CONVEGNO NAZIONALE CONGIUNTO SIN - SID
La Malattia Renale Diabetica (DKD): Presente e Futuro dell'Approccio Integrato Nefro-Diabetologico
TEAM WORK FOR WORK SUCCESS
RIMINI, 2 OTTOBRE 2019

Diabete e trapianto renale

Lorenzo Piemonti, MD

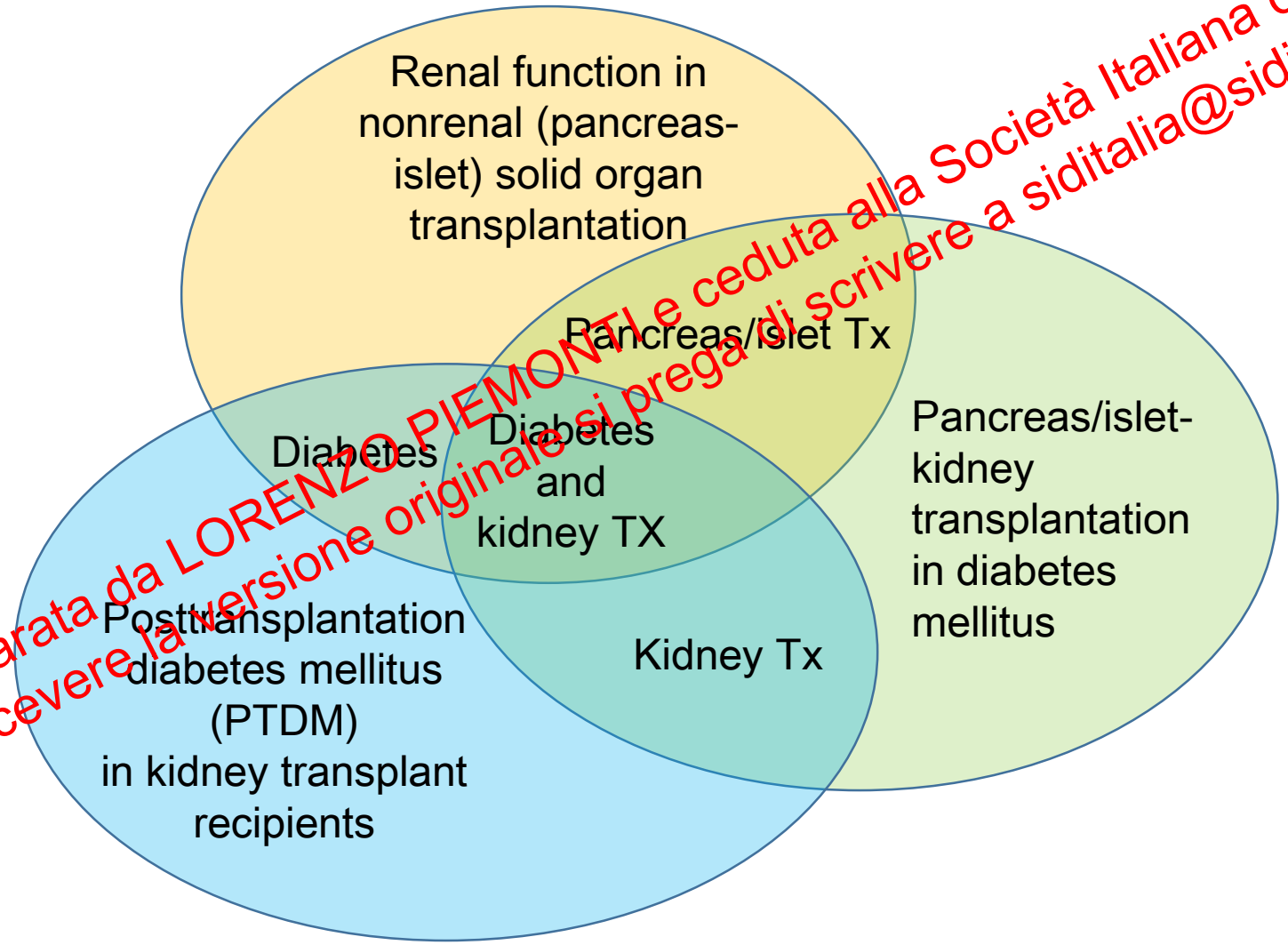
Professor of Endocrinology
Vita-Salute San Raffaele University

Director Diabetes Research Institute
San Raffaele Scientific Institute, Milan

DIABETES RESEARCH INSTITUTE

http://dri.hsr.it

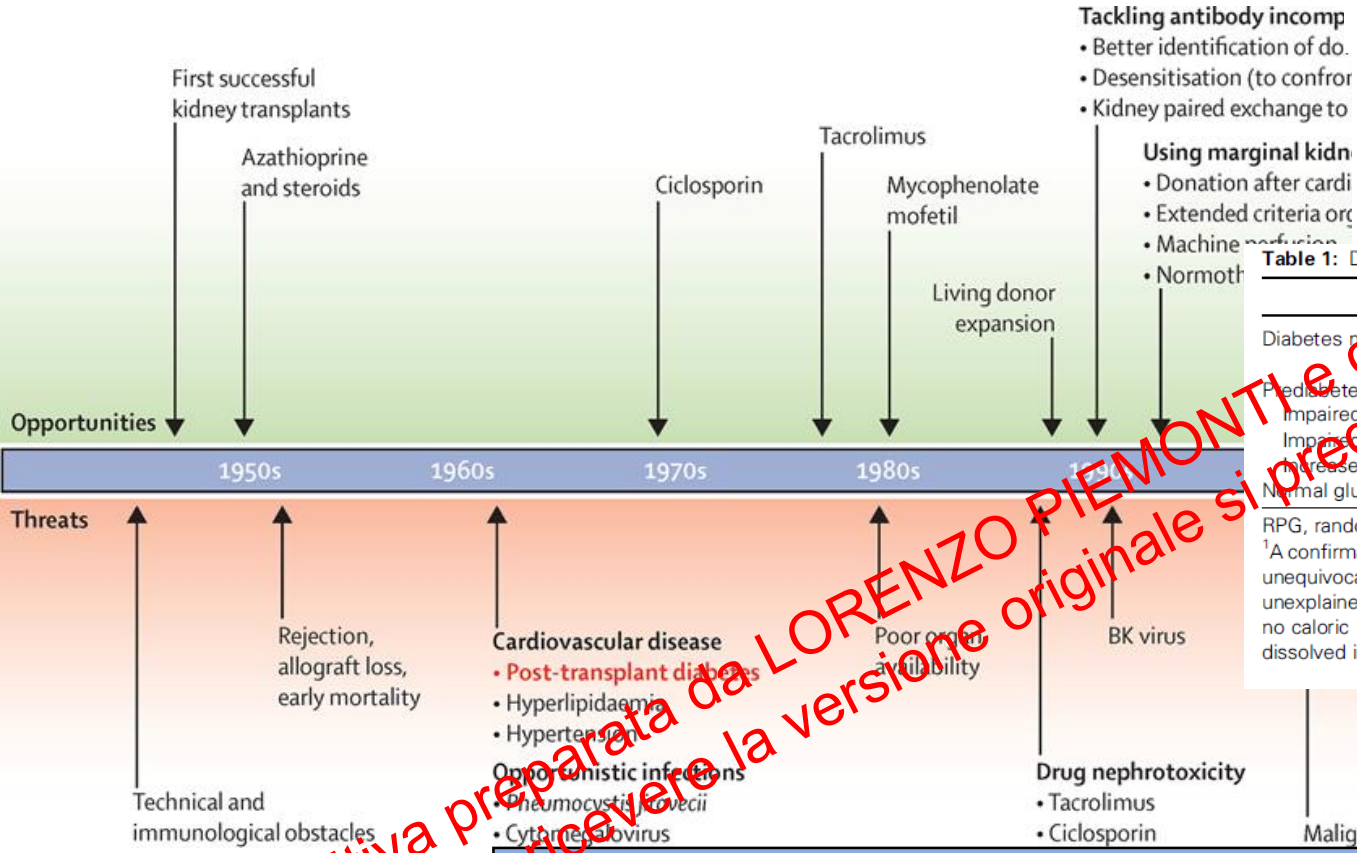
Diabetes and kidney transplant



Posttransplantation diabetes mellitus (PTDM)

- Definition and diagnosis
- Epidemiology
- Pathogenesis
- Risks Factors
- Sequelae
- Management
- Controversies and area of uncertainty

PTDM: definition and dia



American Journal of Transplantation 2014; 14: 1992–2000
Wiley Periodicals Inc.

doi: 10.1111/ajt.12850

May 27, 2003
Supplement

Meeting Report

Proceedings From an International Consensus Meeting on Posttransplantation Diabetes Mellitus: Recommendations and Future Directions

A. Sharif[1,*], M. Hecking[2], A. P. J. de Vries[3], E. Porrini[4], M. Hornum[5], S. Rasoul-Rockenschaub[2], G. Berlakovich[2], M. Krebs[2], A. Kautzky-Willer[2], G. Schernthaner[2], P. Marchetti[6], G. Pacini[7], A. Ojo[8], S. Takahara[9], J. L. Larsen[10], K. Budde[11], K. Eller[12], J. Pascual[13], A. Jardine[14], S. J. L. Bakker[15], T. G. Valderhaug[16], T. S. Jenssen[17], S. Cohney[1] and M. D. Säemann[2]

*Corresponding author: Adnan Sharif, adnan.sharif@uhb.nhs.uk

A consensus meeting was held in Vienna on September 2–3 2013, to discuss diagnostic and therapeutic challenges surrounding development of diabetes mellitus after transplantation. The International Expert Panel comprised 24 transplant nephrologists, surgeons, diabetologists and clinical scientists, which met with the aim to review previous guidelines in light

Table 1: Diagnostic criteria for diabetes mellitus and prediabetes by the American Diabetes Association (ADA)

	ADA[1]
Diabetes mellitus	Symptoms of diabetes plus RPG ≥ 200 mg/dL (11.1 mmol/L) OR FPG ≥ 126 mg/dL (7.0 mmol/L) OR 2HPG ≥ 200 mg/dL (11.1 mmol/L) during an OGTT OR HbA1c ≥ 6.5%
Prediabetes	
Impaired fasting glucose	FPG 100–126 mg/dL (5.6–6.9 mmol/L)
Impaired glucose tolerance	FPG < 7.0 mmol/L AND 2HPG 7.8–11.0 mmol/L
Increased risk of diabetes	HbA1c 5.7–6.4%
Normal glucose tolerance	FPG < 110 mg/dL (5.6 mmol/L) AND 2HPG < 140 mg/dL (7.8 mmol/L) AND HbA1c < 5.7%

RPG, random plasma glucose; FPG, fasting plasma glucose; 2HPG, 2-h plasma glucose after an oral glucose.
[1]A confirmatory laboratory test based on measurements of venous plasma glucose must be done on any subsequent day in the absence of unequivocal hyperglycemia accompanied by acute metabolic decompensation. Symptoms of diabetes include polyuria, polydipsia and unexplained weight loss. Random plasma glucose is defined as any time of day without regard to time since last meal. Fasting is defined as no caloric intake for at least 8 h. The oral glucose tolerance test should be performed using a glucose load of 75 g anhydrous glucose dissolved in water.

HALLER,[6] KRENTZ,[10] WOUDE,[14] WHEELER[15]

s or

ual is

ms

7.0 mmol/l) = IFG

ucose tolerance

g/dl (11.1 mmol/l) = IGT

e the 2 hour OGTT cut-off will identify more

rom the FPG test.

nce; OGTT, oral glucose tolerance test; PG, plasma

Post transplant diabetes: rates ranging from 2 to 53 percent. Lack of consensus regarding the definition and diagnosis: a) random glucose levels greater than 200 mg/dL; b) fasting glucose levels greater than 140 mg/dL; c) need for insulin or oral hypoglycemic agents in the posttransplant period

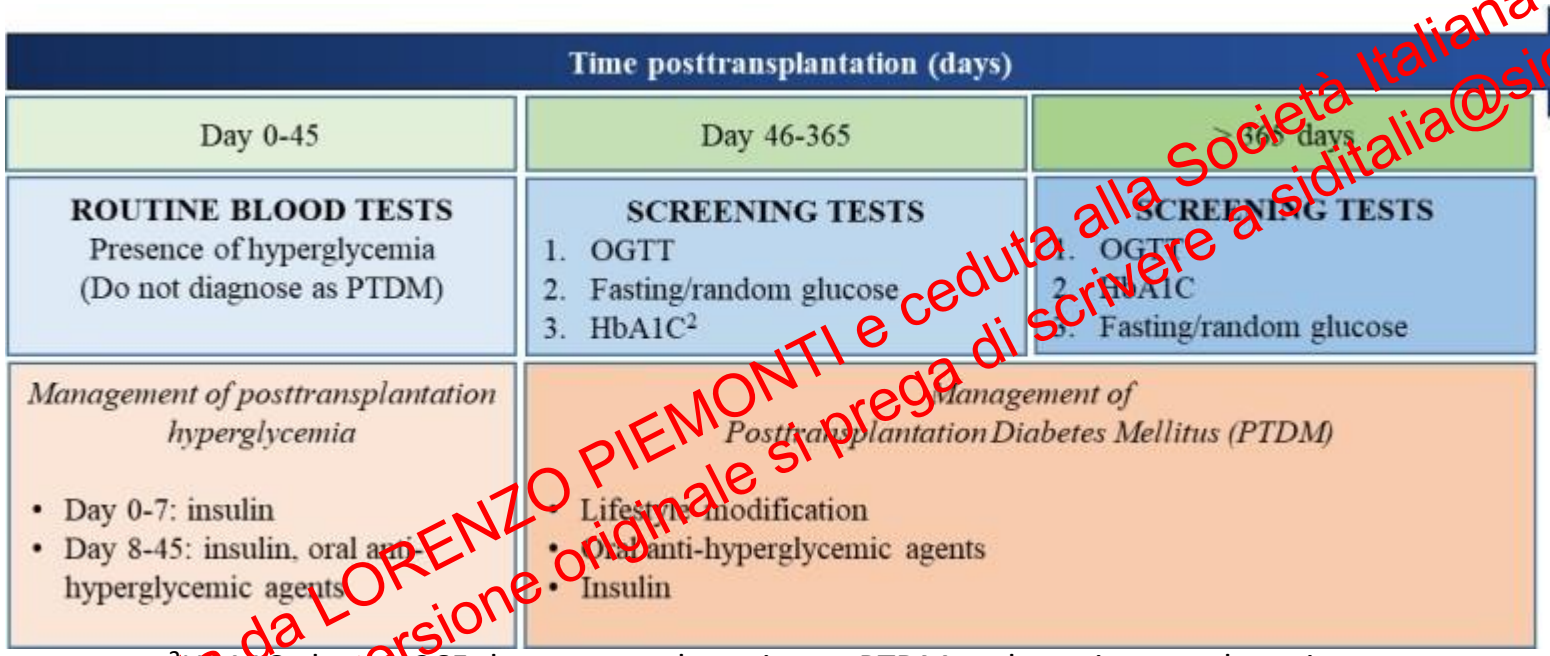
2003

New-onset diabetes after transplant (NODAT); consensus on definition and diagnosis

From New-Onset Diabetes After Transplantation (NODAT) Back to Posttransplantation Diabetes Mellitus (PTDM)

2014

PTDM: definition and diagnosis



[2] HbA1C alone < 365 days may underestimate PTDM and require corroborating.

TEST[1]	PREDIABETES	DIABETES	COMMENTS
Random glucose *plus* classic hyperglycemia symptoms or crisis		≥ 200 mg/dL ≥ 11.1 mmol/L	Random glucose: Any time of the day without regard to time since last meal Symptoms: Polyuria, polydipsia, unexplained weight loss
Fasting plasma glucose	Impaired fasting glucose ≥ 100 < 126 mg/dL ≥ 5.6 < 7.0 mmol/L	≥ 126 mg/dL ≥ 7.0 mmol/L	No caloric intake for at least 8 hours
2-hour plasma glucose (during an oral glucose tolerance test)	Impaired glucose tolerance ≥ 140 < 200 mg/dL ≥ 7.8 < 11.1 mmol/ L	≥ 200 mg/dL ≥ 11.1 mmol/L	Using glucose load of 75 g anhydrous glucose dissolved in water
HbA1C	Increased diabetes risk HbA1C 5.7-6.4%	≥ 6.5%	HbA1C should be measured in a NGSP-certified laboratory. The purpose of the NGSP is to standardize HbA1c test results to those of the Diabetes Control and Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS) which established the direct relationships between HbA1c levels and outcome risks in patients with diabetes.

Sharif A et al Am J Transplant. 2014;14:1992–2000.

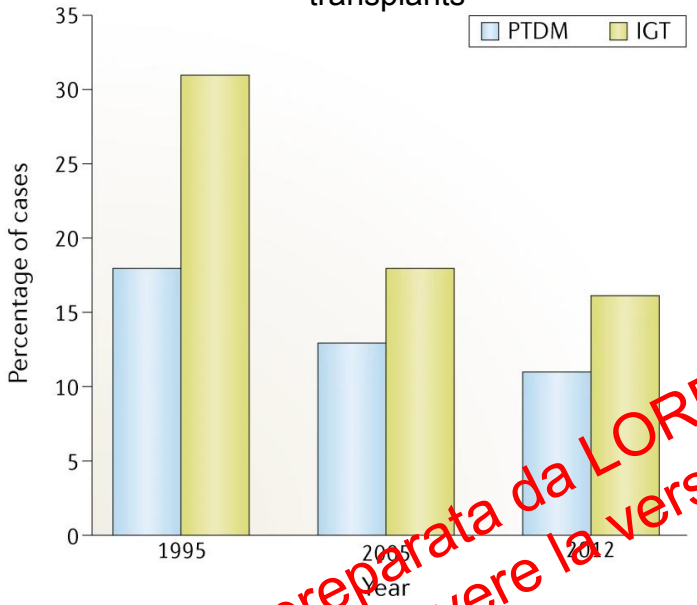
PTDM: epidemiology

Organ	Average accumulated incidence (%)	Evidence for association to mortality	Diagnosis at risk of PTDM	Refs
Kidney	~10–20%	extensive evidence	Autosomal dominant polycystic kidney disease	- Eide IA et al. Transpl. Int. 29, 568–578 (2016). - Valderhaug, TG et al. *Diabetologia* 54, 1341–1349 (2011) - Cosio FG et al. *Kidney Int.* 67, 2415–2421 (2005).
Liver	~30–40%	some evidence	Nonalcoholic steatohepatitis, HCV infection with cirrhosis Non asian	- Roccaro GA et al. Am. J. Transplant. 18, 207–215 (2018)
Heart	~20–30%	some evidence hazard ratio from 1.15 to 1.62	None	- Kim HJ et al. *Circ. J.* 81, 806–814 (2017)
Lung	~20–40%	some evidence hazard ratio from 1.2 and 1.5	Cystic fibrosis	- Hackman KL et al. *Transplantation* 101, 2200–2206 (2017). - Hackman KL et al. *Am. J. Transplant.* 14, 438–445 (2014).

Adapeted from Sharif A et al Am J Transplant. 2014;14:1992–2000.

PTDM: epidemiology

The incidence of early PTDM and impaired glucose tolerance over the past 20 years in a national cohort of recipients of kidney transplants

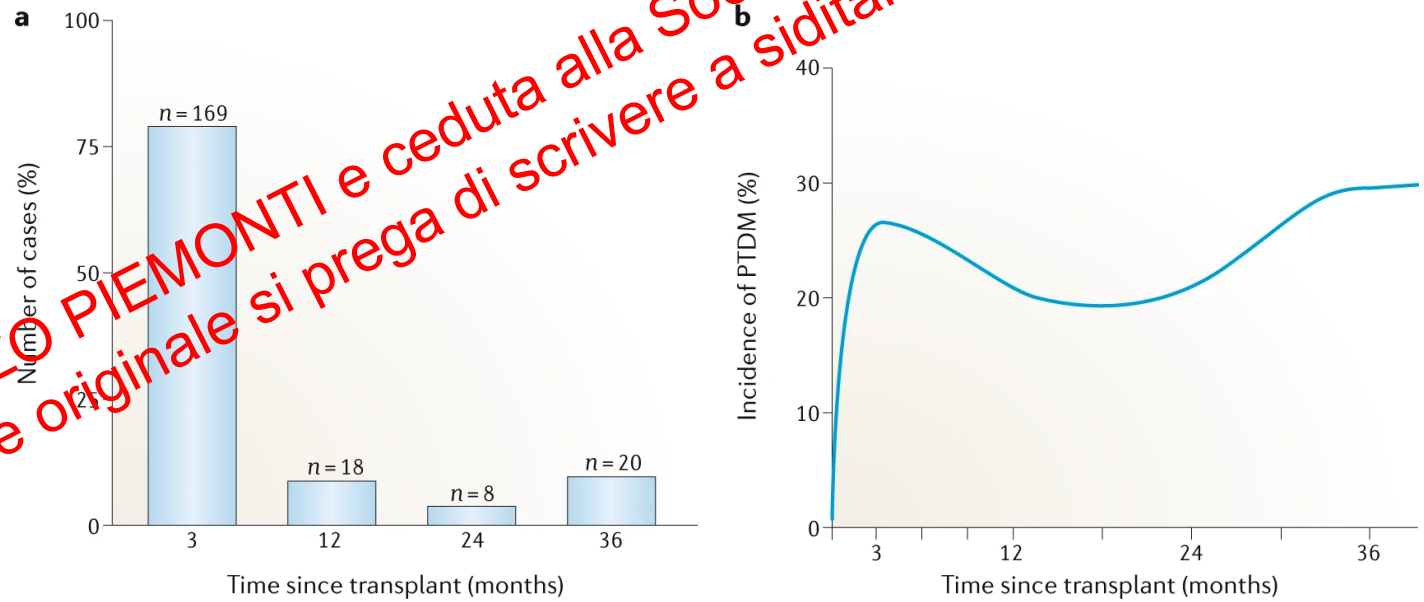


Hjelmesaeth J et al. Transplantation 64, 976–983 (1997)
Valderhaug TG et al. Transplantation 84, 1125–1130 (2007).
von Düring ME et al. Transpl. Int. 28, 1162–1171 (2015).

white people
WHO-based OGTT criteria
8–10 weeks after Tx

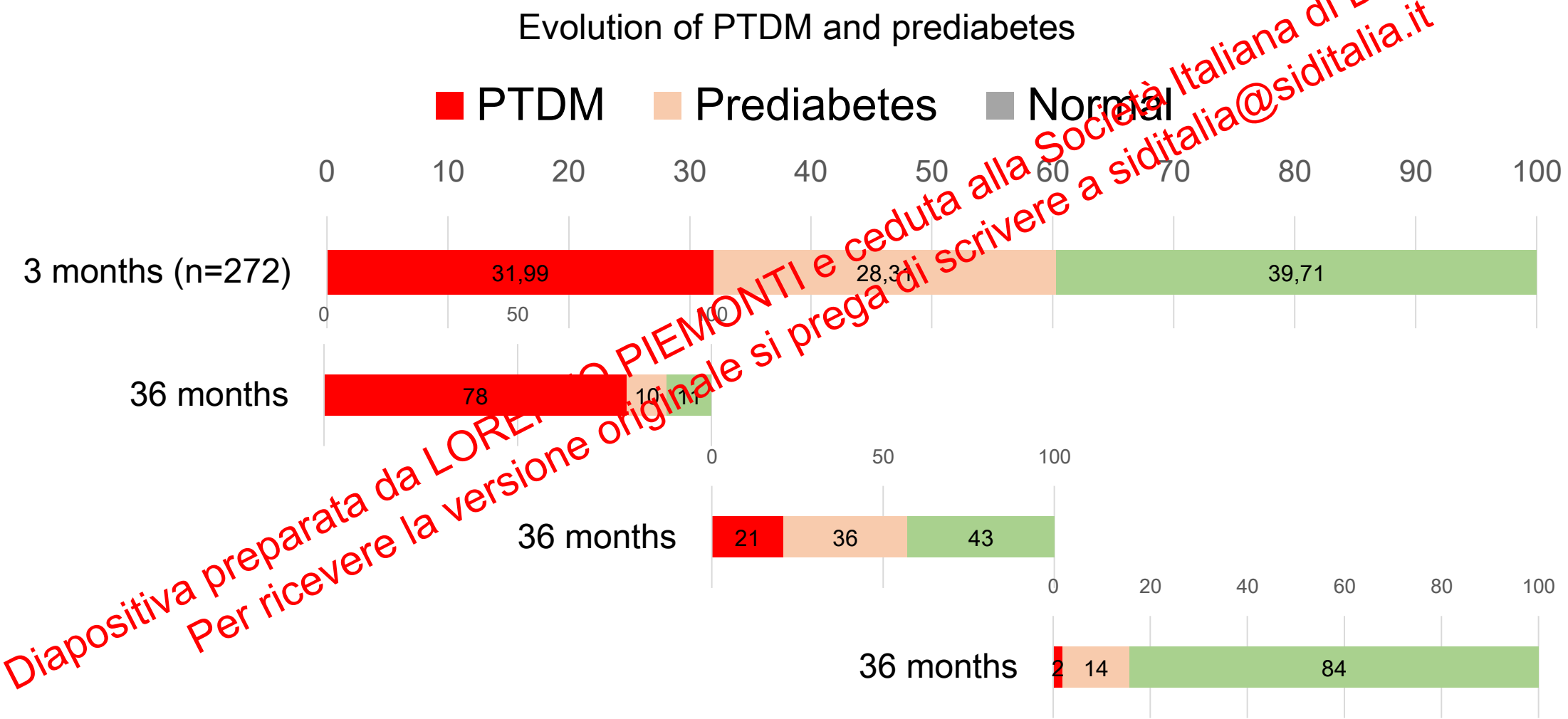
New cases of PTDM at different time points

Accumulated incidence of PTDM over time



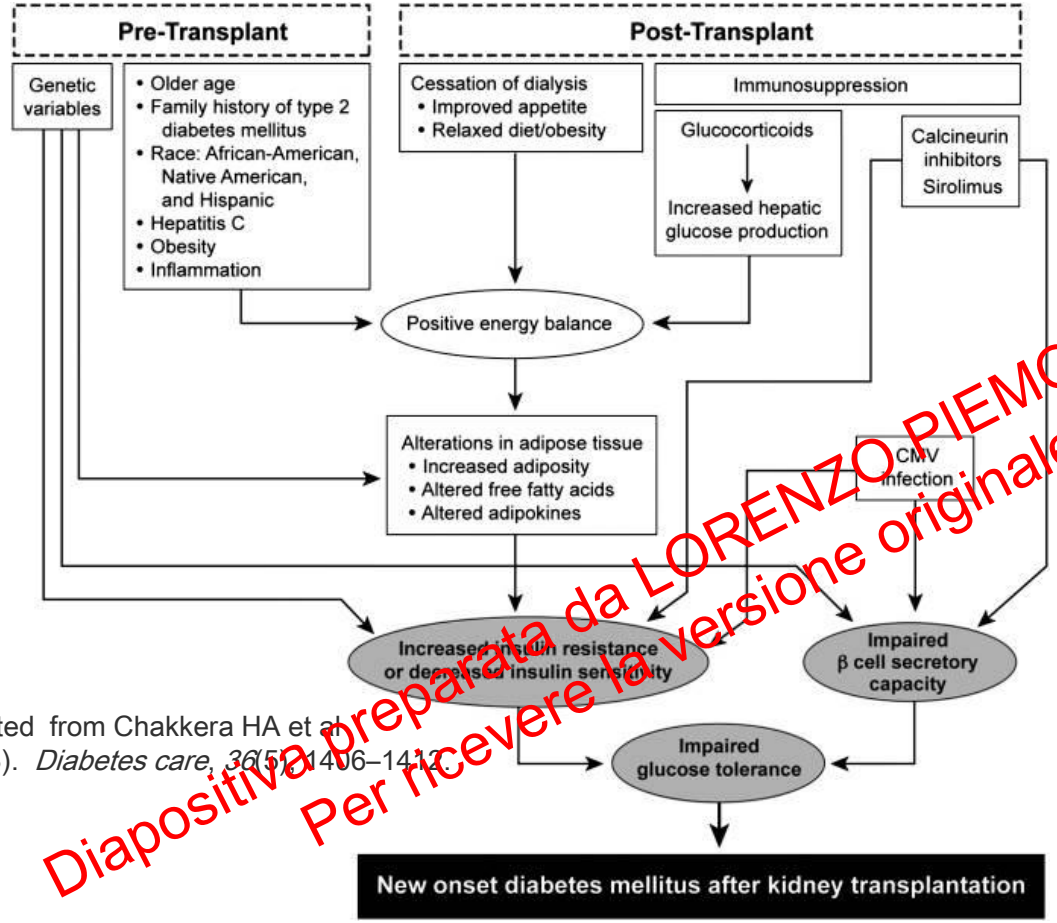
Adapted from Porrini, E. L. et al *Nephrol. Dial. Transplant.* **31**, 495–505 (2016).

PTDM: epidemiology

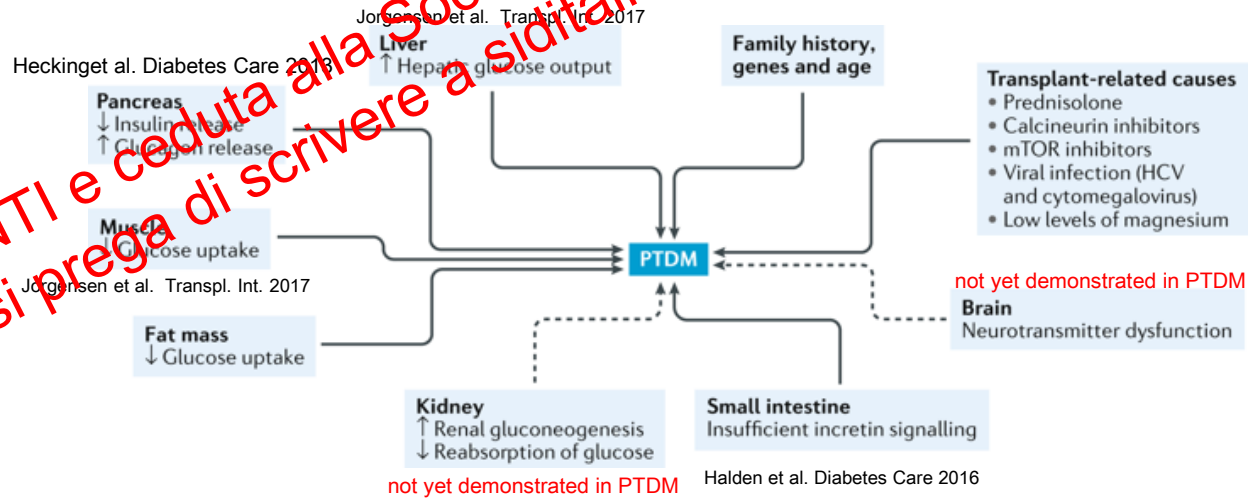


Adapted from Porrini, E. L. et al *Nephrol. Dial. Transplant.* **31**, 495–505 (2016)

PTDM: pathogenesis



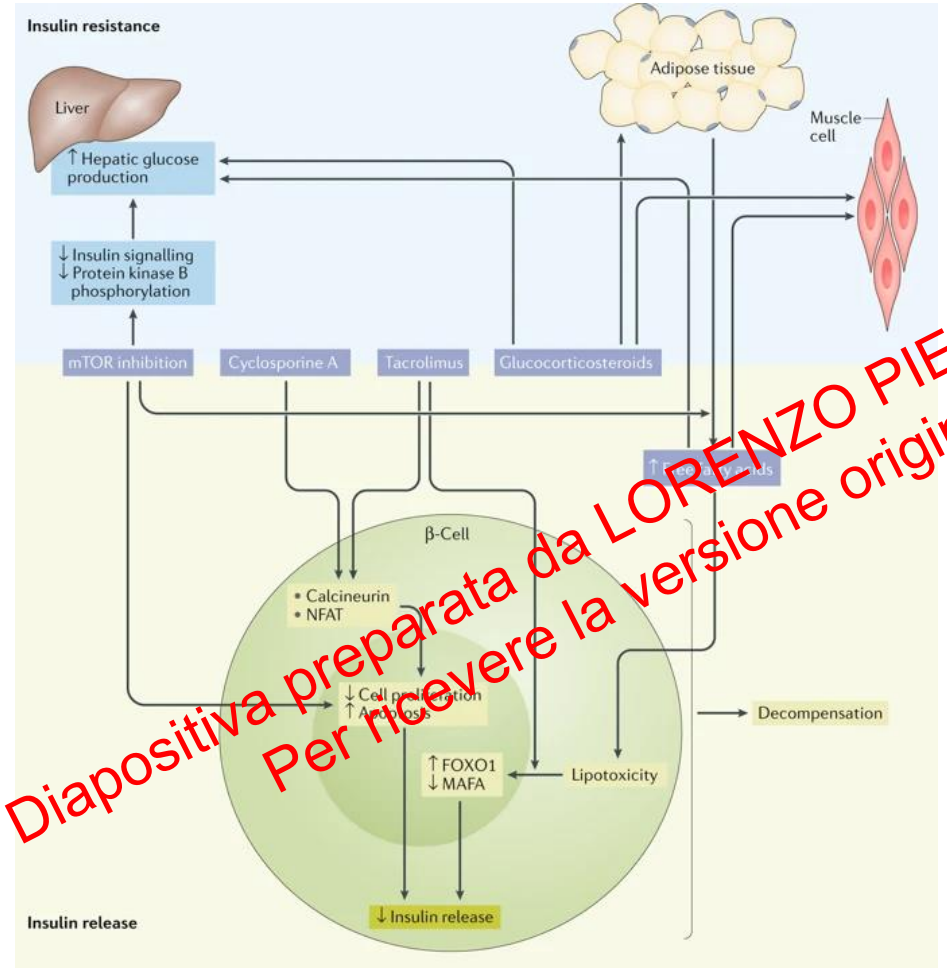
Adapted from Chakkera HA et al. (2013). *Diabetes care*, *36*(5), 1406–1412.

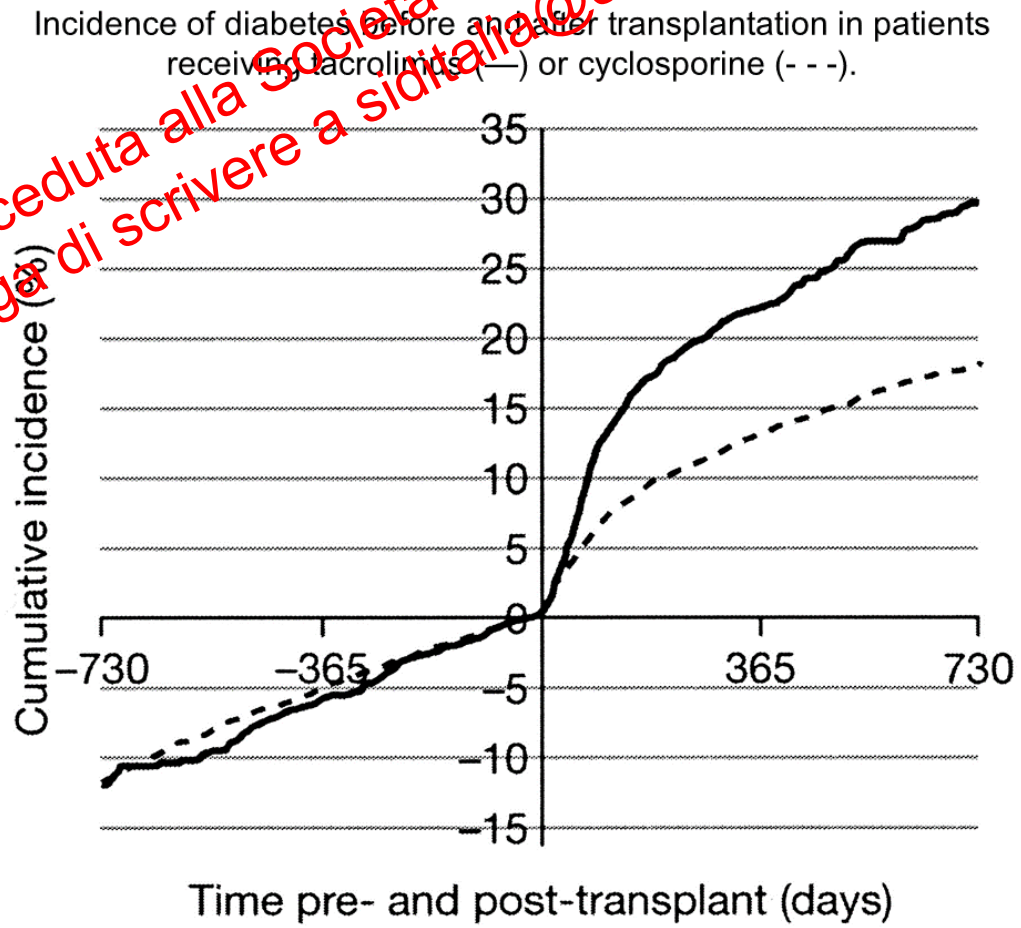


Adapted from Porrini, E. L. et al *Nephrol. Dial. Transplant.* **31**, 495–505 (2016)

PTDM: pathogenesis

Effects of immunosuppressive agents on β-cells and insulin-sensitive tissues that promote PTDM





Jaime A Davidson, and Alan Wilkinson Dia Care 2004;27:805-812

PTDM: risk factors

Non-modifiable	Potentially modifiable	Modifiable[4]	End-organ specific diagnosis
African American, Hispanic Age > 45 years Male recipient Family history of diabetes mellitus Human Leukocyte Antigen (HLA) mismatches HLA A30, B27, B42 Acute rejection history Deceased donor Male donor Genetic polymorphism (e.g. TCF7L2 rs7903146, PPAR-α rs4253728)	Hepatitis C virus[1] Cytomegalovirus[2] Pretransplant IGT/IFG Proteinuria Hypomagnesemia[3]	Obesity (body mass index > 30) LDL cholesterol Steroids, tacrolimus, cyclosporine, sirolimus Vitamin D deficiency	End stage kidney disease due to polycystic kidney disease End stage liver disease due to HCV infection or non-alcoholic steatohepatitis (NASH) End stage lung disease due to cystic fibrosis

Pham PT, Sidhu HS, Pham PM, et al . Endotext April 2019

PTDM: sequelae

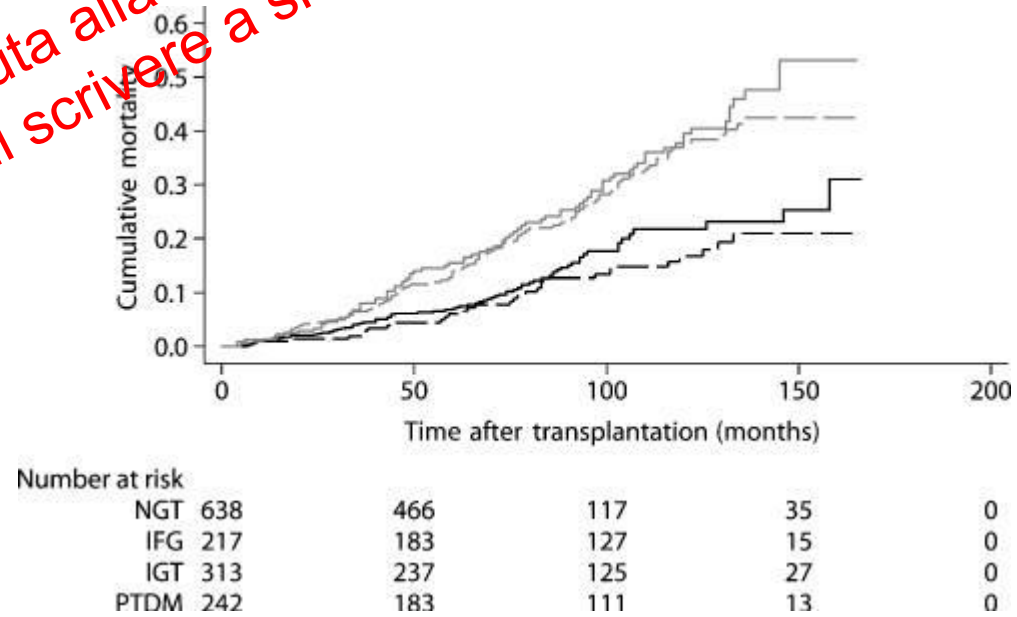
PTDM was associated with:

- mortality of patients
- graft loss
- increased risk for infection and sepsis
- urinary tract infection, pneumonia, and cytomegalovirus (CMV)
- diabetic complications:
  - Ketoacidosis
  - Hyperosmolarity
  - ophthalmic complications
  - neurologic complications
  - hypoglycemia/shock

PTDM: sequelae

The range of complications attributed to PTDM and their evidence base

Cumulative mortality for recipients with NGT (solid black line), IFG (dashed black line), IGT (dashed grey line) and PTDM (solid grey line).



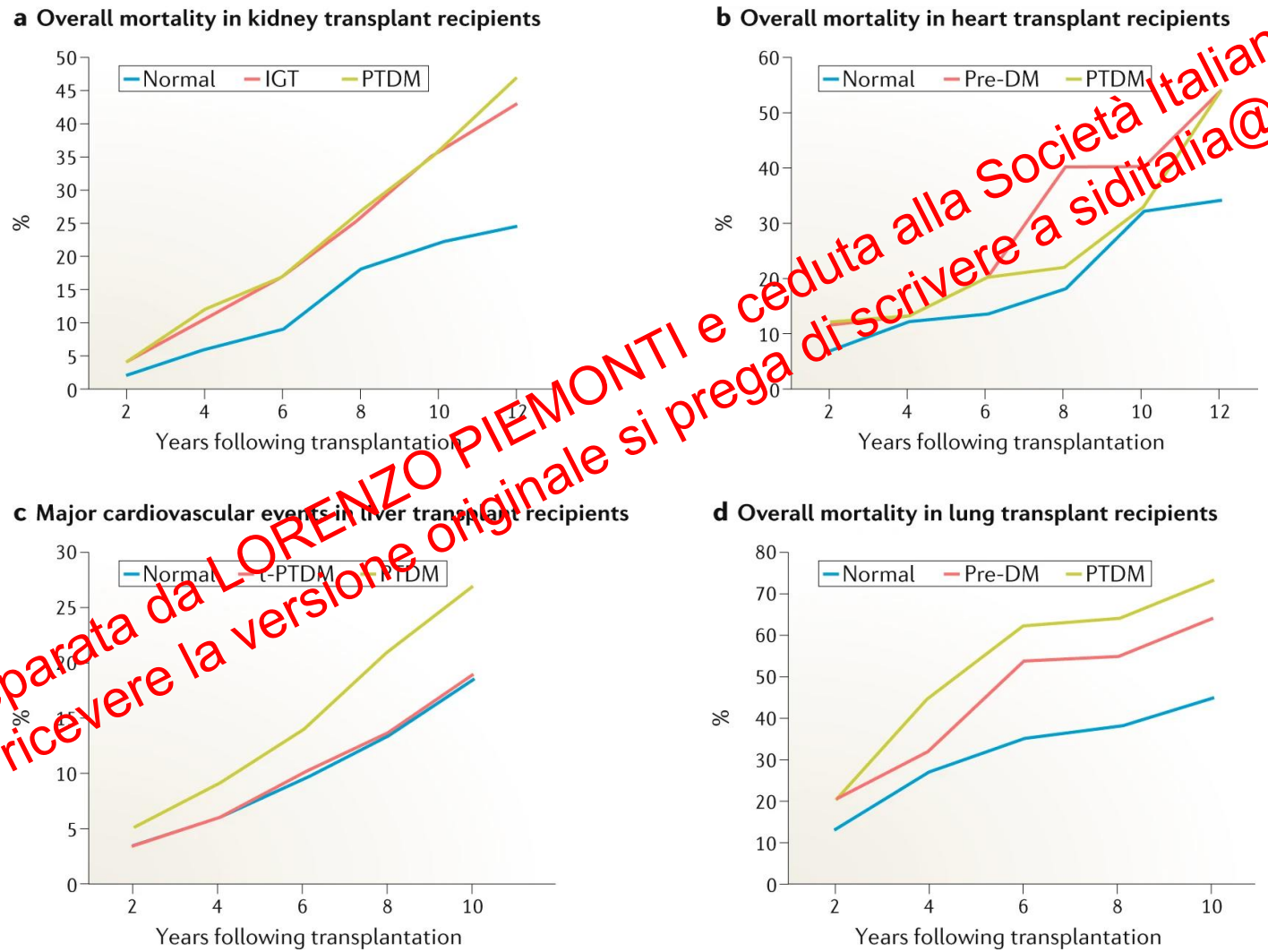
Valderhaug TG et al. Diabetologia (2011)

PTDM: mortality

Study	Study design and data source	Number of renal transplant recipients	Follow-up	Outcomes*		
				Nondiabetic	Pre-existing diabetes	PTDM
Revanuret al. (2001)	Retrospective, single-center	939	14 years	75%‡	39%‡ (insulin-dependent§)	49%‡
Cosio et al. (2002)	Single-center	1,811 (18% with pretransplantation diabetes, 20% with PTDM)	Mean 8.3 years	16%	31%	22%
Kasiskeet al. (2003)	USRDS registry	11,659	3 years	not reported	not reported	RR 1.87, 95% CI 1.60–2.18 (P <0.0001)
Kuo et al. (2010)	OPTN/UNOS database	37,448‖	Median 548 days	not reported	Associated with all-cause and cardiovascular mortality	No associations with all-cause or cardiovascular mortality

* Unless otherwise indicated, outcome data relate to the mortality rate.
‡ 10-year patient survival.
§ The numbers of patients who had pre-existing non-insulin-dependent diabetes mellitus before transplantation and those with coexisting diabetes (patients with end-stage renal disease of other cause but with concomitant diabetes), were too small to analyze.
‖ Individuals with a functioning graft 1 year after transplantation.

PTDM: mortality



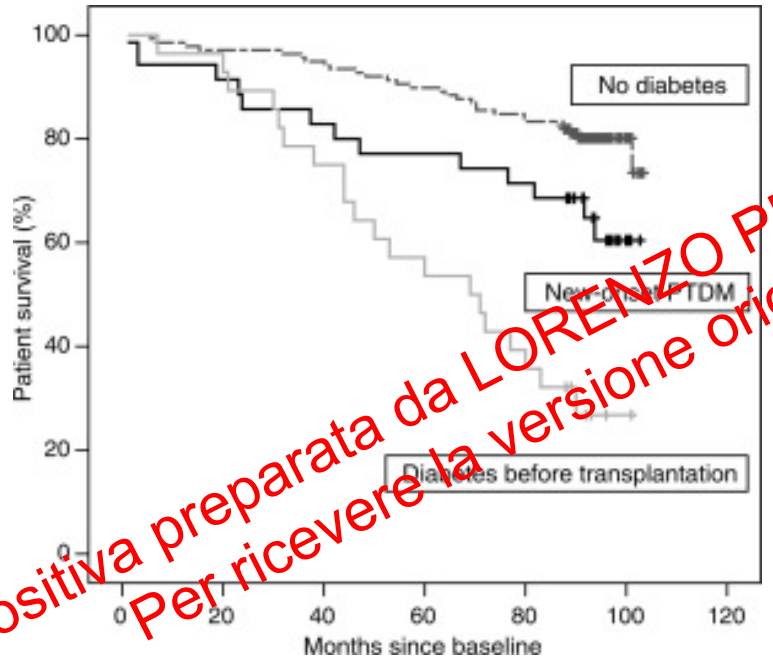
Trond J et al *Nature Reviews Endocrinology* **15**, 172–188 (2019)

Graft failure rates: PTDM and acute rejection

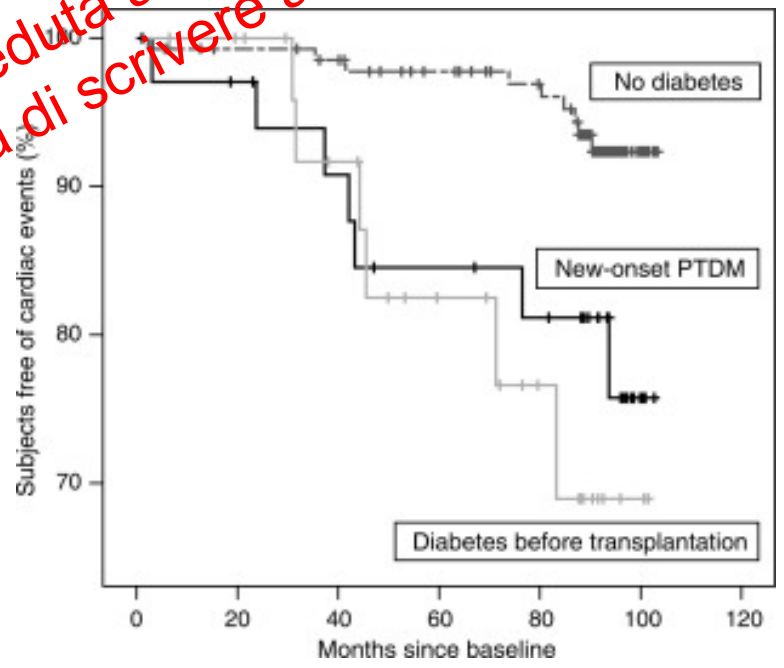
Study	Study design and data source	Number of renal transplant recipients	Outcomes		
			All-cause graft failure	Death-censored graft loss	Death with a functioning graft
Revanuret al. (2001)	Retrospective, single-center	939	Rates similar in nondiabetic transplant and PTDM	not reported	not reported
Kasiskeet al. (2003)	USRDS registry	11,659	PTDM: RR 1.63 P <0.0001	PTDM: RR 1.46 P <0.0001	not reported
Cole et al. (2008)	Retrospective, USRDS registry	27,707 first kidney-only Tx recipients with a graft survival of ≥1 year	Acute rejection: OR 1.43 PTDM: OR 1.24	Acute rejection: OR 1.60 PTDM: OR 1.12	Acute rejection: OR 1.15 PTDM: OR 1.41
Matas et al. (2008)	Retrospective, single-center	1,487 adult renal Tx recipients w/o diabetes at transplantation	Acute rejection more impact than PTDM on 15-year graft survival. Both were independent risk factors	Acute rejection had a greater impact than PTDM on 15-year death-censored graft survival	not reported
Kuo et al. (2010)	OPTN/UNOS database	37,448 patients with a functioning Txfor more than 1 year	Not associated with PTDM	Associated with acute rejection, but not with PTDM	Not associated with PTDM

PTDM: mortality and cardiovascular disease

Kaplan–Meier estimates of patient survival in the three different groups of renal transplant recipients



Kaplan–Meier estimates of renal transplant recipients free of cardiac events in the three different groups.



Hjelmesaeth J et al. Kidney Int. 2006 Feb;69(3):588-95

Study	Study design and data source	Number of renal graft recipients	Follow-up	Results	
				Risk factors for CVD	CVD events
Kasiske et al. (1996)	Single-center	706	Mean 7 yrs	Pretransplantation diabetes, but not PTDM PTDM associated with development of ischemic heart disease, but not independent of other variables: RR 2.22	not reported
Cosio et al. (2005)	Single-center	351 patients w/o diabetes. 1 m post-Tx: 255 euglycemic 44 persistentPTDM 31 resolution of transient PTDM	Mean 40 ± 14M	FG 5.0–5.5 mmol/l: HR 1.0 (reference group) FG 6.1–6.9 mmol/l: HR 2.4 PTDM group with FG >6.9 mmol/l: HR 2.9 Persistent PTDM at 1 month: HR 1.7	Incidence of CVD events significantly higher in patients with IFG or persistent PTDM (23% for both combined), compared with those who were euglycemic (11%) or had resolved PTDM (10%)
de Mattos et al. (2006)	Single-center cohort study	922	5 yrs	Prior CVD event: HR 4.59, Diabetes mellitus*: HR 3.94 Tobacco use: HR 2.89 Obesity at transplantation: HR 2.67, Multiple rejection episodes: HR 2.05, Pretransplantation dialysis >1 year: HR 1.79	176 patients (19%) experienced 201 cardiovascular events (4.42 events per 100 patient years) 29% of deaths attributed to CVD
Hjelmesaeth et al. (2006)	Single-center observational study	138 w/o diabetes 35 PTDM 28 pre-existing diabetes	8 yrs	PTDM associated with increased risk of a major cardiovascular event: HR 3.27, but no significant change in all-cause mortality Pretransplantation diabetes not associated with increased risk of a major cardiovascular event, but strongly associated with all-cause mortality: HR 5.09	8-year cumulative incidence of cardiac death or nonfatal acute myocardial infarction: 7%: No diabetes 20%: PTDM 21%: pre-existing diabetes
Israni et al. (2010)	Multicenter, retrospective analysis of pooled data	23,575	Median 4.5 yrs	Cox proportional hazard analysis for coronary heart disease within 3 years: pretransplantation diabetes, adjusted HR 2.41; PTDM, adjusted HR 1.86	not reported

PTDM: Management

- Pre transplant risk assessment
- Correction of modifiable risk factor
- Regular posttransplantation monitoring of all patients
- Early treatment of post transplantation hyperglycaemia
- Immunosuppression according to risk
- Therapy of diabetes mellitus
- Management of other cardiovascular risk factors such as hypertension and dyslipidemia

PTDM: Pre transplant risk assessment

- Gold standard: OGTT before putting patients on the waiting list for renal transplantation
- Mandatory screening for:
  - risk factors for PTDM
  - fasting plasma glucose (performing an OGTT in KTx candidates with a FPG of 92–125 mg/dL should be considered)
  - other evidence of the metabolic syndrome
  - other cardiovascular risk factors
- Pre-transplantation risk scores for PTD were proposed, but no data are available on their use
- HbA1c testing could be a useful and convenient pre-transplantation screening tool to identify patients at increased risk for PTDM.
- Patients with evidence of risk factors should be counseled of their risk for PTDM.
- Patients with evidence of prediabetes should be counseled of lifestyle modifications including dietary modifications, thirty minutes of moderate intensity physical activity, and overall five to ten percent weight reduction

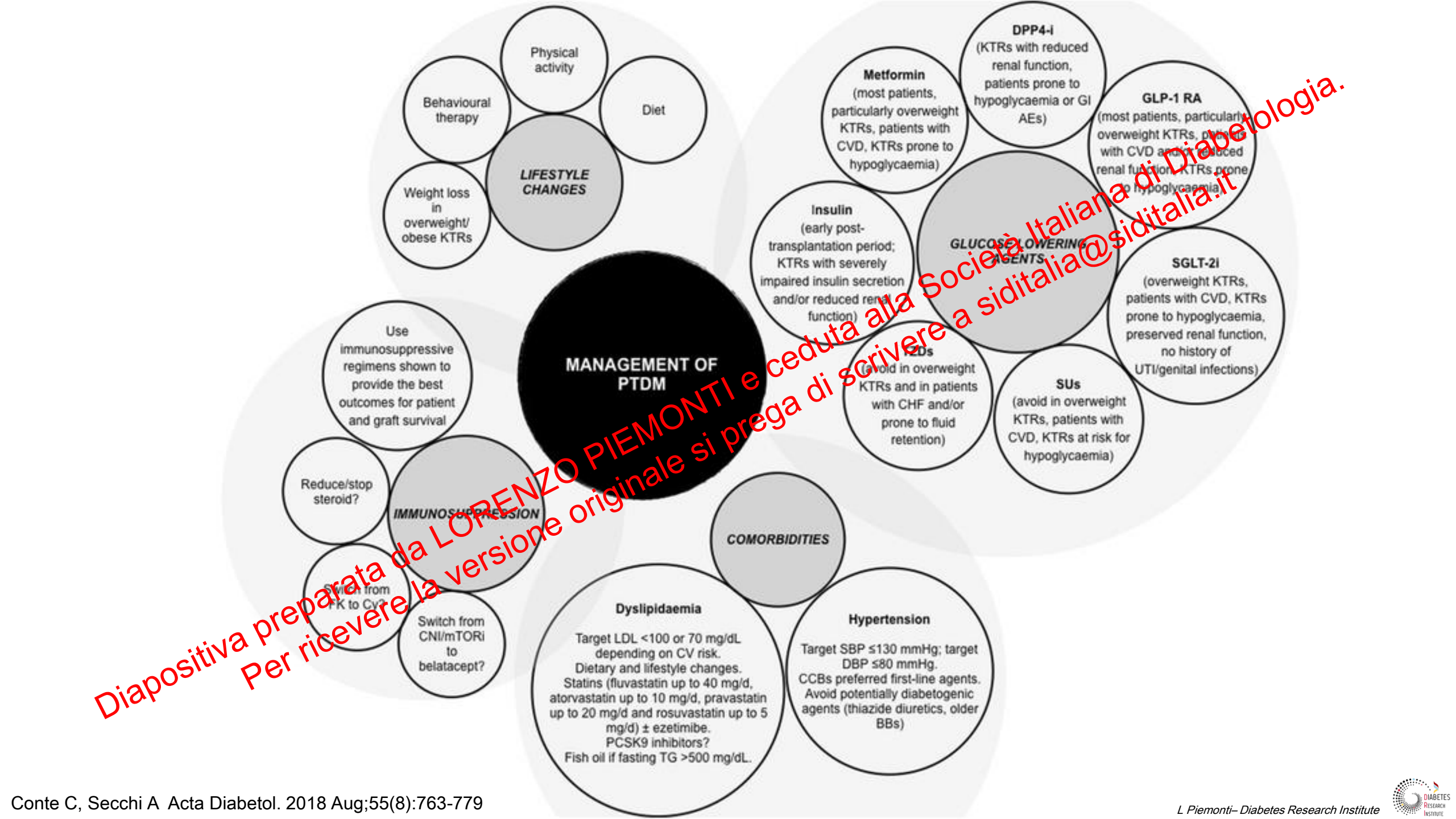
PTDM: regular postTx monitoring of all patients

Evidence-based screening guidelines for the early detection of PTDM are lacking

	Month 1	Month 3	Month 6	Month 12	Yearly
FBG	weekly	yes	yes	yes	yes
HbA1c	-	yes	yes	yes	yes
OGTT	-	In case of prediabetes, or high risk			
SMBG	perioperative hyperglycemia, particularly for those with blood sugars ≥200 or those requiring insulin administration	If HbA1c >6%			

A suggested algorithm for glucose lowering in PTDM

First month	Second month	Long term
Treatment iniziation: If FPG consistently ≥ 126 mg/dl or more than half of random glucose recordings are ≥180 mg/dl	**Treatment iniziation:** If FPG consistently ≥ 126 mg/dl or more than half of random glucose recordings are ≥180 mg/dl	**Treatment iniziation:** standard glucose criteria
Treatment: • Dietary advice and promote physical activity when possible • Insulin	**Treatment:** • Dietary advice and promote physical activity when possible • Considering tapering the dose of prednisolone to 5 mg/daily • Prescribe low dose FK506 if considered safe or switch to CyA • Insulin (consider withdrawal if appropriate, ie insulin dose <20 units per day) • Consider oral Agent	**Treatment:** • Dietary advice and promote physical activity • Considering tapering the dose of prednisolone to 5 mg/daily • Prescribe low dose FK506 if considered safe or switch to CyA • Oral agents • Insulin if needed
Treatment goal: Inpatient: target glucose range of 140-180 mg/dl Outpatient: FPG <126 mg/dl (80-130 mg/dl) Postprandial glucose < 180 mg/dl	**Treatment goal:** FPG <126 mg/dl ((80-130 mg/dl) Postprandial glucose < 180 mg/dl	**Treatment goal:** HbA1c <7-7.5%; avoiding targeting HBA1c ≤ 6



Conte C, Secchi A Acta Diabetol. 2018 Aug;55(8):763-779

	Disadvantages	Advantages	Evidence in PTDM	Potential drug–drug interaction
Metformin	Contraindicated if eGFR <30 GI side effects Possible vitamin B12 deficiency Caution if eGFR 30–59	No hyopglycaemia, No weight gain, Reduction in microvascular and macrovascular endpoints, Low cost	Neutral effect on patient or graft survival Efficacy in PTDM not demonstrated	None known
Sulfonylurea glinides	Hypoglycaemia, weight gain, increased CV risk Dose adjustment in renal impairment	Rapid onset of action, Low cost	SU not effective Gliquidone and repaglinide safe	Glibenclamide—cyclosporine (↑ glibenclamide) Repaglinide—cyclosporine (↑ repaglinide)
Thiazolidinediones				None known (pioglitazone)
DPP4-i				Sitagliptin-cyclosporine (↑ Cy trough levels) Vildagliptin—tacrolimus (↓ FK trough levels)
Insulin				None known
GLP-1 RA	not recommended in ESRD (liraglutide)	(liraglutide, albiglutide) nor ESRD (semaglutide)		None known
SGLT2-i	Not effective in renal impairment (eGFR<45 for empagliflozin, canagliflozin and <60 for dapagliflozin); polyuria, increased risk for UTIs, genital infections (all); increased risk for amputations and fractures (canagliflozin)	Reduction in MACE (empagliflozin, canagliflozin) and CV mortality (empagliflozin)	N/A	Canagliflozin—cyclosporine (↑ canagliflozin)

If insulin can be withdrawn, a DPP4 inhibitor with a proven safety profile is initiated (for example, sitagliptin). Metformin can be used as a supplement if glomerular filtration rate (GFR) is ≥ 30 ml/min/1.73 m^2. Use of SGLT2 inhibitors or GLP1 receptor agonists is pending until safety studies are available.

Adapted from Conte C, Secchi A Acta Diabetol. 2018 Aug;55(8):763-779

Controversies and area of uncertainty

Priority 1: mechanistic studies to understand post-transplant diabetes pathophysiology

- The relation between β-cell dysfunction and insulin resistance in the development of post-transplant diabetes needs to be understood
- The relative importance of β-cell dysfunction and insulin resistance remains unclear (and might differ in early *vs* late post-transplant diabetes), although both are probably necessary for post-transplant diabetes to occur
- Understanding of the underlying pathophysiology is of interest because:
  - it will enable the similarity or difference of post-transplant diabetes with type 1 or type 2 diabetes to be discerned
  - it will provide some rationale for choosing insulin secretagogues versus insulin sensitisers as therapy
  - it might highlight the measures that might be effective for prevention and risk stratification of post-transplant diabetes

Controversies and area of uncertainty

Priority 2: Observational studies of glycaemic metabolism after transplantation and identifycation of optimum diagnostic criteria to link to adverse clinical outcomes

We do not have data for the following:

- optimum test (and when)
- frequency of testing
- risk stratification
- link to outcomes
- usefulness of HbA1c for monitoring and intervention (ie, is HbA1c reduction in post-transplant diabetes associated with improved long-term outcomes?)

Controversies and area of uncertainty

Priority 3: clinical trials for prevention and management of post-transplant diabetes

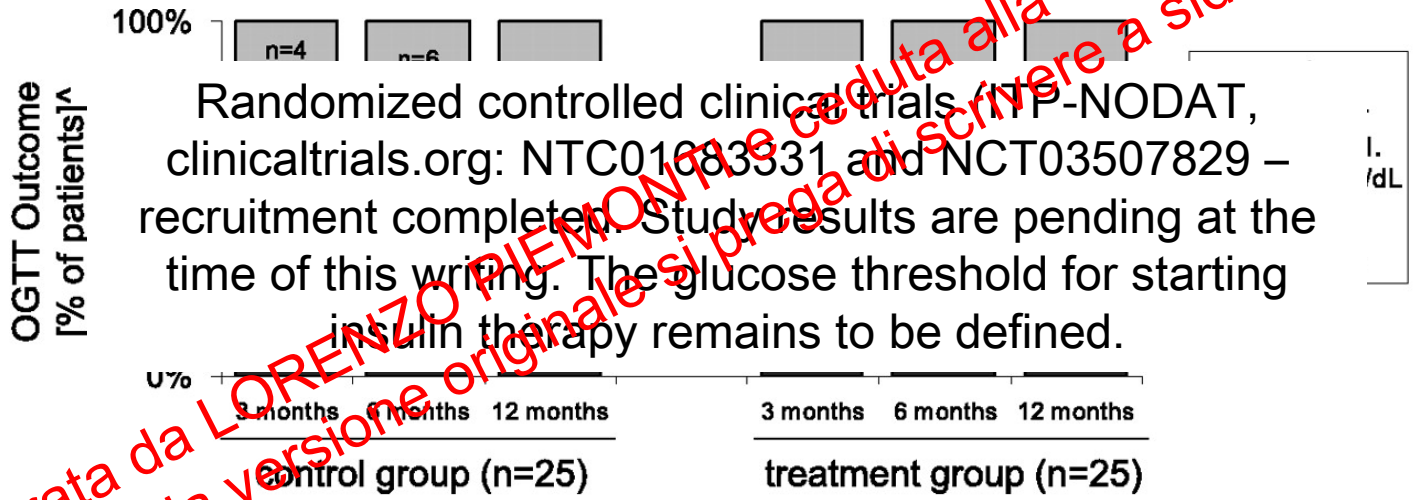
- Little data exist for whether lifestyle modification (in the mileu of immunosuppression) has any benefit on attenuation of adverse cardiometabolic risk
- Despite emerging data for use of glucose-lowering therapy and reduction of HbA1c, no data are available to suggest that any therapy reduces any long-term adverse outcomes (or even surrogate cardiovascular endpoints)
- Head-to-head trials of glucose-lowering therapy (and many other cardio-metabolic interventions) and assessment of safety and efficacy in the context of solid organ transplantation for adverse cardiovascular events have not been done
- The effect of post-transplant diabetes in the contemporary era of immunosuppression and competing risks of infection, cancer, and allograft attrition needs to be clarified
- More information is needed about microvascular complications and the health economics of post-transplant diabetes
- No data exist for the effect of post-transplant diabetes on patient-reported outcome measures such as quality of life, situational motivation scores, and health-related questionaires

Study description	Number of patients	Status	Date last updated	Registration number
Effects of insulin or oral anti-diabetes mellitus drugs				
Early insulin therapy to prevent new-onset diabetes	251	Completed	March 2018	NCT01683331
	276	Completed recruitment	May 2018	NCT03507829
Sitagliptin to prevent new-onset diabetes in kidney patients	50	Recruiting	May 2018	NCT01928199
Sensor-augmented insulin-pump therapy in new-onset diabetes	85	Completed	June 2018	NCT01680185
Empagliflozin in renal transplant recipients (EMPA-RenalTx)	50	All recruited	June 2018	NCT03157414
Empagliflozin in PTDM	16	Recruiting	April 2018	NCT03113110
Studies focusing on the effects of glucocorticosteroids				
Different steroid withdrawal groups and new-onset diabetes	152	Recruiting	March 2014	NCT02095418
Budesonide for liver transplant immune suppression	40	Recruiting	October 2018	NCT03304626
Steroid avoidance and low-dose CNI and ATG-induction (SAILOR)	200	Recruiting	November 2016	NCT02083991
Steroid free immunosuppression and CNI minimization and PTDM	300	Recruiting hold	January 2015	NCT01560572
Studies focusing on other immunosuppression				
Pilot study comparing low-target and conventional target Advagraf	30	Recruiting	June 2016	NCT01265537
DSA formation, diabetes and more, everolimus regimen (ADVISE)	90	All recruited	October 2018	NCT02316938
Everolimus and low-dose tacrolimus in renal recipients (PROTECT)	234	Unknown	September 2014	NCT02036554
TRODAT in kidney transplant patients receiving belatacept	32	Unknown	2013	NCT01875224
Studies with vitamin D and magnesium supplementation				
Vitamin D supplementation in renal transplant recipients (VITALE)	320	All recruited	December 2017	NCT01431430
Magnesium supplement and insulin in renal transplant recipients	70	All recruited	January 2017	NCT01291030
Lifestyle intervention				
Active versus passive lifestyle on glycaemic benefits in renal transplant recipients (CAVIAR)	130	Recruiting	October 2017	NCT02233491

Controversies and area of uncertainty: early treatment of post transplantation hyperglycaemia

Hecking *et al.* demonstrated that early basal insulin therapy following detection of early posttransplantation hyperglycemia (defined as < 3 weeks) reduced the subsequent odds of developing PTDM within the first year after transplantation by 73%

- Conventional antihyperglycemic treatment in the control group: treatment was not encouraged at nonfasting blood glucose levels <180 mg/dl.
- Severe hyperglycemia (blood glucose levels ≥250 mg/dl) had to be at least intermittently corrected with short-acting insulin.
- The sulfonylurea gliclazide (Diamicron)was suggested as the pharmacologic oral agent of choice



Randomized controlled clinical trials (INP-NODAT, clinicaltrials.org: NTC01683331 and NCT03507829 – recruitment completed. Study results are pending at the time of this writing. The glucose threshold for starting insulin therapy remains to be defined.

Odds Ratios [95% CI]

	Diabetic versus Non-diabetic	Diabetic + Prediabetic versus Normal
3 months	0.36 [0.11-1.16]	0.29 [0.08-1.09]
6 months	**0.13 [0.03-0.53]**	0.56 [0.16-1.92]
12 months	**0.27 [0.08-0.95]**	0.51 [0.16-1.61]
Overall^^	**0.27 [0.10-0.72]**	0.43 [0.16-1.14]

- Basal insulin treatment was initiated with a morning dose of 6, 8, or 10 IU of isophane insulin if the blood glucose on the previous evening was >140, 180, or 240 mg/dl, respectively.
- The normoglycemic goal was 110–120 mg/dl.
- Rapid downward titration of the isophane insulin dose was prespecified

Hecking *et al.* JASN April 2012, 23 (4) 739-749

Thank you