cinacalcet cessation on the urinary calcium excretion, the graft function, and also the PTG function [3, 20, 47].

Meanwhile, recent reports indicate that cinacalcet increases calciuria only temporary, during the first 8 hours after intake; the decrease in kidney function is relatively minor and temporary, being reversal after the drug withdrawal, and this decrease is most likely related to renal hemodynamic shifts, rather than structural disorders. The drug displays no adverse interactions with standard immunosuppressive therapies [7, 58, 59]. However, the question of the cinacalcet administration and therapy duration remains open.

Conclusion

HPT is associated with mineral bone disorders after kidney transplantation and has a significant effect on the long-term recipient and transplant survival rates. Its highest incidence is recorded in the first postoperative year. The post-transplant HPT pathogenesis is complicated; the key risk factor for its development and progression is the pre-existing diffuse-nodular hyperplasia of the PTG, other risk factors include a long-term dialysis therapy, a suboptimal renal transplant function, vitamin D and magnesium deficiencies. Patients who underwent kidney transplantation should be regularly monitored for the laboratory parameters of the mineral metabolism and bone turnover aimed at an earlier detection of HPT and close monitoring of the HPT course. The current strategy of the post-transplant HPT prevention and treatment is based on the principles of an individual approach, the assessment of risk factors, and minimization of the factors causing its development. An integrated approach to the post-

transplant HPT correction includes careful monitoring of this disease in the patients awaiting for kidney transplantation, replenishing the vitamin D deficiency by administering the native vitamin D preparations or its active metabolites in the postoperative period, performing the PTE (subtotal or partial PTG resection) at indications.

The authors state there is no conflict of interests to declare

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