

Elevated Plasma High Sensitive C-Reactive Protein and Triglyceride/High-Density Lipoprotein Cholesterol Ratio are Risks Factors of Diabetes Progression in Prediabetes Patients After Kidney Transplant: A 3-Year Single-Center Study in Vietnam

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Purpose: Determination the rate of developing post-transplant diabetes mellitus (PTDM) in prediabetic patients and the relationship with plasma hs-CRP levels and TG/HDL-C ratio in patients after kidney transplantation from living donors followed for 3 years.

Subjects and Methods: A total of 206 post-transplant patients diagnosed with prediabetes by oral glucose tolerance test (OGTT) were included in the study. At the time of diagnosis of prediabetes, all patients were clinically examined, paraclinical tests were performed, plasma hs-CRP was quantified, and the TG/HDL-C ratio was determined. Patients are individualized and given a reasonable diet and exercise regimen. Patients had their fasting blood glucose measured monthly or had an OGTT every 3 months. Patients meeting the criteria for diagnosis of PTDM according to the American Diabetes Association (ADA)-2018 were collected during 3 years of follow-up.

Results: The study group had an average age of 39.46 ± 10.26 years old, including 74.8% males and 25.2% females. The rate of patients who had a development of PTDM from prediabetes was 29.6% (61/206 patients). BMI, plasma TG, HDL-C, hs-CRP, and TG/HDL-C ratio at the time of prediabetes diagnosis were factors related to the progression of PTDM, in which hs-CRP and TG/HDL-C ratio were good predictors (with AUC = 0.85 and 0.874, respectively; $p < 0.001$).

Conclusion: After 3 years of follow-up, nearly one-third of prediabetic patients developed PTDM post-living donor kidney transplantation. BMI, plasma TG, HDL-C, hs-CRP, and the TG/HDL-C ratio were linked to DM progression, with hs-CRP and TG/HDL-C being the strongest predictors.

Keywords: prediabetes, post-transplant diabetes mellitus, plasma hs-CRP, kidney transplantation, TG/HDL-C ratio

Introduction

Post-transplant diabetes mellitus (PTDM) is a disease seen in patients after solid organ transplantation, including kidney.^{1,2} PTDM replaced the term new-onset diabetes after transplantation (NODAT) after the first international consensus in 2003.³ Several reasons explain this name change: 1) many cases of diabetes first detected after transplantation may not be new; 2) the timing of PTDM diagnosis was re-evaluated because the diagnosis of NODAT immediately after admission or surgery could not be ruled out. Like type 2 diabetes mellitus (DM), the pathogenesis of PTDM is also

related to insulin resistance and reduced pancreatic beta cell function.^{1,4} Regarding risk factors for developing PTDM, in addition to factors similar to type 2 DM, there are also factors related to the characteristics of patients after kidney transplant such as: eating habits and no physical exercise that cause weight gain; long-term and high-dose use of immunosuppressive drugs (Tacrolimus and Corticosteroids are drugs in the treatment regimen that cause hyperglycemia); post-transplant infections (Cytomegalo Virus: CMV or Hepatitis C Virus: HCV).⁴⁻⁷ PTDM is associated with loss of kidney graft function, cardiovascular events, and mortality in patients after kidney transplantation.⁸⁻¹¹

The incidence of prediabetes after kidney transplantation often varies between studies, in which about 50% have impaired glucose tolerance (IGT), 30% have impaired fasting glucose (IFG), and 20% have a combination of both IGT and IFG.^{12,13} Prediabetes has been considered a risk factor for developing type 2 DM both in the general population and in patients after kidney transplantation.^{14,15} To reduce the development of diabetes mellitus, prediabetic patients must control risk factors as well as change lifestyle and physical activity. Dyslipidemia, especially the balance between harmful blood lipids such as triglycerides (TG) and beneficial blood lipids such as high-density lipoprotein cholesterol (HDL-C), is significant in predicting the progression of type 2 DM from prediabetes. Sun et al observed 15,017 Chinese prediabetic adults, the mean follow-up time was 3.05 years, 11.46% (1731/15,017 people) converted to diabetes, and high TG/HDL-C ratio at the time of prediabetes diagnosis had predictive value for progression to diabetes (HR = 1.111, 95% CI 1.061–1.164).¹⁶ Inflammation (expressed by C-reactive protein) is also confirmed as a pathogenesis-related to prediabetes and PTDM.^{17,18} Cheng et al found that high levels of hs-CRP (high-sensitivity C-reactive protein) were predictive of progression from prediabetes to diabetes after conducting a study on 2874 middle-aged and elderly people with prediabetes, observed for 4 years.¹⁸ Thus, in prediabetic subjects, both high TG/HDL-C ratio and hs-CRP have predictive value for progression to diabetes, however, in post-kidney transplant patients, this has not been confirmed. Based on the above reasons, in this study we hypothesize that elevated plasma hs-CRP levels and high TG/HDL-C ratio at the time of prediabetes identification are related to the progression of type 2 DM from prediabetes after transplant in patients after kidney transplantation.

Subjects and Methods

Subjects

A cross-sectional, non-interventional, non-controlled longitudinal descriptive study was conducted on 206 patients diagnosed with prediabetes in the first year after kidney transplantation from a living donor at the Organ Transplant Center, Military Hospital 103, Vietnam Military Medical University, from January 2018 to December 2022. Inclusion criteria: Patients >18 years old, both male and female. Diagnosed with prediabetes in the first year after kidney transplantation. Fully followed up for 3 years after diagnosis of prediabetes. No impaired glucose tolerance before transplantation. No diabetes before transplantation. No acute infection at the time of data collection. Followed up and treated after transplantation at the Organ Transplant Center. We excluded patients <18 years old, having acute infection, pregnant or breastfeeding women. Eligible patients signed a consent form to participate in the study.

All patients had anthropometric, clinical, and paraclinical data collected at the time of post-transplant prediabetes diagnosis (after the oral glucose tolerance test). The patients measured blood pressure, height, weight, BMI calculated and daily prednisolone dose collected. Fasting peripheral venous blood was taken for measuring complete blood count and quantifying biochemical indicators such as: glucose, urea, creatinine, protein, albumin. Tacrolimus C0 concentration was also quantified. Patients were also quantified hs-CRP concentration and 4 blood lipid indices including: Cholesterol, TG, LDL-C and HDL-C. Estimated GFR was calculated according to the MDRD formula based on plasma creatinine concentration. Proteinuria and renal transplant rejection status were collected in this study. Plasma TG/HDL-C ratio was calculated as the ratio of TG concentration divided by HDL-C concentration measured in the same plasma sample.

Maintenance Immunosuppressive Therapy

Maintenance immunosuppressive therapy was applied for all patients according to the recommendations of the Vietnam Society of Organ Transplantation and the International Society of Organ Transplantation. Maintenance immunosuppression consisted of a combination of calcineurin inhibitor (tacrolimus: 0.1–0.2 mg/kg/24 hrs or cyclosporine: 10.0 mg -

15.0 mg/kg/24 hrs, dose adjusted according to blood levels; maintain a tacrolimus target level of 8.0 to 12.0 ng/mL; Co of cyclosporine target level of 300 to 350 ng/mL and C2 of cyclosporine target level of 1300 to 1500 ng/mL for the first 10 days) and sodium mycophenolate 1000–2000 mg/24 hrs, adjusted according to body surface, gastrointestinal tolerance, and white and red cell count in peripheral blood.

Follow Up and Management of Prediabetes Patients

All prediabetic patients are continuously monitored and re-examined monthly. In addition to maintaining anti-rejection drugs, treating hypertension, dyslipidemia, hyperuricemia. Prediabetic patients are prescribed to change their diet, lifestyle, and use hypoglycemic drugs (individualized for each patient) according to the recommendations of the American Diabetes Association's guidelines for prediabetic patients.¹

PTDM patients were diagnosed monthly as follows: (1) Patients with fasting blood glucose concentrations ≥ 126 mg/dL (7.0 mmol/L); (2) Patients with any blood glucose concentration ≥ 200 mg/dL (11.1 mmol/L) accompanied by symptoms of frequent urination, increased appetite, and weight loss. These patients continued to receive dietary and lifestyle adjustments, immunosuppressants, and hypoglycemic drugs.¹

The remaining patients underwent a 75 g oral glucose tolerance test (OGTT) with 2-hour blood glucose test ≥ 200 mg/dL (11.1 mmol/L) and continued to be diagnosed with PTDM.¹ The number of PTDM patients was collected during 3 years of follow-up (OGTT was performed every 3 months). At the end of 3 years of follow-up, we divided 206 patients into 2 groups: Group 1 (n=61): PTDM and Group 2 (n=145): Non-PTDM

Statistical Analysis

In the case of a normal distribution, continuous data were expressed as mean and standard deviation and compared using a Student's *t*-test or one-way ANOVA. All bias distributions were expressed as median (interquartile range) and compared using the Mann–Whitney U or Kruskal–Wallis test. Categorical data were expressed as the frequency (percentage) and compared using the Chi-square or Fisher's exact tests. Analysis of independent risk factors for progression of diabetes from prediabetes was performed based on multivariate adjusted regression analysis. Receiver operating characteristic (ROC) curves with the area under the curve (AUC) were calculated to predict the progression of diabetes from prediabetes in all patients. Data were analyzed using the Statistical Package for Social Science (SPSS) software version 22.0 (Chicago, IL, USA). A *p*-value < 0.05 was considered significant.

Results

Table 1 shows age, BMI, levels of Cholesterol, Triglyceride, LDL-C, TG/HDL-C ratio, hs-CRP, prednisolone dose, Tacrolimus C0, ratio of hepatitis B and or C virus infection, lipid disorder, acute graft rejection, proteinuria were higher, while eGFR and HDL-C concentration were lower in PTDM group compared to those of non-PTDM group, $p < 0.05$ to $<$

Table 1 Comparison of Clinical Characteristics and Laboratory Parameters of Patients with PTDM and Non-PTDM

Characteristics	All, (n=206)	PTDM (n=61)	Non-PTDM (n=145)	p
Ages (Average)	39.46 \pm 10.26	47.11 \pm 10.46	36.24 \pm 8.31	< 0.001
Sex (n, %)				
– Males	154 (74.8)	48 (78.7)	106 (73.1)	0.400
– Females	52 (25.2)	13 (21.3)	39 (26.9)	
Hypertension (n,%)	98 (47.6)	34 (55.7)	64 (44.1)	0.128
– Systolic BP	130.49 \pm 7.7	131.92 \pm 8.66	129.89 \pm 7.2	0.111
– Diastolic BP	79.71 \pm 4.80	79.92 \pm 5.95	79.62 \pm 4.25	0.686

(Continued)

Table I (Continued).

Characteristics	All, (n=206)	PTDM (n=61)	Non-PTDM (n=145)	p
Hepatitis virus infection (n,%)				
– None infection	139 (67.5)	45 (73.8)	94 (64.8)	0.032
– HBV	16 (7.8)	3 (4.9)	13 (9.0)	
– HCV	32 (15.5)	4 (6.6)	28 (19.3)	
– HBV+HCV	19 (9.2)	9 (14.8)	10 (6.9)	
BMI (kg/m ²)				
– < 18.5	47 (22.8)	3 (4.9)	44 (30.3)	< 0.001
– 18.5–22.9	95 (46.1)	22 (36.1)	73 (50.3)	
– 23 - < 25	43 (20.9)	17 (27.9)	26 (17.9)	
– ≥ 25	21 (10.2)	19 (31.1)	2 (1.4)	
– Average	21.35 ± 3.56	23.97 ± 4.1	20.25 ± 2.64	< 0.001
Glucose (mmol/L)	5.53 ± 0.58	5.65 ± 0.63	5.49 ± 0.55	0.08
Creatinine (μmol/L)	90.19 ± 14.69	96.02 ± 15.49	87.74 ± 13.66	< 0.001
eGFR (mL/min/1.73m ²)	90.47 ± 18.84	82.72 ± 16.32	93.72 ± 18.92	< 0.001
Albumin (g/L)	40.88 ± 4.58	40.88 ± 4.32	40.89 ± 4.7	0.986
Cholesterol (mmol/L)	4.23 ± 0.98	4.58 ± 1.11	4.09 ± 0.88	0.003
Triglyceride (mmol/L)	1.86 (1.2–2.79)	3.64 (2.12–5.44)	1.51 (1.13–2.16)	< 0.001
HDL-C (mmol/L)	0.94 ± 0.25	0.80 ± 1.45	1.01 ± 0.26	< 0.001
LDL-C (mmol/L)	2.72 ± 0.77	2.91 ± 0.82	2.63 ± 0.74	0.018
TG/HDL-C ratio	1.92 (1.22–3.54)	4.39 (2.78–6.53)	1.57 (1.1–2.28)	< 0.001
hs-CRP (mg/L)	1.41 (0.66–2.17)	2.4 (1.78–3.18)	0.98 (0.47–1.77)	< 0.001
Lipid disorder (n,%)				
– Yes	176 (85.4)	59 (96.7)	117 (80.7)	0.003
– No	30 (14.6)	2 (3.3)	28 (19.3)	
Uric Acid (μmol/L)				
– Increase (n,%)	109 (52.9)	28 (45.9)	81 (55.9)	0.191
– No (n,%)	97 (47.1)	33 (54.1)	64 (44.1)	
Hemoglobin (g/L)	138.42 ± 17.05	140.84 ± 14.56	137.4 ± 17.94	0.187
Anemia (n,%)	48 (23.3)	17 (27.9)	31 (21.4)	0.314
WBC (G/L)	6.67 (5.5–7.81)	7.4 (6.09–8.05)	6.54 (5.4–7.79)	0.087
Acute graft rejection (n,%)	18 (8.8)	9 (14.8)	9 (6.3)	0.049
Proteinuria (n,%)	9 (4.4)	6 (9.8)	3 (2.1)	0.021
Prednisone dose (mg/24 hours)	5.46 ± 1.45	5.90 ± 1.93	5.27 ± 1.14	0.021
Tac C0 (ng/mL)	6.5 (5.7–7.52)	7.6 (6.5–8.7)	6.2 (5.6–6.8)	< 0.001

Notes: Bold value: significant differences.

Abbreviations: PTDM, Post-transplant diabetes mellitus; BP, Blood pressure; HBV, Hepatitis B Virus; HCV, Hepatitis C Virus; BMI, Body mass index; eGFR, estimated Glomerular Filtration Rate; HDL-C, High-Density Lipoprotein Cholesterol; LDL-C, Low-Density Lipoprotein Cholesterol; TG/HDL-C, Triglyceride/High-Density Lipoprotein Cholesterol; hs-CRP, high sensitivity C-Reactive Protein; WBC, White Blood Cell; Tac C0, Trough concentration of Tacrolimus.

Table 2 Multivariate Analysis of Independent Factors Related to Progression from Prediabetes to PTDM

Variable	Adjusted OR	95% CI	p
Age	1.105	1.028–1.188	0.006
BMI	1.338	1.045–1.714	0.021
TG/HDL-C ratio	2.676	1.700–4.213	< 0.001
hs-CRP	7.585	2.920–19.703	< 0.001
Tac C0 (ng/mL)	2.221	1.343–3.671	0.002

Notes: Bold value: significant differences.

Abbreviations: PTDM, Post-transplant diabetes mellitus; BMI, Body mass index; TG/HDL-C, Triglyceride/High-Density Lipoprotein Cholesterol; hs-CRP, high-sensitivity C Reactive Protein; Tac C0, Trough concentration of Tacrolimus.

0.001. In contrast, the results did not show statistically significant differences in gender, blood pressure, albumin, uric acid, anemia, and white blood cell count between the two groups, $p > 0.05$.

Table 2 shows old age, high BMI, TG/HDL-C ratio, hs-CRP, and high Tac C0 are independent factors associated with the progression of PTDM from prediabetes ($p < 0.05$ to < 0.001).

Figure 1 shows age, BMI, hs-CRP, Triglyceride, HDL-C, and TG/HDL-C ratio were good indicators for predicting progression from prediabetes to PTDM in patients after kidney transplantation, in which TG/HDL-C ratio was the best index with AUC=0.874, $p < 0.001$, sensitivity = 80.3%, and specificity = 82.8%.

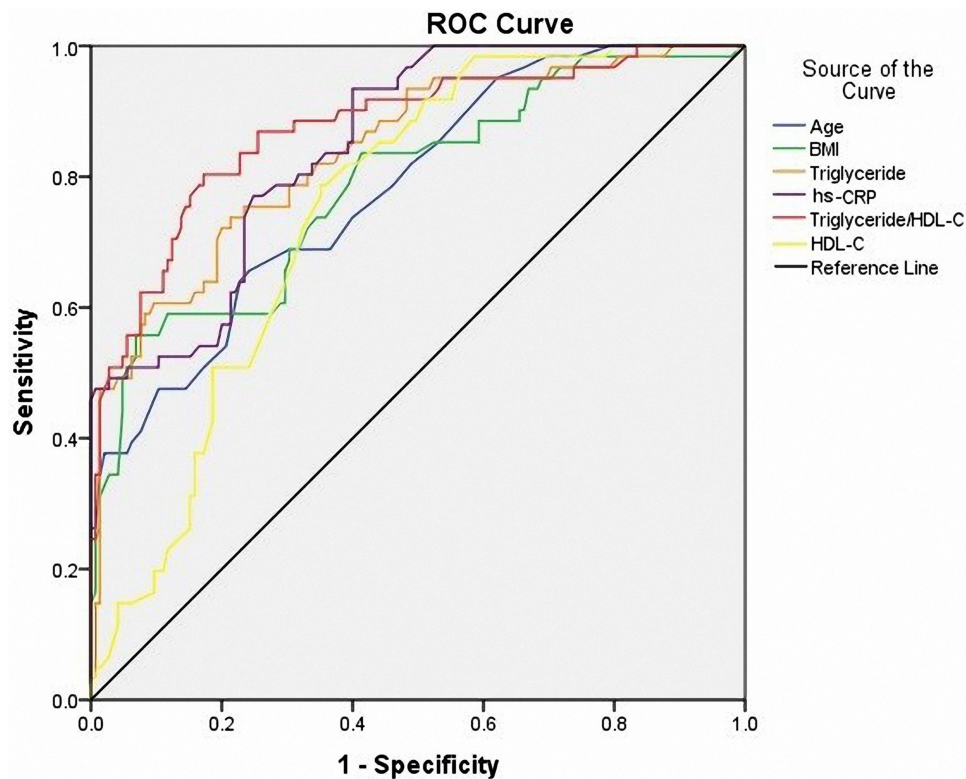


Figure 1 ROC curve of factors predicting progression from prediabetes to PTDM in kidney recipients during 3 years follow-up. Age: AUC = 0.782; $p < 0.001$; Cut-off value = 41.5 years, Sensitivity = 65.6%, Specificity = 75.9%; BMI: AUC = 0.788; $p < 0.001$; Cut-off value = 23.8 kg/m², Sensitivity = 55.7%, Specificity = 93.1%; hs-CRP: AUC = 0.85; $p < 0.001$; Cut-off value = 1.19 mg/l, Sensitivity = 93.4%, Specificity = 60%; Triglyceride: AUC = 0.838; $p < 0.001$; Cut-off value = 2.19 mmol/l, Sensitivity = 73.8%, Specificity = 78.6%; HDL-C: AUC = 0.75; $p < 0.001$; Cut-off value = 0.89 mmol/l, Sensitivity = 78.7%, Specificity = 64.8%; Triglyceride/HDL-C ratio: AUC = 0.874; $p < 0.001$; Cut-off value = 2.61, Sensitivity = 80.3%, Specificity = 82.8%.

Discussion

Despite diet and exercise restrictions, 29.6% of patients (61/206 patients) still developed PTDM from prediabetes after kidney transplantation (Table 1). Prediabetes has been identified as a risk factor for developing type 2 DM because prediabetes is associated with the simultaneous presence of insulin resistance (IR) and β -cell dysfunction (two pathogenesis of type 2 DM). Among prediabetic patients, approximately 10% will progress to DM each year,^{19,20} and it is predicted that up to 70% of people with prediabetes will eventually develop into DM.¹⁴ Our results suggest that multiple factors are involved in the progression from prediabetes to diabetes in kidney transplant recipients. In addition to the classic factors, such as old age, overweight, obesity, and dyslipidemia that have been confirmed in the literature, patients after kidney transplantation also have other typical factors including: hepatitis virus infection, low eGFR, positive proteinuria, as well as high levels of corticosteroids, tacrolimus, and graft rejection, which are also shown in our study results (Table 1). In addition to the progression to DM, prediabetes is also a risk factor and related to cardiovascular events (which are the leading causes of death in prediabetes patients).²¹ Prediabetes is also associated with heart failure, coronary artery disease, and peripheral artery disease.^{22–24} Treatment intervention is necessary to reduce the development of prediabetes into DM and reduce cardiovascular events. There is currently no specific evidence to develop clinical guidelines for the treatment of prediabetes. The use of pharmacotherapy should be based on a case-by-case approach. In kidney post-transplant patients, pharmacotherapy needs to be considered more carefully. It is still best to adjust immunosuppressant medication, reduce the dose, or remove corticosteroids from the anti-rejection maintenance treatment regimen and lifestyle intervention for kidney post-transplant patients with prediabetes. Lifestyle interventions may ultimately improve quality of life, morbidity, and mortality, as well as prolong the lifespan of the transplanted kidney.^{3,4,20,21}

Inflammation is considered a factor related to IR and pancreatic β -cell dysfunction in patients with prediabetes and DM.^{25,26} Chronic, low-level inflammation causes pancreatic β -cell damage, which then causes insufficient insulin production and leads to hyperglycemia.²⁷ Recently, Yousef et al²⁸ showed an association between increased inflammatory cytokines such as Interleukin 10 and CRP and the development of DM from prediabetes. Our study results also showed that the group progressing to PTDM had higher hs-CRP concentrations than non-PTDM, $p < 0.001$ (Table 1). Moreover, increased plasma hs-CRP is an independent factor related to the progression of PTDM from prediabetes after kidney transplantation (Table 2 shows OR=7.585, $p < 0.001$). At the cut-off point = 1.19 mg/L, hs-CRP has predictive value for the progression of PTDM from prediabetes in patients after kidney transplantation, AUC = 0.85, $p < 0.001$ (Figure 1). hs-CRP has been confirmed to be related and predictive of PTDM progression in patients after kidney transplantation¹⁷ through the mechanism of inflammation associated with IR and reduced pancreatic beta cell function.

Blood lipid components, especially TG and HDL-C, play a role in the pathogenesis of patients with prediabetes and type 2 DM. The ADA has recommended that in addition to controlling blood glucose, it is necessary to control other lipid disorders, especially in patients with increased TG and decreased HDL-C.¹ Similar recommendations exist for patients after kidney transplants.^{9–11} The relationship between increased plasma TG and decreased HDL-C concentration, especially the TG/HDL-C ratio, is closely related to IR and central obesity,²⁹ both of which are associated with prediabetes and type 2 DM. The TG/HDL-C ratio related to progression from prediabetes to DM has been confirmed in several studies in non-kidney transplant populations. Sun et al studied the progression from prediabetes to DM after 3.05 years of follow-up of 15,017 prediabetes adults, with a progression rate of 11.46%. Increased TG/HDL-C ratio was related to this progression, $p < 0.001$.¹⁶ In older people without prediabetes, the TG/HDL-C ratio also has predictive value for the new development of DM.³⁰ Our study results showed that TG was higher and HDL-C was lower in the PTDM group compared to the Non-PTDM group, $p < 0.05$ (Table 1). In particular, the TG/HDL-C ratio was higher in the PTDM group than the Non-PTDM one, $p < 0.001$ (Table 1). On multivariate analysis, only the TG/DHL-C ratio was an independent factor related to the progression of PTDM from prediabetes in post-kidney transplant patients continuously monitored for 3 years. As demonstrated, high TG and low HDL-C levels are associated with insulin resistance and type 2 DM. This relationship is not strong when each index is used alone. The relationship will be closer if these two indexes are

combined (TG/HDL-C ratio).³¹ In kidney transplant patients, the role of hs-CRP and blood lipid components in the development of cardiovascular events has also been studied.^{32,33} However, the role in the development of DM from prediabetes after transplantation has not been studied much. Lima et al demonstrated that dyslipidemia and high BMI were associated with the development of PTDM in a study using 258 renal transplant patients.³⁴ High TG and low HDL-C concentrations are also factors associated with the occurrence of PTDM in many recent studies, with the mechanism also related to IR and reduced pancreatic beta cell function such as hs-CRP.^{35,36} Figure 1 in our study shows hs-CRP and TG/HDL-C ratio are good indicators for predicting progression from prediabetes to PTDM in patients after kidney transplantation, $p < 0.001$. From the results of this study, we found that it is necessary to control inflammation and treat dyslipidemia (reduce TG and increase HDL-C) to reduce the rate of PTDM development from prediabetes in patients after kidney transplantation.

Although our study results achieved the objectives, the study still has some limitations as follows: The study was conducted in a single center, limiting the ability to generalize the findings to other population groups. The study has not considered all the genetic factors and lifestyle characteristics of Vietnamese people as well as post-renal transplant factors affecting the progression of PTDM. In particular, the study has not clarified all the potential mechanisms linking these factors to the progression of diabetes from pre-diabetes in patients after kidney transplantation.

Conclusion

The rate of PTDM development from prediabetes was 29.6% (61/206 patients) after 3 years of follow-up in patients who underwent living donor kidney transplantation. Factors such as BMI, plasma TG, HDL-C, hs-CRP, and the TG/HDL-C ratio at the time of prediabetes diagnosis were related to the progression to DM, with hs-CRP and the TG/HDL-C ratio being the strongest predictors, showing AUC values of 0.85 and 0.874, respectively, with $p < 0.001$.

Data Sharing Statement

The data presented in this study are available on request from the corresponding author.

Ethics Approval

All kidneys were donated voluntarily with written informed consent, and that these were conducted in accordance with the Declaration of Istanbul. This study was also approved by the Ethical Committee of Military Hospital 103 (No: 51/CNChT-HĐĐĐ).

Consent for Publication

Informed consent was obtained from all the participants.

Human and Animal Rights

Animals did not participate in this research. All human research procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2008.

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The authors have no relevant financial or non-financial interests to disclose.

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