Therapeutics and Clinical Risk Management

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Open Access Full Text Article

REVIEW

Genetic factors in pathogenesis of diabetes mellitus after kidney transplantation

This article was published in the following Dove Press journal:
Therapeutics and Clinical Risk Management
6 April 2017
Number of times this article has been viewed

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Abstract: Posttransplant diabetes mellitus (PTDM) is one of the major metabolic complications after transplantation of solid organs including the kidney. This type of diabetes mellitus affects allograft survival, cardiovascular complications and overall patient survival. The modifiable risk factors that contribute to PTDM include obesity, some viral infections (eg, hepatitis C virus, cytomegalovirus) and especially immunosuppressive drugs including corticosteroids, tacrolimus, cyclosporine and sirolimus. Currently, predisposing genetic factors have been considered important in PTDM development. The commonly evaluated genetic determinants include genes encoding transcription factors, cytokines, chemokines, adipokines, ionic channels, glucose transporters, cytochrome P450 enzymes and other enzymes metabolizing drugs, drug transporters. Unfortunately, the results of studies are inconclusive and differ between populations. There is a need for large genome-wide association study to identify the genetic risk factors associated with PTDM development.

Keywords: diabetes mellitus, kidney, transplantation, gene polymorphism, SNP

Introduction

Posttransplant diabetes mellitus (PTDM) is one of the major metabolic complications after transplantation of solid organs including the kidney. This type of diabetes mellitus affects allograft survival and also cardiovascular complications and overall patient survival. The incidence of PTDM after kidney transplantation varies from 5.5% to 60.2% of recipients.[1,2] The occurrence of PTDM in the early posttransplant period suggests that the risk factors exist or develop at the time of or prior to transplantation. The PTDM risk factors are divided into 2 groups: modifiable and non-modifiable. Common modifiable risk factors include obesity, sedentary lifestyle, other metabolic syndromes associated with obesity, some viral infections (eg, hepatitis C virus, cytomegalovirus), drugs used in posttransplantation therapy including corticosteroids, which are a mainstay of immunosuppression after transplantation of solid organs, and other immunosuppressive agents (eg, tacrolimus, cyclosporine and sirolimus).[3–9] The non-modifiable risk factors are advanced age, black race including African, Hispanic or South Asian descent, genetic background (eg, HLA B27 phenotype), previously diagnosed glucose intolerance and adult polycystic kidney disease.[3,10–13] All of these risk factors contribute to beta-cell dysfunction in the pancreas prior to or after kidney transplantation. Previous studies suggest that genetic background plays an important role in the pathogenesis of PTDM. Moreover, the differences between populations in prevalence of PTDM were observed. The studies suggest that African, Hispanic and South Asian have higher incidence of PTDM.[3,10–13]

Solid organ transplantation (including kidney) requires the use of immunosuppressive drugs such as steroids and calcineurin inhibitors (CNIs) to maintain graft function.

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Dovepress
http://dx.doi.org/10.2147/TCRM.S129327

Unfortunately, these drugs contribute to the development of PTDM.[3] The corticosteroids are well documented to cause hyperglycemia by inducing insulin resistance, increasing hepatic gluconeogenesis and stimulating appetite resulting in increased weight. The impact of corticosteroids is dose dependent. For example, a low dose of prednisone (5 mg/day) for 5 years after kidney transplantation minimally impacted the incidence of PTDM.[14–16] CNIs, such as cyclosporine and tacrolimus, also are diabetogenic. Cyclosporine increases the synthesis of polyamines, which regulate the function of pancreatic beta cells, inhibiting insulin secretion.[17] The diabetogenic effect of tacrolimus is mainly caused by impaired insulin secretion by pancreatic beta cells and beta-cell toxicity.[17–19] Tacrolimus induces beta-cell damage through induction of beta-cell apoptosis. Cyclosporine and tacrolimus can also increase insulin resistance by inhibiting the glucose transporter GLUT4, which leads to hyperglycemia.[20] Tacrolimus also reduces glucokinase activity and suppresses insulin release by pancreatic islets. Both cyclosporine A and tacrolimus reduce insulin release, increase insulin resistance and reduce insulin gene expression, which lead to the development of PTDM.[7,8,17,21] Both insulin secretion and insulin tissue action are decreased in PTDM. Hyperglycemia increases inflammatory reaction and expression of alloantigens as well as activates endothelial cells and the migration and adhesion of leucocytes. These factors induce an increase in circulating inflammatory mediators, which can contribute to transplant rejection. Hyperglycemia can also influence drug action including cyclosporine, which causes nephrotoxicity.[22,23] In the end, PTDM contributes to cardiovascular complications and frequent inflammatory complications, which lead to a shortened lifespan.[24,25] Therefore, it is important to minimize the incidence and impact of PTDM through pretransplant and posttransplant screening to identify patients with risk factors and improve the modified immunosuppressive regiments during and after transplantation coupled with glucose-lowering therapies with insulin or oral hypoglycemic agents. The efforts of researchers are directed on identifying genetic determinants to predict an increased probability of PTDM.

Genetic polymorphisms and risk of diabetes mellitus

Many studies have investigated the genetic polymorphisms associated with increased risk of type 2 diabetes mellitus (T2DM). The commonly evaluated genetic determinants include genes encoding transcription factors and inflammation-associated genes. The gene products are mostly involved in beta-cell proliferation and apoptosis. However, the results obtained from evaluation of specific gene polymorphisms are inconclusive. The selected genetic observations are presented in Table 1.

One of the most intensively studied genes is *TCF7L2*, which was initially shown to be significantly associated with type 2 diabetes by genome-wide association study

Table 1 Results and statistical power for selected studies of associations between genetic polymorphisms and PTDM

Gene	Study	Association	MAF (%)	Number of patients			Power of the study (MDD)[a] for PTDM vs non-PTDM	
				All	Non-PTDM group	PTDM group	OR when MAF is lower in PTDM vs non-PTDM group	OR when MAF is higher in PTDM vs non-PTDM group
TCF7L2	Kang et al[28]	Yes	2	511	392	119	–	3.073
	Kurzawski et al[20]	Yes	6	234	168	66	0.027	2.779
	Ghisdal et al[29]	Yes	13	1,034	958	118	0.483	1.701
	Yang et al[32]	No	21	303	170	133	0.520	1.717
	Khan et al[30]	Yes	25	140	98	42	0.335	2.249
SLC30A8	Khan et al[30]	Yes	23	140	98	42	0.314	2.282
	Kang et al[57]	Yes	39	624	450	174	0.682	1.440
NFATC4	Chen et al[36]	Yes	4	319	157	162	0.087	2.710
HNF-4A	Yang et al[32]	Yes	48	303	170	133	0.618	1.608
IRS-1	Yang et al[32]	Yes	2	158	170	133	–	3.416
IL-6	Bamoulid et al[37]	Yes	13	349	290	59	0.301	2.109
	Babel et al[39]	No	43	275	221	54	0.516	1.871
	Weng et al[40]	Yes	0.4	278	251	27	–	19.619
IL-10	Babel et al[39]	No	34	256	205	51	0.471	1.917
TGF-β	Babel et al[39]	No	27	276	219	57	0.452	1.899
TNF-α	Babel et al[39]	No	13	273	220	53	0.256	2.233
TNF-α	Kao et al[49]	No	2	314	241	73	–	3.987
IL-28B	Duca et al[41]	Yes	39	99	71	28	0.338	2.564

(*Continued*)

Table 1 (*Continued*)

Gene	Study	Association	MAF (%)	Number of patients			Power of the study (MDD)[a] for PTDM vs non-PTDM	
				All	Non-PTDM group	PTDM group	OR when MAF is lower in PTDM vs non-PTDM group	OR when MAF is higher in PTDM vs non-PTDM group
	Veldt et al[42]	Yes	34	221	152	69	0.503	1.833
IL-2	Kim et al[43]	Yes	51	306	253	53	0.532	1.893
IL-7R	Kim et al[43]	Yes	57	306	253	53	0.537	1.935
IL-17R	Kim et al[43]	Yes	59	306	253	53	0.537	1.955
IL-17RB	Kim et al[43]	Yes	46	306	253	53	0.524	1.871
CCL5	Jeong et al[44]	Yes	30	311	255	56	0.474	1.866
	Nicoletto et al[45]	No	14	270	187	83	0.371	1.987
	Dabrowska-Zamojcin et al[46]	No	24	315	272	43	0.379	2.054
CCL2	Dabrowska-Zamojcin et al[46]	Yes	31	315	272	43	0.431	1.993
IL-17F	Romanowski et al[47]	Yes	3	169	146	23	–	6.192
IL-17F	Romanowski et al[47]	No	9	169	146	23	–	3.564
IL-17A	Romanowski et al[47]	No	35	169	146	23	0.311	2.556
IFN-γ	Babel et al[39]	Yes	28	278	221	54	0.446	1.919
GPX1	Dutkiewicz et al[50]	Yes	32	159	138	21	0.265	2.677
SOD1	Dutkiewicz et al[50]	No	49	159	138	21	0.351	2.793
SOD2	Dutkiewicz et al[50]	No	5	159	138	21	–	4.590
PPARα	Elens et al[53]	Yes	25	101	76	9	–	4.562
	Kurzawski et al[54]	No	21	241	177	64	0.410	1.955
P450	Elens et al[53]	Yes	8.1	101	76	9	–	6.455
	Kurzawski et al[54]	No	26	241	177	64	0.454	1.890
P450	Gervasini et al[55]	Yes	35	164	130	34	0.382	2.235
KCNQ	Yang et al[32]	Yes	36	303	170	133	0.597	1.615
	Kang et al[57]	Yes	62	624	589	145	0.685	1.495
KCNJ11	Tavira et al[61]	Yes	35	50	405	40	0.449	1.984
	Parvizi et al[62]	Yes	37	120	60	60	0.423	2.148
Angiotensin	Lee et al[66]	Yes	10	302	253	49	0.158	2.428
	Özdemir et al[67]	Yes	33	50	27	23	0.183	3.414
CAPN10	Kurzawski et al[70]	Yes	8	214	158	56	0.071	2.683
ENPP1	Szuszkiewicz et al[71]	Yes	13	115	79	36	0.091	2.848
eNOS	Ergün et al[72]	Yes	5	82	73	9	–	8.867
Adiponectin	Nicoletto et al[45]	Yes	28	270	187	83	0.511	1.767
PAI-1	Chang et al[78]	Yes	59	376	295	81	0.598	1.725
ADIPOQ	Kang et al[74]	Yes	30	575	421	154	0.641	1.493
Adiponectin	Yu et al[77]	Yes	66	398	301	97	0.615	1.713
IGF2	Vattam et al[73]	Yes	20	140	98	42	0.278	2.347
PPARγ	Wang and Hudspeth[79]	No	11	123	72	51	0.107	2.788
INFγ	Wang and Hudspeth[79]	No	54	123	72	51	0.463	2.222
IL-1β	Weng et al[40]	No	45	278	251	27	0.402	2.348
MTHFR	Weng et al[40]	No	25	278	251	27	0.273	2.402
VDR	Yao et al[75]	Yes	38	105	89	16	0.231	3.180
Leptin	Romanowski et al[76]	Yes	10	323	278	45	0.139	2.475

Notes: [a]MDD: the true effect size measured as OR for minor vs major allele, which can be detected with 80% probability for the presented sample sizes and MAF (calculated with PS version 3.0.43 software); –, MAF in non-PTDM group was too low for the detection of even lower MAF in PTDM group with 80% statistical power.
Abbreviations: MAF, minor allele frequency; MDD, minimal detectable difference; OR, odds ratio; PTDM, posttransplant diabetes mellitus; PS, power and sample size calculation software.

(GWAS).[26] Further studies implicated *TCF7L2* rs7903146 (T allele) as the most common susceptible gene for T2DM.[18] The TCF7L2 protein belongs to a T-cell transcription factor family that regulates cell proliferation and differentiation through the Wnt signaling pathway, which controls pancreas development and maturation as well as islet function. The T allele has been associated with increased protein expression, impaired insulin secretion, impaired incretin effects and hepatic insulin resistance.[19,27]

The association between *TCF7L2* rs7903146 single-nucleotide polymorphism (SNP) and PTDM is inconclusive. Studies on renal transplanted patients of Korean[28]

(511 patients) or white European ethnicity (total 1,320 patients)[20,29] and 140 Indian Asians[30] showed a significant association with the T allele; however, other studies did not support these data.[31–33] Nonetheless, recent meta-analysis and further genotyping of 464 patients, mostly of white ethnicity treated with tacrolimus, revealed that the rs7903146 T variant confers a higher risk of PTDM in an allele dose-dependent manner.[34]

Another gene associated with T2DM that contributes to PTDM pathogenesis is activating transcription factor 6 (*ATF6*). Fougeray et al did not find an association between 6 *ATF6* SNPs and PTDM. However, the *ATF6* rs2340721 SNP was associated with increased body weight and body mass index (BMI).[35] Another transcription factor that was shown to be associated with PTDM is nuclear factor of activated T cells (NFAT) 4 (NFATC4). Chen et al showed that the *NFATC4* T-T-T-T-G haplotype in Hispanic origin renal transplant patients had a reduced adjusted risk for PTDM. Specifically, the rs10141896 SNP T allele was associated with a lower cumulative incidence of PTDM.[36]

The second group of genes evaluated in the context of PTDM consists of interleukins (ILs) and inflammation-related factors. Both peripheral insulin action and insulin secretion appear to be affected in PTDM.[36] Inflammatory chemokines and cytokines are involved in this process. ILs and other molecules are secreted by T cells and by stimulating the production of inflammatory cytokines (tumor necrosis factor [TNF]-α, IL-1B and IL-6) mediate inflammation. There are several published studies of IL-6-174 SNP in relation to PTDM.[37–39] Work by Bamoulid et al[37] involving 349 patients documents a statistically significant association between GG homozygotes and PTDM, and Weng et al[40] showed that the *IL-6* G/G genotype experienced a lower risk of developing PTDM in the Taiwanese population. Furthermore, there was a significant association between the G allele and serum IL-6 levels.[37] A study of 99 patients after liver transplantation showed that almost one-third (28 patients) developed PTDM.[41] A statistically significant association was observed between *IL-28B* rs12979860 SNP and PTDM,[41] which supported previous observations by Veldt et al in a similar study including 221 patients.[42]

Another study that included 18 different SNPs in 10 different genes encoding ILs was performed by Kim et al.[43] It was found that 61% of the evaluated SNPs (11/18) were significantly associated with PTDM in a Korean population of 306 renal transplant recipients. The evaluated SNPs include the following: *IL-1B* (rs3136558), *IL-2* (rs2069762), *IL-4* (rs2243250, rs2070874), *IL-7R* (rs1494558, rs2172749), *IL-17RE* (rs1124053), *IL-17R* (rs2229151, rs4819554) and *IL-17RB* (rs1043261, rs1025689). These genes were recently reported to be associated with type 1 diabetes mellitus and could be associated with the pathogenesis of PTDM in renal transplant recipients.

Another study from Korea[44] shows that *CCL5* gene polymorphisms, rs2107538, rs2280789 and rs3817655 were significantly associated with increased risk of PTDM. This association was confirmed in multiple logistic regression analysis. The TCA haplotype was associated with higher frequency of PTDM.[44]

A study of 270 Caucasian kidney transplant recipients did not confirm previous observations regarding *CCL5* SNPs (rs2280789 and rs3817655), but researchers found an association between the *276G/T* adiponectin gene polymorphism (rs1501299) and PTDM.[45] In addition to *CCL5*, other chemokines such as CCL2 or monocyte chemoattractant protein-1 were studied. A recent study by Dabrowska-Zamojcin et al on 315 patients of Caucasian origin showed that *CCL2* rs1024611 polymorphism is an independent risk factor for posttransplant diabetes, but not rs2107538 of *CCL5*.[46]

A study by Romanowski et al[47] conducted on 169 Caucasian patients (23 with PTDM) revealed an association between *IL-17F* SNP (rs763780) and PTDM. No significance was found for *IL-17A* polymorphism (rs2275913) and 2 other evaluated SNPs of *IL-17F* (rs11465553 and rs2397084).[47]

The genes involved in regulating lipid homeostasis and carbohydrate metabolism may also be involved in PTDM. Yang et al included 303 kidney transplant patients of Hispanic ethnicity and revealed that polymorphism of 2 alleles of the *HNF-4A* gene encoding transcription factor 14 (rs2144908 and rs1884614) and insulin receptor substrate 1 (rs1801278) are significantly associated with PTDM.[32] Subsequent research by Chen et al revealed that the IRS-2 Gly1057Asp and IRS-1 Gly972Arg genotypes are not related to tacrolimus-induced PTDM in the Chinese population.[48] Further analyses by Babel et al and Kao et al revealed no association between PTDM and the following polymorphisms: −1082IL-10, −308TNF-α, TGF-β1 (codon 10, 25), −174IL-6 and +874IFN-γ, and G-238A SNP.[39,49]

In a study involving 159 patients after kidney transplant, 21 developed PTDM, and a set of genes involved in oxidative stress (*SOD1*, *SOD2*, *CAT* and *GPX1*) was evaluated. Only *GPX1* SNP rs1050450 was associated with increased risk of

PTDM.[50] The functional polymorphisms in this gene were shown to be associated with increased intima-media thickness of carotid arteries and risk of cardiovascular and peripheral vascular diseases in type 2 diabetic patients.[51,52]

Recent investigations have focused on SNPs of genes that play an important role in tacrolimus metabolism, such as peroxisome proliferator-activated receptor α (*PPARα*) and P450 oxidoreductase (*POR*), both of which are involved in control of energy uptake, lipid and carbohydrate metabolism. Elens et al observed an association between a coding POR variant (rs1057868) and 2 single-nucleotide substitutions in *PPARα* (rs4823613 and rs4253728) and increased risk for PTDM.[53] However, this result was not confirmed by Kurzawski et al in a subsequent study.[54] Recently, Gervasini et al focused on cytochrome P450 enzymes in 164 patients and showed that a valine-to-methionine amino acid change in residue 433 of the *CYP4F2* gene (rs2108622) is an independent risk factor of PTDM.[55] The *CYP4F2* gene encodes a ω-hydroxylase that is involved in the synthesis of arachidonic acid active metabolites that regulate kidney function. In patients after heart transplantation, no associations were found between SNPs in cytochrome P450 3A isoenzymes and tacrolimus-induced PTDM.[56]

GWAS on an Asian population identified new loci associated with diabetes type II development. A study including 589 patients in a Korean population after kidney transplantation revealed 8 SNPs in 6 genes significantly associated with PTDM development with odds ratios ranging from 1.33 to 2.32.[57] The 6 genes and 8 SNPs included *TCF7L2* (rs7903146), *SLC30A8* (rs13266634), *HHEX* (rs1111875, rs7923837 and rs5015480), *CDKAL1* (rs10946398), *CDKN2A*/B (rs10811661), *IGF2BP2* (rs4402960), *FTO* (rs8050136), *WFS1* (rs734312), *JAZF1* (rs864745), *CDC123/CAMK1D* (rs12779790), *TSPAN8* (rs7961581), *THADA* (rs7578597), *ADAMTS9* (rs4607103), *NOTCH2* (rs1092391) and *KCNQ1* (rs2237892). Interestingly, there was no association between the same SNPs and PTDM in a Polish population (235 patients).[58] Similar negative results were obtained by Chakkera et al[31] after analyzing similar sets of genes and SNPs in 91 patients.

Numerous studies have analyzed the association between *KCNJ11* and *KCNQ1* gene polymorphisms and diabetes type 2. The *KCNJ11* gene is a member of the potassium channel gene family, which maps to chromosome 11p15.1. This gene encodes an inward-rectifier potassium ion channel (Kir6.2). Mutations in the *KCNJ11* gene are associated with defective insulin secretion and development of diabetes mellitus.[59,60] The associations between *KCNJ11* and *KCNQ1* gene polymorphisms and PTDM are not widely investigated.

Tavira et al examined the contribution of the rs5219 *KCNJ11* gene polymorphism to PTDM after transplantation among patients treated with tacrolimus.[61] The AA + AG genotypes were significantly associated with increased risk of PTDM. Parvizi et al observed an association between the KCNJ11 KK variant and an increased risk for PTDM.[62] This study showed that polymorphisms in KCNJ11 might predispose the patients treated with tacrolimus to development of PTDM after liver transplantation. However, in the previously mentioned study by Kurzawski et al,[58] there was no significant association between PTDM and rs5219 in *KCNJ11*.

Tavira et al performed an interesting study on Spanish patients who received a cadaveric kidney graft and developed PTDM in the first year posttransplant and on patients who remained nondiabetic.[63] Three *KCNQ1* SNPs were genotyped. SNP rs2237895 (genotype CC) was associated with an increased risk for new-onset diabetes after transplantation (PTDM) in the studied population, independently of other risk factors such as BMI, recipient age, or tacrolimus dosage. Other *KCNQ1* variants were not associated with PTDM. Kang et al analyzed the association between PTDM development and *KCNQ1* rs2237892. This polymorphism was significantly associated with PTDM in a cohort of renal allograft recipients in Korea.[57]

Insulin signaling pathways, blood flow, oxidative stress and adipogenesis may be affected by the renin-angiotensin system, which recently has attracted interest with regard to the pathogenesis of insulin resistance and diabetes mellitus in the general population.[64,65] The study by Lee et al conducted on 302 Korean patients revealed an association between the AGT polymorphism (rs4762), but no association in the case of AGT SNP rs699 and angiotensin-converting enzyme rs4291.[66] These results are in contrast to a previous relatively small study conducted on 50 patients of Turkish origin in which these SNPs were associated with PTDM.[67]

Among other genetic factors predisposing to PTDM, there is a polymorphism in the gene that encodes a nonlysosomal cysteine protease – calpain-10 (*CAPN10*). It is expressed in tissues important for the regulation of glucose homeostasis like fat, skeletal muscle, liver and pancreatic islets.[68] What is more, *CAPN10* gene expression or mRNA stability may be affected by *CAPN10*.[69] Kurzawski et al showed an interesting association "between PTDM and *CAPN10* SNP-63 (rs5030952) polymorphism, as well as the 1-1-2 haplotype [derived from SNP-43 (rs3792267), SNP-19 (rs3842570) and SNP-63 (rs5030952)]".[70]

In a study of insulin resistance-related factors including 115 patients of mixed origin (white, Hispanic, black), Szuszkiewicz et al observed an association between the *ENPP1* gene K121Q polymorphism and PTDM with an OR of 1.4.[71] *ENPP1* encodes a class 2 membrane glycoprotein that negatively influences sensitivity to insulin action by inhibiting insulin tyrosine-kinase receptor signaling. Another insulin-resistance gene that showed an association with PTDM is endothelial nitric oxide synthase (*eNOS*). Carriers of the intron 4 allele of *eNOS* (4a allele) in a Turkish population of kidney allograft recipients treated with cyclosporine A had a higher risk of developing PTDM.[72]

Additional studies that also evaluated insulin-resistance genes focused on polymorphisms in IGF, leptin, adiponectin, adiponectin receptor, plasminogen activator-1 and vitamin D receptor genes. Significant associations were found in all of the cases.[73–79] However, not all of them were confirmed in other studies.[33,40]

There is only one GWAS conducted on PTDM patients that investigated the clinical and genetic factors associated with PTDM in a relatively large, white renal transplant population. This study by McCaughan et al included 529 patients of which 57 developed PTDM. It was the first study to utilize an exploratory GWAS with confirmation by de novo genotyping.[33] What is interesting and confusing at the same time is that the authors did not find any association between PTDM and previously described SNPs. However, they found 26 new SNP candidates out of which 8 were verified by genotyping. The 8 SNPs associated with PTDM were mostly involved in the PI3K-Akt signaling pathway.[33]

Conclusion

Solid organ transplantation may lead to serious metabolic complication occurring mainly due to immunosuppressive therapy known as PTDM. This disorder is of particular concern because it is associated with poor graft survival and increased risk of cardiovascular complications, chronic rejection and renal failure.[47] The influence of PTDM on graft function and the circulatory system prompted a search for predictors of PTDM development. The identification of genetic factors predisposing to PTDM development may aid in deciding the proper immunosuppressive therapy in patients with increased risk of PTDM. The effective regimens of immunosuppressive therapy may help to prevent the development of PTDM, chronic allograft dysfunction and cardiovascular complications and improve graft survival. The patients who are carriers of some genetic variants should be considered as renal transplant recipients at higher risk of PTDM development, especially during therapy with immunosuppressive drugs with diabetogenic action such as tacrolimus. Their tacrolimus plasma levels and glycemia should be carefully monitored after transplantation. It would also be reasonable to avoid the use of other drugs with diabetogenic action. It can be speculated that the presence of some genetic variants with other independent risk factors of PTDM (higher BMI, older age) should be considered as the contraindication for treatment with strongly diabetogenic immunosuppressive regimens.

There is a need for large GWAS to identify the genetic risk factors associated with PTDM development. These studies should take into account candidate genes associated with diabetes type 2 and gene encoding enzymes involved in glucose metabolism and pancreatic beta cell function.

Disclosure

The authors report no conflicts of interest in this work.

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