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Genetic Factors Associated with Posttransplant Diabetes Mellitus (PTDM) in Renal Transplant Patients: A Synthesis of Current Knowledge

Genetički faktori povezani s razvojem posttransplantacijske šećerne bolesti u pacijenata s transplantiranim bubregom: sinteza trenutnih spoznaja

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Abstract. Posttransplant diabetes mellitus (PTDM) is a major metabolic complication that can occur after a solid organ transplant. While much about this condition is still unknown, genetic variants have been demonstrated as important factors regarding increased risk of disease development. Based on pathogenic mechanism, these variants can be divided into several categories. These include glucose and lipid metabolism variants (leptin and adiponectin genes), inflammatory response variants (*IL-17*, *CCL2*, and *CCL5* genes), tacrolimus-related pharmacogenetic variants (*CYP3A5* gene), and various metagenomic factors. Renal transplant patients might benefit from optimized therapy and lifestyle, based on the findings of proactive targeted genetic testing.

Keywords: diabetes mellitus; kidney transplantation; polymorphism; genetic; risk factors

Sažetak. Posttransplantacijska šećerna bolest teška je metabolička komplikacija transplantacije solidnih organa. Iako se o bolesti puno ne zna, pokazano je da su genetičke varijante važni faktori koji povećavaju rizik za njezin razvoj. Na temelju patogenog mehanizma ove se varijante mogu podijeliti u nekoliko kategorija. One uključuju varijante metabolizma glukoze i lipida (geni za leptin i adiponektin), varijante upalnog odgovora (geni *IL-17, CCL2* i *CCL5*), farmakogenetičke varijante povezane s takrolimusom (gen CYP3A5) te različite metagenomske faktore. Pacijenti s transplantiranim bubregom mogli bi imati koristi od prilagođene terapije i životnog stila koji su temeljeni na proaktivnom ciljanom genetičkom testiranju.

Ključne riječi: faktori rizika; genetički polimorfizmi; šećerna bolest; transplantacija bubrega

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INTRODUCTION

Posttransplant diabetes mellitus (PTDM) entails the development of diabetes mellitus after a solid organ transplantation. Previously called new-onset diabetes after organ transplantation (NODAT), the clinical entity was renamed due to a number of patients having undiagnosed diabetes mellitus before transplantation[1]. Now, the criteria are defined by the timeframe of the condition, excluding patients with previous diabetes. It has been shown that PTDM affects between 10% and 40% of solid organ recipients and that a wide range of factors accounts for this variance. Diagnostic screening for PTDM includes the usual tests used for diabetes, such as random plasma glucose (RPG), fasting plasma glucose (FPG), two-hour plasma glucose (THPG) after oral administration of glucose, and glycated haemoglobin (GH)[2]. However, it is recommended that the screening tests be conducted once the patient has achieved a stable level of immunosuppression[3].

Posttransplant diabetes mellitus is a dangerous metabolic complication in transplant patients. Studies have explored potential genetic predispositions for this condition.

PTDM has been shown to be a contributor to poor outcomes in transplant patients. Mainly, it increases the risk of infection, graft damage, and rejection. For kidney transplant patients specifically, research by Shivaswamy V et al. stated that the difference in 1-year survival between non-PTDM and PTDM patients was 15%[3]. A study conducted by Cosio FG et al. also described a significant mortality increase in renal transplant patients who developed PTDM[4]. Poor outcomes were noted in other PTDM organ recipients, such as hypertension, infection, and transplant rejection. A significant mortality increase was noted in liver transplantations, while the mortality increase in lung and heart transplantations remains less pronounced[3].

When considering potential risk factors for the development of PTDM, incidence by transplanted organs must be observed. According to research published by Driscoll CJ, heart and lung transplantations are associated with greater rates of PTDM occurrence than kidney transplantations[5]. However, considering the absolute number of kidney transplantations as opposed to the heart and lung, there are still many more kidney recipients who suffer from PTDM. Secondly, Driscoll CJ shows how the risk of PTDM gradually increases over time, up to 15 years after the transplantation, demonstrating the necessity for a continuous follow-up. Finally, the author mentions other risk factors such as a greater recipient age, weight gain after transplantation, non-Caucasian ethnicity, family history of diabetes, etc[5]. Another study published by Driscoll CJ et al. observed risk factors in liver transplant recipients. The authors concluded that hepatitis C virus and cytomegalovirus infections also increased PTDM development risk in these patients[6].

The development of clinical genetics and next-generation sequencing technologies has led to the investigation of potential genetic factors that could contribute to PTDM occurrence in renal transplant patients. The genes in question can be categorized into several groups, depending on their role in glucose metabolism, drug metabolism, or the inflammatory response[7]. Many large-scale studies have identified certain single nucleotide polymorphisms (SNP) that are significantly more frequent in PTDM patients. This review aims to provide a synthesis of the results generated around this topic and perhaps assist in devising a viable genetic screening option for renal transplant patients. Additionally, we analysed if any metagenomic factors might be related to increased PTDM risk. This, in turn, might be the first step to a personalized treatment approach in renal posttransplant care.

GLUCOSE AND LIPID METABOLISM GENETIC FACTORS

As PTDM is primarily a metabolic disorder, it can be expected that certain genetic alterations in the glucose, lipid, or protein metabolic pathways can influence or create a predisposition for this condition.

A study published by Mota-Zamorano S et al. analyses potential metabolic genetic variants

that might pose a risk for developing PTDM[8]. The authors included renal transplant patients and performed genotyping for three polymorphisms in the leptin receptor gene (*LEPR*). The Gln223Arg variant showed a significant association with PTDM development and a generally increased body mass index. Additionally, the authors state that BMI at transplant is a more significant factor for PTDM than BMI increase posttransplant[8]. The role of leptin in glucose and lipid metabolism and in maintaining body mass is somewhat straightforward and can be summarized as glucose-lowering and anti-lipogenic through central and peripheral interactions[9]. Therefore, patients with leptin deficiency or pathogenic leptin receptor variants are usually heavily obese and exhibit a series of systemic complications involving the endocrine, reproductive, immune, and cardiovascular systems. Leptin replacement therapy has shown promising results in the general population of lipodystrophy patients[10]. Regarding the specific aforementioned variant, another study published by Li YY et al. demonstrated that the Gln223Arg leptin receptor polymorphism is directly associated with an increased risk of type 2 diabetes development in the general population[11]. This finding further supports the hypothesis of increased PTDM risk in renal transplant patients. Romanowski M et al. also investigated the link between PTDM and both leptin gene and adiponectin gene polymorphisms, in a cohort of renal transplant patients treated with tacrolimus or cyclosporine[12]. The results revealed a positive association with PTDM for the leptin rs2167270 polymorphism (increased risk in patients with the polymorphism).

A study published by Kang ES et al. investigated the increased risk for PTDM development that may potentially be a result of adiponectin (*ADIPOQ*) and adiponectin receptor-1 (*ADIPOR1*) receptor variants[13]. The study included renal transplant patients who underwent genetic testing for several single nucleotide polymorphisms in the *ADIPOQ* and *ADIPOR1* genes. The results revealed an increased risk for homozygous male patients with the *ADIPOQ* rs1501299 TT-genotype. Adiponectin has several key roles in glucose and lipid metabolism[14]. Regarding glucose metabolism, the functions of adiponectin include the protection of pancreatic beta-cells, increasing

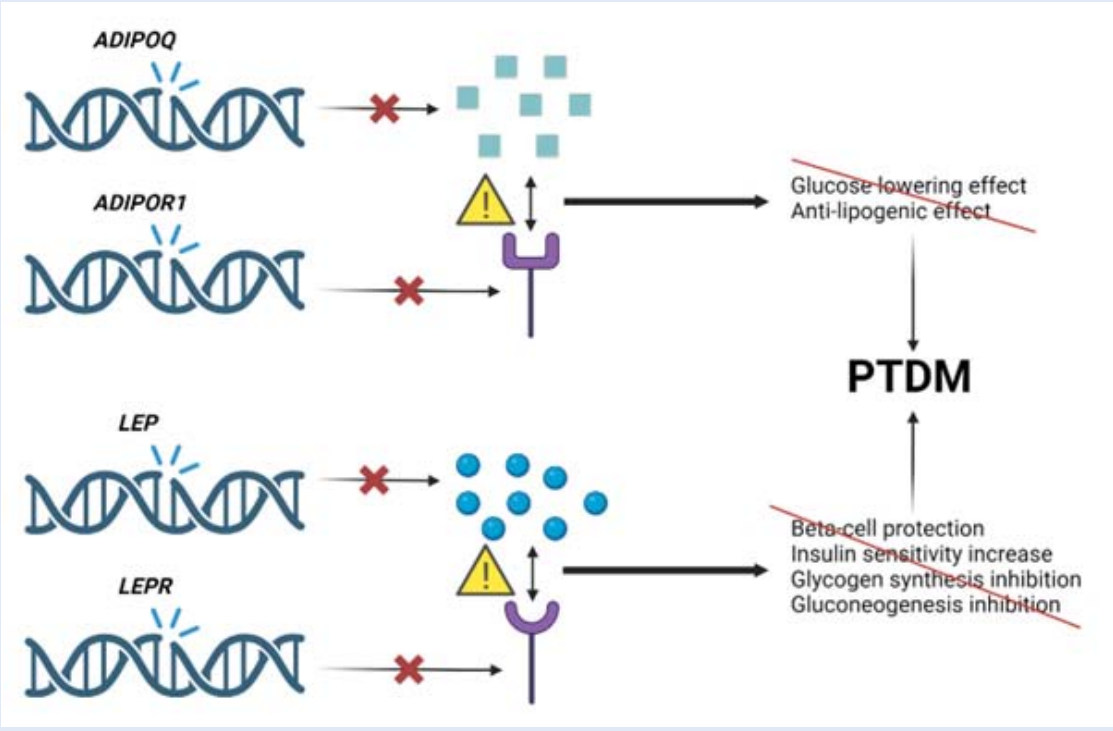

Figure 1. Effects of adiponectin and leptin pathway genetic variants on PTDM development (created with Biorender.com)

glucose uptake via the GLUT4 transporter, inhibiting glycogen synthesis and gluconeogenesis. In terms of lipid metabolism, adiponectin promotes the oxidation and clearance of free fatty acids. Additionally, it increases insulin sensitivity, a lack of which is a key pathogenic mechanism in type 2 diabetes mellitus[14]. Another study, published by Yu AR et al., also investigated the impact of adiponectin polymorphisms on risk for PTDM development in renal transplant patients, finding significant correlations for the SNP-45 and SNP-276 polymorphisms[15].

A meta-analysis published by Xu S et al. investigated a wider range of genes related to PTDM in kidney transplant patients[16]. *TCF7L2* rs7903146, *KCNQ1* rs2237892, and *KCNJ11* rs5219 polymorphisms were associated with PTDM predisposition. *TCF7L2* is a transcription factor in the Wnt signalling pathway and is considered one of the crucial genes for type 2 diabetes risk[17]. Diabetes type 2 associations have also been established for potassium channel encoding genes, such as *KCNQ1* and *KCNJ11*[18, 19].

The findings of the studies above demonstrate that certain genetic polymorphisms related to key components of glucose and lipid metabolism regulation can significantly increase the risk of PTDM development in renal transplant patients. Such examples are leptin and adiponectin, as well as their receptor molecules, which if deficient can generally impact the development of metabolic disorders like type 2 diabetes mellitus (Figure 1). Renal transplant patients with known variants related to glucose and lipid metabolism might benefit from a specialized diet. Gomes-Neto AW et al. demonstrated that increased vegetable intake is associated with a lower risk of PTDM development[20].

INFLAMMATORY RESPONSE GENETIC FACTORS

One of the critical aspects of posttransplant physiology is the immune system and its specifics, as well as optimal immunosuppressive therapy. Many complications in the posttransplant period arise due to inflammatory response activation. As an individual's inflammatory response characteristics are significantly influenced by genetics, many studies have attempted to discover associations between certain genetic variants and said complications. A study published by Dou M et al. developed a prediction model for posttransplant kidney graft loss based on genetic variants related to the immune system[21]. The model based on this data was well calibrated, demonstrating an association between these variants and posttransplant complications. Following the same train of thought, immune system genetic variants might be worth investigating as potential contributory factors to PTDM development.

Romanowski M et al. investigated how specific interleukin-17 (*IL-17A* & *IL-17F*) polymorphisms affect PTDM development in renal transplant patients[22]. Statistical analysis revealed a significant association between PTDM and the *IL-17F* rs763780 polymorphism. The IL-17F molecule acts as a proinflammatory cytokine, stimulating other inflammatory cytokines, chemokines, and the expression of adhesion molecules. Its proinflammatory role has been shown in the pathogenic mechanisms of asthma[23].

Jeong KH et al. analysed the effect of *CCL5* polymorphisms on PTDM development in renal transplant patients[24]. Three *CCL5* polymorphisms, rs2107538*T, rs2280789*C, and rs3817655*A, had a significant association with PTDM. The CCL5 molecule also has a proinflammatory role. It acts as a chemokine, attracting a wide range of immune cells, such as B-lymphocytes, T-lymphocytes, natural killer cells, granulocytes, monocytes, mast cells, etc[25]. Another study, published by Dabrowska-Zamojcin E et al., investigated both *CCL2* and *CCL5* gene polymorphisms regarding risk for PTDM development in renal transplant patients treated with tacrolimus or cyclosporine[26]. Interestingly, no associations were found between PTDM and *CCL5* polymorphisms. However, a significant association was discovered with the *CCL2* rs1024611 G polymorphism. Much like CCL5, CCL2 is a proinflammatory chemokine that promotes immune cell migration[27].

The findings suggest that proinflammatory cytokines and chemokines play a role in the pathogenesis of PTDM. This might occur through mechanisms similar to autoimmune diabetes development or another mechanism entirely[22]. Regardless, more precise inflammatory response

regulation could be beneficial in avoiding this complication.

PHARMACOGENETIC FACTORS RELATED TO TACROLIMUS

Another factor that contributes to the development of PTDM in renal transplant patients is the metabolism of tacrolimus. It is a commonly used immunosuppressive drug that works by inhibiting the calcineurin pathway. One of its primary indications is immunosuppression following organ transplant, including liver, heart, lung, and kidney. Several studies have investigated how the metabolism of tacrolimus may affect glucose metabolism and the development of PTDM. This is closely related to its pharmacogenetic properties, including genetic variants in the genes of its metabolizing enzymes – the *CYP3A* subfamily.

A study published by Jehn U et al. investigated PTDM following a kidney transplant induced by tacrolimus on a cohort of patients with no previous history of diabetes[28]. The authors compared fast and slow tacrolimus metabolizers, which were assessed by experimental kinetics modelling in cultured insulin pancreatic cells. No difference was noted in PTDM occurrence or pancreatic cell viability between the two groups and the authors concluded that fast tacrolimus metabolism is not associated with increased occurrence of PTDM.

Another study, published by Liang S et al., analysed the association between tacrolimus metabolism and PTDM after kidney transplant using DNA sequencing for single nucleotide polymorphism genotyping of a large cohort of patients[29]. Out of all patients who were on tacrolimus immunosuppression, only 18% developed PTDM. Polymorphisms in the *CYP3A4* and *CYP3A5* genes were analyzed to determine their contribution to the risk of PTDM development. Following statistical analysis, the authors concluded that the *CYP3A5* rs776746 polymorphism carried an increased risk for PTDM development, implying the importance of tacrolimus pharmacogenetics in developing this condition. The rs776746 polymorphism can generally be associated with higher levels of *CYP3A5* metabolites, indicating that these patients were poor metabolizers and likely had abnormally high tacrolimus levels concerning the administered dose[30]. A similar result was produced by another study published by Cheng F et al[31]. The authors analysed *CYP3A5* polymorphisms (alongside polymorphisms in other genes such as *CYP3A4*, *ABCB1*, *ABCC2*, *POR*, and *PXR*) in a population of kidney transplant patients. Results showed that certain *CYP3A5* polymorphisms were associated with higher tacrolimus levels, which increased the risk for the development of PTDM. Zhang X et al. published a study that also investigated PTDM risk and certain pharmacogenetic variants[32]. The cohort consisted of renal transplant patients treated with tacrolimus tested for polymorphisms in the *CYP3A5*, *CYP24A1*, and *PPARG* genes. Interestingly, no significant correlations were found for polymorphisms in the *CYP3A5* and *PPARG* genes, while a significant correlation was discovered for the *CYP24A1* rs2296241 A polymorphism in patients of advanced age.

We believe that a synthesis of knowledge, such as our review, is prudent for the implementation of targeted preventive genetic testing in these patients, leading to better outcomes.

Considering these findings, the question of utility regarding *CYP3A5* genotyping in kidney transplant patients arises. Based on the principles of pharmacogenomics, through CYP3A5 genotyping, the metabolism rate for each kidney transplant patient can be determined. With this information, immunosuppression doses could be adjusted for each patient based on their metabolism, thus avoiding higher tacrolimus blood levels, which increase the risk of PTDM development. Yu M et al. supported this reasoning in their review[33]. In their conclusion, the authors state that the additional information provided by pharmacogenomic testing and its understanding can aid clinicians in determining the optimal starting dose for their patients. The consensus report published on personalized tacrolimus therapy, published by Brunet M et al., states that *CYP3A4* and *CYP3A5* genotyping will be considered a component of treatment protocol guidance[34].

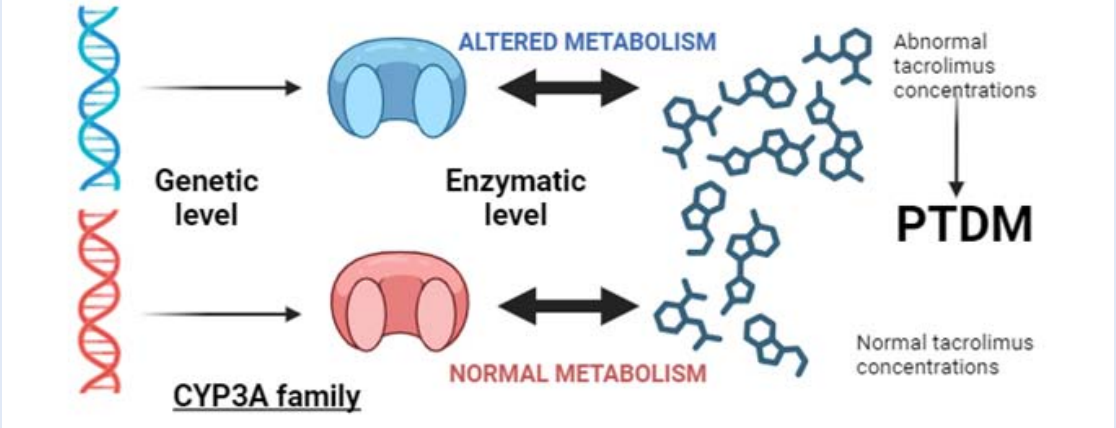

Figure 2. Pharmacogenetic background of tacrolimus therapy in the context of PTDM (created with Biorender.com)

The impact of metabolic and pharmacogenetic properties of tacrolimus on the development of PTDM after kidney transplantation has been demonstrated (Figure 2). Additionally, certain authors have expressed a positive opinion regarding the role of *CYP3A* genotyping in clinical practice. Given these findings, it is reasonable to assume that pharmacogenomic testing might be a great asset in the personalized treatment of kidney transplant patients and PTDM prevention.

METAGENOMIC FACTORS

Metagenomics is a branch of genomic medicine that has become increasingly popular recently. Its focus is the genetic analysis of our collective microbiome, the metagenome, and how it relates to certain clinical entities or predispositions. Certain studies have investigated how variations in the metagenome relate to the occurrence of PTDM.

A study published by Swarte JC et al. analysed the gut microbiome in renal transplant patients[35]. The authors observed how different therapeutic agents affect the presence of certain bacteria. The most significant ones were considered to be proton-pump inhibitors and mycophenolate mofetil. Compared to the control group, these patients had an increase in *Proteobacteria* count and a reduction in *Actinobacteria* and butyrate-producing bacteria. The result showed that the renal transplant group suffered from dysbiosis. A review by Faucher Q et al. postulated the association between gut dysbiosis and PTDM onset, building on the association between PTDM and immunosuppression[36]. The authors conclude that more research in this field is required and suggest that specific dietary supplementation might benefit PTDM mitigation.

In 2024, Li P et al. published a research article in which they demonstrated the effect of the microbiome and metagenome on PTDM[37]. Using metagenomic analysis, the authors showed that bacteria producing beta-glucuronidase are present in the tacrolimus-induced hyperglycaemia mouse model in a much larger quantity. Considering these are vancomycin-sensitive bacteria, the authors attempted to reduce this hyperglycaemic effect by antibiotic administration. The strategy proved effective, as the count of beta-glucuronidase-producing bacteria was significantly reduced, and the hyperglycaemia was eliminated. Due to its effectiveness, the authors propose this metagenomic-based approach as a novel way to avoid tacrolimus therapy cancellation.

Based on these findings, it can be assumed that gut dysbiosis contributes to the pathophysiological mechanism of PTDM. Personalized treatment of renal transplant patients might also include gut microbiome regulation, which could reduce PTDM incidence.

CONCLUSION

The development of PTDM in renal transplant patients is significantly associated with a wide range of genetic factors, including glucose metabolism-

related genes, inflammatory response-related genes, tacrolimus pharmacogenetics, and metagenomic factors. The utility of whole genome sequencing (WGS) in translational medicine and clinical practice has been positively discussed in recent literature[38]. Due to the huge amount of data, it provides, WGS might have the potential to revolutionize personalized patient care in all fields of medicine. Additionally, a study by Matišić V et al. emphasizes the utility of pharmacogenomic testing in avoiding adverse drug reactions and optimizing treatment guidelines[39]. It is worth noting that most of the literature presented in this article is comprised of single studies investigating specific genes and polymorphisms. This demonstrates the gap in synthetic research in the form of comprehensive meta-analyses, which is needed before implementation into clinical practice. Still, based on the findings presented in this review, it is reasonable to conclude that renal transplant patients could greatly benefit from these advanced diagnostics, particularly in preventing difficult and dangerous complications such as PTDM.

Conflicts of Interest: Authors declare no conflicts of interest.

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