Can the analysis of gene polymorphisms improve prediction models of new onset diabetes after kidney transplant? The pivotal role of TCF7L2 rs7903146

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BACKGROUND

Post-Transplant Diabetes Mellitus (PTDM) is a serious complication which develops in 10-30% of kidney transplant (KTx) recipients and exerts a heavy impact on patient and graft survival.

GWASs in the general population identified more than 40 risk loci for type 2 diabetes (T2DM) : most exert a small effect (OR < 1.20), but the most common susceptible variant for T2DM is the rs7903146 of transcription factor 7-like 2 (TCF7L2) gene.

The TCF7L2 protein regulates cell proliferation and differentiation through Wnt signaling pathway, which controls pancreas development and islet function. T allele has been associated with impaired insulin secretion, incretin effects and hepatic insulin resistance.

Some studies on KTx recipients confirmed this association, while other investigations - including a GWAS- did not, making results inconclusive. Therefore, although association of this TCF7L2 polymorphism with PTDM remains highly plausible from a biological point of view, its clinical role remains to unclear.

On this basis, we analyzed the association of TCF7L2 rs7903146 C>T with PTDM in KTx recipients (KTR) and built a predictive model of PTDM including this polymorphism and clinical parameters.

METHODS

Included patients

We proposed this study to all patients without diabetes at KTx transplanted in a our Center at the time of KTx since 2009 or at a follow up visit if they were transplanted earlier.

Data collection

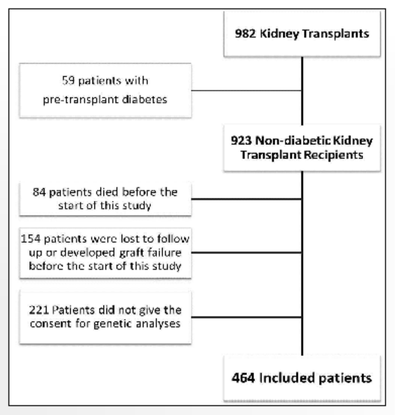
Diabetes was defined according to the 2013 ADA Guidelines before KTx and after KTx.

A diagnosis of PTDM was made only once the transplant was stable and first evidence of hyperglycemia was employed as "event date".

Statistical analysis

Event-free survival analysis was performed with an actuarial Kaplan-Meyer method (event=PTDM; censored=graft failure, death or last visit).

Risk factors were analyzed with a multivariate Cox model (forward stepwise inclusion).



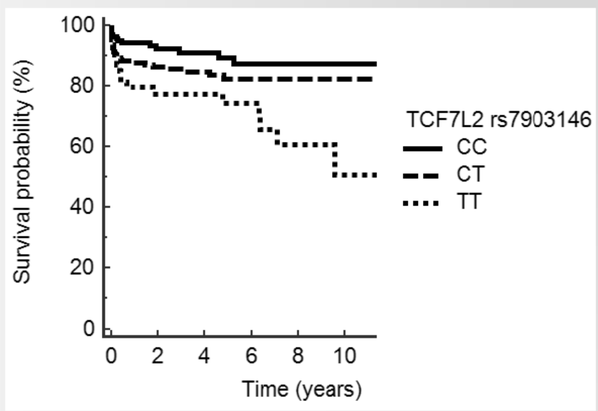
Score development

Only variables with statistically significant hazard ratios were considered. The regression were converted into an integer risk score. To evaluate the predictive accuracy, a ROC curve for each model was derived and the area under the ROC curve (AUROCs) was calculated.

RESULTS

The genotype frequency distribution of TCF7L2 rs7903146 was in accordance with Hardy-Weinberg equilibrium (p=0.13).

As for TCF7L2 rs7903146 genotype, the 1-year and 2-year-risks were respectively 5.82% and 7.83% in CC patients, 11.92% and 13.3% in CT patients and 20.47% and 22.74% in TT patients (p for trend <0.001).



However, *restricting the analysis to 20/66 (30.3%) patients who were first treated for PTDM within 14 days of surgery, TCF7L2 rs7903146 genotype was not a significant risk factor,* as 5/163 (3.1%) patients with a CC genotype, 12/237 (5.1%) with a CT genotype and 3/64 (4.7%) with a TT genotype developed this "early-onset" PTDM (p=0.619).

Sixty-six patients (14.2%) developed PTDM, after a mean time of 16.2±30.4 months from surgery.

TCF7L2	N	2-wk risk (ns)	2-yr risk (p<0,001)
CC	163	3.1%	7.8%
CT	237	5.1%	13.3%
TT	64	4.7%	22.7%

Risk Factor (reference)	HR	95% CI	p
Age (per year)	1.027	1.0037-1.0518	0.024
BMI (≥25 vs. < 25)	2.916	1.735-4.900	<0.001
TCF7L2 (per each T allele)	1.926	1.343-2.762	0.0004
Previous KTx (vs. first KTx)	2.635	1.316-5.279	0.006

Multivariate analysis of risk factors for PTDM

Among analyzed risk factors, only age, sex, TCF7L2 rs7903146 polymorphism, BMI, previous transplants and CIT significantly affected the multivariate risk model (Table 2). Moreover rs7903146 was evaluated as an effect modifier of the other risk factors, and it is not an effect modifier of any other variable. The TCF7L2 rs7903146 polymorphism was not collinear with the other risk factors

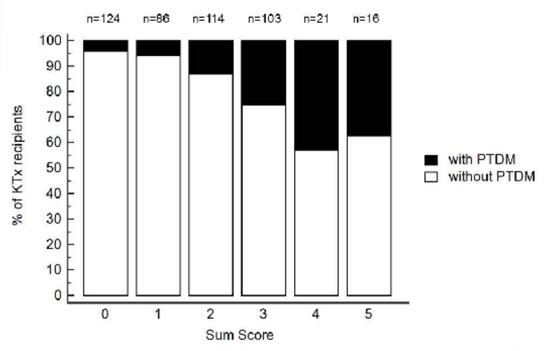
Predictive models for PTDM

Model 1: only clinical risk f.; AUROC: 0.69

Model 2: M1+TCF7 (domin); AUROC: 0.70

Model 2: M1+TCF7 (recess); AUROC: 0.74

When applying the score developed in Model 3, the proportion of patients with PTDM in each score group (from 0 to 5) progressively increased with the score values: 4.0% (score 0), 5.8% (score 1), 13.2% (score 2), 25.2% (score 3), 42.9% (score 4) and 37.5% (score 5).



	Model 1 (clinical)			Model 2 (clinical+dominant)			Model 3 (clinical+recessive)		
Predictor	*Beta*	*HR (95%CI)*	*Score*	*Beta*	*HR (95%CI)*	*Score*	*Beta*	*HR (95%CI)*	*Score*
Age ≥56	0.56	1.75 (1.07-2.87)	1	0.56	1.75 (1.07-2.87)	1	0.61	1.83 (1.11-3.03)	1
BMI ≥25	1.11	3.03 (1.82-5.03)	2	1.08	2.96 (1.78-4.91)	2	1.20	3.32 (1.98-5.57)	2
Previous Transplants	0.89	2.44 (1.24-4.83)	2	0.82	2.28 (1.15-4.53)	1	1.00	2.73 (1.37-5.45)	2
TCF7L2 CC				0.66	1.93 (1.07-3.48)	1			
TCF7L2 TT							1.12	3.05 (1.78-5.22)	2

STUDY POPULATION

Parameter	Overall (n=464)
Age (years)	52.4 ± 12.3
Male	303 (65.3%)
Caucasian	452 (97.4%)
TCF7L2 rs7903146 C>T	
CC	163 (35.1%)
CT	237 (51.1%)
TT	64 (13.8%)
Ever Peritoneal Dialysis	112 (24.1%)
Previous transplants	44 (9.5%)
Deceased Donor	444 (95.7%)
BMI (Kg/m2)	24.1 ± 3.4
BMI ≥ 25 Kg/m2	183 (39.4%)
Delayed Graft Function	103 (22.2%)
1+ acute rejection	32 (6.9%)
Induction therapy:	
None	27 (5.8%)
Anti IL2 receptor	379 (81.7%)
ATG	58 (12.5%)
IS therapy at discharge	
Tacrolimus	421 (90.7%)
Mycophenolate	436 (94.0%)
Sirolimus or Everolimus	32 (6.9%)
Steroid withdrawal	85 (18.3%)

Parameter	Patients with PTDM (n=66)	Patients without PTDM (n=398)	p
Age (years)	55.4 ± 10.2	51.9 ± 12.6	**0.008**
Male	39 (59.1%)	264 (66.3%)	**0.252**
Caucasian	64 (97.0%)	388 (97.5%)	**0.806**
TCF7L2 rs7903146			
CC	14 (21.2%)	149 (37.4%)	
CT	33 (50.0%)	204 (51.3%)	
TT	19 (28.8%)	45 (11.3%)	**<0.001**
Ever Peritoneal Dialysis	11 (16.7%)	101 (25.4%)	**0.125**
Previous transplants	10 (15.2%)	34 (8.5%)	**0.090**
Deceased Donor	66 (100%)	378 (95.0%)	**0.063**
BMI (Kg/m2)	26.4 ± 3.8	23.7 ± 3.2	**<0.001**
BMI ≥ 25 Kg/m2	42 (63.6%)	141 (35.4%)	**<0.001**
Delayed Graft Function	19 (28.8%)	84 (21.1%)	**0.164**
1+ acute rejection	8 (12.1%)	24 (6.0%)	**0.071**
Induction therapy:			
None	4 (6.1%)	23 (5.8%)	
Anti IL2 receptor	53 (80.3%)	326 (81.9%)	
ATG	9 (13.6%)	49 (12.3%)	**0.716**
IS therapy at discharge			
Tacrolimus	63 (95.5%)	358 (89.9%)	**0.159**
Mycophenolate	62 (93.9%)	374 (94.0%)	**0.992**
Sirolimus or Everolimus	5 (7.6%)	27 (6.8%)	**0.814**
Steroid withdrawal	13 (19.7%)	72 (18.1%)	**0.755**

DISCUSSION

TCF7L2 rs7903146 C>T polymorphism is strongly and independently associated with PTDM in KTRs in an allele dose-dependent manner.

Furthermore, it appears to improve risk stratification for PTDM when added into a model including the main relevant clinical variables.

The association of rs7903146 with PTDM is biologically plausible given that most immunosuppressive drugs (tacrolimus, steroids and mTOR inhibitors) promote the apoptosis of pancreatic beta-cells: consequently, genes involved in their proliferation and apoptosis (such as TCF7L2) are excellent candidates to play a role in PTDM, probably to a larger extent than in T2DM

As previously described, we also confirm that TCF7L2 rs7903146 has a major role only in the subset of patients who developed PTDM after two weeks from surgery.

PTDM-risk score.

rs7903146 significantly improved predictive ability of the risk model based only upon clinical factors under the recessive mode of inheritance.

Availability of this genetic information prior to surgery would have important consequences: patients could be preemptively informed about their risk of PTDM and immunosuppression could be tailored to minimize the risk of PTDM in high risk patients

Future studies: validation and interventional studies based on PTDM-risk stratification are nevertheless required before predictive models including TCF7L2 rs7903146 can be implemented in clinical practice.

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M2) Renal transplantation. Clinical.

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