In the name of GOD

MTOR-I and NODAT

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My talk

- Introduction
- NODAT
- MTOR-I Mechanism
- Review of articles

Introduction

- NODAT affects 20–30% of renal transplant recipients.
- increases the risk for cardiovascular events
  infectious events
  metabolic disorders
  diabetic kidney disease
  impaired renal function
  premature graft loss.

- diabetogenic effect of CNIs (tacrolimus) and steroids
- novel immunosuppressive regimens must be carefully evaluated

criteria for NODAT(ADA, WHO)

Table 1. Diagnostic criteria for diabetes mellitus and prediabetes by the ADA

Diabetes	
RPG	≥200 mg/dL (11.1 mmol/L)
FPG	≥126 mg/dL (7 mmol/L)
2hPG	≥200 mg/dL (11.1 mmol/L)
HbA1c	≥6.5%
Prediabetes	
IFG	FPG 100–126 mg/dL (5.6–6.9 mmol/L)
IGT	FPG <126 mg/dL (7 mmol/L) 2hPG 140–200 mg/dL (7.8–11 mmol/L)
Increased risk of diabetes	HbA1c 5.7–6.4%
Normal glucose tolerance	FPG <100 mg/dL (5.6 mmol/L) 2hPG <140 mg/dL (7.8 mmol/L) HbA1c <5.7%

ADA, American Diabetes Association; RPG, random plasma glucose; FPG, fasting plasma glucose; 2hPG, 2-h plasma glucose after an oral glucose; IFG, Impaired fasting glucose; IGT, impaired glucose tolerance.

Limitations of HbA1c

- Use of HbA1c after transplantation is not recommended
- Anaemia, which is common in the early post-transplant period, may lead to false low HbA1c levels
- erythropoietin treatment or blood cell transfusions can change HbA1c levels independently of glycaemic changes
- it is not unusual that a patient may have normal glucose levels (or in the prediabetic range) whereas the levels at 120 min are in the diabetic range, that is, ≥200 mg/dL.
- an OGTT is necessary to detect “occult” PTDM

Transient Post-Operative hyperglycemia **Is Not NODAT**

- About 80% of the patients may experience transient hyperglycaemia early after surgery, which is commonly related to perioperative stress
- This should not be confused with NODAT but must be taken into account since it is associated with future development of the disease
- *diagnosis of NODAT should be made in clinically stable patients*

Risk factors of NODAT

Pre-transplant modifiable

- overweight
- dyslipidemia
- hypertension
- poor physical exercise
- GD

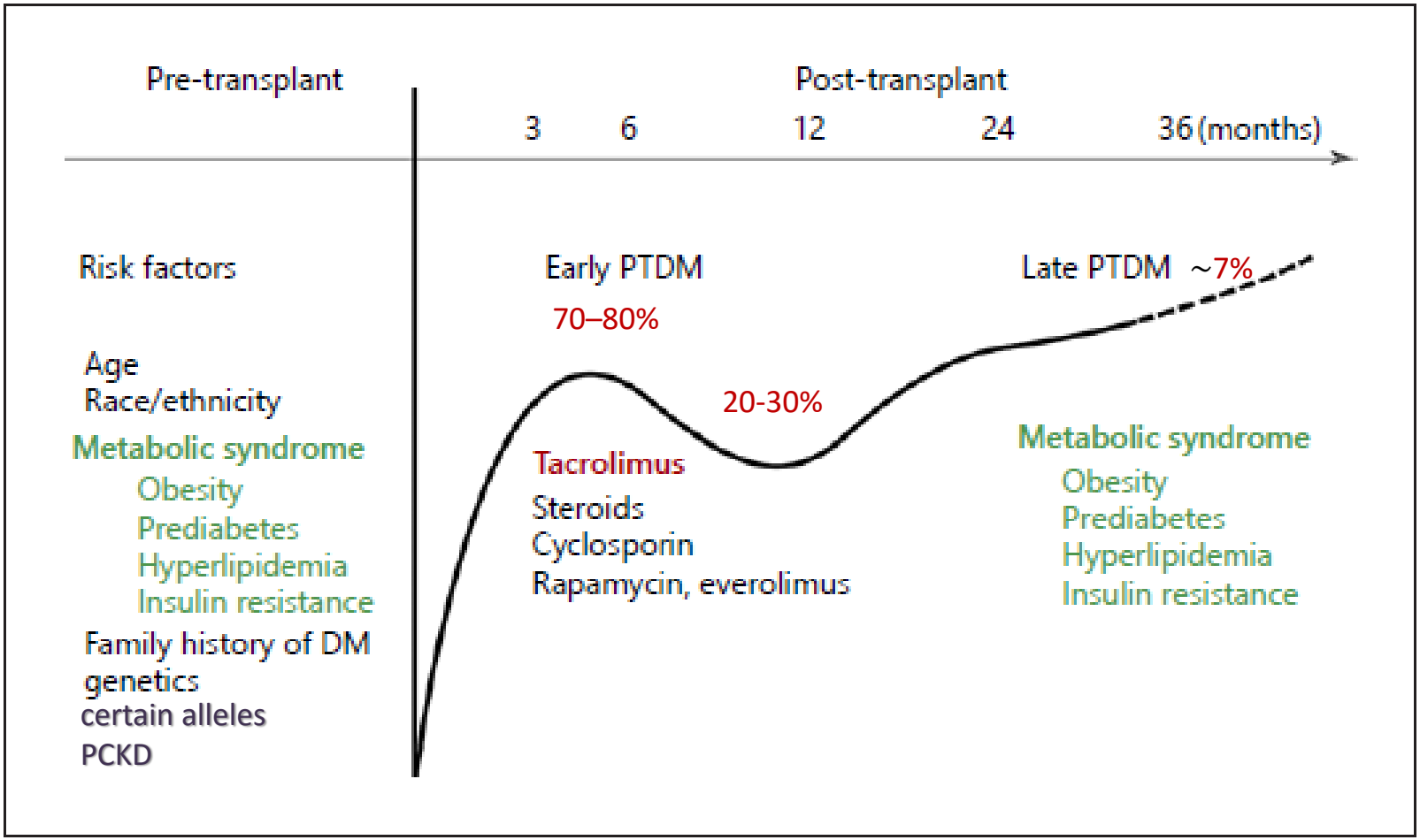
Post-transplant modifiable

- Peri-operative stress
- infections (HCV,CMV)
- Vit D defeciency
- hypo Mg
- HLA mismatch
- IS med

Non-modifiable

- familial history
- older age
- ethnicity
- sex

Timeline of risk factors for NODAT



Nephron 2021;145:317–329

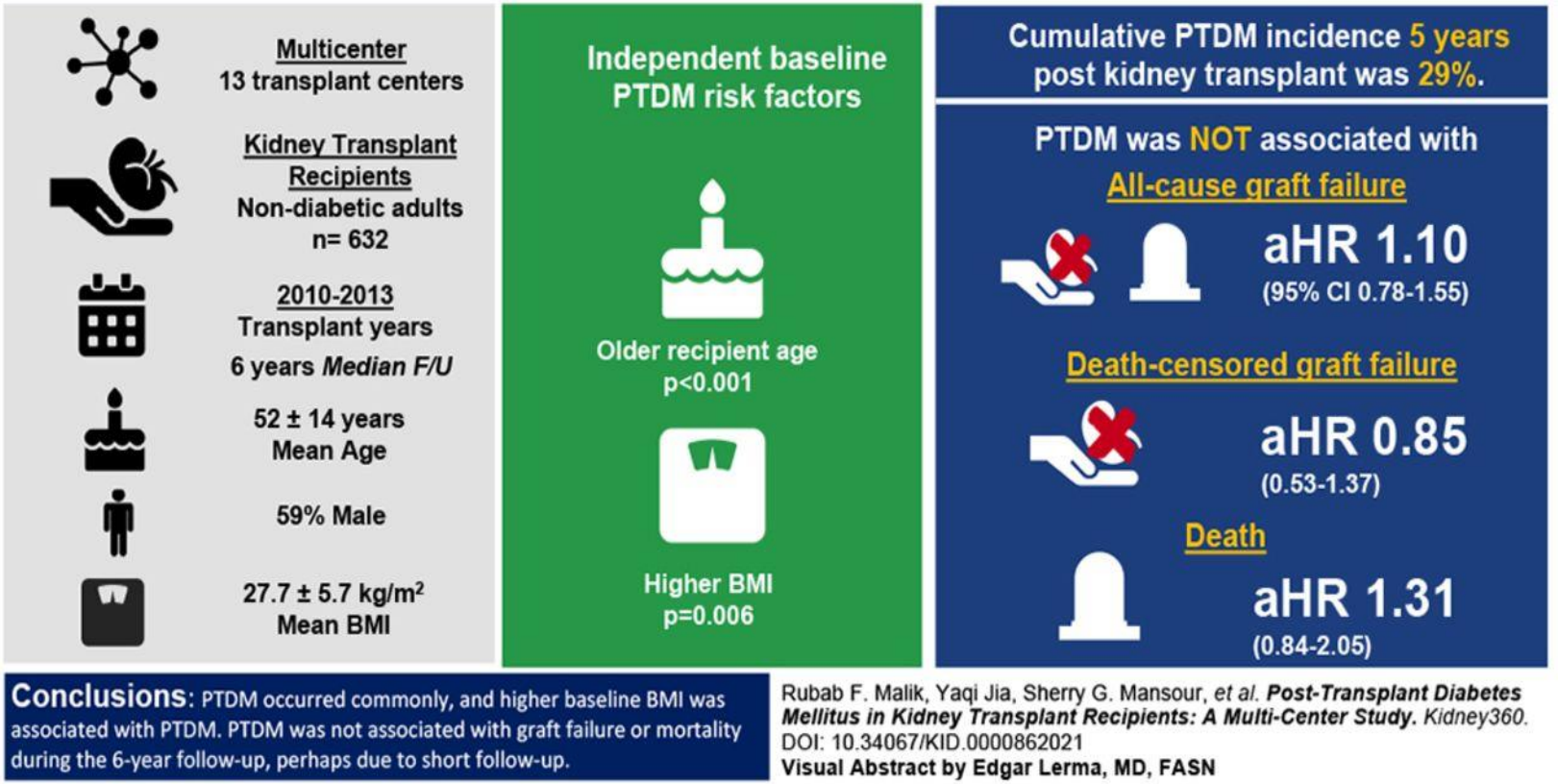
Table 1. Main immunosuppressive medications and their diabetogenic potential.

Drug	Diabetogenic Effect
Maintenance immunosuppression:	
Glucocorticoids	+++++
Tacrolimus	++++
Cyclosporine	+++
Sirolimus	+++
Everolimus	++
Azathioprine	-
Mycophenolic acid	-
Induction immunosuppression:	
Basiliximab	-
Rabbit anti-thymocyte globulin	-
Rituximab	-

Medicina 2021, 57, 250. doi.org/10.3390

Association of post-transplant diabetes mellitus (PTDM) with graft outcomes and mortality

Kidney360



Conclusions: PTDM occurred commonly, and higher baseline BMI was associated with PTDM. PTDM was not associated with graft failure or mortality during the 6-year follow-up, perhaps due to short follow-up.

Rubab F. Malik, Yaqi Jia, Sherry G. Mansour, *et al.* ***Post-Transplant Diabetes Mellitus in Kidney Transplant Recipients: A Multi-Center Study.*** *Kidney360.*
DOI: 10.34067/KID.0000862021
Visual Abstract by Edgar Lerma, MD, FASN

Rubab F. Malik et al. Kidney360 2021;2:1296-1307

Kidney360

Common adverse effects of mTORI

Table 1: Most common adverse events in mTOR-I-treated renal transplant recipients.

Adverse events	Rate of occurrence (%)	References
Pulmonary toxicity	2–11	[20, 21, 24, 33]
Hematopoietic adverse effects		
Anemia	13–58	[6, 36, 44–47, 50, 56, 57, 70, 72, 135, 147]
Leukopenia	5–39	[6, 45, 46, 56, 66, 117, 121, 147]
Thrombocytopenia	4–45	[6, 45–47, 56, 66, 70, 117, 118, 121, 122, 147]
Metabolic disorders		
Hyperlipidemia	8–87	[6, 45–47, 57, 66, 70–72, 115, 117, 118, 121, 135, 147]
Posttransplantation diabetes	3–33	[56, 70, 72, 78, 80, 115, 121, 138, 147]
Hypophosphatemia	15–20	[45, 46, 57]
Lymphedema	<5	[99–102]
Cardiovascular disease	1–6	[80, 100, 117, 122, 124, 128]
Hypertension	8–58	[46, 57, 70, 72, 115, 117, 121, 122, 135]
Cutaneous adverse effects		
Acne, folliculitis	9–25	[6, 57, 70, 116–118, 135, 147]
Stomatitis and mucous membrane disorders	9–64	[6, 118, 138, 147]
Edema	2–70	[6, 56, 57, 70, 121, 122, 135, 147]
Nail and hair pathologies	74	[116]
Gonadal complications	<5	[123–126]
Surgical wound complication	2–20	[56, 70, 72, 133–136]
Infections	2–60	[6, 72, 117, 122, 136]
Gastrointestinal complication	2–51	[6, 46, 47, 56, 57, 70, 72, 117, 118, 121, 135, 147]

MTOR mechanism

- mammalian target of rapamycin (mTOR) is a cytoplasmic serine/threonine protein kinase that belongs to PI3K-related kinase family, which operates as a central regulator of cell metabolism, growth, proliferation, and survival.

- activated by nutrients (glucose, amino acids, and lipids), growth factors, insulin, and inflammatory cytokines

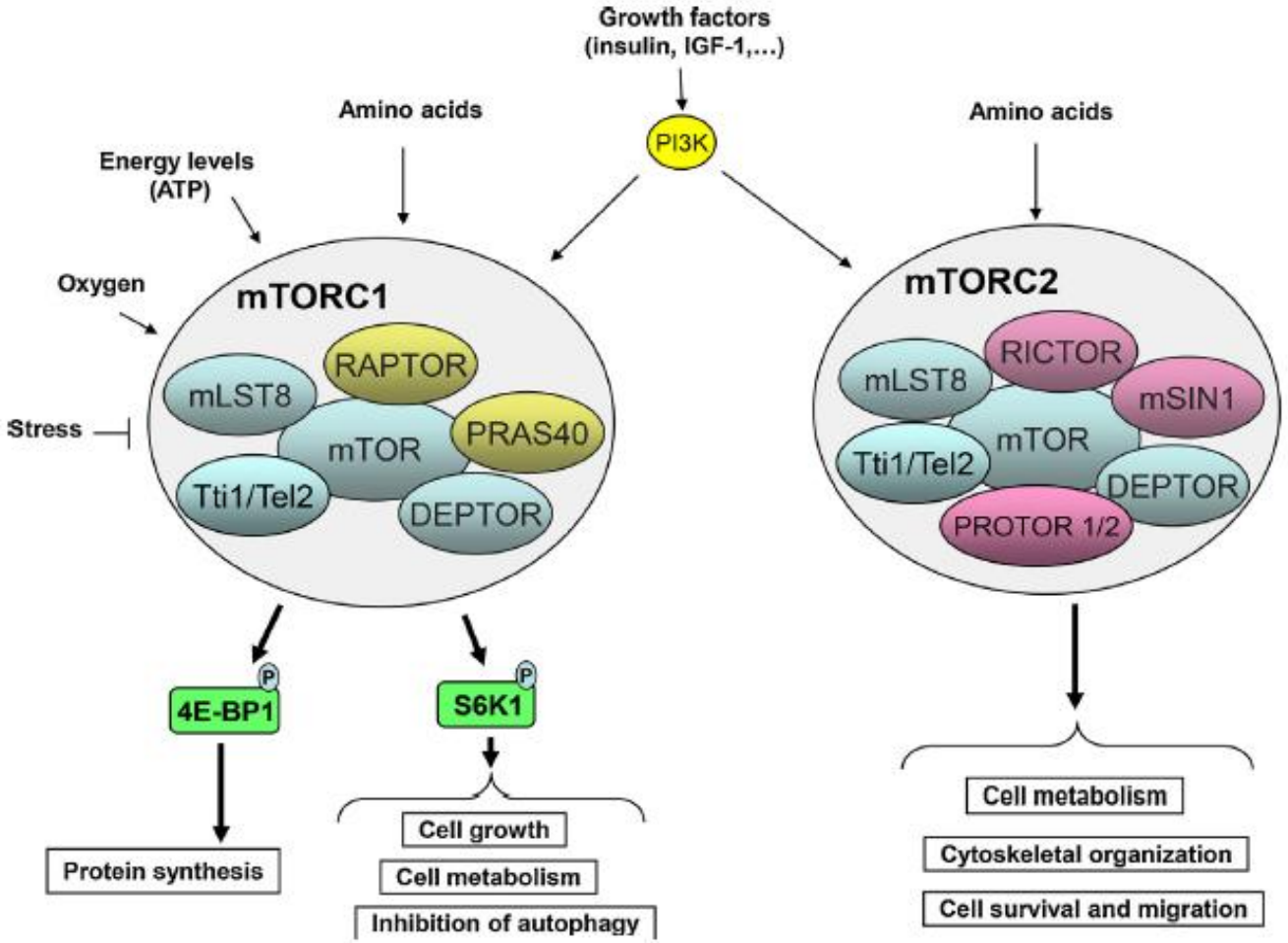


Fig. 1 – mTORC1 and mTORC2 complexes. mTORC1 is composed of 6 protein components (mTOR, mLST8, DEPTOR, Tti1/Tel2, RAPTOR, PRAS40) and responds to various stimuli, such as amino acids, stress, growth factors, energy and oxygen. mTORC2 is composed of 7 protein components (mTOR, mLST8, DEPTOR, Tti1/Tel2, RICTOR, mSIN1, PROTOR1/2) and responds to growth factors and amino acids. S6K1: ribosomal S6 kinase 1; 4E-BP1: eukaryotic translation initiation factor 4E binding protein.

doi.org/10.1016/j.diabres.2015.09.014

MTOR & Hyperglycemia

- mTORC1 promotes insulin resistance in adipose tissue, skeletal muscle, and liver.

- mTORC1 in liver, promoting gluconeogenesis
- Inhibitors of mTOR would therefore be expected to prevent development of insulin resistance through this mechanism
- Conversely, mTORC1 promotes the oxidative metabolism of skeletal muscle.

- mTORC1 is a positive regulator of β cell function, insulin secretion and decreases blood glucose levels, linked to an increase of both β cell size and number.

mTORC1 Signaling: A Double-Edged Sword

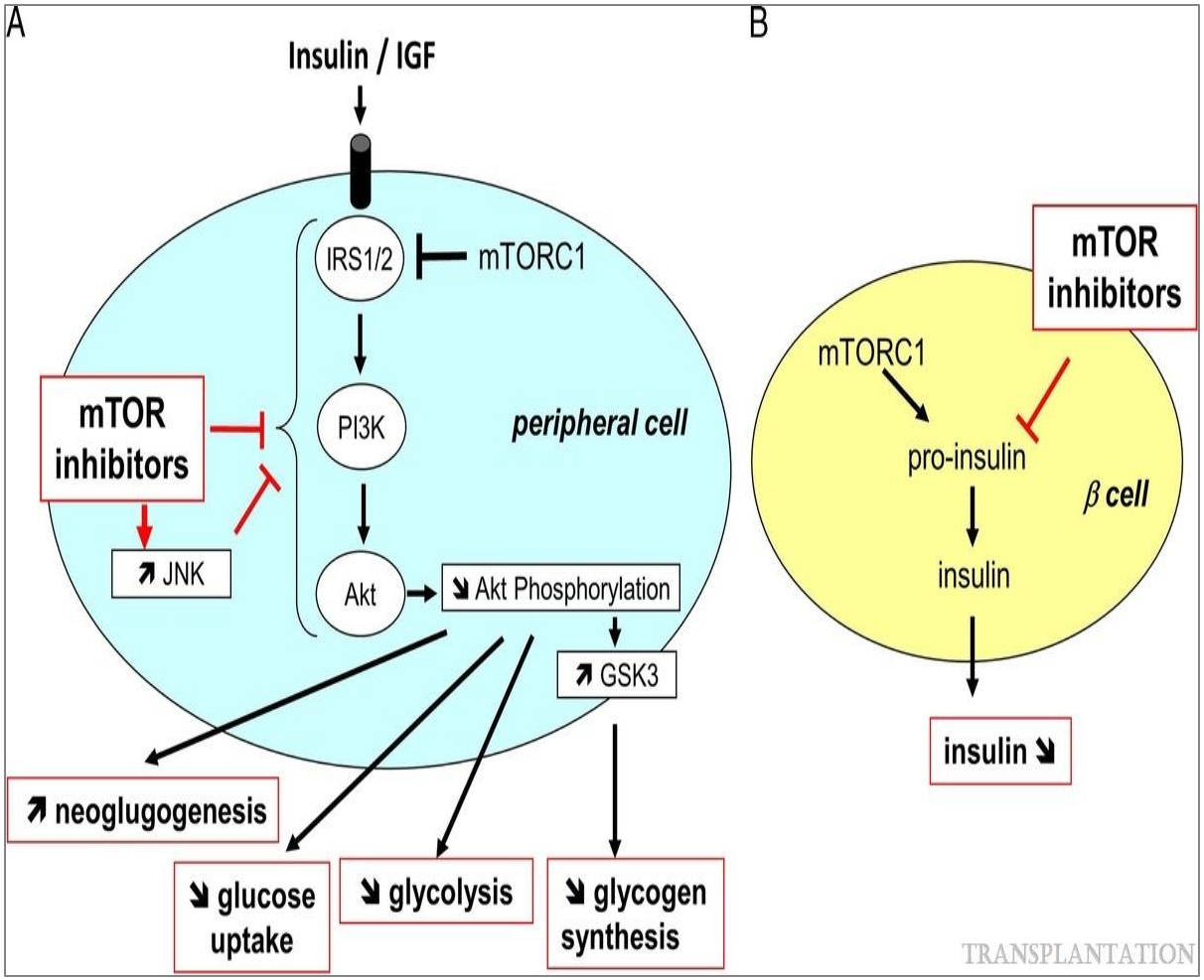
- It seems that mTOR inhibitors exert a ‘‘Janus effect’’ on glucose metabolism.

- mTORC1 activity and metabolic homeostasis probably follows a U-shaped curve, where too little or too much mTORC1 activity has a deleterious effect on systemic metabolism.

MTOR-I mechanism

[mTOR and Cardiovascular Diseases: Diabetes Mellitus]

Vergès, Bruno
Transplantation102(2S):S47-S49, February 2018.
doi: 10.1097/TP.0000000000001722



Pathophysiology of hyperglycemia induced by mTOR inhibitors. A, mTOR inhibitors promote insulin resistance by reducing the activity of the post insulin receptor signaling proteins IRS1/2, by inhibiting the PI3-kinase pathway and by increasing Jun N-terminal kinase (JNK) activity which also reduces the activity of the insulin PI-3 kinase pathway. B, mTOR inhibitors reduce insulin secretion by reducing the upregulating action of mTORC1 on insulin secretion. IRS indicates insulin receptor substrate; PI3K, phosphoinositide 3-kinase; JNK, Jun N-terminal kinase; GSK3, glycogen synthase kinase 3β; IGF, insulin-like growth factor.

Review of articles

American Journal of TRANSPLANTATION

AST AMERICAN SOCIETY OF TRANSPLANTATION ASTS

Original Article | Free Access

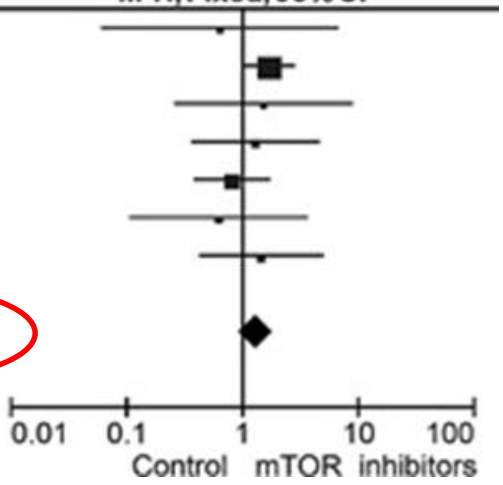
Risk of Metabolic Complications in Kidney Transplantation After Conversion to mTOR Inhibitor: A Systematic Review and Meta-Analysis

RR of NODAT

Study or Subgroup	mTORinhibitors Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Stallone, 2005	1	33	2	42	3.3%	0.64 [0.06, 6.72]
Schena, 2009	62	551	18	273	45.7%	1.71 [1.03, 2.83]
Lebranchu, 2009	3	96	2	97	3.8%	1.52 [0.26, 8.87]
Guba, 2010	5	69	4	71	7.5%	1.29 [0.36, 4.59]
Weir, 2011	11	148	14	153	26.1%	0.81 [0.38, 1.73]
Budde, 2011	2	155	3	145	5.9%	0.62 [0.11, 3.68]
Holdaas, 2011	6	127	4	123	7.7%	1.45 [0.42, 5.02]
Total (95% CI)		**1179**		**904**	**100.0%**	**1.32 [0.92, 1.87]**
Total events	90		47			

Heterogeneity: Chi² = 3.68, df = 6 (P = 0.72); I² = 0%

Test for overall effect: Z = 1.52 (P = 0.13)



NODAT

BPAR

Proteinuria

American J Transplantation, 2014, DOI: (10.1111/ajt.12852)

PLoS One. 2017; 12(1): e0170246.
Published online 2017 Jan 20. doi: 10.1371/journal.pone.0170246
PMCID: PMC5249216
PMID: 28107397

Efficacy and Safety of Everolimus for Maintenance Immunosuppression of Kidney Transplantation: A Meta-Analysis of Randomized Controlled Trials

Jinyu Liu,[1] Dong Liu,[1] Juan Li,[1] Lan Zhu,[2] Chengliang Zhang,[1] Kai Lei,[1] Qiling Xu,[3] and Ruxu You[4,*]

Incidence of the most common adverse events up to 1 year after transplant.

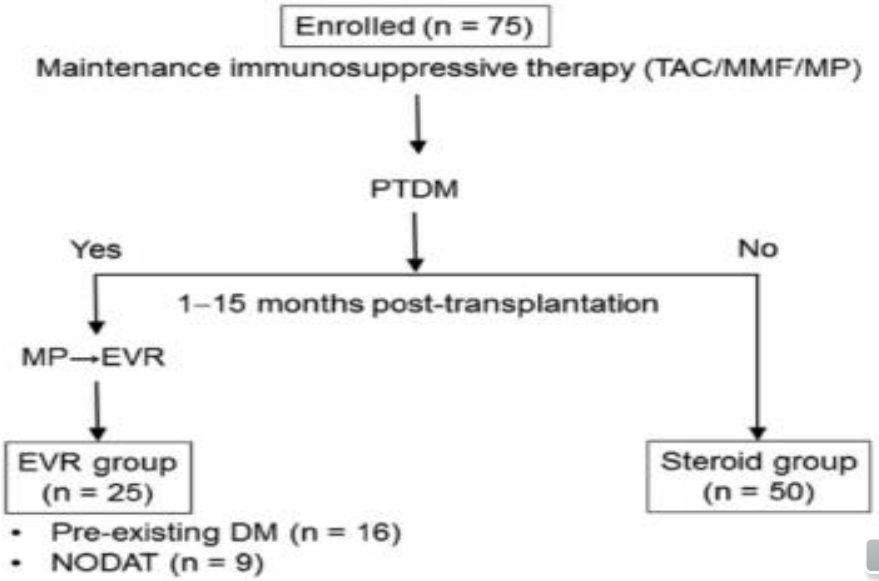
Adverse events	Incidence of adverse events (%)		p-Value
	Everolimus	CNI	
cytomegalovirus	8.90	11.59	0.11
BK virus	2.85	4.88	0.14
urinary tract infection	21.48	25.61	0.27
diabetes mellitus	4.92	8.29	0.16
hypertriglyceridaemia	2.16	2.51	0.77

Conversion From Steroid to Everolimus in Maintenance Kidney Transplant Recipients With Posttransplant Diabetes Mellitus

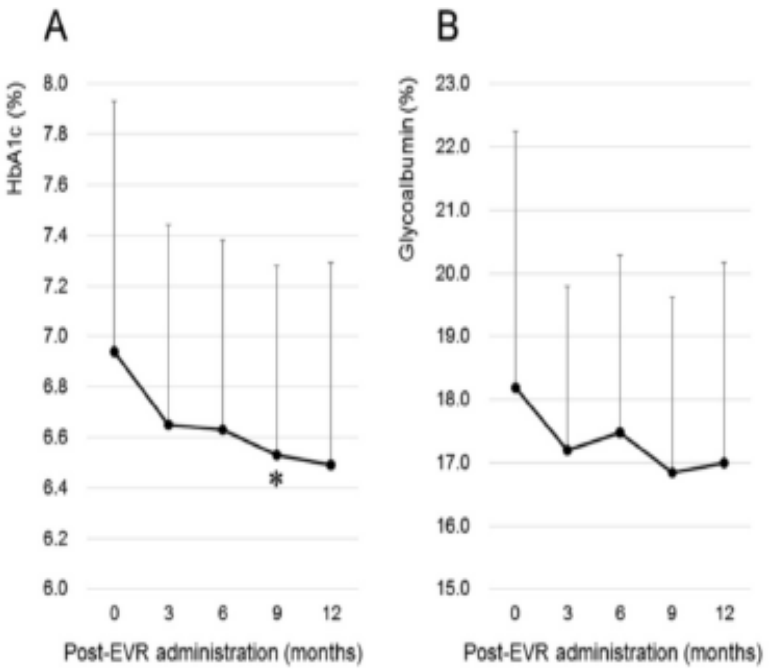
Koji Nanmoku, Akira Kurosawa, Taro Kubo, Takahiro Shinzato, Toshihiro Shimizu, Takaaki Kimura, Takashi Yagisawa

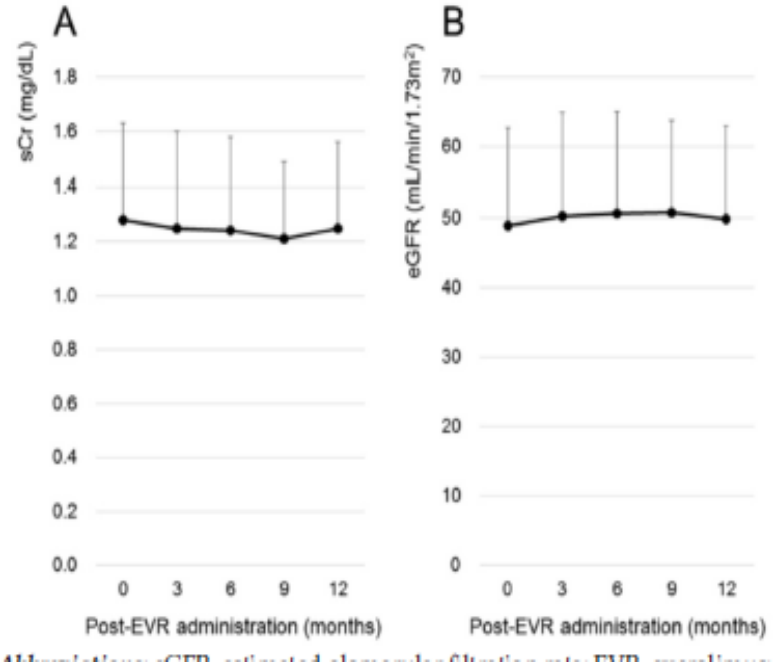
- use of steroids is associated with a potential risk of not only the deterioration of preexisting diabetes and NODAT

- steroid withdrawal can reduce the incidence of PTDM, this strategy has been associated with an increased risk of graft rejection



Experimental and Clinical Transplantation (2019) 1: 47-51





all graft survival ,
biopsy-proven acute rejection rates
did not significantly differ between the groups (16%vs 12%; P = .72).
no acute rejection occurred after everolimus administration.
In the everolimus group, hemoglobin A1c significantly declined at 9 months after everolimus administration (6.94% vs 6.53%; P = .047).
Prospective study

Experimental and Clinical Transplantation (2019) 1: 47-51

Xie et al. BMC Nephrology (2015) 16:91
DOI 10.1186/s12882-015-0078-5

BMC Nephrology

RESEARCH ARTICLE Open Access

mTOR inhibitor versus mycophenolic acid as the primary immunosuppression regime combined with calcineurin inhibitor for kidney transplant recipients: a meta-analysis

11 RCT = 4930 patients

Group1= CNI + MMF

Group 2= CNI + MTORI

immediate post-transplant period

MTORI vs MPA

- mTOR-I-treated patients showed an increased risk of NODAT(RR = 1.32)
- mTOR-I significantly reduced the risk of CMV infections (RR = 0.43), and malignancy (RR = 0.64) compared with MPA
- mTOR-I showed no particular superiority compared with MPA, but in fact had an increased risk of graft loss(RR = 1.2) when combined with CNI.

Transplantation

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Outline

Images

ORIGINAL ARTICLES: CLINICAL TRANSPLANTATION

Posttransplant Diabetes Mellitus in Kidney Transplant Recipients Receiving Calcineurin or mTOR Inhibitor Drugs

Araki, Motoo[1]; Flechner, Stuart M.[1,3]; Ismail, Hazem R.[1]; Flechner, Lawrence M.[2]; Zhou, Lingmei[1]; Derweesh, Ithaar H.[1]; Goldfarb, David[1]; Modlin, Charles[1]; Novick, Andrew C.[1]; Faiman, Charles[1]

TABLE 2. Incidence of PTDM among the three study groups

	Group I: cyclosporine	Group II: tacrolimus	Group III: sirolimus	*P* value
n	263	60	205	
All PTDM	40	14	40	0.2378
Insulin use plus FBS >126 mg/dl BS >200 mg/dl	15.2%	23.3%	19.5%	
Insulin use only	20 (7.6%)	7 (11.7%)	12 (5.9%)	
Insulin use the first year	12 (4.5%)	5 (8.3%)	9 (4.3%)	0.3120

FBS, fasting blood sugar; BS, blood sugar.

TRANSPLANTATION

N=528

39.2 (9.0–103.8) months follow up

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

Clinical Transplantation

Glucose Metabolism in Renal Transplant Recipients: Effect of Calcineurin Inhibitor Withdrawal and Conversion to Sirolimus

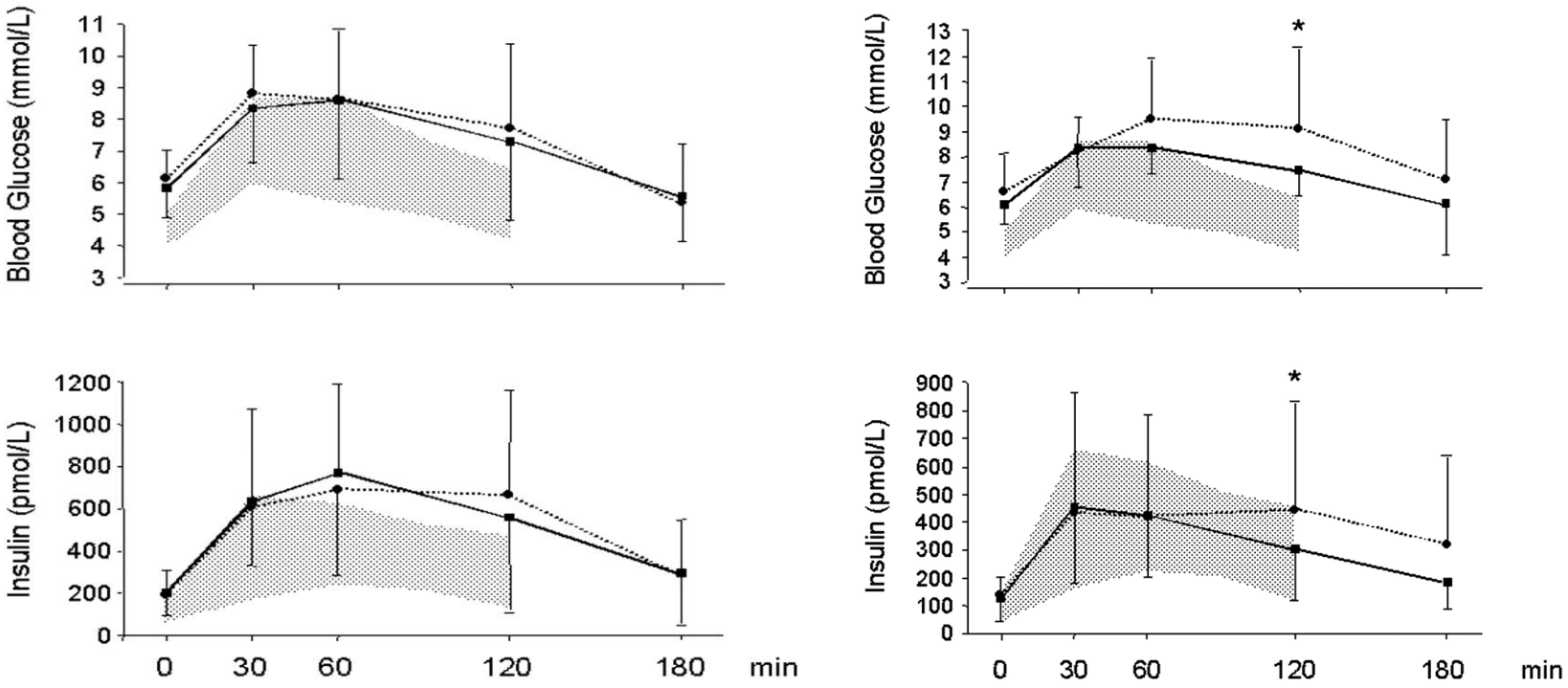
Annalisa Teutonico, Paolo F. Schena and Salvatore Di Paolo

JASN October 2005, 16 (10) 3128-3135; DOI: https://doi.org/10.1681/ASN.2005050487

Prospective study
Group 1: 26 patients discontinued CsA and were converted to sirolimus

Group 2: 15 recipients of suboptimal kidneys who were treated with tacrolimus plus sirolimus for the first 3 mo after grafting and converted to sirolimus alone

Test: OGTT and intravenous insulin tolerance test before and 6 mo after conversion



Switch to sirolimus :

associated with a 30% increase of incidence of IGT and with 4 pt NODAT

In conclusion:

discontinuation of CNI and their replacement by sirolimus fail to ameliorate the glycometabolic profile of kidney transplant recipients.

it is associated with a worsening of insulin resistance and an inappropriately low insulin response.

ANNALS OF TRANSPLANTATION

ORIGINAL PAPER

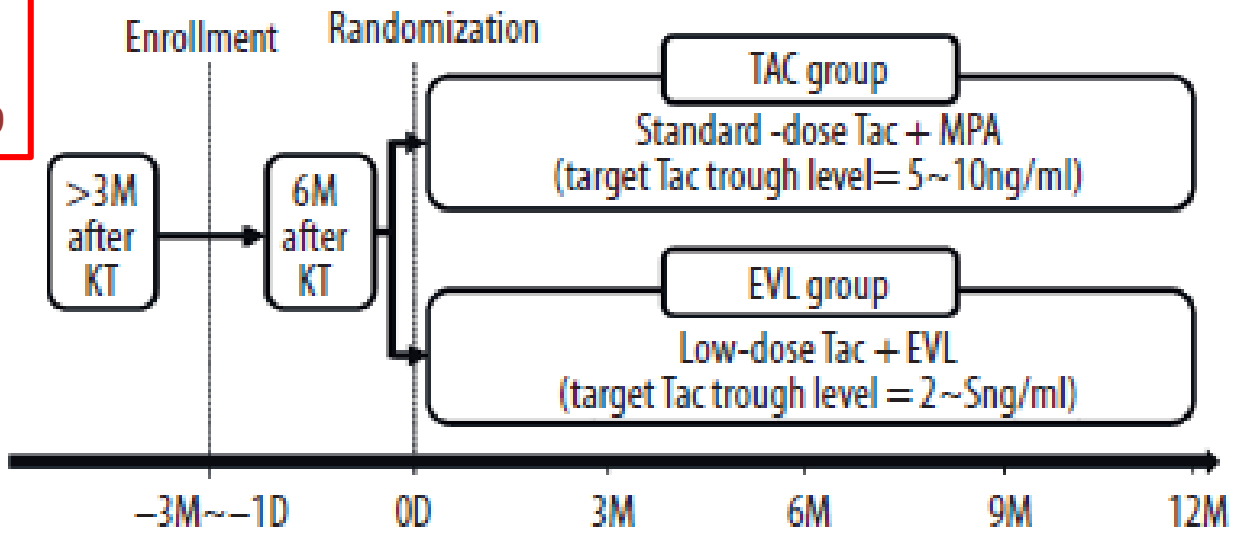
e-ISSN 2329-0358
© Ann Transplant, 2021; 26: e927984
DOI: 10.12659/AOT.927984

Received: 2020.08.13
Accepted: 2020.11.17
Available online: 2020.11.30
Published: 2021.01.22

Effect of Everolimus with Low-Dose Tacrolimus on Development of New-Onset Diabetes After Transplantation and Allograft Function in Kidney Transplantation: A Multicenter, Open-Label, Randomized Trial

12 months
NODAT
no significant difference
13.16% vs. 2.56%, **p=0.0819**

no significant difference
eGFR
BPAR



findings suggest that the addition of EVL with a low dose of Tac is an acceptable strategy for maintenance immunosuppression in KT

Sommerer et al. BMC Nephrology (2018) 19:237
https://doi.org/10.1186/s12882-018-1031-1

BMC Nephrology

RESEARCH ARTICLE Open Access

Onset and progression of diabetes in kidney transplant patients receiving everolimus or cyclosporine therapy: an analysis of two randomized, multicenter trials

Claudia Sommerer[1*], Oliver Witzke[2], Frank Lehner[3], Wolfgang Arns[4], Petra Reinke[5], Ute Eisenberger[6], Bruno Vogt[6], Katharina Heller[7], Johannes Jacobi[7], Markus Guba[8], Rolf Stahl[9], Ingeborg A. Hauser[10], Volker Kliem[11], Rudolf P. Wüthrich[12], Anja Mühlfeld[13], Barbara Suwelack[14], Michael Duerr[15], Eva-Maria Paulus[16], Martin Zeier[1], Martina Porstner[16†] and Klemens Budde[15†] on behalf of the ZEUS and HERAKLES study investigators

Results from this post hoc analysis

- do not suggest any difference in the incidence or severity of PTDM in patients who were converted early post-transplant from a CsA-based regimen to everolimus, or in the progression of pre-existing diabetes.
- eGFR in patients with everolimus in patients with PTDM improved by 14 mL/min/1.73m2 in the ZEUS study and by 4.9 mL/min/1.73m2 in HERAKLES by month 12.
- Among patients with pre-existing diabetes, there was a numerically greater improvement

Sirolimus vs everolimus

- data from a review of 12 RT show that the incidence of NODAT from 11.0% to 27.6% in patients treated with sirolimus + low dose of tacrolimus and from 17.8% to 38.1% in patients treated with everolimus and low dose of tacrolimus.
- in some RCT of everolimus with low-dose cyclosporine in renal transplant recipients, the incidence of NODAT was low (≤5%).

Prevention of NODAT

2 possibilities:

1) treat patients with MS in the waiting list to improve β-cell dysfunction before transplantation

2) identify these patients and select a less diabetogenic therapy after transplantation.

- in all patients, FPG and HbA1c before starting a treatment
- an mTOR inhibitor : FPG every 2 weeks/ 1 month then every month and HbA1c every 3 months.
- OGTT
- SMBG should be intensified.
- In early period after TX , insulin is the preferable choice
- Metformin (in the absence of renal failure)

Take home massage

- MTOR-I seems exert a ‘‘Janus effect’’ on glucose metabolism.
- we can consider everlimus based regim for patients with a risk of PTDM (not high risk for rejection).

- NODAT with MTOR-I : Metformin is a good choice

- discrepancies in results may be related to timing of conversion and the dose of mTOR inhibitors.

Thank you