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CLINICAL STUDY

The role of proteinuria, paricalcitol and vitamin D in the development of post-transplant diabetes mellitus

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ABSTRACT

INTRODUCTION: Post-transplant diabetes mellitus (PTDM) occurs most frequently during the first year after transplantation. We focused on parameters of calcium-phosphate metabolism and proteinuria as possible new risk factors for PTDM after kidney transplantation.

MATERIALS AND METHODS: We have prospectively identified risk factors for post-transplant diabetes mellitus with follow-up of 12 months in a set of 167 patients after kidney transplantation. Patients with diabetes mellitus type 1 and type 2 as well as patients using ciclosporin A or mTOR inhibitor have been excluded from the monitoring. From the perspective of immunosuppression it was a homogeneous set of patients.

RESULTS: We identified the following independent risk factors for PTDM in our set: average proteinuria > 0.300 g/24 h (HR 3.0785, (95 % CI 1.6946–5.5927), p=0.0002), level of vitamin D<20 ng/ml (HR 5.4517, (95 % CI 2.3167–11.8209), p<0.0001) baseline serum level of phosphorus >1.45 mmol/l (HR0.0821, (95 % CI0.0042–1.5920), p=0.0439). The lowest occurrence of PTDM and proteinuria was recorded in patients whose treatment included paricalcitol (p<0.0001) and these patients had at the same time the highest level of vitamin D (p<0.0001).

CONCLUSION: Deficit of vitamin D, proteinuria and hyperphosphatemia have been independent risk factors for the development of PTDM in our set. We identified the usage of paricalcitol as protective factor with regard to the PTDM development *(Tab. 6, Fig. 4, Ref. 29)*. Text in PDF *www.elis.sk.*

KEYWORDS: post-transplant diabetes mellitus, proteinuria, vitamin D, paricalcitol, kidney transplantation.

Abbreviations: PTDM – post-transplant diabetes mellitus, oGTT – oral glucose tolerance test, CKD – chronic kidney disease, HPTH – hyperparathyreosis, PTH – parathormone, KT – kidney transplantation, ADA – American diabetes association, DM2 – diabetes mellitus type 2, APKD – polycystic kidney disease, CKD-MBD – bone disease, BMI – body mass index, HbA1c – glycated hemoglobin, ACEI – angiotensin-converting-enzyme inhibitors

Introduction

Diabetes mellitus after transplantation is a serious and frequently occurring metabolic complication and both the name and the definition have developed during the last fifty years. The post-transplant diabetes mellitus (PTDM) occurs most frequently during the first year after transplantation and does not affect the patient and graft survival (and even the function of the graft) during the first years after the transplantation in any significant way. However, this difference becomes significant in a long-term horizon from 7–10 years after the transplantation (1). Taking into account the improved quality of healthcare, advanced immunosuppressive protocols, surgery techniques and especially well-functioning donor programme, it is clear that numbers of transplanted patients will grow. Development of transplantation programme and development of new immunosuppressants improve the survival of both the graft and the patient after the transplantation, the risk of acute rejection is reduced, but the risk of other complications that affect especially the long-term survival of the patient, graft as well as the patient's quality of life, increases in the population of transplanted patients.

The graft survival is significantly affected from the long-term perspective by cardiovascular morbidity and mortality. We know at the present era of modern and effective immunosuppression that post-transplant diabetes mellitus is an independent predictor of cardiovascular events (2). Valderhaug et al followed 1410 consecutive kidney recipients transplanted between years 1995 and 2006 and examined the predictive value of an oral glucose tolerance test (oGTT) at 10 weeks. Patients in whom the oGTT demonstrated PTDM had a 1.8 fold increase in cardiovascular disease mortality and a 1.5-fold increase in overall mortality (3).

We have proven in the already published analysis of risk factors for PTDM in a homogeneous set of patients from the perspective of immunosuppression that the age at the time of transplantation, positive family anamnesis for diabetes mellitus type 2, body mass index at the time of transplantation more than 30 kg/m^2, predia-

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betes before transplantation and proteinuria > 0.15 g/day are independent risk factors for PTDM development (follow-up – 12 months) (4). We have therefore focused in the said set of patients on proteinuria and parameters of calcium-phosphate metabolism including the level of vitamin D, which could be identified as further risk factors for the PTDM.

Vitamin D deficiency has been associated with poor outcomes in the general population and in CKD (chronic kidney disease) patients (5, 6, 7). An univocal definition of 25(OH)D deficiency is still lacking, as no randomized controlled trials (RCTs) have yet been designed to investigate the best 25(OH)D targets to improve hard endpoints in humans. In the general population, serum 25(OH)D levels < 20 ng/ml are considered deficient, 20–29.9 ng/ml insufficient, and levels ≥ 30 ng/ml sufficient (8, 9). Optimal vitamin D levels may vary according to the specific disease and outcome of interest. 25(OH)D levels > 10 ng/ml were shown to be adequate to prevent rickets and osteomalacia, whereas 25(OH)D levels > 30 ng/ml may be required to prevent secondary hyperparathyreosis (HPTH) or osteoporosis (10).

Proteinuria is a common problem occurring in up to 45 % of renal transplant recipients. Proteinuria is associated with worse clinical outcomes including an increased risk of death, cardiovascular events, and graft loss (11).

We determined through a thorough analysis of the set that proteinuria in our set can be significantly linked with the usage of paricalcitol. Paricalcitol, a selective vitamin D receptor activator, is indicated in the prevention and treatment of secondary hyperparathyroidism. Several analyses (however, only in small sets of patients) confirmed that paricalcitol in patients after kidney transplantation reduces the values of parathormone (PTH), has a positive effect on proteinuria, and is easily tolerated. When compared with any other analogs, paricalcitol causes less significant hypercalcemia and hyperphosphatemia, which is related to the lower effect on the transport proteins for calcium and phosphorus in the bowels (12). There is little information on the use of paricalcitol in patients after renal transplantation.

Material and methods

We have been prospectively evaluating selected risk factors for PTDM in the set of 167 patients (Europids) after primary kidney transplantation (KT) from a dead donor in Transplant center Martin. PTDM was diagnosed according to the ADA (American diabetes association) criteria, oral glucose tolerance test (oGTT) was realised in the 10th – 12th week after transplantation and in the 12th month after transplantation.

We determined in the already published study for all patients the age at the time of transplantation, sex, family history of diabetes mellitus type 2 (DM2) – parents, siblings, grandparents, compatibility index and number of HLA-mismatches, presence of risk HLAs (A30, B27, B42), basic diagnosis of kidney failure (we have differentiated patients with polycystic kidney disease – APKD). Monitored parameters were completed in this analysis with the examination of serum concentration of calcium, phosphorus, intact parathormone (iPTH) and levels of vitamin D. Values of vitamin D and iPTH were determined before the transplantation and subsequently in 3rd, 6th and 12th month after the transplantation. Proteinuria, serum value of calcium, phosphate and level of tacrolimus were determined during each check-up in the transplant centre (at average 22 times during the monitored period).

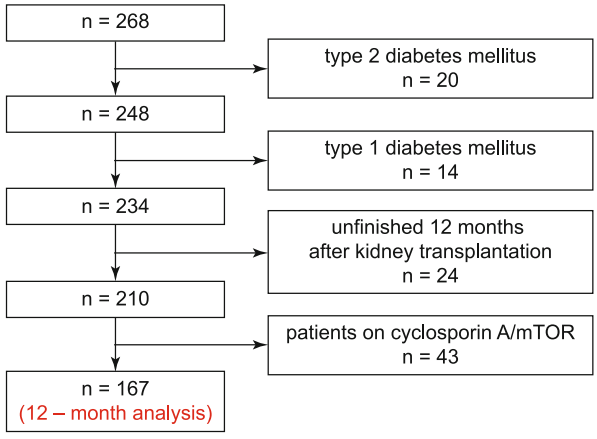

Fig. 1. Inclusion criteria.

We further focused on the treatment of bone disease (CKD-MBD): cinalacet, cholecalciferol, paricalcitol or none (or combined treatment) before the transplantation, 6 months after the transplantation and 12 months after the transplantation. We have found the influence of CKD-MBD treatment on the development of PTDM in the monitored period 12 months after the transplantation.

Only patients using tacrolimus in immunosuppressive mode were included in the monitoring (Fig. 1) and patients with diabetes mellitus type 1 or type 2 diagnosed before the transplantation were excluded from the monitoring.

We used a certified statistical program MedCalc version 13.1.2. (MedCalc Software's VAT registration number is BE 0809 344 640, Member of International Association of Statistical Computing, Ostend, Belgium) for statistical evaluation and we used following statistical analyses: Student's t-test, chi-square test, Cox proportional hazard model. We consider the value $p < 0.05$ to be statistically significant.

Ethical approval

All procedures performed in studies involving human participants are approved with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Results

There were 167 patients in this set of patients, out of which 103 (61.7 %) patients formed the control set and 64 (38.3 %) patients formed the set with PTDM diagnosed in monitored period (12 months after primary kidney transplantation). Basic set characteristics are shown in Table 2.

Tab. 1. Comparison of control set vs. PTDM set in terms of immunosuppression (12 months after transplantation).

12-month analysis	control set n=103	PTDM set n=64	p
average level of TAC (ng/ml)	4.7±0.9	4.8±1.2	0.5592
average dose of prednisone/day (mg)	8.2±2.3	8.8±2.0	0.0877
average dose of MMF/day (mg)	849.4±264.2	911.7±175.4	0.0919
average dose of mycophenolate sodium/day (mg)	670.7±292	721.9 ±113	0.1734

TAC – tacrolimus, MMF – mycophenolate mofetil

Tab. 2. Patients characteristics.

	control set n=103	PTDM set n=64	p
age at the time of transplantation (years)	43±12.1	50.5±9.6	< 0.0001
dialysis before transplantation (months)	34.1±19.2	37.3±14.9	0.2572
positive family history of DM2 (%)	29.8	78.1	< 0.0001
male sex (%)	62.1	59.4	0.8627
HLA A30 (%)	2.9	0	0.4375
HLA B27 (%)	9.6	10.9	0.9937
HLA B42 (%)	1	0	0.8335
average number of HLA mismatches	3.5±1.2	3.7±1.4	0.3266
APKD (%)	10.4	17.2	0.2839
ECD donor (%)	17.3	21.9	0.5926
treatment with methylprednisolone (g) - induction	1000	1000	1.0000
pulse treatment with methylprednisolone (%) except for induction	36.4	34.9	0.9792
average dose (g) except for induction	2.0±0.7	2.3±0.7	0.0086
BMI at the time of transplantation (kg/m^2)	24.9±4.1	26.5±4.3	0.0170
weight at the time of transplantation (kg)	73.7±15.1	78.3±14.5	0.0533
BMI 12 months after transplantation (kg/m^2)	26.8±5.3	28.5±4.1	0.0318
weight 12 months after transplantation (kg)	78.5±15.6	83.5±13.1	0.0361
weight gain 12 months after transplantation(kg)	5.6±5.1	6.2±5.6	0.4834
average level of TAG (mmol/l)	2.0±0.7	1.9±0.5	0.3262
average level of cholesterol (mmol/l)	4.4±0.7	4.5±0.5	0.3262
artery hypertension (%)	96.2	98.4	0.7277
basiliximab in induction (%)	52.4	84.4	0.0001
average level of magnesemia (mmol/l)	0.79±0.1	0.78±1.3	0.9393
prediabetes before transplantation (%)	0	15.6	0.0001
HCV PCR positivity (%)	0.9	4.7	0.2914
CMV replication (%)	45.8	45.2	0.9286
average number of copies (cop/ml)	3500	3800	0.9763
average proteinuria (g/24 h)	0.18±0.13	0.23±0.16	0.0308

DM2 – diabetes mellitus type 2, APKD – polycystic kidney disease, ECD – expanded criteria donor, BMI – body mass index, TAG – triacylglycerols, HCV – hepatitis C, CMV – cytomegalovirus, prediabetes – impaired glucose tolerance, impaired fasting glucose

Average level of tacrolimus (during the 12 monitored months after kidney transplantation) was without statistically significant difference in both sets (p = 0.5592), similarly the average dose of prednisone/day (p = 0.0877). Average level of mycophenolate mofetil/day (or mycophenolate sodium) was also without statistically significant difference between the monitored sets (p = 0.0919 – mycophenolate mofetil and p = 0.1734 – mycophenolate sodium (Tab. 1). In view of the above, both sets were homogenous in terms of the administered immunosuppression and individual monitored parameters were not distorted by the administered immunosuppression (4).

Patients who developed PTDM during the monitored period were compared to patients in the control set significantly older, had significantly more frequently positive family history for diabetes mellitus type 2, higher value of body mass index (BMI) at the time of transplantation and 12 months after the transplantation, more frequent prediabetes before the transplantation (impaired glucose tolerance or impaired fasting glucose) and significantly higher value of proteinuria.

We subsequently added parameters of bone metabolism at the baseline at the time of transplantation, 6 and 12 months after the transplantation (Tabs 3, 4, 5).

Patients who developed PTDM during the monitored period had as compared to the control set significantly lower base line levels of vitamin D and higher levels of phosphorus in the serum. We identified in the set of patients with PTDM 6 months after the

transplantation significantly lower levels of vitamin D as compared to the control set. We further determined that treatment of patients in the control set included cholecalciferol significantly more often as compared to patients with PTDM. Significantly lower levels of vitamin D in the set of patients with PTDM were determined also 12 months after the transplantation.

We found out that 62 patients had constantly (during each monitoring) value of vitamin D less than 30 ng/ml.

We identified by means of multivariate analysis following independent risk factors for PTDM in our set: average proteinuria during the monitored period more than 0.300 g/24 hours, value of vitamin D less than 30 ng/ml (ng each monitoring) and serum value of phosphorus at the time of transplantation more than 1.45 mmol/l (Tab. 6).

We learned by using the correlation coefficient that the occurrence of PTDM negatively correlates with the level of vitamin D – baseline (r = –0.6210 (95% CI for r: –0.7886 to –0.3674), p < 0.0001), what means that lower base line level of vitamin D increases the occurrence of PTDM in our set. We analogically applied the correlation coefficient also in the case of proteinuria and again confirmed that the occurrence of PTDM significantly rises with the average value of proteinuria (r = 0.3809 (95% CI for r: 0.2134 to 0.5266), p < 0.0001). However, we did not confirm significantly higher occurrence of PTDM with higher value of phosphorus at the time of transplantation (r = 0.01690, (95% CI for r: –0.4536 to 0.4800), p < 0.9469).

We further analyzed the impact of treatment of secondary hyperparathyroidism (cholecalciferol, cinacalcet and paricalcitol) on the PTDM development (Fig. 2). The average dose (i.e. during 12 monitored months after the transplantation) of cholecalciferol was 17 ± 6 drops/week, paricalcitol 2.8 ± 1.8 μg/week and cinacalcet 42.3 ± 12 mg/day. We learned that the highest occurrence of PTDM was in the set of patients who did not use any preparation in their treatment, or used only cholecalciferol in monotherapy, and that at the baseline, 6 months after the transplantation as well as 12 months

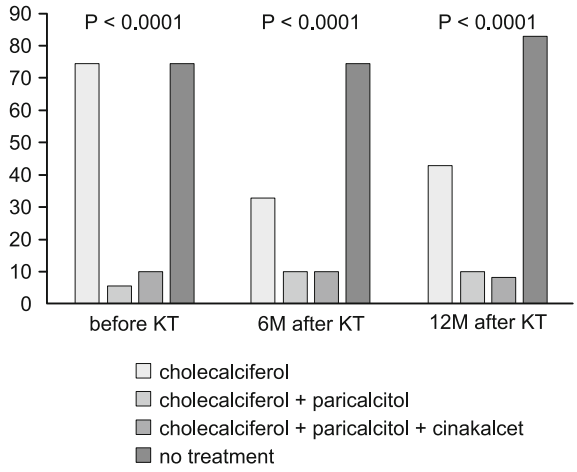

Fig. 2. Impact of the treatment type on the PTDM development – graph shows % of patients with PTDM development.

Tab. 3. Characteristics of the set after parameters of bone metabolism are added – base line.

base line	control set n=103	PTDM n=64	p
vitamin D (ng/ml)	32.4±9.7	23.1±7.6	0.0282
iPTH (pg/ml)	346.8±250.3	211.2±182.2	0.1830
Ca (mmol/l)	2.2±0.2	2.2±0.3	1.000
P (mmol/l)	1.2±0.9	1.9±0.4	0.0374
cinacalcet (%)	31.1	12.5	0.3262
cholecalciferol (%)	34	10.9	0.2276
paricalcitol (%)	78.6	35.9	0.0600

Tab. 4. Characteristics of the set after parameters of bone metabolism are added – 6 months after the transplantation.

6M after transplantation	control set n=103	PTDM n=64	p
vitamin D (ng/ml)	38.5±8.8	22.7±10.9	0.0022
iPTH (pg/ml)	202.5±153.8	129.9±58,4	0.1798
Ca (mmol/l)	2.5±0.2	2.4±0.1	0.1744
P (mmol/l)	0.8±0.2	1.0±0.2	0.0382
cinacalcet (%)	19.4	7.8	0.4648
cholecalciferol (%)	77.7	29.7	0.0359
paricalcitol (%)	29.1	10.9	0.3214

Tab. 5. Characteristics of the set after parameters of bone metabolism are added – 12 months after the transplantation.

12M after transplantation	control set n=103	PTDM n=64	p
vitamin D (ng/ml)	41.2±13.1	23.5±9.6	0.0029
iPTH (pg/ml)	113.9±81.7	92.7±39.7	0.4700
Ca (mmol/l)	2.5±0.1	2.5±0.2	1.000
P (mmol/l)	0.9±0.2	1.0±0.2	0.2783
cinacalcet (%)	21.4	3.1	0.2238
cholecalciferol (%)	78.6	46.9	0.1530
paricalcitol (%)	24.3	15.6	0.6352

Tab. 6. Cox's regression Hazard model.

	Hazard ratio	CI 95 %	p
proteinuria (average) ≥ 0.300 g/24 hours	3.0785	1.6946–5.5927	0.0002
vitamin D < 20 ng/ml*	5.4517	2.3167–11.8209	< 0.0001
vitamin D 21–30 ng/ml**	1.3167	1.0057–1.8741	0.0322
vitamin D 31–40 ng/ml	1.1185	0.8955–1.2353	0.0786
vitamin D > 40 ng/ml	0.4500	0.2552–1.6932	0.6585
phosphorus at the time of transplantation < 0.81 mmol/l	0.0565	3.4926– 4.9317	0.8364
phosphorus at the time of transplantation 0.81–1.45 mmol/l	0.0366	1.7556–4.5512	0.2192
phosphorus at the time of transplantation > 1.45 mmol/l	0.0821	0.0042–1.5920	0.0439

* patients with continuous level of vitamin D < 20 ng/ml (n = 29), ** patients with continuous level of vitamin D (n = 33)

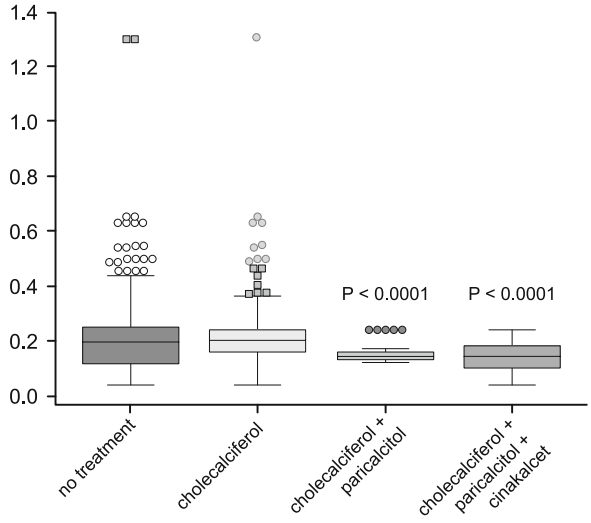

Fig. 3. Average value of proteinuria (g/day) according to treatment.

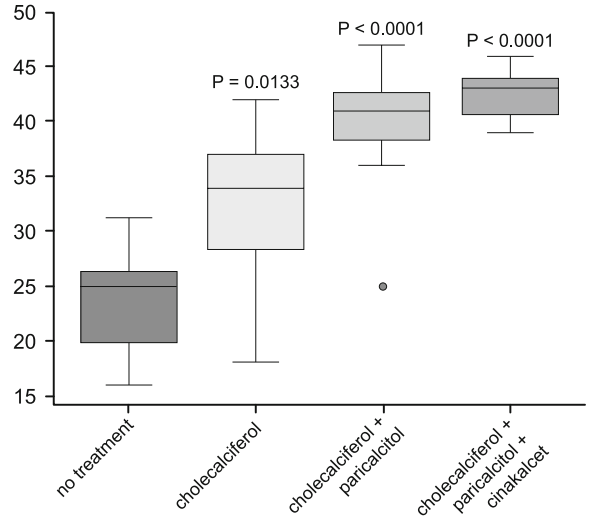

Fig. 4. Average level of vitamin D (ng/ml) according to treatment

after the transplantation. On the other hand, the lowest incidence of PTDM was recorded in the set of patients whose treatment included (again at the base line, 6 months after the transplantation as well as 12 months after the transplantation) cholecalciferol + paricalcitol or cholecalciferol + paricalcitol + cinacalcet.

We similarly evaluated also the impact of treatment of the secondary hyperparathyroidism (cholecalciferol, cinacalcet and paricalcitol) on the average value of proteinuria during the monitored period (Fig. 3). The significantly lowest proteinuria was recorded for patients whose treatment included cholecalciferol and paricalcitol with or without cinacalcet.

Figure 4 shows average levels of vitamin D during the monitored period according to the treatment of secondary hyperparathyroidism. We learned that significantly highest levels of vitamin D had those patients who were treated with cholecalciferol and paricalcitol with or without cinacalcet or whose treatment included only cholecalciferol. Patients with no treatment had clearly lowest levels of vitamin D.

Discussion

The most important finding arising from our analysis is the fact that hypovitaminosis D is an independent risk factor for the development of PTDM. Vitamin D deficit is associated with higher occurrence of diabetes mellitus type 2 and it is also known that substitution treatment with vitamin D acts as a prevention of progression of prediabetes conditions to diabetes mellitus type 2 (8, 13). Vitamin D insufficiency is associated with increased glycated hemoglobin (HbA1c) levels and resistance to insulin (14, 15). Authors Tabesh et al described the impact of supplementing vitamin D and calcium on the reduction of serum level of interleukin 6 and tumor necrosis factor-α in patients with diabetes mellitus type 2 (16). Meta-analysis of authors George et al points out that supplementation with vitamin D improves values of fasting blood glucose and reduces insulin resistance, but does not affect the value of glycosylated hemoglobin (HbA1c) (17). To the contrary, another meta-analysis did not confirm the effect of supplementation of vitamin D on the glucose metabolism. However, authors of this meta-analysis point out that results can be influenced by high heterogeneity of studies and short follow-up duration (18).

No randomized study has so far confirmed whether the vitamin D deficit is a risk factor for the PTDM development. The ongoing randomized controlled study VITALE with follow up of 12–48 months, which follows the effect of substitution treatment with calcitriol after kidney transplantation, can have results that can shed more light on the issue (19). We have clearly confirmed in our set that the deficit of vitamin D with average value during the monitored 12 months after the transplantation less than 30 ng/ml is an independent risk factor for PTDM development. We also confirmed negative correlation of average value of vitamin D and occurrence of PTDM 12 months after the transplantation, what confirms that long-term deficit of vitamin D is a risk factor not only for diabetes mellitus type 2 but also for PTDM.

Proteinuria is known to be an independent risk factor for cardiovascular disease and mortality as well as a predictor of allograft damage and loss after kidney transplantation (20, 21). The prevalence of proteinuria in kidney transplant recipients varies considerably from 7.5 to 45.0 %, depending on the threshold used to define proteinuria (22). Proteinuria in the first week after the transplantation can be induced by hyperglycaemia with osmotic diuresis when high doses of corticosteroids are administered, or also the residual proteinuria of native kidneys can be present. However, the proteinuria and albuminuria 3–6 months after the kidney transplantation is a more important factor. Authors Roland et al proved the relationship between albuminuria (30–300 mg/day in a sample of 24-hour urine) and the development of PTDM. Patients with proteinuria (> 300 mg/day in a sample of 24-hour urine) (23, 24) had even higher risk of PTDM occurrence. We confirmed in our set that the average proteinuria of more than 300 mg/24 hours (determined from 20–22 samples of 24-hour urine) is an indepen-

dent risk factor for the PTDM development and its higher value correlates with higher occurrence of PTDM. An important information is the usage of angiotensin-converting-enzyme inhibitors – ACEI or sartans in our set. Of patients having proteinuria below 150 mg/24 hours the ACEI or sartan was used by 15 % of patients as compared to 18 % of patients with average value of proteinuria higher than 150 mg/24 hours (p = 0.8955) and results were therefore not distorted by this treatment.

It is known that patients with CKD have low serum levels of vitamin D related to higher mortality and quicker progression of CKD (25). Authors de Borst et al confirmed in their review, mentioning 6 studies, the reduction of proteinuria in case paricalcitol was used in non-transplanted population with CKD (26). The VITAL study showed that treatment for 24 weeks with 2 μg of paricalcitol reduced residual albuminuria in patients with type 2 diabetes mellitus and kidney disease that were being treated with stable doses of ACEIs or sartans (27).

Kanter Berga et al did not confirm the improvement of either proteinuria or albuminuria in 110 patients after the kidney transplantation in case calcidiol was used (28).

The work which deals with the effect of paricalcitol on proteinuria after kidney transplantation is carried out in a limited number only and in very small sets. A study carried out in 58 patients who were monitored for a period of 18 months while taking paricalcitol is available. The authors confirmed a significant decrease of proteinuria in the monitored set by more than 50 %. In addition to proteinuria, that analysis confirmed the effect of paricalcitol on significant decrease of PTH (29). We assume that it is the treatment with paricalcitol with the fall of proteinuria that affects the occurrence of PTDM. We unambiguously confirmed in our set a lower occurrence of PTDM in the set of patients treated with paricalcitol as compared to patients who did not have paricalcitol in their treatment.

The limitation of our analysis is the fact that it is a retrospective analysis where we had to exclude patients using in CKD treatment other preparations (such as calcitriol) from the monitoring, but the number of such patients was negligible (n = 3). We also excluded from the monitoring in evaluating the impact of treatment of the secondary hyperparathyroidism on the development of PTDM patients whose treatment substantially changed (n = 10). Only those patients whose treatment did not change during the 12 months after the transplantation thus remained in the set for the evaluation of the treatment of secondary hyperparathyroidism. A large benefit of the study is the homogeneity of the set from the perspective of immunosuppression where results and development of PTDM were not affected by used immunosuppression.

Conclusion

We identified in our set the deficit of vitamin D, proteinuria of more than 300 mg/24 hours and hyperphosphatemia at the time of transplantation as independent risk factors for the development of PTDM after the kidney transplantation. Usage of paricalcitol seems to be a protective factor probably with regard to the significant impact on proteinuria as well as significantly higher levels of vitamin D in patients who were treated with paricalcitol. However, to confirm our findings further especially randomized controlled studies will be required, similar as those performed with non-transplanted patients with CKD or patients with diabetes mellitus type 2.

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