Review article

Adipocytokines and new onset diabetes mellitus after transplantation

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ABSTRACT

Background and aim: Diabetes mellitus is a very common metabolic disease with a rising incidence. It is one of the most serious comorbidities in renal transplant recipients. New-onset diabetes after renal transplantation (NODAT) is associated with poor graft function, higher rates of cardiovascular complications and a poor prognosis. Adipocytokines, synthetized by adipose tissue influence metabolic pathways and disorders in various ways. In this review article, we chose the most researched adipocytokines and evaluated their relationship to posttransplant diabetes mellitus. The aim of this paper is to summarize current knowledge and discuss their perspective role in diagnostics or therapy of the new onset diabetes mellitus after transplantation.

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Introduction

Kidney transplantation is the treatment of choice in patients with end stage renal disease. Modern medicine with the new immunosuppressive regimens has minimized the rejection incidence of transplanted organs and increased patient survival. Therefore, more attention is being paid to non-immunological complications that influence patient’s morbidity, mortality and a quality of life. These include, for example, hypertension, infections, calcineurin inhibitor toxicity, anemia, surgical complication and last but not least diabetes mellitus.

MEDLINE search was performed to retrieve both original and review articles addressing adipocytokines and NODAT. We used the information from various papers published by April 2018. We worked with the following terms as keywords: new onset/posttransplant diabetes mellitus, adipocytokines (including adiponectin, leptin, TNF-α, PAI-1, IFG2, FGF-21, visfatin, resistin), organ transplantation and adipose tissue.

NODAT

New-onset diabetes mellitus after transplantation (NODAT) or post-transplant diabetes mellitus (PTDM) is a major complication after renal transplantation, leading to recipient’s shorter survival, especially due to cardiovascular and infectious complications, as well as of graft’s function.

New-onset of diabetes mellitus occurs in approximately one third of renal transplant recipients, with the rate ranging between 7 and 46% (Chadban, 2008; Cosio et al., 2001; Davidson and Wilkinson, 2004; Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003; Heisel et al., 2004; Kasiske et al., 2003). The prevalence depends on the diagnostic criteria of DM, study design, immunosuppressives and time from transplantation.

Although the etiology of NODAT is still not understood, insulin resistance and insulin deficiency have been identified as the key metabolic abnormalities that may develop through a variety of biochemical pathways (Krentz et al., 1995). There is an important relationship between adipose tissue and pancreas. Both, traditional Type 2 DM risk factors and risk factors unique to transplant recipients are associated with NODAT (Chadban, 2008; Cosio et al., 2001; Davidson and Wilkinson, 2004; Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003; Heisel et al., 2004; Kasiske et al., 2003). Since NODAT is a very serious complication in patients after renal transplantation, identification of those risk factors may help to prevent its development.

Adipocytokines

Adipose tissue is well-known essential endocrine organ. Its main function is to store triglycerides under condition of

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calories excess and their release during periods of fasting, thermoregulation and mechanical organ protection (Blüher, 2013a; Klötting and Blüher, 2014). It produces a wide range of hormones (adipocytokines) that play a signal role in metabolic homeostasis and their dysfunction leads to many metabolic disorders. They can regulate appetite and satiety, fat distribution, insulin secretion and sensitivity, energy expenditure, endothelial function, inflammation, blood pressure, homeostasis and endothelial function (Blüher and Mantzoros, 2015; Nagy et al., 2016). Adipokines also regulate or modulate different biological processes in target organs, including the brain, liver, muscle, vasculature, heart and pancreas, immune system and others (Blüher, 2014; Blüher and Mantzoros, 2015).

Therefore, alterations in adipokine secretion may link obesity to inflammatory, metabolic and cardiovascular comorbidities (Blüher and Mantzoros, 2015). The adipokine secretion pattern reflects adipose tissue function and seems to be important for determining the individual risk to develop metabolic and cardiovascular comorbidities of obesity (Blüher, 2009; Van Gaal et al., 2006). The expansion of adipose tissue leads to adipocyte hypertrophy (rather than hyperplasia), ectopic fat deposition, hypoxia, and chronic stress in adipose tissue, which subsequently causes an adverse adipokine secretion profile (Klöting and Blüher, 2014). Associated with a loss of insulin sensitivity in both lean and obese conditions (Björntorp and Sjöström, 1971; Cotillard et al., 2014; Klötting and Blüher, 2014). The full set of human adipokines is still not entirely characterised, it has become clear that adipose tissue is a source of more than 600 potentially secretory proteins (Lehr et al., 2012).

Adipocytokines could serve as a new diagnostic tool or novel pharmacological treatment strategies. Some adipokines are considered as innovative biomarkers for screening, diagnosis and therapeutic monitoring of obese, insulin-resistant individuals and patients, as well as for the prediction of disease recurrence (Kusminski and Scherer, 2009). The purpose of this review is to summarise the relationship between adipocytokines and new-onset diabetes mellitus after renal transplantation. Although we know dozens adipokines having an influence to diabetes mellitus, we aimed at those with proven or expected relationship to NODAT. We rank leptin, adiponectin, fibroblast growth factor (FGF-21), tumour necrosis factor alpha (TNF-α), insulin-like growth factor (IGF), resistin, visfatin as well known adipocytokines with effects on diabetes mellitus (see Table 1).

Adipocytokine gene polymorphisms have been investigated in patients with diabetes mellitus in various populations. The results are variable and are dependent on the studied population. In most cases, these polymorphisms seem to be factors predisposing to diabetes mellitus or diabetic complications.

### Table 1
Summary of adipocytokines with potential effects on diabetes mellitus.

<table>
<thead>
<tr>
<th>Adipocytokine</th>
<th>Effects</th>
<th>Insulin resistance</th>
<th>Beta-cell function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptin</td>
<td>Satiety signals, energy expenditure</td>
<td>Improves insulin sensitivity</td>
<td>Improves</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>Antidiabetic, antiatherogenic, anti-inflammatory</td>
<td>Stimulates insulin secretion</td>
<td>Improves (proliferation and inhibits apoptosis)</td>
</tr>
<tr>
<td>TNF-alpha</td>
<td>Proinflammatory</td>
<td>Worsens</td>
<td>Improves GSIS</td>
</tr>
<tr>
<td>PAI-1</td>
<td>Prothrombotic</td>
<td>No data</td>
<td>Inhibits GSIS</td>
</tr>
<tr>
<td>IGF2-1</td>
<td>Growth and metabolism</td>
<td>Contradictory data</td>
<td>No data</td>
</tr>
<tr>
<td>FGF-21</td>
<td>Stimulates glucose uptake into adipocytes, energy expenditure, fat utilization</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Resistin</td>
<td>Related to obesity, insulin resistance, inflammation</td>
<td>Worsens</td>
<td>Improves (cell viability)</td>
</tr>
<tr>
<td>Visfatin</td>
<td>Insulin-like, proinflammatory, antiapoptotic</td>
<td>Insulin sensitizer</td>
<td>Increases insulin secretion</td>
</tr>
</tbody>
</table>

* GSIS – glucose stimulated insulin secretion.
leptin to arterial stiffness as a marker of cardiovascular risk has shown that leptin is an independent predictor of arterial stiffness in kidney transplant patients. Therefore, serum fasting leptin level could predict the development of central arterial stiffness of kidney transplant patients (Tsai et al., 2015). Kidney transplant recipients also show higher concentrations of leptin in combination with parameters evaluating endothelial dysfunction, among which we rank nitric oxide and hs-CRP (Ocak et al., 2016).

Studies show that mean serum levels of leptin were higher in pre-transplant patients (Souza et al., 2008) and it significantly decreases in the first 3 months after the renal transplantation (Souza et al., 2008). It is usually attributed to an improvement of the renal function.

However, some studies have found an increased level of serum leptin in a longer follow (El Haggan et al., 2004; Kayacan et al., 2003). Other studies observed that latter in the posttransplant course (average time of 2.5 year) serum level of leptin are higher in renal transplant patients than in healthy individuals (Kokot et al., 1999). The inhibitory effect of leptin may enhance the inhibition of insulin secretion caused by calcineurin inhibitors (tacrolimus and cyclosporin). They both display a significant diabetogenesis effect, although the effect of tacrolimus is more potent than cyclosporine. The diabetogenic effect of tacrolimus is mainly caused by β-cell toxicity and impaired insulin secretion by β-cells (Drachenberg et al., 1999; Li et al., 2009).

Adipocytokine gene polymorphisms have been investigated in patients with diabetes mellitus in various populations. The results are variable and are dependent on the studied population. In most cases, these polymorphisms seem to be factors predisposing to diabetes mellitus or diabetic complications. Polymorphisms of the leptin gene are associated with obesity, insulin resistance and diabetes mellitus (Al-azzam et al., 2014). Several studies have indicated an association between the leptin gene polymorphism rs2167270 and serum leptin levels as well as diabetes mellitus. It was shown that the A allele is associated with increased serum leptin levels (Mammès et al., 2000; Sahin et al., 2013) and that rs2167270 leptin gene polymorphism influences gene transcription and leptin expression at the transcriptional level, and therefore also secretion levels of this hormone (Hoffsted et al., 2002). In a study of 323 patients who received kidney transplants, the association between the LEP gene polymorphism rs2167270 and serum leptin levels was found (Romanowski et al., 2015).

Adiponectin

Adiponectin is an adipokine synthesized within adipose tissue, it is considered to be an antiinflammatory adipocytokine that improves insulin sensitivity and also has cardioprotective benefits (Liu and Liu, 2014). Studies showed an inverse correlation between adiponectin, inflammation and nutrition in kidney transplant recipients (Gnacinska et al., 2010; Kaisar et al., 2009). Adiponectin is metabolised by the liver and metabolites are eliminated by the kidneys (Tacke et al., 2005). In patients with Type 2 diabetes, increased plasma adiponectin levels are associated with risk of concurrent diabetic nephropathy and the prevalence of progression to dialysis was significantly increased among patients with higher adiponectin level (Chen et al., 2018).

Adiponectin is an abundantly expressed adipokine that exerts a potent insulin-sensitising effect through binding to its receptors AdipoR1 and AdipoR2, leading to signalling pathways. In obesity-linked insulin resistance, both adiponectin and its receptors are downregulated (Clarke and Mohamed-Ali, 2005). Unlike most other adipokines, plasma adiponectin levels were reduced in animal models of obesity and insulin resistance (Hotta et al., 2001; Hu et al., 1996). Administration of recombinant adiponectin to rodents resulted in increased glucose uptake and fat oxidation in muscle, reduced hepatic glucose production, and improved whole-body insulin sensitivity (Berg et al., 2001; Fruebis, 2001; Yamauchi et al., 2001). In humans, plasma adiponectin levels were correlated negatively with adiposity (Chop et al., 2003; Tschritter et al., 2003; Weyer et al., 2001), insulin resistance and Type 2 diabetes (Weyer et al., 2001), yet positively correlated with markers of insulin sensitivity in frequently sampled intravenous glucose tolerance testing (Hanley et al., 2007).

There is a substantial evidence of adiponectin effects on β-cell function and survival. Both adiponectin’s receptors are expressed in primary and clonal beta-cells (Brown et al., 2010; Kharroubi et al., 2003). It was shown that adiponectin has an effect to preserve beta-cell mass either by inhibiting apoptosis of β-cells (Hanley et al., 2007; Weyer et al., 2001) or by increasing proliferation (Chetboun et al., 2012).

A study on 174 patients who underwent kidney transplantation studied the development of NODAT and its relationship to adiponectin (Bayés et al., 2007). Statistically significant differences between NODAT and non-NODAT patients were found for insulin level, HOMA-IR index and adiponectin serum concentrations. NODAT patients showed higher pre-transplant plasma insulin concentrations and lower adiponectin concentrations than non-NODAT patients. Pre-transplant adiponectin was inversely related to BMI, insulin and HOMA-IR index (Bayés et al., 2007). This relationship was also shown in a stable hemodialysis patient population (Zoccali et al., 2002). Therefore, higher pre-transplant adiponectin concentrations constitute a protective factor against NODAT in patients with kidney transplants. Another study was aimed at the relationship between fat areas and the adiponectin fraction, post-transplant diabetes mellitus and cardiovascular diseases. 57 Japanese patients who underwent renal transplantation were included. Serum adiponectin levels inversely correlated with glomerular filtration and the higher low molecular weight adiponectin ratio and the visceral fat were aggravating factors of post-transplant diabetes mellitus (Adachi et al., 2016).

Adiponectin gene polymorphisms are also under investigation. It is reported that adiponectin levels are partly determined by genetic factors. Previous studies reported an association between the T allele of 276G/T SNP and increased plasma adiponectin concentrations in healthy (Hara et al., 2002) and obese (Bayés et al., 2007) individuals. Also, higher adiponectin levels are related to a reduced risk for NODAT in kidney transplant recipients (Bayés et al., 2007). The adiponectin rs1501299 polymorphism represents a risk factor for Type 2 diabetes mellitus, insulin resistance and lower plasma adiponectin concentration (Hara et al., 2002). Nicoletto et al. examined the rs1501299 adiponectin gene polymorphism in 270 Caucasian kidney transplant recipients, the TT genotype was significantly more frequent in patients with post-transplant diabetes mellitus than non-PTDM patients (Nicoletto et al., 2013). This was confirmed by two other studies (Kang et al., 2012; Yu et al., 2011).

TNF-α

TNF-α is a proinflammatory adipokine that is produced by monocytes and macrophages and it is highly expressed and secreted in adipose tissue. It has a central role in inflammation and autoimmune diseases (Fasshauer et al., 2014) and correlates with obesity and decreases with weight loss (Brown et al., 2010; Cawthorn and Sethi, 2008; Hotamisligil et al., 1993). TNF-α has been shown to directly impair both insulin signalling in insulin-sensitive tissues and insulin secretion (Brown et al., 2010; Cawthorn and Sethi, 2008). Inhibition TNF-α action (by antibodies or genetic ablation) had insulin-sensitising effects in various rodent models of obesity and diabetes (Hotamisligil et al., 1993).
and in other studies it reduced inflammation and improved fatty liver disease (Cawthorn and Sethi, 2008). A few studies reported some improvement of insulin sensitivity or glucose homeostasis in insulin resistant individuals during prolonged treatment with the anti-TNF-α antibody (infliximab or etanercept) (Stanley et al., 2011; Yazdani-Biuki et al., 2004). In contrast, this treatment has not been associated with changes in insulin sensitivity and obesity in humans (Ofei et al., 1996; Paquot et al., 2000).

Both peripheral insulin action and insulin secretion appear to be affected in NODAT. inflammatory cytokines and chemokines are involved in this process. Interleukins and other molecules are secreted by T-cells and by stimulating the production of inflammatory cytokines (TNF-α, IL-1B and IL-6). In the study of Bayés et al. (2007) on 199 patients who underwent kidney transplantation, in agreement with other studies (Blüher et al., 2001), there were no differences in TNF-α levels corrected by BMI between NODAT and non-NODAT patients, when data from all individuals were analysed.

**PAI-1**

Plasminogen activator inhibitor-1 (PAI-1), a main physiological inhibitor of the fibrinolytic system, is expressed in rodent and in human adipose tissue (Alessi et al., 1997; Samad and Loskutoff, 1996; Shimomura et al., 1996). Its levels in plasma are increased in obesity and reduced with weight loss. Adipocyte-derived PAI-1, predominantly expressed in visceral fat, is released into the circulation in parallel with increased fat mass, and it functions as a crucial adipokine that negatively affects physiological metabolism and vascular biology. Type 2 Diabetes mellitus is a genetically heterogeneous disease resulting from a complex interaction of genetic and environmental factors. High plasma plasminogen activator inhibitor (PAI-1) concentrations have been linked to the development of type 2 diabetes mellitus, insulin resistance, atherosclerosis, dyslipidemia, hypertension, obesity and hyper-insulinemia (Herlihy et al., 2002; Julan-Vague et al., 2000).

Increased PAI-1 activity in stable pediatric renal transplants is determined by genetic factors and metabolic factors, it significantly associated with metabolic factors including CRP, body mass index, fasting insulinemia, the latter mainly linked to the insulin resistance syndrome (Aldamiz-Echevarria et al., 2003). It was also reported that serum PAI-1 activity significantly associates with chronic allograft damage index score in kidney allografts (Chang et al., 2009). Several polymorphisms at position 675 in the promoter region of the gene have been shown to exert the greatest impact on plasma PAI-1 concentration. The study of Chang et al. (2011) of 458 kidney transplant recipients receiving triple drug immunosuppression (cyclosporine/tacrolimus, mycophenolate mofetil, with or without prednisolone) showed that 21.5% developed NODAT. In the NODAT group, the patients were older, with higher BMI and more patients used tacrolimus-based immunosuppression. The genotype distribution was significantly different, non-NODAT patients were significantly more often homozygous for the 5G/5G genotypes than patients with post-transplant diabetes. Therefore, PAI-1 5G/5G genotype had a significant preventing role on the occurrence of NODAT compared to the PAI-1 4G/4G and 4G/5G genotypes ($p = 0.0058$).

**IGF2**

Insulin-like growth factors (IGFs) regulate growth and metabolic processes. IGF2 is synthesized primarily by the liver, but it is also produced locally by many tissues including adipose tissue, where it acts in an autocrine/paracrine manner (LeRoith and Roberts, 2003). IGF1 and IGF2 contribute to pancreatic beta-cell growth and development by regulating beta-cell replication, renewal, and apoptosis (t Hart et al., 2004). Dysbalance between beta-cell renewal and apoptosis due to alterations in IGF levels is potentially of great importance in the development of glucose intolerance, a major characteristic of Type 2 diabetes (Vattam et al., 2013). IGF2 polymorphisms have been associated with weight gain, body mass, obesity and adiposity (Sandhu et al., 2003). In the study of Apa1 polymorphism of IGF2 of 364 individuals who have undergone renal transplant, it was reported that a new onset of diabetes mellitus patients showed a significant difference for the G allele and AG genotype when compared to the end-stage renal disease patients (Vattam et al., 2013). In conclusion, Apa1 polymorphism of IGF2 can help indentify individuals at a high risk of developing NODAT in renal transplant recipients.

**FGF-21**

Fibroblast growth factor-21 is a member of the FGF family that is produced in liver and adipose tissue and has recently been marked as an important metabolic regulator (Gaich et al., 2013). FGF-21 has significant glucose and lipids lowering as well as thermogenic effects. There is an evidence demonstrating that the FGF-21 enhances insulin sensitivity by regulating the selective expansion of subcutaneous fat. In animals, decreased insulin sensitivity mice is associated with reduced subcutaneous fat, whereas the replenishment of FGF-21 to a level similar to those occurring in diet-induced obesity can reverse insulin resistance as well as increase the amount of subcutaneous fat. In humans, an independent association between FGF-21 levels and the amount of subcutaneous fat was found in insulinsensitive obese individuals (Li et al., 2018). Administration of FGF-21 showed diverse metabolic effects, on body weight reduction, fasting insulin level, improvements in dyslipidemia in animal models (Gaich et al., 2013). Furthermore, FGF-21 was also shown to improve pancreatic beta-cell function and survival (Wente et al., 2006).

In the study on 176 renal transplant recipients, Bagheri et al. (2016) investigated the correlation of serum FGF-21 levels with metabolic syndrome (MS) in renal transplanted subjects. They observed no significant differences in serum FGF-21 levels between MS and non-MS groups even with a history of hemodialysis or peritoneal dialysis before transplantation, living donor or deceased donor recipients. There were no significant correlations between the FGF-21 level and sex, age, BMI, waist circumference, TG, HDL cholesterol, FBS, uric acid, duration of dialysis before transplantation and frequency of transplantation.

**Other adipocytokines**

Resistin is an adipocytokine synthetized by macrophages. There is considerable controversy about the role of resistin in humans. Several groups suggested resistin levels to be associated with obesity, insulin resistance, and Type 2 diabetes (Degawa-Yamauchi et al., 2003; Heilbronn et al., 2004; Ochi et al., 2007; Osawa et al., 2004, 2007; Youn et al., 2004). However, other groups failed to identify changes in resistin levels in these conditions (Chen et al., 2005; Gerber et al., 2005; Kielstein et al., 2003; Lee et al., 2003; Pfützer et al., 2003). Resistin’s role in diabetes mellitus is still under investigation, Shu et al. (2014) demonstrated strong association between the presence of the metabolic syndrome and higher serum resistin levels.

Visfatin is largely synthetized and secreted by granulocytes. Originally isolated as a presumptive cytokine that enhances the maturation of beta-cell precursors (Samal et al., 1994) was reported to be highly correlated with the amount of visceral fat in humans and in a mouse model of obesity and insulin resistance, to exert insulin-mimetic effects in cultured cells, and to lower plasma glucose levels in mice (Fukuhara, 2005). Observational
studies have not yet demonstrated an association between visfatin and glucose metabolism, but in animal studies visfatin was found to have a protective effect on pancreatic cells (Kim et al., 2014; Olszanecka-Glinianowicz et al., 2014; Xiang et al., 2015). Unfortunately, there are no studies aimed at the relationship between resistin and visfatin and NODAT.

Conclusions

In conclusion, a growing number of hormones and other active circulating factors secreted by adipose tissue have been found to have an established role in metabolic pathways leading to diabetes mellitus. We aimed at new-onset diabetes mellitus after transplantation, which belongs to the serious non-immunological complications that occurs after organ transplantation. NODAT can dramatically affect patient’s quality of life, survival and prognosis through poor graft function, increased risk of cardiovascular complications, chronic rejection and organ failure.

Although, the relationship between adipocytokines and NODAT has not been thoroughly explored, the data found about their function on insulin sensitivity and beta cell function. Most known adipocytokines – leptin and adiponectin affect beta-cell function and survival and they also have an insulin sensitising effect. Leptin levels are reduced with decreasing the renal function and it was shown that the type of leptin gene allele has an association with NODAT. Leptin gene polymorphisms contribute to obesity, insulin resistance and diabetes mellitus. Higher levels of adiponectin were found in patients with NODAT in comparison with non-NODAT patients and adiponectin gene polymorphisms are associated with diabetes mellitus. The role of other mentioned adipocytokines (TNF-α, PAI-1, IGF2, FGF21, resistin, visfatin) is still under investigation and their effects on diabetes mellitus or NODAT are still controversial. All the known or supposed effects of these adipocytokines are summarized in Fig. 1.

Future directions

Future studies should be conducted on investigating the association between adipocytokines’ levels in plasma and the new-onset diabetes mellitus after transplantation, which is surely practically more usable than gene polymorphisms. On the other hand, gene polymorphisms could be used in association with serum levels of the adipocytokines and homeostasis model assessment (HOMA) of insulin resistance or beta cell function. This approach could explore the possible mechanisms of these adipokines in the pathogenesis of NODAT.

Since NODAT is a very serious complication in patients after renal transplantation, identification of the risk factors may help prevent the condition. The risk factors can be divided into two groups, modifiable and non-modifiable. The non-modifiable risk factors are age, ethnic and genetic background, family history of type 2 diabetes mellitus and previous impaired glucose tolerance. The modifiable risk factors are obesity, viral infection, immunosuppressive drugs, human leukocyte antigen mismatch, donor gender and underlying renal disease. Immunosuppressive regimens include calcineurin inhibitors (tacrolimus, sirolimus), glucocorticosteroids, mycophenolate mofetil, sirolimus or azathioprine. Tacrolimus has usually been observed to be more diabetogenic. A meta-analysis published in 2004 found that insulin-treated diabetes mellitus occurred in 9.8% of renal transplant recipients on tacrolimus versus 2.7% of those on cyclosporine-based regimen (Heisel et al., 2004). In a recent study, it was found, that replacement of tacrolimus with cyclosporine significantly improves glucose metabolism and it has the potential to reverse diabetes during the first year after conversion (Wissing et al., 2018). Sirolimus is a diabetogenic agent. Calcineurin inhibitors to sirolimus conversion therapy in a regimen consisting of tacrolimus and sirolimus were associated with a 30% increased incidence of impaired glucose tolerance (Schold et al., 2005). The combination of either calcineurin inhibitor with sirolimus may be particularly diabetogenic, compared with the combination of a calcineurin inhibitor with mycophenolate mofetil (Luan et al., 2011). Glucocorticoids are well known as potent immunosuppressive drugs with a number of side effects including new onset diabetes mellitus. They are regular part of therapeutic regimens after transplantation but it is also possible to use the glucocorticoids-free regimens. Studying plasma levels of adipocytokines is a possible method of predicting...
a patient’s risk for developing NODAT and would be a valuable device in selecting appropriate immunosuppressive regimens for these individuals.

Adiponectin and leptin, as well known and researched adipokines, seem promising. However, less explored PAI-1 and IGFB2 showed possible effect on metabolic pathways connected to NODAT and therefore we need further research to objectify it.

Another discussed topic is possible use of adipocytokines or adipokin targeting antibodies as therapeutic target. Recombinant leptin treatment is available in a few selected centers on research-protocol basis. Metreleptin (analog of the human hormone leptin) has been approved for the treatment of lipodystrophy in Japan. It has also been suggested for the treatment of obesity (Blüher, 2014). Administration of recombinant adiponectin to rodents resulted in increased glucose uptake and improved insulin sensitivity. A few studies reported improvement of insulin sensitivity in rodents treated with anti-TNF-α antibodies but not in humans. Administration of FGF-21 showed metabolic effects on body weight, insulin levels or dyslipidemia in animal models. Adipocytokines are promising candidates for novel treatment concepts but there is a long way ahead.

It remains to be seen if these factors play a causative role in the development of diabetes mellitus or if they contribute to the progression of the disease by affecting beta-cell function, insulin sensitivity or insulin resistance. Further studies are needed to understand the role of all adipocytokines in the development of diabetes mellitus in organ transplant recipients. Unravelling the pathophysiological roles of adipocytokines can lead to the development of new diagnostic or pharmacotherapeutic approaches.

Conflict of interests

The authors have no conflict of interests to declare.

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