BMC Nephrology

RESEARCH

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Pulse wave parameters as a predictor of the development of post-transplant diabetes mellitus after kidney transplantation

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Abstract

Background Kidney transplantation is the preferred treatment for patients with end-stage renal disease, significantly preserving kidney function and patient quality of life. However, post-transplant diabetes mellitus (PTDM) is a common complication, occurring in approximately one-third of renal transplant recipients. This study aims to evaluate the role of pulse wave parameters in predicting PTDM and to identify other pre-transplant risk factors.

Methods This prospective cohort study included 105 patients on the kidney transplant waiting list from 2017 to 2022. Exclusion criteria included any pre-existing diabetes mellitus. Patients underwent physical examinations, laboratory analyses, and pulse wave analysis before transplantation and one year post-transplant. PTDM diagnosis followed International Consensus Guidelines. Data were analyzed using Wilcox test, Bonferroni correction, May-Whitney U-test, and Fisher's exact test, with $p < 0.05$ considered statistically significant.

Results Post-transplant, 21% of patients were diagnosed with PTDM, increasing to 35% 3months post-transplant and 43% at one year post-transplant. Significant findings included: **Pre-transplat risk factors for developing PTDM:** Proteinuria ($p = 0.037$, OR = 3.942) and perioperative hyperglycemia ($p = 0.003$, OR = 4.219 at 3 months; $p = 0.001$, OR = 4.571 at 1 year). **Pulse wave parameters for developing PTDM:** Pre-transplant Aortic PP > 45 mmHg (AUC = 0.757) and PWV > 8.5 m/s (AUC = 0.730) were strong predictors of the development of PTDM after 3 months ($p < 0.0001$). Moreover, we found significant improvements in aortic pulse pressure (Aortic PP) and pulse wave velocity (PWV) post-transplant ($p < 0.0001$).

Conclusion Our study confirms that pulse wave parameters, such as Aortic PP and PWV, are significant predictors of PTDM in kidney transplant recipients (KTR). These findings support incorporating pulse wave analysis into routine pre-transplant evaluations to identify high-risk patients. Additionally, monitoring these parameters post-transplant may aid in early intervention and prevention of PTDM, ultimately improving patient outcomes.

Trial registration Ethical approval was obtained from the Ethics Committee of Medical faculty and University Hospital Olomouc (approval no. 94/15).

Keywords Kidney transplantation, Post-transplant diabetes mellitus, Pulse wave analysis, Aortic pulse pressure, Pulse wave velocity, Cardiovascular complications.

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Introduction

Kidney transplantation (Tx) is the treatment of choice for end-stage renal disease patients. With the increasing number of kidney tranplantats and the extended survival of grafts, attention is shifting towards non-immunological complications that significantly impact morbidity and mortality. One such complication is post-tranplant diabetes mellitus (PTDM).

Post- transplant diabetes mellitus is among the most frequent complications following Tx. It occurs in approximately one-third of renal transplant recipients, with an incidence rate ranging from 7 to 46% [1–4]. This wide range reflects the heterogeneity in reports due to a historical lack of diagnostic criteria, variation in follow-up duration, study design, and immunosuppressive regimens. Both insulin resistance and insulin deficiency play roles in the pathogenesis of PTDM. Insulin resistance alone does not cause hyperglycemia; it is the dysfunction of pancreatic beta cells, which fails to secrete sufficient insulin under persistent insulin resistance, to achieve normoglycemia. Both traditional type 2 diabetes risk factors and transplantation-specific factors contribute to the development of PTDM. Traditional non-modifiable risk factors include age, ethnic and genetic background, family history of type 2 diabetes, polycystic kidney disease, and previous impaired glucose tolerance. Modifiable risk factors include obesity, proteinuria, and infections (such as hepatitis C and cytomegalovirus). Additionally, transplantation-specific factors such as the use of immunosuppressive drugs (glucocorticoids, calcineurin inhibitors, and mammalian target of rapamycin inhibitors - mTOR inhibitors) significantly contribute to the development of PTDM.

Given the complex pathogenesis of PTDM and the identification of multiple risk factors, some of which are modifiable, there is an opportunity to perform metabolic evaluations of high-risk patients before transplantation. We selected pulse wave analysis evaluating arterial stiffness as an additional tool to assess metabolic risk in KTR. Previous studies have demonstrated that endothelial dysfunction, arterial stiffness, and accelerated atherosclerosis are prevalent among stable kidney transplant patients and may contribute to the high rate of cardiovascular event rate [5]. Furthermore, pulse wave analysis recognized as a biomarker of vascular damage and may contribute to high rate of cardiovascular event rate in the diabetic population [6]. Studies have also suggested that increased arterial stiffness is associated with insulin resistance and beta-cell dysfunction, both of which are pivotal in the development of diabetes. If we look at studies evaluating vascular stiffness parameters in KTR, it has been found that patients diagnosed with diabetes (whether type 2 diabetes or PTDM) exhibit worse vascular stiffness values [7–9]. Our hypothesis posited that patients at increased metabolic risk, including those at risk of developing PTDM, already exhibit worse pulse wave parameters before transplantation. The aim of our study was to evaluate the impact of already known risk factors on the development of PTDM and to assess whether pulse wave analysis could also be included as one of these factors.

Materials and methods

Study design

This prospective cohort single-center study involving patients with end-stage renal disease on waiting list for Tx. The study was performed in accordance with the principles of the Declaration of Helsinki for experiments involving humans at the University Hospital Olomouc. All participants initially signed an informed consent to the scheduled examinations. An exclusion criterion was the diagnosis of any type of diabetes mellitus, including positive oral glucose tolerance test (oGTT). All patients who underwent Tx within the specified time frame were included in the study.

Patients

Our study included 105 patients (69 males; 36 females; mean age 55 +- 13 years) on waiting list for Tx collected between years 2017 and 2022. A thorough history of each patient was recorded, focusing on traditional metabolic risk factors as smoking, family history, history of hypertension or cardiovascular events or body mass index (BMI). The causes of end-stage renal disease were as follows: chronic glomerulonephritis ($n = 44$), chronic tubule-interstitial nephritis ($n = 18$), autosomal dominant polycystic kidney disease ($n = 14$), nephrosclerosis ($n = 16$), Alport syndrome ($n = 1$), and unknown cause ($n = 12$). None of the patients were taking vitamin supplements (folic acid, vitamin C and E). No participants had active viral hepatitis B of C.

These patients underwent a basic physical examination, laboratory analyses and pulse wave analysis. The diagnosis of post-transplant diabetes mellitus was based on the International Consensus Guidelines on PTDM published in 2024 [3]. These criteria include: (1) Symptoms of diabetes mellitus (polyuria, polydipsia, unexplained weight loss) and random plasma glucose over 11.1 mmol/l. (2) Fasting plasma glucose over 7 mmol/l (8 h of fasting). (3) Using oGTT with 2-hour plasma glucose over 11.1 mmol/l (this test was performed using a glucose load containing the equivalent of 75 g of anhydrous glucose dissolved in water). We performed the diagnosis of PTDM three times. First, in stable patients after setting the immunosuppressive therapy on maintenance doses during hospitalization after the Tx. Then we repeated it after 3 months and after one year. After the transplantation, we also recorded the anamnesis of perioperative hyperglycemia (> 11.1 mmol/l).

Patients enrolled in the study received induction therapy in the form of anti-CD25 monoclonal antibody ($n = 93$) or anti-thymocyte globulin ($n = 12$) in the recommended dosage, and an initial pulse of methylprednisolone was also administered (Day 0: 500 mg iv perioperatively, Day 1: 250 mg iv). Subsequently, maintenance therapy was based on a triple combination of immunosuppressants, including calcineurin inhibitor tacrolimus ($n = 88$) or mTOR inhibitor everolimus ($n = 17$) alternatively sirolimus ($n = 1$), antimetabolite mycophenolate mofetil or sodium mycophenolate and prednisone. The initial tacrolimus dose of 0.1 mg/kg was administered 4 h before the operation. Further dosage was maintained with regard to the levels and time from transplantation (Days 1–14: 10–15 ng/ml; Days 15–30: 7–12 ng/ml; >30 Days: 5–10 ng/ml). The starting dose of everolimus was 0.75 mg twice a day. The dose was subsequently adjusted to target an everolimus trough concentration of 3–8 ng/ml. Sirolimus, on the other hand, is initiated at 4 mg orally as a single dose, followed by 1–2 mg/day, targeting a trough level of 3–8 ng/mL. Mycophenolate mofetil was given in starting dose 2 g/day, starting dose of enteric-coated mycophenolate sodium was 1,44 g/day, which could be reduced after week 2 to keep target levels 1–3.5 mg/. All patients were given prednisone in the dose of 30 mg from Day 2 to Day 14, 20 mg from Day 15 to Month 2 after Tx, 15 mg from Month 3 to Month 5 after Tx, 10 mg from Month 6 to Month 12 after Tx, and then after 1 year 5 mg a day.

In cases of biopsy proven acute cellular rejection we administered pulse iv methylprednisolon 500 mg daily every other day to standard total dosage 2 g. In more fragile patients, a reduced dosage of 1.5 g was occasionally used ($n = 3$), and in four cases, a dosage of 3 g was selected ($n = 4$).

Most patients in our study were treated with antihypertensive medications as follows: RAAS blockers (renin-angiotensin-aldosterone blockers) ($n = 33$), calcium channel blockers ($n = 69$), beta-blockers ($n = 60$), central antihypertensive drugs ($n = 48$), and diuretics ($n = 62$). Additionally, we recorded the number of patients treated with statins ($n = 43$) and antiplatelet therapy ($n = 49$).

Laboratory analyses

Venous blood samples were drawn in the morning after a 12-h-fasting period using a closed system Vacuette® tube with a clotting activator. After centrifugation, the serum was used for analyses. Hemoglobin A1c (HbA1c) was determinated from whole blood (K3EDTA). Routine biochemical parameters (lipid parameters, glucose, C-reactive protein and HbA1c) were performed on the day of blood collection.

Glucose levels were determined using the hexokinase method on an Atellica automated analyzer (Siemens). Total cholesterol (TC) was determined on an Atellica analyzer (Siemens) based on the enzymatic colorimetric assay principle. High-density lipoprotein cholesterol (HDL-C) levels were determined on an Atellica analyzer (Siemens) using an enzymatic HDLC kit. Low density lipoprotein cholesterol (LDL-C) was calculated using Friedewald formula (LDL-C = TC - TG*0.4537 - HDL-C for TG < 4.5 mmol/l). A calculation was used to obtain the value of non-HDL cholesterol (nonHDL = TC – HDL-C). Triacylglycerol concentrations were determined using the Triglycerides_2 enzymatic assay. HbA1C levels were measured by ion exchange chromatography on an Arkray Adams HA-8180 V analyzer. C-peptide levels were determined using a commercially available C-peptide immunochemiluminescence assay on the immunochemistry module of an Atellica analyzer (Siemens). CRP was assessed using an immunoturbidimetric method on an automatic analyzer Atellica. The immunoturbidimetric method on the Atellica automatic analyzer was also used to measure apolipoproteinB. All these assays meet the requirements of the EN ISO 15189:2013 accreditation standard.

Pre-transplant proteinuria was evaluated as a potential risk factor in this study. It was assessed using a single urine sample, measuring the albumin-to-creatinine ratio (ACR). This method provides a reliable estimate of protein secretion. An ACR > 30 mg/g (> 3 mg/mmol) was considered positive.

Pulse wave analysis

Patients underwent further non-invasive measurement of vascular wall stiffness parameters using pulse wave analysis. The measured parameters included aortic systolic, diastolic and pulse pressure (Ao SBP, DBP, PBK), augmentation pressure (AP), augmentation index corrected for heart rate 75 beats/min (AiX/75 bpm) and pulse wave velocity (PWV). The measurements were conducted using the SfygmoCor instrument (AtCor Medical Pty Ltd. Head Office, West Ryde, NSW, Australia). The examination was performed after instructing patients not to use caffeine and alcohol or smoke 12 h before the test and it was conducted during the hospitalization prior to being placed on the kidney transplant waiting list. Patients were examined in a temperature-controlled room after a minimum of 15 min of rest. The first part of the pulse wave analysis was conducted while the patients were seated, during which peripheral parameters (radial artery) were measured. The device then performed a mathematical conversion to obtain the aortic pulse wave. PWV was measured in the supine position by recording the pulse wave at the carotid and femoral arteries in conjunction with an electrocardiogram (ECG). The software processed data from each pulse wave and acquired ECG to calculate the time difference between the heart

and peripheral arteries, averaging 10 consecutive cycles. A measuring tape was used to measure the distance between the points of sensor application on the carotid and femoral arteries and the jugular fossa. PWV was then calculated using the formula: PWV (m/s) = carotid-femoral distance (m) / carotid-femoral transmission time (s) [10, 11].

Statistical analyses

All values were expressed as median and interquartile range (IQR). Wilcoxon test with Bonferroni correction was used for the statistics of quantitative data and McNemar test with Bonferroni correction was used for the statistics of qualitative data. Furthermore, we evaluated predictive data for the development of diabetes using Mann-Whitney U-test for quantitative data and Fisher's exact test for qualitative data. Probability values of $p < 0.05$ were considered as statistically significant.

Results

Our study was performed on the cohort of 105 patients placed on waiting list for kidney transplantation (see Fig. 1). After the transplantation, 21% patients were diagnosed with PTDM ($n = 22$); this increased to 35% at 3 months post-transplant ($n = 35$) and to 43% at one year post-transplant ($n = 40$).

First, we evaluated clinical and laboratory findings and their change throughout our study. The results are shown in Table 1. Our cohort exhibited statistically significant decrease in body mass index (BMI) at 3 months post-transplant as well as increased levels of total cholesterol, LDL cholesterol, nonHDL cholesterol, apolipoprotein B and apolipoproteinB/apolipoproteinA ratio. Conversely, there was a significant improvement in levels of HDL cholesterol, C-reactive protein (CRP), and C-peptide.

We also investigated whether the use of medications (antihypertensive drugs, statins, antiplatelet therapy) influenced pulse wave parameters in our patients before Tx. It was found that the use of RAAS blockers ($n = 33$), calcium channel blockers ($n = 69$), diuretics ($n = 62$), and antiplatelet therapy ($n = 49$) did not have a significant effect on pulse wave parameters. In contrast, patients using beta-blockers ($n = 60$) demonstrated worse Aortic PP and PWV parameters compared to those not using beta-blockers (AoPP: $p = 0.039$; PWV: $p = 0.043$). Similarly, patients on central antihypertensive drugs ($n = 48$) exhibited worse Aortic PP values ($p = 0.003$). Patients using statins ($n = 43$) also had worse PWV values ($p = 0.031$), as shown in Table 2. When we compared the use of individual medication groups (antihypertensive drugs, statins, and antiplatelet therapy) between patients with and without PTDM, no statistically significant

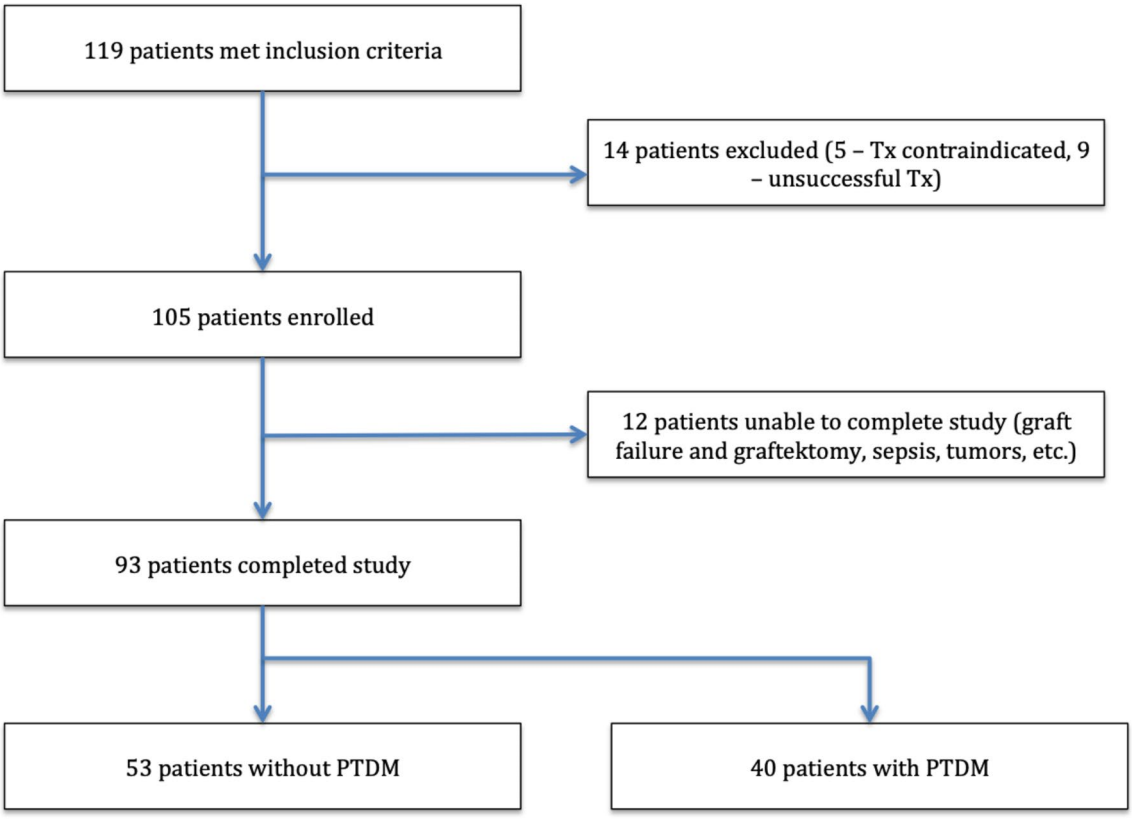

Fig. 1 Flow diagram of study participants

Table 1 Comparison of clinical and laboratory findings in patients before Tx, 3 months post-transplant and 1 year post-transplant

	Before Tx	3 months post-transplant	1 year post-transplant
BMI (kg/m2)	27.65 (23.9–31.1)	27.00 (24-30.5)**	28.00 (24–31)
TC (mmol/l)	4.27 (3.54–4.88)	5.46 (4.42–6.14)***	5.12 (4.11–5.76)***
HDL-C (mmol/l)	1.12 (0.95–1.48)	1.36 (1.04–1.68)**	1.28 (1.08–1.6)**
LDL-C (mmol/l)	2.08 (1.54–2.62)	2.92 (2.09–3.53)***	2.59 (1.98–3.31)**
nonHDL-C (mmol/l)	2.9 (2.4–3.8)	3.7 (3.1–4.8)***	3.5 (2.8–4.35)***
ApoB	0.82 (0.67–1.06)	0.98 (0.86–1.26)***	0.99 (0.79–1.21)**
ApoB/ApoA	0.59 (0.44–0.79)	0.78 (0.55–0.88)*	0.69 (0.55–0.9)*
CRP	3.9 (1.3–5.2)	1.7 (0.6-4)*	3.6 (1.65-5)
C-peptide (pmol/l)	2327 (1554–4077)		1115 (840–1542)**
HbA1C (mmol/mol)	31 (28–34)		39 (35–44)**

Data were statistically processed using Wilcoxon test with Bonferroni correction. Tx – kidney transplantation; BMI - body mass index; TC - total cholesterol; HDL-C - HDL-cholesterol; LDL-C - LDL-cholesterol; non-HDL-C - non-HDL-cholesterol; ApoB – apolipoprotein B; ApoB/ApoA – apolipoprotein B and A ratio; CRP – C-reactive protein; Hb1C - glycated hemoglobin. Values are expressed as median (25 and 75 percentile). * $p < 0.05$, ** $p < 0.001$, *** $p < 0.0001$

Table 2 Effect of medication on pulse wave parameters

Betablockers		***N***	**Mean**	**Std. Deviation**	***p***
Aortic PP	0	48	41,96	12,19	0,039*
	1	60	46,92	12,26	
PWV	0	48	10,11	3,11	0,043*
	1	60	11,38	3,26	
Central antihyper.					
Aortic PP	0	60	41,57	11,28	0,003**
	1	48	48,65	12,78	
PWV	0	60	10,38	3,03	0,119
	1	48	11,36	3,44	
Statins					
Aortic PP	0	65	43,923	11,3994	0,419
	1	43	45,907	13,8818	
PWV	0	65	10,272	3,1138	0,031*
	1	43	11,642	3,2916	

Data were statistically processed using Shapiro-Wilkov test. N – number; Central antihyper. – Central antihypertensive drugs. * $p < 0.05$, ** $p < 0.001$

differences were found (assessed as a comparison of two independent groups for qualitative variables using Fisher's exact test).

We divided our cohort of patients into two groups (patients with and without PTDM). There was no significant difference between these groups in terms of age, sex, BMI, duration of dialysis treatment prior to Tx, type of induction or immunosuppression therapy used or whether they received corticosteroid pulse therapy post-transplant (Table 3).

Table 3 Comparison of baseline characteristics between groups of patients without and with PTDM

	Patients without PTDM *n* = 53	**Patients with PTDM *n* = 40**
Age	51 (25–74)	60 (19–71)
Gender	F = 20 M = 33	F = 12 M = 28
BMI	26,6 (17–35,9)	28,7 (18,3–38,7)
Duration of dialysis treatment prior to Tx (months)	17 (0–88)	22,5 (0–96)
Induction therapy	A = 9 B = 44	A = 3 B = 37
Immunosuppression therapy	T = 45 E = 7 S = 1	T = 32 E = 8 S = 0
Pulses of corticosteroids	*n* = 13	*n* = 12
Dosage of corticosteroids in pulses (mg)	2000 (1500–3000)	2000 (1500–3000)

Quantitative data were statistically processed using Mann-Whitney U-test and qualitative data were statistically processed using Fisher test. F - female; M – male; BMI – body mass index; A = atntithymocyte globulin; B – basiliximab; T – tacrolimus; E – everolimus; S – sirolimus. Values are expressed as median (25 and 75 percentile). All presented data are statistically non-significant ($p > 0.05$)

Table 4 Occurrence and statistical prediction of examined risk factors for developing PTDM

	Occurence (%)	**Prediction of the development of PTDM**	
		3 months after the Tx	1 year after the Tx
Smoking	24.8%	non-sign.	non-sign.
Arterial hypertension	93.3%	non-sign.	non-sign.
Possitive family history of CVD and DM	17.1%	non-sign.	non-sign.
Proteinuria	78.1%	$p = 0.037$ OR = 3.942	non-sign.
Perioperative hyperglycemia	55.2%	$p = 0.003$ OR = 4.219	$p = 0.001$ OR = 4.571
Treatment of corticosteroids	100%		
Pulses of corticosteroids	25.7%	non-sign.	non-sign.
Delayed onset of graft function	36.2%	non-sign.	non-sign.
Dialysis after the Tx	36.2%	non-sign.	non-sign.

Data were statistically processed using McNemar test with Bonferroni correction and Fisher exact test for the prediction of PTDM. CVD – cardiovascular disease; DM – diabetes mellitus; Tx – kidney transplantation

Quantitative data and results are shown in Table 4. First, we examined the influence of traditional risk factors (smoking, arterial hypertension and positive family history) on the development of PTDM. The influence of these factors was found to be non-significant. In contrast, pre-transplant proteinuria was shown to be a significant risk factor for predicting PTDM development 3 months post-transplant ($p = 0.037$) with OR = 3.942

(95% CI for OR 1.066–14.576). Similarly as perioperative hyperglycemia was proven to be a significant risk factor for PTDM development at 3 months and 1 year post-transplant ($p = 0.003$, OR = 4.219; 95% CI for OR 1.660-10.718 and $p = 0.001$, OR = 4.571; 95% CI for OR 1.853–11.276 respectively). The influence of other investigated factors (pulses of corticosteroids, delayed onset of graft function and dialysis after the Tx) was not proved (non-significant).

Since the main goal of our study was to determine if pulse wave parameters differ before and after kidney transplantation and if they can be considered another risk factor for the development of PTDM, we performed pulse wave analysis before transplantation and then one year later. All measured parameters significantly improved 1 year after the transplantation ($p < 0.0001$), as is shown in Table 5.

Pre-transplant Aortic pulse pressure (Aortic PP, AUC = 0.757) and pulse wave velocity (PWV, AUC = 0.730) are the best prognostic indicators for predicting the development of PTDM three months after transplantation. The most favorable cut-off value for Aortic PP is 45mmHg (sensitivity SE = 0.714 and specificity SP = 0.698). Cut-off value for PWV is 8.5 m/s (SE = 0.857, SP = 0.6). The statistical significance was high ($p < 0.0001$), results are shown in Fig. 2. Similar results were obtained when diagnosing PTDM 1 year after the transplantation.

Table 5 Comparison of pulse wave parameters before Tx and 1 year post-transplant

	Before Tx	1 year post-transplant
AP (mmHg)	10	8***
AiX (%)	18.5	16***
AiX75 (%/75 bpm)	20	17***
AoSP (mmHg)	132.5	124***
AoPP (mmHg)	43	39***
PWV (m/s)	10.45	8.9***

Data were statistically processed using Wilcoxon test with Bonferroni correction

AP – augmentation pressure, AIx – augmentation index, AiX75 – augmentnation index corrected on 75 beats per minute, AoSP – aortic systolic blood pressure, AoPP – aortic pulse blood pressure, PWV – pulse wave velocity, Tx – transplantation. *** $p < 0.0001$

The cut-off value was set at 42mmHg for Aortic PP (SE = 0.750, SP = 0.585, $p = 0.002$) and 11 m/s for PWV (SE = 0.600, SP = 0.717, $p = 0.001$), as seen in Fig. 3.

Discussion

PTDM is one of the most common long-term complications after kidney transplantation. It is associated with major cardiovascular events [12] and even premature death [13, 14]. A study that monitored KTR in following 5 years found that 5-year survival rate was 87% in patients with PTDM compared to 93% in non-diabetic patients [15]. Furthermore PTDM is correlated with increased cardiovascular mortality, which is the most prevalent

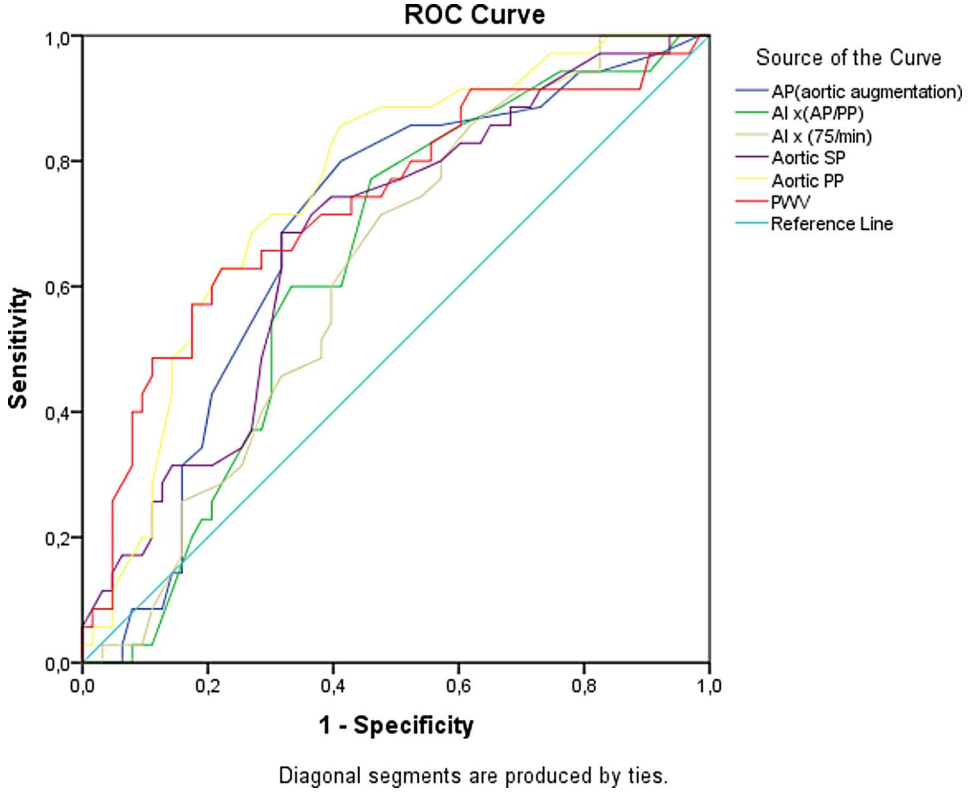

Fig. 2 ROC curve of pulse wave parameters for prediction of PTDM 3months post-transplant

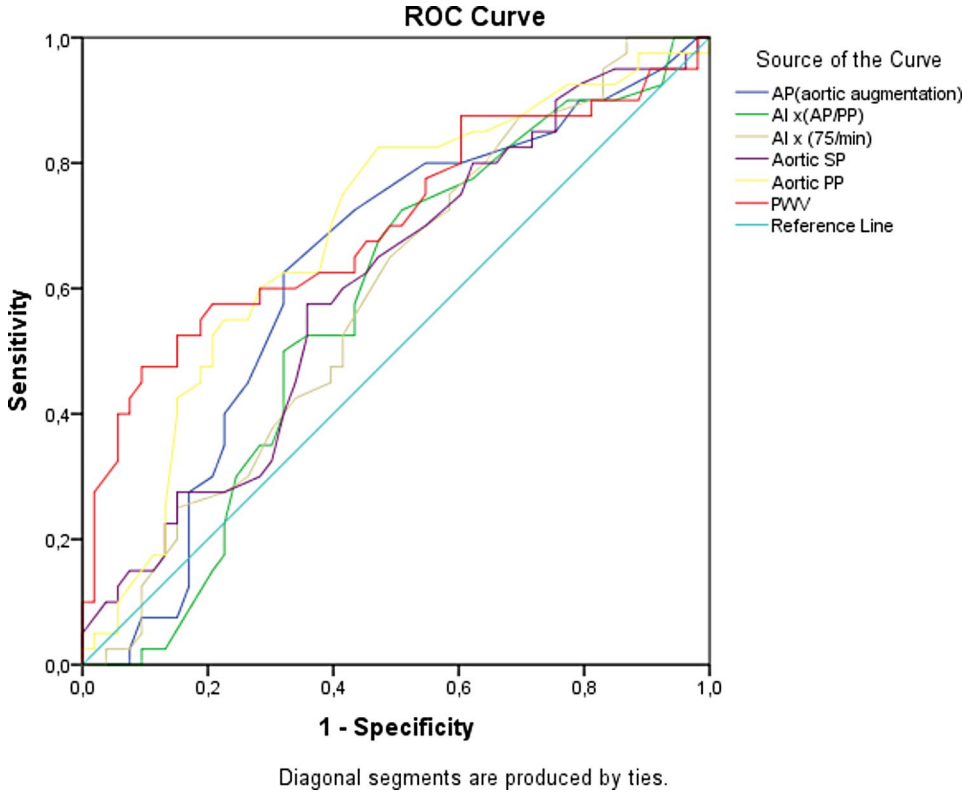

Fig. 3 ROC curve of pulse wave parameters for prediction of PTDM 1 year post-transplant

cause of poor long-term survival rate [1, 16–18]. Moreover, PTDM decreases long-term allograft survival [1, 18, 19] and it is risk factor for infection and sepsis [15, 18, 20].

The incidence of PTDM one year after transplantation was 43% in our study, which corresponds to the upper limit of the incidence reported in previous studies [1–4]. The high incidence of PTDM in our study can be attributed to the generally older age of the patients (median age 55 years) and their pre-transplant BMI (median 27.6, indicating overweight). Another potential explanation for the high incidence of PTDM is the center-specific practice of higher corticosteroid dosing in immunosuppressive regimens and the longer duration required to taper to the maintenance dose of 5 mg/day. All patients on the waiting list underwent oGTT, which ruled out overt diabetes. Patients who exhibited values indicative of prediabetes were advised to make dietary and lifestyle modifications. The diagnosis of PTDM was based on the International Consensus Guidelines on PTDM published in 2024 [3] as mentioned above. HbA1c was not used as diagnostic tool in KTR because it can be affected by various clinical interferences such as bleeding with blood loss, iron deficiency, blood transfusions, infection, renal allograft function or acidosis. HbA1c could be an adequate diagnostic tool in stable patients at least 1 year after transplantation [3, 21]. Since many KTR develop perioperative hyperglycemia and are likely to develop PTDM, the question arises as to when to perform the final diagnosis of PTDM. Current recommendations state that the diagnosis can only be made after 10–13 weeks post-transplant in stable patients [3]. In our study, we identified 21% of KTR with PTDM as early as four to six weeks post-transplant. We confirmed the diagnosis of PTDM in all of these early-diagnosed patients 3 months after the Tx, as recommended. They remained on antidiabetic therapy until the end of the study, which was at least one year post-transplant.

The main goal of our study was to confirm our hypothesis, that the parameters of arterial stiffness could be used as predictive factor for the development of PTDM. Furthermore, we analyzed pulse wave parameters before and 1 year post-transplant. Our results indicate that all measured pulse wave parameters significantly improved one year post-transplant ($p < 0.0001$), suggesting a positive impact of transplantation on vascular function. Pre-transplant Aortic PP and PWV proved to be the best prognostic indicators for the development of PTDM three months after transplantation. Specifically, the AUC for Aortic PP was 0.757 and for PWV 0.730. The most favorable cut-off value for Aortic PP was set at 45 mmHg (SE = 0.714, SP = 0.698) and for PWV at 8.5 m/s (SE = 0.857, SP = 0.6), with high statistical significance ($p < 0.0001$). Similar results were obtained when

diagnosing PTDM one year after transplantation, with a cut-off value of 42 mmHg for Aortic PP (SE = 0.750, SP = 0.585) and 11 m/s for PWV (SE = 0.000, SP = 0.717).

These findings suggest that pulse wave parameters can be useful tools for predicting PTDM in kidney transplant patients. Increased arterial stiffness, as measured by PWV and Aortic PP, may reflect underlying vascular dysfunction contributing to the development of PTDM. High arterial stiffness has previously been associated with a higher risk of cardiovascular diseases (CVD) and diabetes in the general population, and our study confirms this relationship in the context of post-transplant patients. To date, no study has focused on the evaluation of pulse wave parameters in relation to long-term post-transplant complications, including post-transplant diabetes mellitus (PTDM). A study by Cheddani et al. [22] reported that patients with chronic kidney disease (CKD) exhibit higher vascular stiffness compared to kidney transplant recipients. In contrast, our study found that among KTR, those who developed PTDM showed significantly higher vascular stiffness, measured by Aortic PP and PWV. While transplantation has been shown to reduce vascular stiffness compared to patients with kidney failure, our findings indicate that PTDM development post-transplant is associated with increased arterial stiffness, suggesting that PTDM might negate some vascular benefits of transplantation. Our study underscores the importance of monitoring pulse wave parameters in kidney transplant patients. Identifying patients with high Aortic PP and PWV values may aid in early intervention and prevention of PTDM. We recommend incorporating pulse wave analysis into the routine follow-up of post-transplant patients as part of a comprehensive risk management approach.

The other goal of our study was to identify and evaluate risk factors that lead to PTDM. We confirmed perioperative hyperglycemia as a risk factor for the development of PTDM. Perioperative hyperglycemia was observed in 55.2% patients and was significant for PTDM 3 months post-transplant ($p = 0.003$) and 1 year post-transplant ($p = 0.001$). These patients likely had impaired insulin resistance or insulin sensitivity and they were prone to developing PTDM, as mentioned in study of Nagajara et al. [23]. This hypothesis led us to use markers of insulin resistance and insulin sensitivity (HOMA-IR - homeostatic Model Assessment for Insulin Resistance and QUICKI – quantitative insulin sensitivity index) to predict PTDM. However, none of these markers were statistically significant.

We assessed post-transplant proteinuria as the last known risk factor for the development of PTDM. Proteinuria developing within 3–6 months post-transplant is a strong risk factor for PTDM; even low-grade (< 1 g/day) and very low-grade (< 0.3 g/day) proteinuria is independent risk factors [24]. In our study, we confirmed proteinuria (occurred in 78.1% of patients) as a risk factor for the development of PTDM 3 months post-transplant ($p = 0.037$) but it was not significant for PTDM 1 year post-transplant.

Previous studies have shown that traditional risk factors for the development of PTDM include age, gender, BMI, smoking, and a positive family history of diabetes mellitus. The correlation between age and PTDM has been demonstrated in various studies [25–27]. In the study of Cheng et al. the risk of developing PTDM in KTR aged 45–65 years at the time of transplant was 2.9 times higher than that in patients aged < 45 years and the risk in patients aged > 65 years was 4.86 times higher than that in patients aged < 45 years [19]. The incidence of PTDM is considerably higher in male patients and those with BMI > 30 kg/m^2 [28]. Surprisingly, in our study there was shown no significant influence of age, gender, BMI, anamnesis of smoking or positive family history of DM or CVD on the development of PTDM. Our two groups of patients (with and without PTDM) did not differ in the traditional risk factors, which may be interesting for the interpretation of subsequent findings.

There are also post-transplant risk factors of PTDM including the immunosuppressive regimen used to maintain the graft function and treat eventual acute rejection. Initially, all our patients received corticosteroids as part of their immunosuppressive therapy. It is well known that corticosteroids cause hyperglycemia and predispose patients to the development of diabetes. The mechanisms include impaired insulin sensitivity, increased hepatic gluconeogenesis, and appetite stimulation resulting in weight gain. The diabetogenic effect of glucocorticoids is dose-dependent, with induction protocols having a greater diabetogenic potential than long-term maintenance doses [29, 30]. Furthermore, acute rejection has been identified as another risk factor for PTDM in previous studies [31, 32]. The increase in blood glucose levels induced by acute rejection may be related to high doses of corticosteroids but also to the stress response, which can mobilize the secretion of catecholamine, glucocorticoids, growth hormones, glucagon and other insulin antagonistic hormones causing further increase in glycaemia [33]. In our study, 25.7% of patients needed high doses of corticosteroids in pulses to treat acute rejection. Contrary to expectations, this treatment did not significantly influence the development of PTDM. Additionally, 36.2% of patients had delayed graft function onset with the need of dialysis after Tx. None of these complications were correlated with the development of PTDM.

Changes in lipid profile occur after kidney transplantation. In KTR, the main lipid alteration is hypercholesterolemia while hypertriglyceridemia is less pronounced [34, 35]. Furthermore HDL-cholesterol levels significantly

increase [36]. These changes were also confirmed during our study. We observed significant increase of TC, LDL cholesterol, nonHDL cholesterol, apolipoprotein B and HDL cholesterol. These observations suggest an increased cardiovascular risk in KTR.

Finally, we found out that the use of RAAS blockers, calcium channel blockers, diuretics, and antiplatelet therapy did not have a significant effect on pulse wave parameters before Tx. In contrast, patients using beta-blockers demonstrated worse Aortic PP and PWV parameters compared to those not using beta-blockers. Similarly, patients on central antihypertensive drugs exhibited worse Aortic PP values ($p = 0.003$) and patients using statins also had worse PWV values ($p = 0.031$). These findings are supported by studies demonstrating that inhibition of RAAS appears to be superior compared to other antihypertensive medication in reducing arterial stiffness [37, 38]. Calcium channel blockers, diuretics and beta blockers are less effective in reducing arterial stiffness compared to ACE inhibitors and AT-1R antagonists perhaps because of less impact on fibrosis and vascular remodeling [39, 40]. On the contrary, statins seem to reduce arterial stiffness according to recent meta-analysis [41]. The explanation could lie in the fact that these patients were generally more complex, requiring a broader range of medications due to additional comorbidities, which may have contributed to their poorer pulse wave parameter values. However, further analysis did not reveal a significant difference in the use of these medications between patients with and without the development of PTDM.

Despite significant findings, our study has some limitations.

In the context of acute rejection, we evaluated only pulses of corticosteroids as s potential rick factor of PTDM. We did not differentiate between antibody-mediated rejection and acute cellular rejection, nor the impact of their treatment was included (plasmapheresis or administration of intravenous immunoglobulines). Furthermore, our study protocol did not assess echocardiographic findings, such as left ventricular hypertrophy and its thickness, as additional markers of elevated central pressures.

The small sample size and short follow-up period may limit the generalizability of our results. Future research should include larger cohorts and longer follow-up periods to confirm our findings and explore the mechanisms linking arterial stiffness and PTDM.

Conclusion

Efficient prevention is an essential tool for modern medicine. Both the frequency and severity of PTDM justify scientific investigation into PTDM prevention. Establishing an effective prevention strategy requires several key prerequisites: the accurate identification of at-risk patients, a solid understanding of PTDM pathogenesis, and the development of reliable early detection tools. These elements are crucial and must be clarified before any prevention efforts can be initiated. Additionally, prevention strategies must be easy to manage, acceptable to patients, well tolerated, and cost-effective. Our study provides evidence that pulse wave parameters, such as Aortic PP and PWV, are significant predictors of PTDM in KTR. These findings enhance our understanding of PTDM pathophysiology and support the development of preventive and therapeutic strategies aimed at improving vascular function in KTR.

The results of our study have significant implications for clinical practice. The inclusion of pulse wave parameters (Aortic PP and PWV) in routine pre-transplant evaluations may allow for early identification of patients at high risk of PTDM. By integrating this tool into the pre-transplant workup, clinicians could tailor post-transplant monitoring and interventions more effectively. From a therapeutic perspective, the diabetogenic effects of corticosteroids remain a challenge. Adjusting immunosuppressive regimens, such as expediting the tapering of corticosteroids to maintenance doses or considering the use of less diabetogenic immunosuppressive agents, could reduce the incidence of PTDM, especially in high-risk patients. Additionally, lifestyle modifications aimed at improving metabolic health should be emphasized pre- and post-transplant. Encouraging weight management, dietary adjustments, and regular physical activity in patients identified as high risk could mitigate the development of PTDM and its associated complications.

Our findings underline the importance of a multifaceted approach to PTDM prevention and management, incorporating both innovative diagnostic tools and individualized therapeutic strategies to optimize outcomes for kidney transplant recipients.

Acknowledgements
The authors thank study participants, as well as the additional healthcare professionals involved in conducting the study.

Author contributions
DM, JZ, DK: design and methodology; DM: investigation and collecting data; VK: biochemical analysis; DM, LC: writing – original draft preparation; KL: statistics; DK, JZ, LC: writing – review and editing. All authors have read and approved the final manuscript.

Funding
This work was supported by Ministry of Health, Czech Republic – conceptual development of research organization (MH CZ-DRO (FNOI, 00098892) and Internal Grant Agency of the Ministry of Health, Czech Republic (IGA_LF_2024_004) and IGA_LF_2025.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethic approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethical approval was obtained from the Ethics Committee of Medical faculty and University Hospital Olomouc (approval no. 94/15). Informed consent was obtained from all participants.

Consent for publication

Clinical trial number: not applicable. This study did not involve the publication of any identifiable personal data, and therefore consent for publication is not applicable.

Competing interests

The authors declare no competing interests.

Received: 26 September 2024 / Accepted: 30 December 2024
Published online: 16 January 2025

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