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Risk factors for Post-Kidney Transplantation Diabetes Mellitus: a systematic review

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RISK FACTORS FOR POST-KIDNEY TRANSPLANTATION DIABETES MELLITUS – A SYSTEMATIC REVIEW

FATORES DE RISCO PARA DIABETES MELLITUS PÓS TRANSPLANTE RENAL – UMA REVISÃO SISTEMÁTICA

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Abstract

Post-Kidney Transplantation *Diabetes Mellitus* is a common complication of kidney transplantation that has a serious impact on the patient prognosis. As the pathophysiology of PTDM is not fully understood, becomes essential to characterize potential risk factors to prevent, wisely manage and establish future target therapies to this condition.

Our goals were to describe new risk factors for Post-Kidney Transplantation *Diabetes Mellitus*, in the last five years, and search for updates on those previously described in 2003 International Consensus Guidelines.

In order to write this systematic review, we searched on PubMed database from 1st of January 2015 to the 1st of January 2020 and we selected 21 articles for qualitative synthesis with an overall of 9571 patients.

As results of our review, we associated older age, abnormal glucose levels before and right after Kidney Transplantation, family history of *Diabetes Mellitus* and dyslipidemia to increased risk of Post-Kidney Transplantation *Diabetes Mellitus*. Overweight also seems to be a risk factor for Post-Kidney Transplantation *Diabetes Mellitus* but new ways of measuring this parameter are required to create a stronger association. Still controversial, Hypomagnesemia, 25 hydroxyvitamin D deficiency, acute rejection episodes and proteinuria levels seem to play a role in PTDM. We also verified that some immunosuppression therapies such as steroids, tacrolimus and sirolimus are highly diabetogenic. In tacrolimus case, new monitoring methods and genetic studies can optimize its use. In our review, we present new perspectives of therapeutic targets based on Serum proprotein convertase subtilisin/kexin type 9 and Cytochrome P450 enzymes.

The acknowledge of risk factors through a complete anamnesis and a careful pre-and post-transplantation follow up can improve the graft and the patient prognosis. Besides, genetic studies are becoming fundamental tools in management of immunosuppressive therapies and selection of kidney transplant candidates.

Keywords: Post-Kidney Transplantation *Diabetes Mellitus*, kidney transplantation, risk factors, adverse effects**,** immunosuppressive therapies, future perspectives

Resumo

A *Diabetes Mellitus* Pós-Transplante Renal é uma complicação comum da transplantação renal com um impacto importante no prognóstico do doente. Como a fisiopatologia da *Diabetes Mellitus* Pós-Transplante Renal não é totalmente conhecida, torna-se essencial a caracterização de fatores de risco para prevenir, gerir e estabelecer terapias alvo futuras desta doença.

Os nossos objetivos eram descrever novos fatores de risco de *Diabetes Mellitus* Pós-Transplante Renal, nos últimos 5 anos e, procurar atualizações relativas aos fatores descritos nas *Guidelines* Internacionais de 2003.

Para a realização desta revisão sistemática, pesquisámos na base de dados *Pubmed* entre 1 de janeiro de 2015 e 1 de janeiro de 2020, selecionando 21 artigos para análise quantitativa, alcançando no total 9571 transplantados.

Como resultados da nossa revisão, associámos idades mais avançadas, alterações da glicémia pré e pós transplante, história familiar de *diabetes mellitus* e dislipidemia, a risco aumento de *Diabetes Mellitus* Pós-Transplante Renal. Excesso de peso também parece ser um fator de risco para *Diabetes Mellitus* Pós-Transplante Renal, mas novas formas de avaliação deste parâmetro são precisas para criar uma associação mais forte. Apesar de controverso, a hipomagnesémia, a deficiência de 25-hidroxivitamina D, episódios de rejeição aguda e níveis mais elevados de proteinúria também podem ter um papel na *Diabetes Mellitus* Pós-Transplante Renal. Verificámos, igualmente, que determinadas terapias imunossupressoras como o uso de esteroides, tacrolimus ou sirolimus são altamente diabetogénicas. No caso do tacrolimus, novos métodos de monitorização e determinados estudos genéticos podem otimizar a sua utilização. Na nossa revisão, apresentamos novas perspetivas e alvos terapêuticos baseados na proproteína sérica convertase subtilisina/kexina tipo 9 e em enzimas do Citocromo P450.

A identificação de fatores de risco através de uma anamnese completa e de *follow-ups* pré e pós-transplante permitem um melhor prognóstico do enxerto e do doente. Além disso, estudos genéticos estão a tornar-se ferramentas fundamentais na gestão de terapias imunossupressoras e na seleção de candidatos a transplante renal.

Palavras chaves: *Diabetes Mellitus Pós-transplante Renal,* transplante renal, fatores de risco, complicações, imunossupressão, perspetivas futuras

Abbreviations

25(OH)D: 25 hydroxyvitamin D
Ab: Antibody
ARE: acute rejection episodes
ATG: Antithymocyte globulin
AZT: azathioprine
BPAR: biopsy proven acute rejection
CDRs: Concentration to dose ratio
CMV: cytomegalovirus
CNIs: Calcineurin inhibitors
CsA: cyclosporine
CV: Cardiovascular
CYP: cytochrome
DM: Diabetes mellitus
EVR: Everolimus
FPG: Fasting plasmatic glucose
HBV: hepatitis B virus
HCV: Hepatitis C virus
HLA: Human Leukocyte Antigens
HTN: hypertension
IFG: Impaired fasting glucose
IGT: Impaired glucose Tolerance
KT: Kidney transplantation
KTRs: kidney transplant receptors
MMF: Mycophenolate mofetil
mTORi: mTOR inhibitors
NODAT: New-onset Diabetes Mellitus
OGTT: Oral Glucose Tolerance Test
PCKD: Polycystic Kidney Disease
PCSK9: Serum proprotein convertase subtilisin/kexin type 9
PRA: panel- reactive antibody
PTDM: Post-kidney Transplantation Diabetes Mellitus
RBG: random blood glucose
SRL: sirolimus
TAC: tacrolimus
TC: total cholesterol
TG: triglycerides
Treg: Regulatory Lymphocyte T
WHR: Waist to hip ratio

Introduction

Post-transplantation diabetes mellitus (PTDM) is a common metabolic complication of kidney transplantation (KT) which has a serious impact on the outcome of both, the graft and the patient. Although its serious consequences, there is no consensus in the scientific community about this metabolic condition.[1]

This condition was known by different designations across the years due to its complexity and continuous updates. New-onset Diabetes Mellitus (NODAT) was the previous one but this denomination could be misleading because it didn't include patients with pre-existing undiagnosed diabetes.[2]

According to the *2003 International Consensus Guidelines*,[3] PTDM is defined by the same criteria as *diabetes mellitus* and impaired fasting glucose (IFG) in the general population (following American Diabetes Association recommendations).

Epidemiology

The incidence of PTDM in kidney transplantation is 7-39% in the first year(1) and 10-30% in the third year after the transplant [4] and the risk of graft failure in PTDM patients is 65% higher than in patients without this complication. The mortality rate is also 85% higher in PTDM patients.[1]

Pathophysiology

PTDM occurs due to insulin resistance and decrease in insulin secretion but the impact of hyposecretion seems to be crucial in the pathophysiology of the disease.[5]

Prognosis

PTDM has been connected to 3 major adverse consequences: impaired graft function and survival, reduced long-term survival of the patient and higher risk for cardiovascular diseases.[3] When it comes to graft survival, Eide IA *et al.*[6] confirm that there is an increased risk of overall graft loss but not death-censored renal graft loss.

One of the last studies about the long-term survival of the patient(7)describes that there's a two fold increase of mortality in patients with PTDM compared to non-diabetics recipients. Most of the deaths related to PTDM aren't related to graft loss but due to cardiovascular disease events.[8] In fact, an eight-year observational study suggested that when diagnosed in the first 3 months after the transplant, this pathology is a predictor of cardiac death and myocardial infarction.[9]

Risk factors

According to the 2003 Guidelines for PTDM,[3] there are two type of risk factors, non-modifiable and modifiable.

One of the not-modifiable risk factors is age: patients over 40 years old develop more often PTDM.[3] Ethnic backgrounds seem to be also strongly related to PTDM: Hispanic and African American population develop more frequently PTDM due to differences on the pharmacokinetics and diabetogenic effects of immunosuppression.[3]

The 2003 Guidelines also present family history of *diabetes mellitus* and increased body weight as important risk factors for PTDM. However, Montori VM *et al.*[10] reveal a weak connection between body mass index (BMI) and body weight in general. Nevertheless, obesity is proven as a risk factor for DM type 2, so it is possible that the right parameter to connect obesity and PTDM had yet to be found, by the time these Guidelines were written.[3]

Hepatitis C virus (HCV) infection can be associated with KT. In fact, patients infected by hepatitis C virus are at higher risk of PTDM after KT, especially if the chosen immunosuppressor is tacrolimus.[11]

According to the same Guidelines,[3] abnormal regulation of glucose before transplantation, presence of metabolic syndrome components (such as hypertension, hypertriglyceridemia and hyperuricemia) and transplantation from a deceased donor are also related to PTDM.

Immunosuppression has a major role in decreasing graft rejection after KT. Nowadays, the combination of a proper induction therapy and maintenance therapy lead to satisfying early outcomes in graft survival.[8]

However, evidence says that immunosuppression regimens have a serious impact on PTDM arising. Steroids regimens are clearly associated with PTDM due to the induction of insulin resistance in peripheric tissues and decreasing insulin releasing and glucose sensitivity of β pancreatic cells.[1] In fact, the use of prednisolone increases the risk of diabetes on 46%.[12]

Calcineurin inhibitors (CNIs), including tacrolimus (TAC) and cyclosporine (CsA), are the most common agents of immunosuppression used in KT but patients under this therapeutic regimen show higher incidence of PTDM.[3] Tacrolimus inhibits T-cell clonal expansion blocking interleukin-2 syntheses.[5] Maes BD *et al.* [13] described that after one year using tacrolimus, 32% of the patients developed PTDM and 15% developed IFG. Calcineurin is expressed in the β pancreatic cells and using tacrolimus will decrease insulin secretion. Moreover, tacrolimus also blocks the uptake of glucose by the muscle cells and adipocytes.[5] So, levels of tacrolimus >15 ng/ml during the first month are an independent risk factor for PTDM and more often lead to persistent hyperglycemia (after the first year).[13] It's proven that tacrolimus is more effective than Cyclosporine when it comes to acute graft rejection, but it increases the risk of PTDM by 5 times and this effect magnifies in minority patients, such as African American and Hispanics.[3]

New immunosuppression agents have been used in recent transplant protocols such as mammalian targets rapamycin inhibitors (mTORi): sirolimus and everolimus. They have antiproliferative properties and make use of antitumor activities[14] but they also seem to play a role in secretion and resistance to insulin, especially if combined with CNIs.[1]

Diagnosis

The diagnosis of PTDM is made based on the following parameters:

- Symptomatic diabetes (patient presenting polyuria, polydipsia and unexplained weight loss) and casual plasmatic glucose (PG) levels ≥ 200 mg/dl;
- Fasting plasma glucose (FPG) levels ≥126 mg/dl;
- 2 hours oral glucose tolerance test (OGTT) ≥ 200 mg/dl; [3]
- HbA_1c ≥ 6,5%. [2]

Unless hyperglycemia associated with metabolic decompensation occurs, it is required another laboratory test measuring venous plasma glucose on the following days to the first measure to establish the diagnosis.[2]

The OGTT is the gold standard for the diagnosis of PTDM. This test identifies more patients with PTDM than FPG due to differences on the pathophysiology of this condition when compared to DM of the general population:[2] if the insulin clearance is reduced, it is possible to have FPG within the normal levels with a positive OGTT.[4] Using HbA_1c in the early post-transplantation times can be misleading because a normal value in the presence of post-operative anemia, blood transfusion or dynamic renal allograft function is not conclusive. Although, some studies have shown that, 10 weeks after the transplant, FPG levels of 95-124 mg/dl associated to HbA_1c ≥ 5,8% or FPG levels ≥ 90 mg/dl and HbA_1c ≥ 5,7% should lead to an OGTT.[15] Between 10 weeks to 4 months after a kidney transplant, using HbA_1c values of 6,5% and 6,2% to diagnose PTDM has high specificity, however present low sensitivity, requiring further investigation.[16]

Management

When it comes to management of PTDM, there are three periods to approach the condition: pretransplant, perioperative and posttransplant.[17]

In pretransplant period, it's essential to screen known risk factors such as: metabolic syndrome and its factors – BMI and hypertriglyceridemia- which are closely related to PTDM development.[18] Impaired glucose Tolerance (IGT) or IFG increase the incidence of PTDM up to 2.5 times[17] and pretransplant FPG levels of 92-125 mg/dl should lead to an OGTT in order to discover undiagnosed diabetes.[19] However, HbA_1c levels above 5.4% were recently linked

to higher risk and the same study revealed that the risk starts at lower percentage of HbA_1c than prediabetes actual upper limit.[20]

Family history of DM, gout medicines and adult polycystic kidney disease have important consequences on PTDM, as well.[4] There are two scores for predicting DM – the San Antonio Diabetes Prediction Model and the Framingham Offspring Study: *Diabetes Mellitus* algorithm,[21] but they haven't been applied in clinical practice recently.[4] Cardiovascular risk factors should also be taken into account, such as hypertension, smoking and dyslipidemia.[17]

Frequently, hyperglycemia occurs in the perioperative time due to stress of the surgery and the use of high dose steroids to induce immunosuppression. In these cases, insulin infusions are the standard to manage the situation.[17]

During the first 4 weeks, 2009 KDIGO [22] recommends the evaluation of glycemia using FPG, OGTT and/or HbA_1c weekly and then every 3 months until complete one-year posttransplant. After that, an annually evaluation should be done. The same issue also recommends the screening of PTDM once immunosuppressants or corticosteroids are initiated or if there is an update on their doses. The glucocorticoids must be reduced as soon as possible and the risk of PTDM has to be weight against the risk of acute rejection of the graft in every patient, when it comes to the choice of the immunosuppression protocol.[3]

Based on the pathophysiology of the condition, the main efforts of postoperative managing PTDM are preserving the function of the β pancreatic cell and increasing insulin sensitivity.[4]

Initially, patients are advised to adopt a hypoglycemic diet and to practice physical activity. In some cases, lifestyle changes are not enough to reduce the state of hyperglycemia, so pharmaceuticals have to be applied.[23] One way of doing that is using oral antidiabetics such as metformin, sulfonylurea/glinides, thiazolidinediones, DPP4-I, GLP-1 RA and SGLT2-i. Metformin is contraindicated in renal dysfunction with eGFR $< 30mL/min/1.73m^2$, because of the risk of lactic acidosis. Although, an American observational study showed that many kidney transplant recipients used it and both the graft, and the patient survival hadn't worsened[(24)]. Nevertheless, its efficacy in PTDM isn't demonstrated and requires more studies. Sulfonylureas aren't effective in PTDM. Gliquidone and Repaglinide improve the glycose control but interact with cyclosporine. Thiazolidinediones are effective in glucose control. DPP4-I such as Linagliptin, Sitagliptin and Vildagliptin seem to have efficacy and tolerability but Sitagliptin interacts with cyclosporine and Vildagliptin with tacrolimus. When it comes to GLP-1 RA, Liraglutide has a good tolerability and no interactions. About SGLT2-I, there isn't enough data about their efficacy in PTDM. Insulin injections are the best option to kidney transplant receptors (KTRs) in the early post-transplantation period and patients who present severe impaired insulin secretion and abnormal renal function.[4]

Aim

PTDM has an important impact on patient prognosis therefore, the report and evaluation of risk factors seem to be crucial in prevention, effective management, and future target therapeutics.

With this review, we aim to do an extended data survey and analysis, in order to describe new risk factors for PTDM and verify if there's new data concerning the ones described in 2003 International Consensus Guidelines,[3] in the last five years.

Methods

We wrote this Systematic Review based on the The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Using the following Medical Subjects Heading Terms: “Kidney Transplantation/adverse effects” AND “diabetes mellitus” AND “risk factors”, the Pubmed Database was searched from the 1st of January 2015 to the 1st of January 2020.

As inclusion criteria, we used: clinical study, clinical trials, comparative study, controlled clinical trial, meta-analysis, multicenter study, observational study, randomized controlled trial. Journal articles were also taken in account and search on the same database. The selected articles were restricted to English language and had a full text availability in the database. The population that we choose for this review were adults who were eighteen years old or older.

In this review we analyze NODAT and PTDM related articles, despite the 2014 International Consensus Meeting on Post-transplantation Diabetes Mellitus Recommendation, first recommendation.[2]

Results

We identified eighty-four articles through online database searching. Only 34 of those were selected for full-text assessment and 21 were selected for qualitative synthesis. [1, 5, 25-43] Figure 1 shows the PRISMA flow diagram for inclusion of articles.

In Table I, we present the characteristics of the included studies. Six studies were observational longitudinal prospective cohort studies, 1 was a cross-sectional study and 14 were observational longitudinal retrospective cohort studies. Overall, the presented articles involve 9571 patients. Studies with less than 100 patients were excluded due to small size sample limitations.

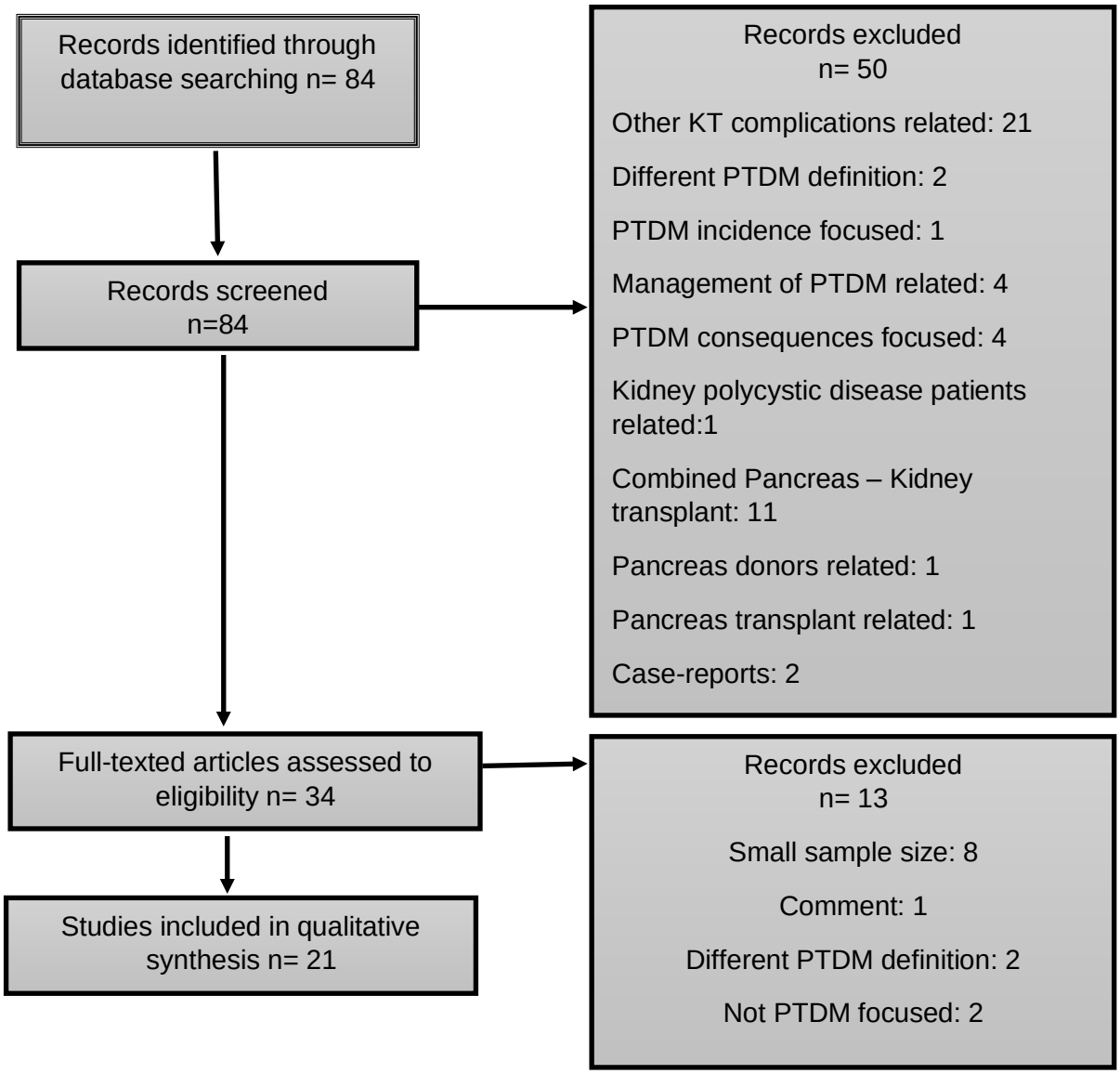

Figure 1. PRISMA flow diagram for inclusion of articles. KT: Kidney transplantation PTDM: Post-transplantation *diabetes mellitus*

Table 1. Characteristics of included studies

Study	Type of study	Participants	Potencial Risk factors	Statistical Tests	Results
Cascais de Sa D *et al.*[1] (2019, Portugal)	Unicentric Observational Longitudinal Retrospective Cohort	659 Included: 577	Recipient age/ sex/ donor age/ type of donor/ expanded criteria donor/ BMI/ FPG on the fifth day after KT/ time of dialysis previous KT/ delayed graft function/panel reactive antibodies/ active or previous smoker/ HCV chronic infection/ use of: beta-blockers, diuretics, statins and TAC	Independent risk factor: Logistic regression P<0.05	PTDM: 61 (10,6%) 93.5% diagnosed after 1 year PTDM group: lower use of statins and beta-blockers Univariate analysis: higher fasting glucose in the 5th day post-transplant, recipient age and recipient BMI, Independent risk factors: recipient BMI (>28Kg/m^2); fasting glucose in the 5th day post-transplant (>110 mg/dl)
Lima C *et al.*[5] (2018, Brasil)	Unicentric Observational Longitudinal Retrospective Cohort	Included: 258	BMI prior and post-transplantation/ causes of renal failure prior to transplantation (chronic glomerulonephritis, HTN, PCKD, pyelonephritis and lithiasis, IgA nephropathy)/ donor type/ CMV and HCV infection/ dyslipidemia/ HTN/ ethnicity	Continuous variables: unpaired t test; Mann-Whitney test Categorical variables: χ^2 test; Fisher exact test Independent risk factor: Logistic regression P<0.05	**1-year analysis** PTDM: 31,2% PTDM group: higher in elderly patients, African - American, patients with hypertension and dyslipidemia Independent risk factors: African – American, dyslipidemia, hypertension
Paek JH *et al.*[25] (2019, Korea)	Multicenter, Observational Longitudinal Prospective Cohort	1080 Included: 723	Donor and recipient age at KT/sex/comorbidity/ BMI/ WHR/ HbA_1c/ FPG/ ferritin/ transferrin saturation/ immunosuppressants (TAC, CsA, MMF, SRL, EVR)/ induction therapy (ATG, Basiliximab)/ number of HLA mismatches/ presence of donor specific Ab/ proportion of acute rejection/ delayed graft function/	Continuous variables: Student t test Categorical variables: χ^2 test Independent risk factor: Logistic regression p <0.05 SPSS version 20.0	PTDM group: higher recipient age, proportion of smokers, number of HLA mismatches, BMI, WHR, HbA_1c PTDM group: lower transferrin saturation **1- year analysis** PTDM: 85 patients (11.8%) PTDM group: higher WHR, HbA_1c, episode of acute rejection, FPG, proportion of prednisolone prescription Independent risk factors: higher age; WHR; HbA_1c before KT

Xu J *et al*. [26] (2018, China)	Unicentric Observational Longitudinal Retrospective Cohort	482 Included:358	Recipient age/ sex/ family history of DM/ BMI/ IFG/ Hyperglycemia first week/ Hypomagnesemia/ HCV infection/ CMV infection/ PCKD/ TAC use and concentration levels/ acute rejection episodes (ARE)	Continuous variables: Student t test Categorical variables: χ^2 test Independent risk factor: Logistic regression p <0.05 SPSS version 21.0	**3-years analysis** PTDM: 110 patients (30.73%) Cumulative incidence 1st, 2nd, 3rd years: 24.58%, 27.93%,30,73% PTDM group: higher family history of DM, use of tacrolimus, pre-transplantation hypomagnesemia, acute rejection episodes 3 month after transplantation, pre-transplantation IFG, BMI, hyperglycemia during the first week after transplantation, pre- and post-transplantation FPG. Independent risk factors: BMI≥ 25 Kg/m^2, family history of DM, hypomagnesemia pre-transplantation, ARE 3 months after transplantation, tacrolimus use, IFG pre-transplantation, hyperglycemia during the first week after transplantation ≥ 100mg/dL
Xie L *et al.*[27] (China, 2016)	Unicentric Observational Longitudinal Retrospective Cohort	421 Included: 397	Age /BMI/family history of DM FPG pre-transplant/ positive OGTT/ TAC vs CsA	Continuous variables: Student t test, rank test Categorical variables: χ^2 test Independent risk factor: Logistic regression p <0.05 SAS 9.2 software.	**Follow up time: 53.5 _ 10.4 months** PTDM: 37 patients (9,3%) PTDM group: higher family history of DM, use of tacrolimus, age≥40, BMI, FPG, positive OGTT Independent risk factors: pretransplant BMI≥ 24 Kg/m^2; family history of DM, FPG pretransplant
Yu H *et al.*[28] (2016, Korea)	Unicentric Observational Longitudinal Retrospective Cohort	567 Included: 418	Sex/ age/donor age/ donor sex/ HTN/ prior kidney transplantation/rejection history within 1 year/ BMI pre-KT/ family history of DM/ cold ischemic time/ FPG levels pre-KT/ PCKD/ immunosuppressants (TAC, CsA, MMF, AZT: % and levels)/ corticosteroids dose/ magnesium serum levels	Continuous variables: Student t test Categorical variables: χ^2 test Independent risk factor: Logistic regression P<0.05 SPSS version 20.0	**1-year analysis** PTDM: 85 patients – incidence: 20.4% 83% within 3 months of KT PTDM group: higher age, BMI, family history of DM, high plasma glucose levels, weight chance 3 month after KT Independent risk factors: higher age, family history of DM, FPG level pretransplant and BMI≥ 25 Kg/m^2.

Dedinska I *et al.* [29] (2015, Slovakia)	Unicentric Observational Longitudinal Retrospective Cohort	1-year analysis Included: 167 5 years analysis Included:117	Age at time of transplantation, population, positive family history of DM2, male sex, HLA mismatches, HLA A30, B27, B42, PCKD, BMI pre-KT and 1 year after KT, weight gain, hypertriacylglycerolemia and cholesterol – average levels, HTN, Hypomagnesemia Prediabetes before transplantation (hyperglycemia, IGT) VHC, CMV infection, Induction therapy: Basiliximab, Proteinuria	Continuous variables: Student t test Categorical variables: χ^2 test p <0.05 Independent risk factor: correlation coefficient, Cox proportional hazard model p <0.05 Medcalc version 13.1.2	**1-year analysis:** PTDM: 64 patients - incidence of 38,3% 1st 6 months: 70% were diagnosed PTDM group: higher age, average dose of methylprednisolone, BMI at time of transplant and 1 year later, weight 1 year after KT, higher proteinuria, positive family history of DM2 and administration of basiliximab, average dose of prednisolone except induction Independent risk factors: age> 50, family history of DM2, BMI at time of transplant > 30kg/m^2, pre-diabetes, proteinuria > 0.15 g/d. **5-year analysis:** PTDM: 53 patients (9 developed PTDM between the 12th and the 60th month) PTDM group: higher age, higher average levels of proteinuria, positive family history of DM2, pre-diabetes. PTDM between the 12th and the 60th month: older and higher doses of methylprednisolone Independent risk factors: age> 50 at the time of transplantation
Baron PW *et al*. [30] (2017, USA)	Unicentric Observational Longitudinal Retrospective Cohort	486 Included: 279 Hispanic:155 Caucasians:124	Recipient age and sex; BMI; HCV infection; type of donor; FPG; ethnicity	Continuous variables: Student t test Categorical variables: χ^2 test p <0.05 SPSS 23.0	**1-year analysis:** Hispanic PTDM vs non-PTDM PTDM: incidence of 14.2% 10 years older and higher BMI Higher FPG after 3,6,12 month Caucasians PTDM vs non-PTDM PTDM: incidence of 10.5% higher BMI Higher FPG after 3,6,12 month

Dedinska I *et al.*[31] (2015, Slovakia)	Unicentric Observational Longitudinal Retrospective Cohort	Included: 167	Waist circumference/ BMI 1 year after KT/ weight gain from the transplantation/ average levels of TG and cholesterol/ type of immunosuppression (TAC, CsA, mTORi)/ average dose of prednisone	Continuous variables: Student t test Categorical variables: χ^2 test Independent risk factor: correlation coefficient, Cox proportional hazard model p <0.05 Medcalc version 13.1.2	**1-year analysis:** PTDM: 64 patients – incidence of 38,2% 1st 6 months: 70% were diagnosed PTDM group: higher age, waist circumference, average levels of sirolimus Independent risk factors: age> 50 at the time of transplantation, waist circumference in men > 94 cm, waist circumference in women> 80, greater waist circumference
Okumi M *et al.* [32] (2017, Japan)	Unicentric Observational Longitudinal Retrospective Cohort	Included: 849	Recipient age/sex/ duration of dialysis/ BMI at transplant/ Blood pressure/Triglycerides/ HDL/ FPG/ IGT/ HLA mismatches/AB0-incompatible/ total ischemic time/donors age, and sex, unrelated/ TAC dose and trough/ MMF dose/ methylprednisolone dose/ induction therapy: basiliximab/ rituximab	Cumulative probabilities of PTDM: Kaplan–Meier method Optimal threshold of TAC: ROC analysis with the Youden index Independent risk factor: Cox proportional hazards model p <0.05 SAS system version 9.4	**5-year analysis:** PTDM: 127 patients 1st 6 months: 12% / 1 year: 13% / 3 years: 14,4%/ 5 years: 15.1%(cumulative) PTDM group: higher age, BMI, elevated blood pressure, high triglycerides, low HDL levels, higher IGT and FPG, an unrelated donor, TAC dose at 2 weeks, TAC trough levels from 2 weeks through 6 months and methylprednisolone dose at 1 month after KT A TAC **once daily formulation** was associated to lower MP doses and low trough level of TAC Independent risk factors: recipient age, BMI≥ 25 Kg/m^2 at transplant, TAC trough levels at 2 weeks Protective factor: use of MMF
Gervasini G *et al.* [33] (2016, Spain)	Unicentric Observational Longitudinal Retrospective Cohort	175 Included: 164	Recipient age/ BMI pretransplant and average in the first year/ SNPs: CYP2C8*3, CYP2C8*4, CYP2C9*2, CYP2C9*3, CYP2J2*7, CYP4A11 F434S and CYP4F2 V433M/ TAC vs CsA	Continuous variables: Student t test/ ANOVA/ Kruskal-Wallis Categorical variables: χ^2 test Independent risk factor: Logistic binary regression p <0.05 SPSS 15.0	**1-year analysis:** PTDM: 34 patients – incidence of 20,73% PTDM group: CYP2C8*3 carriers, higher age, higher BMI Higher CDRs of Tacrolimus: higher risk of PTDM Independent risk factors: recipient age, higher average first year BMI, CYP4F2 V433M

Mohammad KG *et al.* [34] (2018, Pakistan)	Unicentric Cross-sectional Study	Included: 191	Recipient age/ recipient sex/ BMI/ family history of DM/HCV infection/ CMV infection/ TAC/ steroids/ serum creatinine at 6th and 12th months	Categorical variables: χ^2 test p <0.05 SPSS version 15.0 software	**6th month analysis** PTDM: 30 patients – incidence of 15.8% PTDM group: higher serum creatinine levels, use of TAC
Le Fur A *et al*.[35] (2016, France)	Observational Longitudinal Prospective Cohort	1083 Included: 444	Recipient age and sex; ethnicity, BMI, history of CV event, PCKD, levels of 25(OH)D, HCV, dialysis pretransplant, type of donor, graft characteristics and season of transplantation, type of immunosuppression (CsA, TAC, MMF, AZT, mTORi) and steroids	Continuous variables: ANOVA Categorical variables: χ^2 test Independent risk factor: Cox proportional regression model p <0.05 r software version 2.14.1	**1-year analysis:** PTDM: 58 patients – incidence of 13% Cumulative incidence 3rd: 11,8%/12th: 13,2% PTDM group: 25(OH)D deficiency and insufficiency Independent risk factor: levels of 25(OH)D<30ng/ml, age≥55, BMI (1.72 folds which 5kg/m^2), tacrolimus therapy, maintenance corticoids therapy
Eisenga MF *et al.*[36] (2017, Netherlands)	Observational Longitudinal Prospective Cohort	606 Included: 453	Levels of PCSK9 Use of statins (possible protective factor)	Categorical variables: χ^2 test Independent risk factor: Cox proportional hazards model NODAT developing according to tertiles: Mantel-Cox p <0.05 SPSS version 22.0 software	**Follow up of 9.6 years:** PTDM: 70 patients – incidence: 15.5% Upper tertile of PCSK9: incidence of 23% Lower 2 tertiles of PCSK9: incidence of 12% PTDM: upper tertile of serum levels of PCSK9 Independent risk factor: serum PCSK9 The association remained similar after adjusting to sex, age, eGFR, proteinuria, time since transplantation, use of tacrolimus and cyclosporine and trough levels of both

Porrini EL *et al.* [37] (2016, Spain)	Multicenter Observational Longitudinal Prospective Cohort	Included: 631	Recipient Age/ Recipient sex/ pre-KT BMI/ cardiovascular events/ smoking status / renal function/ proteinuria/ acute rejection/ CMV infection/ immunosuppressants/HbA_1c/ levels of TG and glucose/ aspirin/ angiotensin-converting enzyme inhibitors/ insulin insensitivity/ diuretics	Continuous variables: Kruskal-Wallis Categorical variables: Pearson's χ^2 test Independent risk factor: Univariate and multivariate logistic regression	PTDM: 215 patients – cumulative incidence of 32% 3 months: 27% 12 months: 21% 24 months: 21% 36 months: 30% PTDM group at 3 months: more men, higher age, BMI, TG, proteinuria levels, lower renal function, more diuretics, CMV infection Early PTDM risk factors: pretransplant BMI, age Late PTDM risk factors: pretransplant BMI, age, HbA_1c at 3 months Late PTDM protective factors: higher insulin sensitivity at 3 months
Liang J *et al.*[38] (2019, China)	Observational Longitudinal Retrospective Cohort	915 Included: 557 HBV-HCV-: 470 HBV+HCV-:46 HBV-HCV+:34 HBV+HCV+: 7	HBV+HCV- HBV-HCV+ HBV+HCV+ Age, BMI, preoperative FPG, TC, TG, AST, ALT, family history of DM, donor type, history of dialysis, type of dialysis (hemodialysis vs peritoneal dialysis), Induction therapy: IL-2Ra, immunosuppressants (CsA vs TAC), ARE, PCKD.	Continuous variables: Kruskal-Wallis Categorical variables: χ^2 test Independent risk factor: Univariate Cox regression Independent effects of viral status: Stepwise Cox regression models Cumulative incidence of PTDM: Cox regression SPSS version 19.0 software	**Follow up: 7.53 years (median)** PTDM: 120 patients – incidence: 21.5% HBV-HCV+: 55.88% HBV+HCV+: 71.43% Independent risk factors: higher age, BMI, preoperative FPG and TC levels, positive family history of DM and HCV infection and coinfection (unadjusted) Independent effects of viral status: HCV is risk factor for PTDM (3-fold more likely) / HBV infection tend to increase PTDM risk (by 1.8fold) but was marginally significant/ Coinfection is not (adjusted model)

Xue M *et al.*[39] (2018, China)	Unicentric Observational Longitudinal Retrospective Cohort	915 Included: 557	IL-2Ras	Continuous variables: Student t test, ANOVA Categorical variables: Pearson's χ^2 test Independent risk factor: Cox stepwise regression model p <0.05 SPSS version 20.0 software	Cumulative incidence of NODAT (1,3, 5,7,10 years) **IL2Ra group:** 10.61%, 14.09%, 16.92%, 19.96%, 25.48% **Non IL2Ra group:** 13%,20.21%, 23.84%, 27.93%, 35.32% Independent risk factor: IL-2Ras are a protective factor of PTDM adjusted to preoperative and postoperative measurements
Tillmann FP *et al.*[40] (2017, Germany)	Observational Longitudinal Prospective Cohort	187 Included: 141	Prediabetes (OGTT), immunosuppression therapy	Continuous variables: Mann-Whitney U Categorical variables: Pearson's χ^2 test Independent risk factor: multivariate binary logistic regression p <0.05 SPSS version 22.0 software	**5 years follow-up** PTDM group: history of prediabetes Independent risk factor: prediabetes (measure by OGTT pre-transplantation)
Biro B *et al.*[41] (2019, Hungary)	Unicentric Observational Longitudinal Retrospective Cohort	343 Included: 223	Age, BMI, Pre-KT Total cholesterol, LDL, HDL, TG, FPG, random plasmatic glucose before, T reg. presence ($CD4^+$ $CD25^{bright}CD127^{dim}$), graft function, type of donor, history of dialysis, PCKD, HTN, CMV/HVC/HVB infection, induction therapy (ATG, anti-CD25)	Independent risk factor: univariate/ multivariate logistic regression p <0.05 SPSS version 25.0 software	PTDM: 33 patients – incidence: 14.8% (**follow up of 8 years and 6 months**) 1.5-3months: 45.5% 3-6 months: 33.3% 6-12months: 33.0% 12-24months: 18.2% PTDM group: higher age and BMI, delayed graft function, higher total cholesterol, LDL, TG, RBG before transplant, higher average FPG 1 week after transplant, lower absolute values of Treg. Independent risk factor: delayed graft function, total cholesterol, LDL, TG, RBG before transplant, average FPG>7mmol/L 1 week after transplant.

Gaynor JJ *et al.*[42] (2015, USA)	Observational Longitudinal Prospective Cohort	Included: 481	Recipient age, BMI, TAC/SRL, TAC/MMF, CsA/ SRL, pretransplant dialysis, PCKD, CMV/HVC infection, %PRA, BPAR	Continuous variables: Student t test Categorical variables: Pearson's χ^2 test Independent risk factor: Cox stepwise regression model p <0.05	**Follow up of 57 months (median)** PTDM: 108 patients – incidence of 22.5% PTDM group: higher BMI, maintenance with SRL, non-white recipient and older age HCV+: 8 – 5/8 PTDM (1 year after transplant) Freedom-from-PTDM at 36 months: Score risk 0 (BMI≤25, non-white, age < 40): 93% Score risk 1 (BMI ≥ 25, white race, age < 40 or BMI<25, non-white race, age ≥25): 84% Score risk 2 (BMI>25, non-white, age ≥ 40): 52% Without SRL / With SRL Score risk 0: 95% / Score risk: 84% Score risk 1: 88% / Score risk: 69% Score risk 2: 55% / Score risk: 33% PTDM on 9/13 BPAR (<3 months)
Abbas MH *et al*.[43] (2015, Egypt)	Unicentric Observational Longitudinal Retrospective Cohort	1113 Included: 913 HCV-/PTDM-: 511 HCV-/PTDM+: 87 HCV+/PTDM-:230 HCV+/PTDM+: 85	Recipient Age and sex/ donor age and sex/ unrelated donor/ no. of blood transfusions/ Blood group/ pretransplant dialysis/ pre-KT BMI/ Original kidney disease (chronic glomerulonephritis, chronic pyelonephritis nephrosclerosis, obstructive uropathy, hypoplasia amyloidosis, PCKD)/ number of HLA mismatches/ HCV infection/ immunosuppression (ATG, Basiliximab, Daclizumab, Alemtuzumab, TAC, CsA, MMF, AZT, SRL), steroids	Categorical variables: χ^2 test $\boldsymbol{p}$ <0.05 SPSS version 19.0 software	**11 years analysis:** PTDM: 172 patients – incidence of 18.5% PTDM group: higher age, recipient age at the time of transplant between 35-50, unrelated donor, BMI <30 Kg/m^2, history of pretransplant dialysis, number of blood transfusions, higher number of HLA mismatches HCV infected: incidence of 27% HCV infection: higher percentage of pretransplant dialysis, pretransplant schistosomiasis and hypertension Independent risk factor: age, total dose of steroids in the first 3 months, time to diuresis, sirolimus.

25(OH)D: 25 hydroxyvitamin DAb: Antibody/ ARE: acute rejection episodes/ ATG: Antithymocyte globulin/ AZT: azathioprine/ BMI: Body mass index/ BPAR: biopsy proven acute rejection/ CDRs: Concentration to dose ratio/ CMV: cytomegalovirus/ CNIs: Calcineurin inhibitors/ CsA: cyclosporine/ CV: Cardiovascular/ CYP: cytochrome/ DM: *Diabetes mellitus*/ EVR: Everolimus/ FPG: Fasting plasmatic glucose/ HBV: hepatitis B virus/ HLA: Human Leukocyte Antigens/ HTN: hypertension/ HVC: hepatitis C virus/ IFG: impaired fasting glucose/ IGT: impaired glucose tolerance/IL-2RAs: anti-interleukin-2 receptor antibodies/ KT: Kidney transplantation/ MMF: Mycophenolate mofetil/ mTORi: Mtor inhibitors/ OGTT: Oral glucose tolerance test/ PCKD: Polycystic Kidney Disease/ PCSK9: Serum proprotein convertase subtilisin/kexin type 9/ PRA: panel- reactive antibody/ RBG: random blood glucose/ SRL: sirolimus/ TAC: tacrolimus/ TC: total cholesterol / TG: triglycerides/ Treg: Regulatory Lymphocyte T/ WHR: Waist to hip ratio

PTDM incidence

The overall incidence of PTDM after one year of KT was between 11,8% and 38,2% and some studies highlight the fact that the incidence was higher on the first six month,[29, 31, 32] particularly on the first 3 months.[28, 35, 41]

Risk factors:

Age

One of the most common independent risk factor was recipient age.[25, 28, 29, 31, 32, 35, 37, 38, 43] Xie L. *et al.*, [27] Cascais de Sá D. *et al.*[1] and Biro B *et al*. [41] show that the PTDM group had older patients, but the significance wasn't enough to be considered an independent risk factor. Baron Pw *et al*.,[30] in the Hispanic group, verified that in the PTDM group patients were around 10 years older.

Gaynor *et al.*[42] created risk scores based on BMI, ethnicity and age. The scores where patients were 40 years old or older are the ones with lowest percentage of freedom from PTDM at 36 months.

Meanwhile, Dedinska I. *et al.* [31] and Le Fur *et al.*[35] presented as a risk factor an age higher than 50 and 55 years old, respectively.

Abnormal regulation of glucose

States of abnormal regulation of glucose were also frequent as risk factors. In fact, pre-transplantation altered FPG [27,28, 41] and IFG, [26] elevated HbA1c levels[25] and prediabetes[29, 40] plus hyperglycemia on the first week after KT[26, 41] and FPG on the 5th day after KT[1] were also identified as risk factor with statistical significance in several studies. Moreover, family history of DM seems to be an important factor on the development of PTDM.[26-29, 38]

Waist circumference

Only two of the selected articles mentioned waist measurements as possible predictors of PTDM after KT. Both studies[25,31] presented waist to hip ratio (WHR) as an independent risk factor and Dedinska *et al.*[31] mentioned that in cut-offs above 94 cm in men and 80 cm in women the risk of PTDM was higher.

BMI

Obesity was a consistent risk factor throughout this review. In fact, pretransplant BMI $\geq$ 25Kg/m^2 was an independent risk factor in 4 studies.[26, 28, 32, 37] However different cut-offs have been found by different authors as predictors of PTDM such as BMI $\geq$ 28Kg/m^2,[1] $\geq$ 24Kg/m^2, [27] $\geq$ 30Kg/m^2.[29] Le Fur *et al.* [35] described that the risk of PTDM was 1.72 times higher for each 5kg/m^2 increase.

Abbas MH *et al.*[43] stablished that patients with BMI <30 Kg/m^2 were at greater risk of PTDM. Baron PW *et al.*[30] showed that BMI values in PTDM group were higher, both in the hispanic and causacian ethniticy. Gaynor JJ *et al.*[42] presented scores when measuring the freedom from PTDM at 36 months and the scores where BMI was over 25Kg/m^2 were the ones with lowest percentage of freedom from PTDM.

Dyslipidemia

Dyslipidemia was searched as a potential risk factor in six studies. In two of those studies, abnormal average levels of triglycerides (TG) and total cholesterol (TC) were not present in the PTDM group.[29, 31]In contrast, Okumi M *et al*.[32] presented higher levels of TG and lower levels of HDL in PTDM group while Porrini EL *et al*.[37] articles showed higher levels of TG after 3 months, in that same group. Finally, Liang J *et al.*[38] displayed higher levels of TC as an independent risk factor for PTDM and Biro B *et al.*[41] established pre-transplantation TC, LDL and TG abnormal levels as independent predictors of PTDM.

Hypomagnesemia

Three articles[26, 28, 29] mentioned hypomagnesemia as a possible risk factor, but only Xu J *et al*. [26] established pre-transplantation hypomagnesemia as an independent risk factor for PTDM.

Viral infections

Viral infections and PTDM were searched in twelve studies [1, 5, 26, 29, 30, 34, 35, 37, 38, 41-43] but only four found an association between cytomegalovirus (CMV), HCV and HBV and PTDM.

Porrini EL *et al.*[37] established a higher number of patients infected by CMV in the PTDM group at 3 months after KT. Liang J *et al.*,[38] at the univariate model, presented HCV infection and coinfection (HCV/HBV) as independent risk factors. In fact, around 56% of patients infected by HCV and 71% of coinfected patients developed PTDM. In the multivariate adjusted model, HCV was a risk factor for PTDM (3-fold more likely), HBV infection tended to increase PTDM risk by 1.8-fold but was marginally significant and coinfection was not a risk factor. Gaynor *et al.*[42] presented a sample where in 8 patients who were positive for HCV, 5 developed PTDM. Abbas MH *et al.*(43) described an HCV infected group where 27% of the patients developed PTDM however it wasn't an independent risk factor for PTDM.

Immunosuppression

Despite being searched in almost every article of this review, a connection between the type of induction and maintenance therapy used and the risk for PTDM wasn´t always found.[1, 25, 28, 37, 38, 40]

When it comes to induction, Okumi M *et al.*[32] verified that the PTDM group had higher doses of methylprednisolone at 1 month and Dedinska I *et al.*[29] had more patients treated with basiliximab in the PTDM group.

Biro B *et al.*[41] tried to relate the proportion of $CD4^{+}CD25^{bright}CD127^{dim}$ to basiliximab use and to the development of PTDM. They verified that the treatment with this anti-CD25 did not provoke PTDM. Besides, Xue M *et al.*[39] analyzed the effects of anti-interleukin-2 receptor antibodies (IL-2RAs) in PTDM and established that using these antibodies as induction therapy was an independent protective factor adjusted to pre and postoperative conditions.

When analyzing maintenance immunosuppression, Paek JH *et al.*[25] presented a higher proportion of prednisolone used in the PTDM group, one year after the KT. The same happened in Dedinska I *et al.*[29] study, where the average levels of prednisolone were higher in the PTDM. Le Fur *at al.*[35] further determined maintenance corticoids therapy as a predictor of PTDM.

Mohammad KG *et al.*[34] established that the use of tacrolimus(TAC) was more common in the PTDM group and both, Xu J *et al.*[26] and Le Fur *et al.*[35] established TAC use as an independent risk factor.

Different ways of monitoring tacrolimus and different times have been studied by several authors trying to find the best maker for PTDM. For instance, Okumi M *et al.*[32] verified that the PTDM group had higher TAC dose at week 2 and TAC trough levels between the second and sixth months. They also established TAC trough levels at 2 weeks as an independent risk factor. Gervasini G *et al.*[33] also associated higher concentrations to dose ratio of TAC with an increased risk of PTDM.

Okumi M *et al.*[32] presented mycophenolate mofetil (MMF) as an independent protective factor for PTDM

Regarding mTOR inhibitors (mTORi), two of the studies verified higher average levels of sirolimus (SRL) in the PTDM group.[31, 42] In fact, Gaynor JJ *et al.*[42] established that, when using SRL, there was a decrease of freedom from PTDM at 36 months in every risk score. Finally, Abbas MH *et al.*[43] considered SRL as an independent risk factor.

Acute rejection episodes and graft function

The possible connection between acute rejection episodes and PTDM was searched in several articles of this review [25, 26, 28, 36, 42]. Paek JH *et al.*[25] presented a higher proportion of episodes of acute rejection at the first year after KT, in the PTDM group. Besides, Xu J *et al.*[26] established acute rejection episodes (ARE) in the first 3 months as an independent risk factor and their PTDM group also had more ARE in the first 3 months.[26] Finally, Gaynor JJ *et al.* [42] tried to connect biopsy proven acute rejection (BPAR) in the first 3 months to PTDM and, indeed nine out of the thirteen people with positive BPAR developed PTDM.

Three studies evaluated delayed graft function in order to establish it as a possible risk factor for PTDM. [1, 25, 41] Biro B *et al*.[41] observed that, in the PTDM group, the number of patients with delayed graft function was higher and determined delayed graft function as an independent risk factor for PTDM.

Compatibility

When it comes to compatibility, the number of human leukocyte antigens (HLA) mismatches [25, 29, 32, 43], presence of risk HLAs (HLA A30, B27 AND B42)[29], AB0 incompatibility [32, 43], percentage of Panel Reactive Antibodies[1,42] and proportion of donor specific antibodies[25] were tested in a few articles of this review. Paek JH *et al*.[25] and Abbas MH *et al.*[43] presented a PTDM group with a higher number of patients with HLA mismatches.

The type of donor, [1, 5, 29, 30, 35, 38, 41] whether they are related/unrelated to the patient[32, 43] and their features[1, 25, 28, 32, 43] were mentioned in several studies but only one revealed an increased number of patients with unrelated donor in the PTDM group.[43]

Cardiovascular comorbidity and risk factors

The smoker status was evaluated in three studies.[1, 25, 37] Only Paek JH *et al.*[25] presented a higher number of smokers in PTDM group. Another cardiovascular (CV) risk factor analyzed was hypertension (HTN).[5, 32, 41] Lima C *et al.*[5] established HTN as an independent risk factor for PTDM and Okumi M *et al.*[32] revealed in PTDM group, more patients with higher blood pressure. Two articles tried to find a connection between history of CV events, but none had significant results. [35, 37]

Kidney function parameters/Causes of kidney failure

Higher levels of proteinuria were found in PTDM group of two different studies.[29, 37] Only Dedisnka *et al.*[29] established levels above 0.15 g/ dl of proteinuria as an independent risk factor for PTDM.

Mohammad KG *et al.*[34] analyzed serum creatinine at the 6th and 12th months as a potential risk factor but only determined that the patients in PTDM group at the 6th month had higher levels of serum creatinine.

None of the causes of renal failure searched, including polycystic kidney disease [26, 28, 35], were related to PTDM. [5, 26, 28, 35, 43]

Medication and previous treatment (pre-transplant dialysis)

The use of Beta-blockers,[1] diuretics,[1, 37] statins,[1, 36] angiotensin-converting enzyme inhibitors, insulin and aspirin [37] was observed in some studies of this review. Cascais de Sa D *et al.* [1] established that the PTDM group presented less patients treated with statins and beta-

blockers. Porrini EL *et al*.[37] presented a PTDM group at 3 months with less patients treated with diuretics and determined that higher insulin sensitivity at 3 months as a late protective factor.

The history,[30, 35, 38, 41, 43] type (hemodialysis vs peritoneal dialysis), [38] and duration[1, 32] of pre-transplant dialysis were potential predictors of PTDM. However, only Abbas MH *et al.*[43] observed more patients with history of dialysis in the PTDM group.

Ethnicity

The connection between different ethnicities and PTDM wasn't a common feature on this review. Lima C *et al.*[5] established that being African- American was an independent risk factor for PTDM. Besides, Baron PW *et al.*[30] determined that when comparing the Hispanic population and the Caucasian one, the incidence of PTDM was higher in the Hispanic group but the difference was non-significant.

Vitamin D

Le Fur A *et al.*[35] searched a connection between the levels of 25 hydroxyvitamin D (25(OH)D) and the risk of PTDM. They determined the presence of 25(OH)D deficiency and insufficiency in the PTDM group and established the levels of 25(OH)D below 30ng/ml as an independent risk factor.

Serum PCSK9

Serum proprotein convertase subtilisin/kexin type 9 (PCSK9) was considered an independent risk factor adjusted to several patients features by Eisenga MF *et al.*[36] This study also established a higher incidence of PTDM in the upper tertile of serum levels of PCSK9.

Cytochrome P450 (CYP) enzymes

Gervasini G *et al.*[33] evaluated a possible link between mutations on cytochrome P450 enzymes - SNPs: CYP2C8*3, CYP2C8*4, CYP2C9*2, CYP2C9*3, CYP2J2*7, CYP4A11 F434S and CYP4F2 V433M. In conclusion, PTDM group had more CYP2C8*3 carriers and CYP4F2 V433M was an independent risk factor for PTDM.

Discussion

It was consensual during our review that older age is an independent risk factor for PTDM. Several studies showed that higher age is a risk factor although a cut-off age was not unanimous. Nevertheless, the median of ages mentioned as a risk factor by different studies was over 40 years old, which is the cut-off set in 2003 PTDM Guidelines.[3]

Other risk factors identified were abnormal regulation of glucose before KT, hyperglycemia on the first week after KT and family history of DM as described in previous literature. [3, 4] Therefore, the pre and posttransplant tracking of hyperglycemic states and a proper anamnesis are essential.

The selected studies used different cut-offs of BMI as a risk factor but, in general, they verified that BMI over 25Kg/m^2 was strongly linked to the increase of the PTDM incidence. However, BMI does not discriminate fat from muscle. In fact, body composition monitoring (BCM) can help overcome this problem, as it assesses three different components: fat mass status, lean tissue mass and volume status. This method allows a better description of a KT candidate, knowing that, for instance, these patients retain fluids between dialyses sessions which influences the overall weight.[44] Body fat distribution has been suggested to have an important role in the insulin resistance and, in this review, only two reports analyzed a specific measurement of central adiposity: waist circumference. For that, they used different methods, so careful conclusions should be taken, still waist circumferences above 94 cm in men and 80 cm in women were possible risk factors for PTDM. Further investigations are necessary in order to clarify how body composition can be linked to PTDM, using measurement of central, visceral and subcutaneous adiposity.[45]

Although dyslipidemia is clearly linked to PTDM, in our review we did not find any strong association between lower levels of HDL and PTDM, as described by previous studies.[3,8] Higher levels of TG and TC had more significance. We were not able to take clear conclusions about HTN since only three from the selected studies hypothesized that HTN could be a possible risk factor, in which only one showed significant impact in PTDM.

To sum up, as metabolic syndrome seems to play a major role in PTDM, preventive measures in selected patients become essential. In fact, at least 150 minutes of exercise a week, reduction of 7% of body weight and smoking cessation are recommend before the procedure.[23]

Hypomagnesemia does not seem to be consensual as a risk factor, as well. We analyzed three articles about this parameter but only one considered lower levels of pretransplant magnesium as independent risk factor for PTDM. The hypothesis that hypomagnesemia is a risk factor for PTDM is due to magnesium deficiency that can lower the activity of tyrosine kinase of insulin receptors, leading to insulin resistance.[28] However, some

studies stated that the use of tacrolimus is correlated to the induction of hypomagnesemia which might be a confounding factor[8] and, in fact, the studies which analyzed posttransplant hypomagnesemia did not seem to have statistical significance.

Vitamin D receptors (VDR) are present in several human cells, including Langerhans's islets cell, thereby 25(OH)D deficiency can lead to insulin secretion impairment. In fact, VDR transform 25(OH)D into calcitriol which helps insulin secretion because it controls the insulin gene transcription and the intracellular calcium on β-cells.[35] β-cells dysfunction with insulin secretion impaired is one of the explanations for PTDM and thus, Le Fur *et al.* [35] results open space for further investigation, specially related to a possible supplementation and its effect on PTDM.

Although there were many papers studying the influence of infections in the risk of PTDM, the number of patients infected with HCV, HBV and CMV was reduced to take conclusions. However, Liang J *et al.*[38] conducted a large study focusing on HCV infection and that showed an association with PTDM which confirms previous reports. This paper further investigated and brought new perspectives about the HBV infection and coinfection and how they can be correlated to PTDM after KT. HCV infection can lead to PTDM through two mechanisms: β-cell dysfunction and increase insulin resistance. The β-cell dysfunction results of direct cytopathic effect caused by the virus or the immune response it provokes. On the other hand, insulin resistance happens due to downregulation of the insulin receptor substrate (IRS) caused by several different pathways initiated on the adipose tissue, the muscle, the liver or on circulating monocytes.[38]

Siraj *et al.*[46] hypothesized if ARE were a possible cause of PTDM or a consequence. In fact, ARE lead to an increase of steroids use but can also be a consequence of PTDM. Gaynor *et al.*[42] concluded that the bolus of steroids after an ARE is as diabetogenic as the induction of immunosuppression on the first week after KT and recent studies do not related PTDM to graft loss,[8] confirming their hypothesis. Although, ours results were not conclusive, it is possible that states of incompatibility such as higher percentage of Panel Reactive Antibodies or increased number of HLA mismatches lead to more rejection episodes and to the necessity of higher doses of steroids. However transplantation in the presence of a positive crossmatch or circulating donor-specific anti-HLA antibodies is theoretically contraindicated, desensitization techniques are opening new perspectives to high sensitized patients[47] and further investigation about adverse effects in these patients such as PTDM is required.

One of our selected studies, suggested that proteinuria might be a risk factor for PTDM. During the first days after KT, proteinuria can be the result of hyperglycemia through osmotic diuresis due to pulses of steroids or it can be the consequence of residual proteinuria from native kidneys. However, the long-term proteinuria measurement can be a more important factor. Roland *et al.*[48] showed a link between albuminuria or proteinuria and PTDM, suggesting

that these parameters can be markers of generalized endothelial damage which may occur in the pancreas of KT patients.

Previous studies suggested that Polycystic Kidney Disease (PCKD) was strongly linked to PTDM.[4] PCKD patients present increase fluidity and abnormal red cells Na/Li counter-transport which are associated with insulin resistance.[49] In our review, that association was never found. Pietrzak-Nowacka *et al.*[50] claimed that at a molecular level, there is not a total satisfying pathogenetic explanation for the link between PTDM and PCKD and those confounding factors when selecting patients to non-PCKD group might had influenced the results.

In our review, some articles discussed new possible predictors and therapeutic targets such as serum PCSK9 and CYP P450 enzymes. PCSK9 pathway is important in the regulation of hepatic expression of LDL receptors (LDLR). PCSK9 is a protease that targets LDLR toward intracellular degradation, thus reducing LDL apoB catabolism.[36] Given the fact that higher serum levels of PCSK9 are associated to PTDM and this protease is closely related do cholesterol metabolism, more studies and trials are needed due to the potential effect of a PCSK9 inhibitor (possibly, lowering LDL and PTDM itself). CYP450 enzymes transform arachidonic acid into vasoactive eicosanoids. There are two pathways: one that syntheses epoxyeicosatrienoic acids (EETs) which have anti-inflammatory, profibrinolytic and vasodilator properties and other one that metabolizes AA into 20-hidroxyeicosatetraenoic acid (20-HETE) that induces vasoconstriction but has an antihypertension effect because increases the sodium excretion in the kidneys. In the selected study, CYP4F2 V433M SNP was considered a possible risk factor for PTDM. This SNP produce greater expression of 20-HETE which previously has been associated to greater risk of DM2 and metabolic syndrome. However, this study correlating PTDM and CYP450 SNPs is the first one on this area and there is a lot of unknow facts about these molecular pathways.

It is acknowledged the diabetogenic effects of steroids. We found that higher average doses of steroids were present in PTDM groups 1 year after KT. As it seems to be a dose related risk factor, a possible solution for this situation would be an avoidance or early withdrawal of steroids, although some trials exhibited higher rejection rate and not a significant reduction of PTDM or their side effects.(51) Tacrolimus is also known to be highly associated to PTDM as we confirmed in our review. The new discussion is if the effect on PTDM is dose-dependent and which is the best way to monitor this drug effect. Xu J *et al.*[26] by measuring TAC concentration levels on the 1st, 3rd, 6th and 12th months after KT and not finding a statistical difference between the PTDM group and non-PTDM group claimed that this risk factor is not dose dependent. Although some studies showed higher trough levels of TAC as independent risk factors, other present CDRs, explaining that in this case there's a bigger area under the curve for the same trough level, what makes TAC being more diabetogenic.[52] Focusing on the

fact that TAC inter-individual pharmacokinetic variability is so high, studying the variant genes that encode the CYP 3A4 and 5 enzymes (which are responsible for TAC metabolism) can be the key to stablish a standard marker to do an efficient target focused therapy.[53]

Since MMF seems to have a protective effect on PTDM, one study discuss the hypothesis of an association between TAC and MMF, reducing the trough levels of TAC and the dose of steroids.[32] Moreover, SRL also seems to have an impact on PTDM, although the mechanism is not fully understood but insulin resistance and toxicity of β-cells are two hypothesis(54). We found some studies describing IL-2Ras as protective factors so, that is another possibility to reduce the diabetogenic effects of some immunosuppression therapies.

According to our review, in the last five years, there are not a lot of studies focusing on ethnicity as potential risk factor, probably because the association between some ethnic backgrounds and PTDM was well stablished by previous data. For instance, it is known that African American need 37% more tacrolimus doses for the same effect that Caucasians and some immunosuppressants being highly diabetogenic, the risk of PTDM is increased.[55]

This review has some limitations. First, most studies were retrospective which provide low level of evidence. Furthermore, some PTDM groups had a small sample size so taking definitive conclusions from them is not possible.

Conclusion

In our review, we strongly associated older age, abnormal glucose levels before and right after KT and dyslipidemia to PTDM. Overweight was also correlated to PTDM, but new measurements are required to stablish a stronger association. Therefore, pre and posttransplant lifestyle alterations and preventive pharmacological measures can play an important part in reducing PTDM after KT incidence.

In this paper, Hypomagnesemia, 25(OH) deficiency, acute rejection episodes and proteinuria levels seem to play a role in PTDM however scientific evidence is controversial.

New perspectives and therapeutic targets are being studied such as PCSK9 and CYP P450 enzymes that, in the future, can lead to a more effective therapy.

Immunosuppression therapy is a consensual risk factor. We verified that steroids, tacrolimus and sirolimus are the most diabetogenic options and so, adapting the therapeutic regimen to the PTDM risk becomes essential. However, tacrolimus high inter-individual pharmacokinetic variability demands a careful monitorization in order to optimize its use and avoid adverse effects and steroids withdrawal or avoidance increases the risk of graft loss.

The acknowledge of these risk factors by a detailed anamnesis and close pre- and post-transplantation follow up is crucial to improve graft and patient survival. The selection and management of candidates to KT based on their genetic profile seems to be the future of kidney transplantation and a possible solution to PTDM.

References

1. Cascais de Sa D, Santos L, Rodrigues L, Romaozinho C, Guedes Marques M, Macario F, et al. Post-Kidney-Transplant Diabetes: Evaluation of Risk Factors. Transplant Proc. 2019;51(5):1597-600.
2. Sharif A, Hecking M, de Vries AP, Porrini E, Hornum M, Rasoul-Rockenschaub S, et al. Proceedings from an international consensus meeting on posttransplantation diabetes mellitus: recommendations and future directions. Am J Transplant. 2014;14(9):1992-2000.
3. Davidson J, Wilkinson A, Dantal J, Dotta F, Haller H, Hernandez D, et al. New-onset diabetes after transplantation: 2003 International consensus guidelines. Proceedings of an international expert panel meeting. Barcelona, Spain, 19 February 2003. Transplantation. 2003;75(10 Suppl):Ss3-24.
4. Conte C, Secchi A. Post-transplantation diabetes in kidney transplant recipients: an update on management and prevention. Acta Diabetol. 2018;55(8):763-79.
5. Lima C, Grden A, Skare T, Jaworski P, Nisihara R. Risk factors for new-onset diabetes mellitus after kidney transplantation (NODAT): a Brazilian single center study. Arch Endocrinol Metab. 2018;62(6):597-601.
6. Eide IA, Halden TAS, Hartmann A, Dahle DO, Asberg A, Jenssen T. Associations Between Posttransplantation Diabetes Mellitus and Renal Graft Survival. Transplantation. 2017;101(6):1282-9.
7. Cosio FG, Pesavento TE, Kim S, Osei K, Henry M, Ferguson RM. Patient survival after renal transplantation: IV. Impact of post- transplant diabetes. Kidney Int. 2002;62(4):1440-6.
8. Shivaswamy V, Boerner B, Larsen J. Post-Transplant Diabetes Mellitus: Causes, Treatment, and Impact on Outcomes. Endocr Rev. 2016;37(1):37-61.
9. Hjelmesaeth J, Hartmann A, Leivestad T, Holdaas H, Sagedal S, Olstad M, et al. The impact of early-diagnosed new-onset post-transplantation diabetes mellitus on survival and major cardiac events. Kidney Int. 2006;69(3):588-95.
10. Montori VM, Basu A, Erwin PJ, Velosa JA, Gabriel SE, Kudva YC. Posttransplantation diabetes: a systematic review of the literature. Diabetes Care. 2002;25(3):583-92.
11. Bloom RD, Rao V, Weng F, Grossman RA, Cohen D, Mange KC. Association of hepatitis C with posttransplant diabetes in renal transplant patients on tacrolimus. J Am Soc Nephrol. 2002;13(5):1374-80.
12. Gunnarsson R, Lundgren G, Magnusson G, Ost L, Groth CG. Steroid diabetes--a sign of overtreatment with steroids in the renal graft recipient? Scand J Urol Nephrol Suppl. 1980;54:135-8.
13. Maes BD, Kuypers D, Messiaen T, Evenepoel P, Mathieu C, Coosemans W, et al. Posttransplantation diabetes mellitus in FK-506-treated renal transplant recipients: analysis of incidence and risk factors. Transplantation. 2001;72(10):1655-61.

14. Lim LM, Kung LF, Kuo MC, Kuo HT. Risk Factors Associated With Mammalian Target of Rapamycin Inhibitor Withdrawal in Kidney Transplant Recipients. Transplant Proc. 2016;48(3):790-3.
15. Valderhaug TG, Jenssen T, Hartmann A, Midtvedt K, Holdaas H, Reisaeter AV, et al. Fasting plasma glucose and glycosylated hemoglobin in the screening for diabetes mellitus after renal transplantation. Transplantation. 2009;88(3):429-34.
16. Pimentel AL, Cavagnolli G, Camargo JL. Diagnostic accuracy of glycated hemoglobin for post-transplantation diabetes mellitus after kidney transplantation: systematic review and meta-analysis. Nephrol Dial Transplant. 2017;32(3):565-72.
17. Lane JT, Dagogo-Jack S. Approach to the patient with new-onset diabetes after transplant (NODAT). J Clin Endocrinol Metab. 2011;96(11):3289-97.
18. Bayer ND, Cochetti PT, Anil Kumar MS, Teal V, Huan Y, Doria C, et al. Association of metabolic syndrome with development of new-onset diabetes after transplantation. Transplantation. 2010;90(8):861-6.
19. Bergrem HA, Valderhaug TG, Hartmann A, Hjelmesaeth J, Leivestad T, Bergrem H, et al. Undiagnosed diabetes in kidney transplant candidates: a case-finding strategy. Clin J Am Soc Nephrol. 2010;5(4):616-22.
20. Shin JI, Palta M, Djamali A, Astor BC. Higher Pretransplantation Hemoglobin A1c Is Associated With Greater Risk of Posttransplant Diabetes Mellitus. Kidney Int Rep. 2017;2(6):1076-87.
21. Rodrigo E, Santos L, Pinera C, Millan JC, Quintela ME, Toyos C, et al. Prediction at first year of incident new-onset diabetes after kidney transplantation by risk prediction models. Diabetes Care. 2012;35(3):471-3.
22. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant. 2009;9 Suppl 3:S1-155.
23. Goldmannova D, Karasek D, Krystynik O, Zadrazil J. New-onset diabetes mellitus after renal transplantation. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2016;160(2):195-200.
24. Stephen J, Anderson-Haag TL, Gustafson S, Snyder JJ, Kasiske BL, Israni AK. Metformin use in kidney transplant recipients in the United States: an observational study. Am J Nephrol. 2014;40(6):546-53.
25. Paek JH, Kang SS, Park WY, Jin K, Park SB, Han S, et al. Incidence of Post-transplantation Diabetes Mellitus Within 1 Year After Kidney Transplantation and Related Factors in Korean Cohort Study. Transplant Proc. 2019;51(8):2714-7.
26. Xu J, Xu L, Wei X, Li X, Cai M. Incidence and Risk Factors of Posttransplantation Diabetes Mellitus in Living Donor Kidney Transplantation: A Single-Center Retrospective Study in China. Transplant Proc. 2018;50(10):3381-5.

27. Xie L, Tang W, Wang X, Wang L, Lu Y, Lin T. Pretransplantation Risk Factors Associated With New-onset Diabetes After Living-donor Kidney Transplantation. Transplant Proc. 2016;48(10):3299-302.
28. Yu H, Kim H, Baek CH, Baek SD, Jeung S, Han DJ, et al. Risk factors for new-onset diabetes mellitus after living donor kidney transplantation in Korea - a retrospective single center study. BMC Nephrol. 2016;17(1):106.
29. Dedinska I, Laca L, Miklusica M, Galajda P, Mokan M. Twelve-Month and Five-Year Analyses of Risk Factors for New-Onset Diabetes After Transplantation in a Group of Patients Homogeneous for Immunosuppression. Transplant Proc. 2015;47(6):1831-9.
30. Baron PW, Infante S, Peters R, Tilahun J, Weissman J, Delgado L, et al. Post-Transplant Diabetes Mellitus After Kidney Transplant in Hispanics and Caucasians Treated with Tacrolimus-Based Immunosuppression. Ann Transplant. 2017;22:309-14.
31. Dedinska I, Laca L, Miklusica J, Rosenberger J, Zilinska Z, Galajda P, et al. Waist circumference as an independent risk factor for NODAT. Ann Transplant. 2015;20:154-9.
32. Okumi M, Unagami K, Hirai T, Shimizu T, Ishida H, Tanabe K. Diabetes mellitus after kidney transplantation in Japanese patients: The Japan Academic Consortium of Kidney Transplantation study. Int J Urol. 2017;24(3):197-204.
33. Gervasini G, Luna E, Garcia-Cerrada M, Garcia-Pino G, Cubero JJ. Risk factors for post-transplant diabetes mellitus in renal transplant: Role of genetic variability in the CYP450-mediated arachidonic acid metabolism. Mol Cell Endocrinol. 2016;419:158-64.
34. Mohammad KG, Idrees MK, Ali T, Akhtar F. Posttransplant diabetes mellitus among live-related kidney transplant recipients: Sindh Institute of Urology and Transplantation experience. Saudi J Kidney Dis Transpl. 2018;29(6):1320-5.
35. Le Fur A, Fournier MC, Gillaizeau F, Masson D, Giral M, Cariou B, et al. Vitamin D deficiency is an independent risk factor for PTDM after kidney transplantation. Transpl Int. 2016;29(2):207-15.
36. Eisenga MF, Zelle DM, Sloan JH, Gaillard C, Bakker SJL, Dullaart RPF. High Serum PCSK9 Is Associated With Increased Risk of New-Onset Diabetes After Transplantation in Renal Transplant Recipients. Diabetes Care. 2017;40(7):894-901.
37. Porrini EL, Diaz JM, Moreso F, Delgado Mallen PI, Silva Torres I, Ibernon M, et al. Clinical evolution of post-transplant diabetes mellitus. Nephrol Dial Transplant. 2016;31(3):495-505.
38. Liang J, Lv C, Chen M, Xu M, Zhao C, Yang Y, et al. Effects of preoperative hepatitis B virus infection, hepatitis C virus infection, and coinfection on the development of new-onset diabetes after kidney transplantation. J Diabetes. 2019;11(5):370-8.

39. Xue M, Zhao C, Lv C, Chen M, Xu M, Rong R, et al. Interleukin-2 receptor antagonists: Protective factors against new-onset diabetes after renal transplantation. J Diabetes. 2018;10(11):857-65.
40. Tillmann FP, Radtke A, Rump LC, Quack I. Effect of Prediabetes on Allograft Survival and Evolution of New-Onset Diabetes After Transplant in Deceased-Donor Kidney Transplant Recipients During Long-Term Follow-Up. Exp Clin Transplant. 2017;15(6):620-6.
41. Biro B, Szabo RP, Illesy L, Balazsfalvi N, Szollosi GJ, Barath S, et al. Regulatory T Cells in the Context of New-Onset Diabetes After Renal Transplant: A Single-Center Experience. Transplant Proc. 2019;51(4):1234-8.
42. Gaynor JJ, Ciancio G, Guerra G, Sageshima J, Hanson L, Roth D, et al. Multivariable risk of developing new onset diabetes after transplant- results from a single-center study of 481 adult, primary kidney transplant recipients. Clin Transplant. 2015;29(4):301-10.
43. Abbas MH, Ismail MI, El Deeb SA, Nagib AM, Hassan NM, Refaie AF, et al. Effect of pretransplant hepatitis C virus on the development of new-onset diabetes mellitus after transplant in Egyptian living-donor renal allotransplant recipients at Mansoura Urology and Nephrology Center. Exp Clin Transplant. 2015;13(1):26-34.
44. Zhang H, Tao X, Shi L, Jiang N, Yang Y. Evaluation of body composition monitoring for assessment of nutritional status in hemodialysis patients. Ren Fail. 2019;41(1):377-83.
45. Cron DC, Noon KA, Cote DR, Terjimanian MN, Augustine JJ, Wang SC, et al. Using analytic morphomics to describe body composition associated with post-kidney transplantation diabetes mellitus. Clin Transplant. 2017;31(9).
46. Siraj ES, Abacan C, Chinnappa P, Wojtowicz J, Braun W. Risk factors and outcomes associated with posttransplant diabetes mellitus in kidney transplant recipients. Transplant Proc. 2010;42(5):1685-9.
47. Santos C, Costa R, Malheiro J, Pedroso S, Almeida M, Martins LS, et al. Kidney transplantation across a positive crossmatch: a single-center experience. Transplant Proc. 2014;46(6):1705-9.
48. Roland M, Gatault P, Al-Najjar A, Doute C, Barbet C, Chatelet V, et al. Early pulse pressure and low-grade proteinuria as independent long-term risk factors for new-onset diabetes mellitus after kidney transplantation. Am J Transplant. 2008;8(8):1719-28.
49. Ducloux D, Motte G, Vautrin P, Bresson-Vautrin C, Rebibou JM, Chalopin JM. Polycystic kidney disease as a risk factor for post-transplant diabetes mellitus. Nephrol Dial Transplant. 1999;14(5):1244-6.
50. Pietrzak-Nowacka M, Safranow K, Rozanski J, Debska-Slizien A, Domanski L, Dziewanowski K, et al. Autosomal dominant polycystic kidney disease is not a risk factor for post-transplant diabetes mellitus. Matched-pair design multicenter study. Arch Med Res. 2008;39(3):312-9.

51. Augustine JJ, Hricik DE. Steroid sparing in kidney transplantation: changing paradigms, improving outcomes, and remaining questions. Clin J Am Soc Nephrol. 2006;1(5):1080-9.
52. Rodrigo E, Pinera C, de Cos MA, Sanchez B, Ruiz JC, Fernandez-Fresnedo G, et al. Evolution of tacrolimus blood levels and concentration-dose ratios in patients who develop new onset diabetes mellitus after kidney transplantation. Transpl Int. 2005;18(10):1152-7.
53. Mohamed ME, Schladt DP, Guan W, Wu B, van Setten J, Keating BJ, et al. Tacrolimus troughs and genetic determinants of metabolism in kidney transplant recipients: A comparison of four ancestry groups. Am J Transplant. 2019;19(10):2795-804.
54. Johnston O, Rose CL, Webster AC, Gill JS. Sirolimus is associated with new-onset diabetes in kidney transplant recipients. J Am Soc Nephrol. 2008;19(7):1411-8.
55. Neylan JF. Racial differences in renal transplantation after immunosuppression with tacrolimus versus cyclosporine. FK506 Kidney Transplant Study Group. Transplantation. 1998;65(4):515-23.