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Role of sex in post-transplant diabetes mellitus development: Are men and women equal?

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ABSTRACT

Introduction: Sex differences are defined as biology-linked differences between women and men that occur through the sex chromosomes and their effects on organ systems.
Material and methods: The objective of this prospective study was to determine risk factors for post-transplant diabetes mellitus (PTDM) in men and women.
Results: A total of 417 patients (271 men and 146 women) were included in the monitored group. Age at the time of kidney transplantation (KT) >60 years and hypovitaminosis D at the time of KT (<20 μg/l) were identified as independent risk factors for PTDM in both men and women. It was further confirmed as an independent risk factor for men a waist circumference at the time of KT >94 cm, C-peptide at the time of KT >5 ng/ml, HOMA-IR >2 and triacylglycerols at the time of KT >1.7 mmol/l. In case of women, the dominant factor was BMI at the time of KT >30 kg/m2 and menopause at the time of KT. A significant decrease in C-peptide was recorded in women with PTDM.
Conclusion: It was confirmed that there are gender differences with regard to the development of PTDM after KT. Women show pancreas β cell dysfunction, whereas insulin resistance and metabolic syndrome are dominant in men.

1. Introduction

The development of post-transplant diabetes mellitus after kidney transplantation (PTDM) significantly increases kidney graft loss and mortality.[1] Patients with PTDM have significantly higher rates of cardiovascular disease, cardiovascular death, and overall mortality with a doubling in all-cause mortality and a tripling in cardiovascular events.[2,3,4] Despite the fact that the presence of insulin resistance in combination with pancreas βcell dysfunction is known in the case of PTDM, discussions continue about whether PTDM is a separate entity. Insulin resistance does not lead by itself to the development of hyperglycaemia in the case of PTDM. Hyperglycaemia occurs because of the dysfunction of pancreas β cells, which in the case of continuing insulin resistance are no longer able to maintain sufficient insulin secretion to maintain normoglycaemia.[5]

Causes of PTDM development are individual and differ for individual patients. Considerable glycaemic fluctuations are generally observed, especially during the first six months after transplantation, when there is a relatively rapid reduction in immunosuppressive treatment, or when anti-rejection treatment is administered. Although hyperglycaemia is observed in >90% of patients during the first days following transplantation, PTDM develops only in portion of them.[6] PTDM development is influenced by several variables that are specific only to the transplanted population. They include changes in the graft (or in the native kidneys) induced by used immunosuppression, hypomagnesaemia (an adverse reaction to calcineurin inhibitors), cytomegalovirus infection and others.[7,8,9] A role is also played by genetics, as several genes responsible for pancreas β cell apoptosis have been identified. However, obesity, metabolic syndrome, and related insulin resistance remain the key factors responsible for PTDM development.[10]

Another important question we tried to answer in our study is whether the identified risk factors have the same weight for men as compared with women after kidney transplantation. It is generally known that there is evidence of differences between genders regarding the epidemiology, pathophysiology, and treatment of many diseases.[12]

Abbreviations: BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CNI, calcineurin inhibitors; DM2, diabetes mellitus type 2; HbA1c, glycated haemoglobin; HLA, human leukocyte antigen; HOMA-IR, homeostatic model assessment for insulin resistance; IDF, International Diabetes Federation; IRI, immunoreactive insulin; oGTT, oral glucose tolerance test; PTDM, post-transplant diabetes mellitus; KT, kidney transplantation.

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Sex differences are defined as biology-linked differences between women and men that occur through the sex chromosomes, sex-specific autosomal gene expression, sex hormones, and their effects on organ systems. Differences between genders originate in social-cultural processes, such as the different behaviour of men and women, exposure to specific impacts of the environment, various forms of nutrition, lifestyle or stress, but also different attitudes to treatment and prevention.[13,14] Differences between genders are extremely important for development, diagnostics, treatment and prevention in the case of disease, in our case PTDM, which is also associated with lifestyle.[15]

In the case of diabetes mellitus type 2 (DM2), a higher body mass index (BMI) is a predictor for women, whereas the waist circumference dominates in the case of men. Insufficient physical activity leads to the development of DM2 in women, whereas metabolic syndrome with the presence of arterial hypertension together with dyslipidaemia is seen more often in men. A poor level of education facilitates the development of DM2 in more women than in men. In terms of conditions with pre-diabetes, fasting hyperglycaemia is present more frequently in men, whereas impaired glucose tolerance in more often seen in women. Smoking is a risk factor for both genders, but in the case of female smokers with DM2, the cardiovascular risk is significantly higher compared to male smokers with DM2. In general, men have higher occurrence of DM2 at a younger age compared to women. Men have abdominal obesity more often, whereas women can be in a state of so-called metabolically healthy obesity. Women have hypovitaminosis D more frequently, which is associated with the occurrence of DM2.[16] Sex differences with regard to PTDM have yet to be published in any available study and therefore the objective of our multicentre prospective 12-month analysis was to determine whether risk factors for PTDM in patients after kidney transplantation are the same for women and men. Another objective was to determine when PTDM develops in men and in women and to compare graft survival in men with and without PTDM and in women with and without PTDM.

2. Material and methods

This prospective multicentre analysis with 12-month follow-up included 417 patients (all of European racial ancestry) without a diagnosis diabetes mellitus type 1 or 2 or prediabetes (glucose tolerance disorder and fasting hyperglycaemia) at the time of kidney transplantation, who had a kidney transplanted at the transplantation centres in Martin, Bratislava, Banská Bystrica or Košrice; thus, all kidney transplantation centres in the Slovak Republic were engaged in the analysis. All transplant centres use the same immunosuppression protocols. Each patient in induction receives either basiliximab or Thymoglobuline (cumulatively 3.5 mg/kg). Each patient receives as part of induction 500 mg of Solu-medrol before operation and 500 mg of Solu-medrol on the first post-operative day. We have also recorded an average dose of Methylprednisolone in case it was administered as part of anti-rejection treatment.

All patients underwent oGTT before their placing on the waiting list for kidney transplantation – and oGTT was performed 1× per year during waiting for the transplantation.

The examination protocol is shown in Table 1. During the monitored 12 months, we determined in the patients included in the study the risk factors for PTDM; in the case of PTDM development, we recorded when PTDM developed. For the analysis of collected data, we divided the patients into four groups as follows: men – control group, men – PTDM, women – control group, and women – PTDM. We compared individual groups according to gender (men – control group versus men – PTDM and women – control group versus women – PTDM). The control group contained patients who did not develop PTDM in the course of the monitored period. In the case of numeric parameters we also assessed differences between them and their development during the monitored period. At the end of the study, we compared the 12-month survival of grafts among all four groups.

Table 1
Examination protocol.

Monitored parameters	Pre-transplant	6 months after KT	12 months after KT	Each control
Age	X			
Gender	X			
Menopause	X	X	X	
Positive family history (yes/no)[a]	X			
Arterial hypertension (yes/no)	X	X	X	X
HLA A30, B27, B42 (yes/no)	X			
HLA mismatches	X			
Waist circumference (cm)	X	X	X	
Weight (kg)	X	X	X	X
BMI (kg/m^2)	X	X	X	
Type of immunosuppression	X	X	X	
Level of used immunosuppression (ng/ml)		X	X	X
Dose of corticoids (mg/day)		X	X	X
Basiliximab (yes/no)	X			
Fasting glycaemia		X	X	X
C peptide (pmol/l)	X		X	
IRI (uIU/ml)	X		X	
HOMA-IR	X		X	
Triacylglycerols (mmol/l)	X	X	X	X
Cholesterol (mmol/l)	X	X	X	X
HbA1c (%)		X	X	
Magnesaemia (mmol/l)	X	X	X	X
eGFR CKD-EPI (ml/min)		X	X	X
Vitamin D (μg/l)	X		X	

KT – kidney transplantation; HLA – human leukocyte antigen; BMI – body mass index; IRI – immunoreactive insulin; HOMA-IR – homeostatic model assessment for insulin resistance; HbA1c – glycated haemoglobin; CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration.

[a] Siblings, parents, grandparents.

PTDM was diagnosed according to the American Diabetes Association (ADA) criteria, second international consensus panel. An oral glucose tolerance test (oGTT) was performed in 10–12 weeks after transplantation and six months post-transplantation.[17,18] Glycated haemoglobin was not used for PTDM diagnostics, as it is not recommended as a diagnostic criterion for at least the first three months after kidney transplantation.[18]

The homeostasis model assessment-estimated insulin resistance (HOMA-IR), developed by Matthews et al. was used for the estimation of insulin resistance in our research. HOMA-IR is a convenient and beneficial method for evaluating insulin resistance. It is calculated multiplying fasting plasma insulin (FPI) by fasting plasma glucose (FPG), then dividing by the constant 22.5, i.e. HOMA-IR = (FPI × FPG)/22.5. An immunoreactive insulin test system is a device intended to measure immunoreactive insulin in serum and plasma.

Inclusion criteria for the research:

1. Age > 18 years
2. Patient without the diagnosis diabetes mellitus
3. Patient without diagnosis prediabetes (fasting hyperglycemia + impaired glucose tolerance)
4. Primary kidney transplantation
5. Transplantation of kidney from dead donor
6. Transplantation of kidney from living donor
7. Signed informed consent

Exclusion criteria for the research:

1. Secondary/tertiary kidney transplantation
2. Children age
3. Diabetes mellitus
4. Prediabetes (impaired fasting glucose/impaired glucose tolerance)

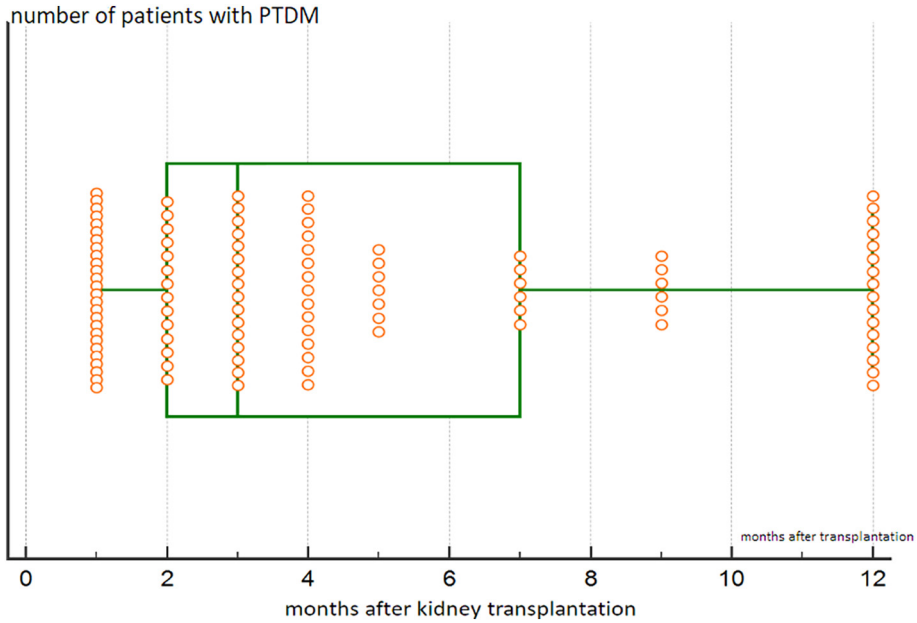

Fig. 1. Time to PTDM development – men. The central box represents the values from the lower to upper quartile (25 to 75 percentile). The middle line represents the median. The horizontal line extends from the minimun to the maximum value. The dots represent number of patients who developed PTDM in certain month after transplantation (x axis).

5. Taking immunosuppressive treatment (tacrolimus/cyclosporin/corticoids) 1/2 year prior to the transplantation and less
6. No consent of the patient.

All patients included in the waiting list for the kidney transplantation have according to the protocol oGTT performed once per year and their fasting blood glucose was checked once per month. This implies that patients included in the study had oGTT max. 12 months before the transplantation and their fasting blood glucose was monitored on regular basis.

We used a certified statistical program, MedCalc version 13.1.2. (MedCalc Software VAT registration number BE 0809 344,640, Member of International Association of Statistical Computing, Ostend, Belgium). Comparisons of continuous variables between groups were carried out using parametric (*t*-test) or non-parametric (Mann-Whitney) tests; associations between categorical variables were analysed using the χ^2 test and Fisher's exact test, as appropriate. Logistic regression was used for multivariate analysis for independent predictors of PTDM. We identified independent risk factors by means of the Cox proportional Hazard model. A P-value <0.05 was considered to be statistically significant.

2.1. Ethical approval

All procedures involving human participants have been approved according to the ethical standards of the institutional and/or national research committee, including the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

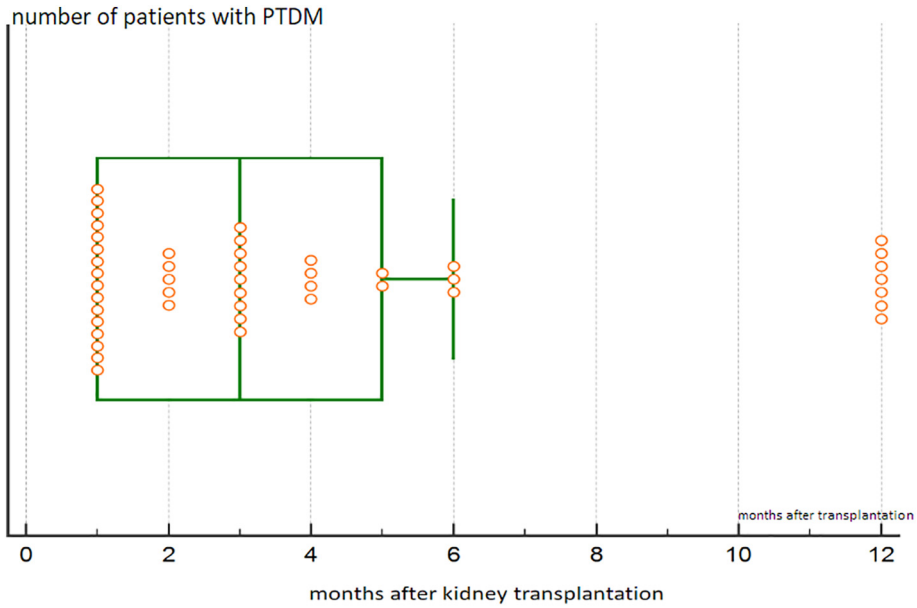

Fig. 2. Time to PTDM development – women. The central box represents the values from the lower to upper quartile (25 to 75 percentile). The middle line represents the median. The horizontal line extends from the minimun to the maximum value. The dots represent number of patients who developed PTDM in certain month after transplantation (x axis).

Table 2
Comparison of Control Group Versus PTDM Group Regarding Immunosuppression (men versus women).

12 months after KT	CG – M n = 165	PTDM – M n = 106	P-value	CG – W n = 100	PTDM – W n = 46	P-value
Average level of tacrolimus (ng/ml)	5.7 ± 1.5	5.8 ± 2.3	0.6651	5.8 ± 1.7	5.7 ± 2.1	0,7601
Average level of ciclosporin A (ng/ml)	70.5 ± 21.3	71.7 ± 15.1	0.6145	68.7 ± 19.1	70.9 ± 19.9	0.5244
Average level of mTOR (ng/ml)	5.8 ± 1.5	5.7 ± 0.1	0.4940	–	5.8 ± 0.1	–
Average dose of prednisone/day (mg)	6.9 ± 2.8	7.1 ± 0.6	0.4695	6.1 ± 1.8	6.4 ± 2	0.3680
Pulse treatment with methylprednisone (%)[a]	39.1	39.6	0.8926	40.2	38.6	0.8545
Average dose (g) except for induction	10.3 ± 2.8	11.3 ± 3.3	0.2170	9.5 ± 2.5	10.1 ± 2.9	0.2027

M – men; W – women; CG – control group; PTDM – post-transplant diabetes mellitus; KT – kidney transplantation.
[a] Except for induction.

The clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul as outlined in the Declaration of Istanbul on Organ Trafficking and Transplant Tourism.

3. Results

A total of 417 patients (271 men and 146 women) were included in the monitored group. PTDM developed during the monitored period in 152 patients, representing 36.5%. PTDM incidence was 39.1% (n = 106) in men and 31.5% (n = 46) in women (P = 0.3737). Men developed PTDM on average 4.6 months ±3.8 after transplantation (median 3 months) and women on average 3.9 months ±3.7 after transplantation (median 3 months); the time of PTDM development is shown in Figs. 1 and 2.

No difference was observed between individual groups with regard to the level of administered immunosuppression and in the dose of corticosteroids (Table 2).

Male patients with PTDM were significantly older, more often had a positive family history for DM2, and more often presented with arterial hypertension, a significantly larger waist circumference, and higher BMI. This group also received basiliximab in induction more often, had higher values of C-peptide, IRI, HOMA-IR, triacylglycerols, cholesterol, and HbA1c (glycated haemoglobin), significantly lower value of vitamin D a significantly less patients received vitamin D substitution treatment (Table 3). Twelve months after transplantation, the group of men with PTDM again showed a significantly larger waist circumference (P < 0.0001), higher BMI (P < 0.0001), and higher values of C-peptide (P < 0.0001), IRI (P < 0.0001), HOMA-IR (P < 0.0001), Hb1Ac (P < 0.0001), and vitamin D (P < 0.0001). Changes in selected numerical parameters during the monitored period were also recorded. A significant increase in BMI, IRI, HOMA-IR, and cholesterol was recorded in the control group of men during the monitored 12 months. A significant increase in waist circumference, BMI, IRI, HOMA-IR, triacylglycerols, and vitamin D was recorded in the group of men with PTDM (Table 4).

Age at the time of KT >60 years and hypovitaminosis D at the time of KT (<20 μg/l) were identified as independent risk factors for PTDM in men as well as women. In addition to that, we confirmed as an independent risk factor for men a waist circumference at the time of KT > 94 cm (according to the International Diabetes Federation criteria for metabolic syndrome), C-peptide at the time of KT > 5 ng/ml, HOMA-IR >2 and triacylglycerols at the time of KT > 1.7 mmol/l (Table 5).

Female patients with PTDM, similar to men with PTDM, were significantly older. This group with PTDM also presented with arterial hypertension more often, had a significantly larger waist circumference and higher BMI, and higher values of C-peptide, IRI, HOMA-IR, and vitamin D and again significantly fewer patients received vitamin D substitution treatment (Table 3).

Table 3
Group characteristics – input data.

Input	CG – M n = 165	PTDM – M n = 106	P-value	CG – W n = 100	PTDM – W n = 46	P-value
Age (years)	42.3 ± 13.2	50.9 ± 9.8	<**0.0001**	40.8 ± 14.9	52.9 ± 4.4	<**0.0001**
Active menstruation (%)	–	–	–	10	13	0.5909
Positive family history for DM (%)[a]	29.1	41.5	**0.0357**	47	30.4	0.0597
Polycystic kidney disease (%)	8	15.1	0.0644	16	26.1	0.1513
Arterial hypertension (%)	93.9	100	**0.0097**	90	100	**0.0268**
HLA A30 (%)	0	1.9	0.0761	5	2.2	0.4305
HLA B27 (%)	6.1	2.8	0.2162	2	0	0.3358
HLA B42 (%)	0	1.9	0.0761	1	0	0.4976
Number of HLA mismatches	4.4 ± 1.4	4.6 ± 1.5	0.2655	3.6 ± 1.6	3.6 ± 1.4	1.0000
Waist circumference at the time of KT (cm)	92.7 ± 10.9	95.9 ± 12.2	**0.0253**	81.7 ± 14.1	90.6 ± 15.7	**0.0008**
BMI at the time of KT (kg/m^2)	24.8 ± 3.5	26.8 ± 3.8	<**0.0001**	23 ± 3.4	28.2 ± 4.4	<**0.0001**
Ciclosporin A (%)	1.8	2.8	0.5839	5	6.6	0.6947
Tacrolimus (%)	93.3	95.3	0.4957	95	91.3	0.3895
mTOR inhibitor + tacrolimus (%)	4.2	2.8	0.5495	0	2.0.2	0.1380
Basiliximab in induction (%)	50.3	73.4	**0.0002**	47	50	0.7369
C-peptide at the time of KT (ng/ml)	4.4 ± 1.9	7.8 ± 6	<**0.0001**	3.4 ± 0.9	5.6 ± 4.7	<**0.0001**
IRI at the time of KT (μIU/ml)	9.4 ± 5.7	14.2 ± 7.5	<**0.0001**	7.1 ± 2.5	10.2 ± 7	**0.0001**
HOMA-IR	2.2 ± 0.2	4.0 ± 0.6	<**0.0001**	1.5 ± 0.5	2.3 ± 1.3	<**0.0001**
Triacylglycerols at the time of KT (mmol/l)	1.9 ± 0.9	3.3 ± 2.8	<**0.0001**	2.3 ± 1.5	2.2 ± 0.5	0.6604
Cholesterol at the time of KT (mmol/l)	4.7 ± 1.3	5.2 ± 1.2	**0.0016**	5.1 ± 1.1	5.5 ± 1.7	0.0904
HbA1c at the time of KT (%)	4.1 ± 0.8	4.6 ± 1.5	**0.0004**	3.7 ± 1	4 ± 1.2	0.1166
Magnesaemia at the time of KT (mmol/l)	0.7 ± 0.1	0.7 ± 0.1	1.0000	0.7 ± 0.1	0.7 ± 0.1	1.0000
Vitamin D (μg/l)	36.7 ± 2.3	23.6 ± 3.5	<**0.0001**	25.7 ± 2.6	19.5 ± 2	<**0.0001**
Cholecalciferol (%)	77.6	32.3	<**0.0001**	71	26.1	<**0.0001**
Paricalcitol (%)	29.1	11.3	**0.0006**	25	10.9	**0.0510**

P-value <0.05 was considered to be statistically significant.
M – men; W – women; CG – control group; PTDM – post-transplant diabetes mellitus; HLA – human leukocyte antigen; KT – kidney transplantation; BMI – body mass index; IRI – immunoreactive insulin; HOMA-IR – homeostatic model assessment for insulin resistance; HbA1c – glycated haemoglobin.
[a] Siblings, parents, grandparents.

Table 4
Development of monitored parameters – PTDM.

PTDM	input - M n = 106	12 months after KT - M n = 106	P-value	input - W n = 46	12 months after KT – W n = 46	P-value
Waist circumference (cm)	95.9 ± 12.2	101.5 ± 10.8	**0.0005**	90.6 ± 15.7	92.5 ± 15.4	0.5594
BMI (kg/m^2)	26.8 ± 3.8	28.3 ± 4.3	**0.0077**	28.2 ± 4.4	29.8 ± 4.8	0.0991
C-peptide (ng/ml)	7.8 ± 6	7.9 ± 5.8	0.9019	5.6 ± 4.7	3.4 ± 0.9	**0.0024**
IRI (μIU/ml)	14.2 ± 7.5	21.5 ± 11.8	<**0.0001**	10.2 ± 7	12.6 ± 8.2	0.1346
HOMA-IR	4.0 ± 0.6	5.5 ± 0.5	<**0.0001**	2.3 ± 1.3	3.4 ± 2.5	**0.0096**
Triacylgycerols (mmol/l)	3.3 ± 2.8	2.1 ± 1.0	<**0.0001**	2.2 ± 0.5	1.8 ± 0.8	**0.0050**
Cholesterol (mmol/l)	5.2 ± 1.2	4.9 ± 1.9	0.1708	5.5 ± 1.7	5.4 ± 0.8	0.7190
Magnesaemia (mmol/l)	0.7 ± 0.1	0.7 ± 0.1	1.0000	0.7 ± 0.1	0.7 ± 0.1	1.0000
Vitamin D (μg/l)	23.6 ± 3.5	25.9 ± 3.3	<**0.0001**	19.5 ± 2	23.9 ± 1.8	<**0.0001**

P-value <0.05 was considered to be statistically significant.
M – men; W – women; KT – kidney transplantation; BMI – body mass index; IRI – immunoreactive insulin; HOMA-IR – homeostatic model assessment for insulin resistance; HbA1c – glycated haemoglobin.

Twelve months after transplantation, the group of women with PTDM did not show any significant differences in waist circumference or in the value of C-peptide compared to the control group, but significantly higher BMI persisted ($P < 0.0001$), as well as HOMA-IR ($P < 0.0001$) and significantly higher values of HbA1c ($P < 0.0001$) and vitamin D ($P < 0.0001$).

A significant increase was recorded in the values of HOMA-IR, triacylglycerols, and vitamin D in women with PTDM. Despite the significant increase in vitamin D levels in the monitored period, both men and women with PTDM had lower values of vitamin D compared to men/women in the control group 12 months after the transplantation. On the other hand, a significant decrease was recorded in the value of C-peptide in the group of women with PTDM, which is one of the most important findings in our analysis (Table 4, Fig. 3).

Men with PTDM and women with PTDM were further compared. It has been confirmed that on input women with PTDM had significantly higher BMI and significantly lower values of C-peptide, IRI, HOMA-IR and vitamin D (Table 6). A year after the transplantation the BMI value of women was no longer significantly higher, but the significantly lower value of C-peptide, IRI and HOMA IR as compared to PTDM persisted (Table 7).

As mentioned before, an age of >60 years at the time of KT and hypovitaminosis D at the time of KT (<20 μg/l) were identified as independent risk factors for PTDM in both men and women. Conversely, the dominating factors in the group of women were BMI at the time of KT >30 kg/m^2 and menopause at the time of KT (Table 5).

Finally, 12-month graft survival in individual groups was compared. Men with PTDM had surprisingly significantly worse graft survival, which is considered to be one of the crucial results of this analysis, followed by women with PTDM. Graft survival in women and men without PTDM development was comparable (Fig. 4).

4. Discussion

Men and women are different in many ways. These differences include both biological phenotypes and psychological traits. Some of these differences are influenced by environmental factors. Yet, there are fundamental differences between the sexes that are rooted in biology.[19] Many organizations now call for the inclusion of the sex and gender dimension in biomedical research, to improve the scientific quality and societal relevance of the produced knowledge, technology, and/or innovation.[16] Sex differences describe biology-linked differences between women and men, which are caused by differences in sex chromosomes, sex-specific gene expression of autosomes, sex hormones, and their effects on organ systems. Women show more dramatic changes in hormones and body due to reproductive factors during lifetime.[14,16]

Data dealing with the PTDM issue from the gender perspective have not yet been published in the available literature. It is a pressing problem with a high incidence, so understanding the mechanisms of development in men and women may lead to the creation of preventive

Table 5
Cox proportional hazard model.

	Hazard ratio men	95% CI men	P-value	Hazard ratio women	95% CI women	P-value
Age at the time of KT ≤ 40 years	2.8870	0.8751–9.5247	0.0817	0.09626	0.006142–1.5084	0.0955
Age at the time of KT 41–50 years	0.3986	0.1201–1.3233	0.1330	0.5000	0.07563–3.3054	0.4719
Age at the time of KT 51–60 years	1.0105	0.2142–4.7678	0.9894	0.3676	0.02598–5.2023	0.4592
Age at the time of KT >60 years	2.2737	1.0988–4.7048	**0.0268**	16.6250	2.4237–114.0375	**0.0042**
Positive family anamnesis for DM[a]	0.9320	0.3593–2.4177	0.8848	0.4848	0.1191–1.9744	0.3123
Menopause	–	–	–	0.1327	0.01879–0.9367	**0.0428**
Polycystic kidney disease	1.1815	0.3236–4.3139	0.8007	1.4667	0.4110–5.2333	0.5551
Waist circumference at the time of KT >94 cm/80 cm	1.6842	1.1083–2.5594	**0.0146**	2.4000	0.5866–9.8189	0.2232
BMI at the time of KT <25 kg/m^2	0.7321	0.2416–2.2185	0.5814	0.3393	0.04946–2.3273	0.2712
BMI at the time of K25–29,9 kg/m^2	1.3493	0.5376–3.3866	0.5235	1.9792	0.8441–4.6406	0.1164
BMI at the time of KT ≥ 30 kg/m^2	1.6071	0.6198–4.1672	0.3291	4.1667	2.0741–8.3703	**0.0001**
Basiliximab in induction	2.0692	0.7334–5.8382	0.1694	1.0769	0.3368–3.4432	0.9005
C-peptide at the time of KT >5 ng/ml	3.2995	1.0836–10.0468	**0.0356**	1.4250	0.4427–4.5866	0.5526
IRI at the time of KT >23 μIU/ml	1.4288	0.5337–3.8255	0.4776	1.1429	0.2052–6.3664	0.8789
HOMA-IR >2	3.3503	1.0832–10.3619	**0.0358**	3.5625	0.7286–17.4193	0.1167
Triacylglycerols at the time of KT >1.7 mmol/l	4.1386	1.1400–15.0002	**0.0308**	2.9474	0.4297–20.2172	0.2712
cholesterol at the time of KT >5.16 mmol/l	1.0173	0.3663–2.8251	0.9738	1.7949	0.5320–6.0560	0.3458
vitamin D 20–30 μg/l	8.4706	0.4944–145.1137	0.1405	1.2324	0.3343–2.9912	0.9989
vitamin D < 20 μg/l	4.7500	1.9885–11.3464	**0.0005**	2.2500	1.3424–3.7714	**0.0021**

P-value <0.05 was considered to be statistically significant.
KT – kidney transplantation; DM – diabetes mellitus; BMI – body mass index; IRI – immunoreactive insulin; HOMA-IR – homeostatic model assessment for insulin resistance.
[a] Siblings, parents, grandparents.

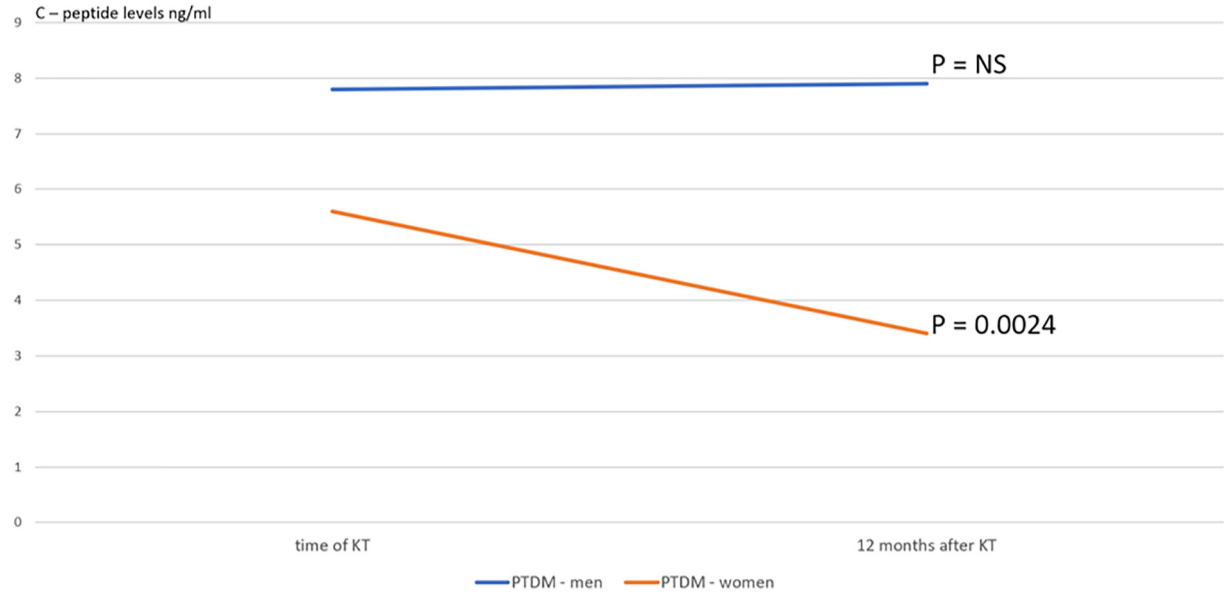

Fig. 3. C-peptide levels development – PTDM men versus PTDM women.

measures or the establishment of a more correct and effective treatment of the disease.

The incidence of PTDM varies with the type of transplant because of differences in age, body mass index (BMI), and the underlying risk of the candidate group. Published data specify that the incidence of PTDM after kidney transplantation is in the range of 10–74%. Such high differences between published papers are primarily related to the inconsistent diagnostics of PDTM.[20] In 2003, the first International Consensus Guidelines for new-onset diabetes after transplantation (NODAT) were published, and in October 2013, the second international consensus panel met to update the criteria.[18] The incidence of PTDM in our group was 36.5%, and PTDM was more often diagnosed in men than in women. PTDM was diagnosed in men on average three weeks later than in women. A significant decrease in the C-peptide value in women with PTDM indicates rapid exhaustion of pancreas β cells in women with increasing insulin resistance. It is this dysfunction of β cells due to exhaustion and the subsequent decrease in C-peptide that explains the earlier development of PTDM in women. Identifying the different mechanism of PTDM in women is essential and may lead to targeted treatment of PTDM. Women will benefit from insulin treatment, while men need to focus on changing lifestyle and weight reduction. The IRI value did not significantly change in women with PTDM, which can be put in relation to the PTDM treatment (exogenous insulin), which can partially distort our results with regard to determination of IRI in patients with PTDM.

Waist circumference dominates as a risk factor for PTDM in men, whereas for women it is BMI. Our findings are in line with the available literature and published papers dealing with sex differences in DM2.[16] Insulin resistance is an independent risk factor for men, but it significantly grows in all four monitored groups.

Another interesting conclusion in our analysis was with regard to hypovitaminosis D. A normal level of vitamin D was found only in men in the control group, and the vitamin D level increased significantly during the monitored period in both men and women with PTDM. We therefore evaluated hypovitaminosis D as an independent risk factor

Table 6
PTDM group characteristics – input data.

Input	PTDM – M n = 106	PTDM – W n = 46	P value
Age (years)	50.9 ± 9.8	52.9 ± 4.4	0.1870
Positive family history for DM (%)[a]	41.5	30.4	0.1970
Polycystic kidney disease (%)	15.1	26.1	0.1092
Arterial hypertension (%)	100	100	–
HLA A30 (%)	1.9	2.2	0.9035
HLA B27 (%)	2.8	0	0.2533
HLA B42 (%)	1.9	0	0.3482
Number of HLA mismatches	4.6 ± 1.5	3.6 ± 1.4	**0.0002**
Waist circumference at the time of KT (cm)	95.9 ± 12.2	90.6 ± 15.7	**0.0260**
BMI at the time of KT (kg/m^2)	26.8 ± 3.8	28.2 ± 4.4	**0.0487**
Ciclosporin A (%)	2.8	6.6	0.2708
Tacrolimus (%)	95.3	91.3	0.3383
mTOR inhibitor + tacrolimus (%)	2.8	2.2	0.8320
Basiliximab in induction (%)	73.4	50	**0.0052**
C-peptide at the time of KT (ng/ml)	7.8 ± 6	5.6 ± 4.7	**0.0287**
IRI at the time of KT (μIU/ml)	14.2 ± 7.5	10.2 ± 7	**0.0025**
HOMA-IR	4.0 ± 0.6	2.3 ± 1.3	<**0.0001**
Triacylglycerols at the time of KT (mmol/l)	3.3 ± 2.8	2.2 ± 0.5	**0.0091**
Cholesterol at the time of KT (mmol/l)	5.2 ± 1.2	5.5 ± 1.7	0.2166
HbA1c at the time of KT (%)	4.6 ± 1.5	4 ± 1.2	**0.0177**
Magnesaemia at the time of KT (mmol/l)	0.7 ± 0.1	0.7 ± 0.1	1.0000
Vitamin D (μg/l)	23.6 ± 3.5	19.5 ± 2	<**0.0001**

P-value <0.05 was considered to be statistically significant.
M – men; W – women; CG – control group; PTDM – post-transplant diabetes mellitus; HLA – human leukocyte antigen; KT – kidney transplantation; BMI – body mass index; IRI – immunoreactive insulin; HOMA-IR – homeostatic model assessment for insulin resistance; HbA1c – glycated haemoglobin.
[a] Siblings, parents, grandparents.

Table 7
Development of monitored parameters – PTDM men and women comparison.

PTDM	12 months after KT - M n = 106	12 months after KT – W n = 46	P-value
waist circumference (cm)	101.5 ± 10.8	92.5 ± 15.4	**0.0001**
BMI (kg/m^2)	28.3 ± 4.3	29.8 ± 4.8	0.0585
C-peptide (ng/ml)	7.9 ± 5.8	3.4 ± 0.9	<**0.0001**
IRI (μIU/ml)	21.5 ± 11.8	12.6 ± 8.2	<**0.0001**
HOMA-IR	5.5 ± 0.5	3.4 ± 2.5	<**0.0001**
triacylgycerols (mmol/l)	2.1 ± 1.0	1.8 ± 0.8	0.0740
cholesterol (mmol/l)	4.9 ± 1.9	5.4 ± 0.8	0.0880
magnesaemia (mmol/l)	0.7 ± 0.1	0.7 ± 0.1	1.0000
vitamin D (μg/l)	25.9 ± 3.3	23.9 ± 1.8	**0.0002**

P-value <0.05 was considered to be statistically significant.
M – men; W – women; KT – kidney transplantation; BMI – body mass index; IRI – immunoreactive insulin; HOMA-IR – homeostatic model assessment for insulin resistance; HbA1c – glycated haemoglobin.

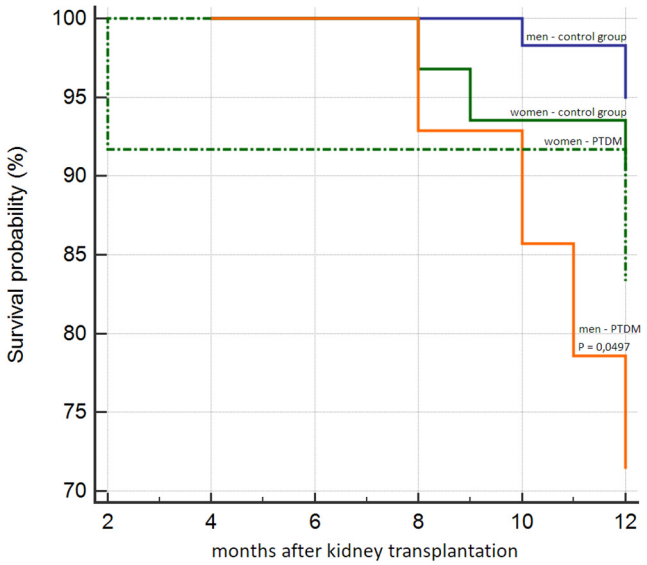

Fig. 4. Twelve - month graft survival.

for PTDM in both men and women. Hypovitaminosis D has been found in middle-aged Caucasians to be independently associated with DM2 in women but not in men[21]; 17-estradiol may influence these associations with variations over time.[22] Vitamin D may directly stimulate expression of the insulin receptor, thereby improving glucose transport in human cells.[23] A significant increase of vitamin D values occurs after the transplantation and it takes ≤18 months for vitamin D status to improve after renal transplantation.[24] We therefore consider the hypovitaminosis D at the time of the transplantation to be the most important risk factor. Proper management of bone metabolism of patients waiting for transplantation is therefore a key momentum.

Menopause (as the permanent cessation of menstruation) was another significant risk factor for PTDM in women. The menopause signals the loss of fertility. Again, no paper has been published so far to describe this association. However, an association has been found between DM2 and early menopause in women under 45 years of age. We therefore assume that this mechanism can also be applied to our female patients because women develop menopause during dialysis treatment without regard to age as a consequence of terminal kidney failure.[25,26]

Finally, we identified significantly worse graft survival in men with PTDM 12 months after transplantation. This is an interesting finding because PTDM has a significant impact particularly on the long-term survival of grafts and patients. The greatest impact of PTDM on graft survival is death with a functioning graft.[27] Only one study has suggested PTDM as be a risk factor for death-censored renal graft failure.[4] We infer that men with PTDM had the worst survival for several reasons that can lead to graft failure. Abdominal obesity is a risk factor for the surgery itself and for wound healing; PTDM is also associated with a more frequent occurrence of infections, in particular urological infections, which cause serious pyelonephritis of the graft, especially in men. However, an unambiguous conclusion cannot be formulated as graft survival is affected by a number of factors. Moreover, no other data are available regarding the graft or patient survival according to gender and PTDM development.

5. Conclusion

It is confirmed that there are gender differences with regard to PTDM development after kidney transplantation. According to our findings, dysfunction of pancreas β cells is a factor in PTDM development in women, whereas insulin resistance and metabolic syndrome prevail in men. We assume that some other parameters that were not included in our analysis could emphasise the differences observed by us. They include, for instance, psychosocial factors (socioeconomic status, psychosocial stress, sleep deprivation, and work stress) and health behaviours (lifestyle, consumption of sugar-sweetened beverages or alcohol, and smoking).

Biomedical basic and clinical research should be useful for both women and men in a balanced way. Modern personal care must consider differences in biological factors such as genetic predisposition, sex hormones, and neurohumoral pathways, as well as behavioural and environmental differences between men and women.

Authorship

Doc. MUDr. Ivana Dedinská, PhD: participated in performing the research and data analysis and writing the paper
MUDr. Karol Graňák: participated in research design
MUDr. Matej Vnučák: participated in writing the paper
Prof. MUDr. Ľudovít Laca, PhD: participated in writing the paper
MUDr. Juraj Miklušica, PhD: participated in data analysis
MUDr. Petra Skalová: participated in writing the paper
MUDr. Lea Kováčiková: participated in research design
MUDr. Dana Prídavková, PhD: participated in data analysis
Prof. MUDr. Peter Galajda, CSc: participated in research design
Prof. MUDr. Marián Mokáň, DrSc FRCP Edin: participated in research design

Conflict of interest

The authors declare no conflicts of interest.

Funding sources

None.

Novelty statement

The important question we tried to answer in our study is whether the identified risk factors have the same weight for men as compared with women after kidney transplantation. Sex differences with regards to PTDM have yet to be published in any available study. A significant decrease was recorded in the value of C-peptide in the group of women with PTDM. A significant decrease in the C-peptide value in women with PTDM indicates rapid exhaustion of pancreas β cells in. Identifying the different mechanism of PTDM in women is essential and may lead to targeted treatment of PTDM.

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