Obesity and Kidney Transplantation: Exploring Crosstalks between Metabolism and Immune Responses

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Abstract

The global prevalence of overweight and obesity is increasing at an alarming rate. Thus, obesity has also become a clinically significant challenge in transplantation medicine. Despite a growing number of clinical reports on inferior outcome and higher complication rates in obese recipients, a more profound understanding of obesity related changes on immune responses relevant to organ transplantation is still lacking. Studies outside of transplantation have clearly demonstrated that obesity impacts several aspects of the immune response linked to a process of chronic low-grade inflammation.
This review addresses the consequences of obesity on transplant outcomes and summarizes relevant data linking obesity to immunity. **(Trends in Transplant. 2014;8:27-34)**

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Key words

Transplantation. Obesity. Immune response. Outcome.

Background

The worldwide prevalence of obesity has progressively increased over the past decades, now reaching epidemic proportions. The latest National Health and Nutrition Examination Survey (NHANES) reports on rapidly advancing rates of overweight and obesity. In detail,

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> one-third of adults in the USA are obese with a body mass index (BMI) $\geq$ 30. Alarmingly, the rate of morbid obesity (BMI $\geq$ 40) has been growing rapidly and doubled over the last two decades to now 6.3%[1]. In line with the NHANES data, the prevalence of obesity has also increased in organ transplant candidates, with 29.8% of kidney allograft recipients in the USA being obese (BMI $\geq$ 30)[2,3]. Moreover, it can be expected that increasing rates of obesity will also be reflected in the donor population.

The clinical impact of obesity on outcomes and complication rates following solid-organ transplantation has been largely recognized. Obese graft recipients have increased risks for complications such as wound infections, delayed wound healing, deep vein thrombosis,

and perioperative cardiovascular events[4,5]. However, obesity related consequences on immune responses and their impact on transplant outcome have so far only received little attention. We will provide a comprehensive overview of the clinical impact of obesity on outcomes following kidney transplantation. Moreover, we will summarize data providing a mechanistic link between obesity and immune responses.

Clinical impact of obesity in kidney transplantation

Delayed graft function

Delayed graft function (DGF) is in general defined as the need for dialysis in the first week after transplantation. DGF, in turn, has been linked to augmented allograft immunogenicity and increased rates of acute rejection[6]. Most clinical studies show more frequent DGF rates in obese transplant recipients[7-10]. These results are in accordance with those of several registry studies: a comprehensive analysis of > 50,000 adult renal transplants between 1988 and 1997 registered in the US Renal Database System (USRDS) revealed a significantly increased risk for DGF in recipients with BMI > 36[11]. In a study of > 10,000 patients listed in the Scientific Registry of Transplant Recipients (SRTR), obesity was reported to be an independent risk factor for DGF[12]. An additional analysis from the Australian and New Zealand Dialysis and Transplant Registry (ANZDATA) confirmed the association between obesity (BMI ≥ 30) and DGF[13]. Moreover, recent large-volume studies from the United Network for Organ Sharing (UNOS) database support the correlation of an augmented risk for DGF in parallel to body weight[2,14].

Although there are certain limitations to these clinical studies, including differences in the definitions of obesity and, on a more general level, a controversial discussion on BMI appropriately reflecting the risks of obesity,

there is a robust and growing body of evidence that obese transplant recipients are at higher risk for DGF. Interestingly, a paired analysis of mate kidneys showed significantly increased rates of DGF in obese recipients[15].

Acute rejection

Both, analysis from the UNOS and the ANZDATA database revealed a link between obesity (BMI ≥ 30) and rates of acute rejections[13,14]. However, other registry and single-center studies failed to associate recipient obesity with increased rates of acute rejections[2,10-11,16].

These controversial findings are noteworthy. Several factors may interfere with a clear cause and effect correlation of obesity and acute rejections: the trend towards more rejections in patients with higher BMI could be explained by lower calcineurin inhibitor exposure as discussed by Chang, et al. in the ANZDATA registry study[13]. Moreover, lymphocyte-depleting agents are more frequently utilized in obese recipients, potentially impacting acute rejection rates[5]. In addition, biopsy proven acute rejections may be underrepresented in obese recipients since technical challenges and increased risks of complications may alter the threshold for biopsies.

In summary, the clinical correlation between recipient obesity and acute rejection rates remains controversial and warrants further in-depth exploration with a detailed analysis of confounding factors.

Graft and patient survival

Several studies have demonstrated detrimental effects of obesity on short-term and long-term graft survival[10,16,17]. This correlation is supported by a large-scale USRDS registry analysis showing significantly worse patient and graft survival in patients at the extremes

of very high (> 36) and very low BMIs (< 18). This U-shaped association between obesity and transplant outcome has also been documented in other studies[11]. A more recent analysis of the UNOS database, including > 70,000 patients, showed a significantly increased risk for graft failure in patients with a BMI ≥ 35. However, patient survival was not impacted by obesity in this analysis[2]. Data from the ANZ-DATA registry analysis also showed a significant impact of obesity on both graft and patient survival in a univariate analysis. Of note, this correlation was not confirmed for patient survival in a multivariate analysis[13].

Cardiovascular risk factors require a precise exploration when analyzing the clinical impact of obesity on patient survival following transplantation as cardiovascular disease (CVD) is the leading cause of death among renal transplant recipients[18]. Several studies have revealed a clear trend towards higher mortality rates in obese transplant recipients[19-21]. One of the major challenges when assessing transplant outcome in obese transplant recipients is the delineation of obesity *per se* compared to obesity related clinical comorbidities. In fact, some clinical reports have been unable to correlate obesity to transplant outcome while other reports suggested protective effects of obesity. Although small in volume, a retrospective single-centre analysis comparing renal transplant outcome in patients carefully screened for CVD was unable to link graft or patient survival to obesity[22]. Interestingly, kidneys from living donors, in general a rigorously selected patient population, demonstrated 100% three-year graft survival rates in morbidly obese recipients (BMI ≥ 35) compared with 91% in patients with BMI < 25[23]. Although based on a small number of patients, those studies point towards the importance of further efforts to disentangle the interactions between obesity and comorbid conditions.

Furthermore, assessing patient and graft outcomes based on BMI alone may be misleading as BMI does not distinguish between visceral and abdominal fat or muscle mass. Assessment of obesity by waist circumference or waist-to-hip ratio may thus be a better predictor for the individual risk profile, with the latter being a stronger independent predictor of CVD and death linked to cardiovascular events[24]. A recent study in obese kidney graft recipients has shown a survival benefit in obese recipients with higher muscle mass[25]. Moreover, in a prospective cohort study of almost 1000 kidney transplant recipients, higher mortality rates linked to BMI were in fact lower when adjusted for waist circumference[26].

In summary, currently available clinical data correlating obesity with graft and patient survival are conflicting and call for an improved delineation of consequences of obesity from confounding risk factors. The concept of obesity as a state of chronic low-grade inflammation, at the same time, provides a mechanistic link between metabolic functions and immune responses and has intriguing implications that require in-depth analysis in models of organ transplantation.

The impact of obesity on immune responses

The concept of obesity as chronic low-grade inflammation

Intriguing recent data have shown that inflammation is critical for the development of obesity related diseases including insulin resistance and type 2 diabetes mellitus[27]. Cytokines, reactive oxygen species, and other agents produced by adipocytes and immune cells are able to activate important stress pathways and disrupt central metabolic processes including the insulin signaling cascade[28]. These processes may, in turn, activate JUN N-terminal kinase (JNK), thus preventing the inhibition of nuclear factor-κB (NFκB) kinase-b signaling pathways in liver, skeletal muscle, and fat. Those mechanisms may finally result

in the inhibition of insulin receptor substrate-1 phosphorylation, leading to insulin resistance.

Excessive nutrient intake is the primary cause of hyperplasia and hypertrophy of adipose tissue. The inflammatory pathways subsequently triggered in adipose tissue may be initiated by adipocytes, previously thought to be a passive storage for triglycerides and energy. More recently, adipocytes have been linked to the production of several hormones, in addition to proinflammatory chemokines and cytokines. Thus, adipose tissue has been conceptualized as an endocrine organ[29]. Cytokines secreted by hypertrophic adipocytes include tumor necrosis factor (TNF)-α, interleukin (IL)-6, resistin and monocyte chemoattractant protein-1 and represent a classical proinflammatory cytokine profile. Those cytokines may lead to the infiltration of immune cells, thus enhancing and stimulating the inflammatory microenvironment. Moreover, saturated fatty acids have been shown to act as danger signals, promoting the activation of macrophages by ligation of the Toll-like receptor-4. These mechanisms may subsequently lead to the activation of signaling cascades mediated by interferon regulatory factor-3, JNK, and NFκB[30].

As obesity progresses, inflammation accelerates gradually. This process is characterized by a significant shift in macrophage subtypes towards proinflammatory M1 macrophages, amplifying the inflammatory signal. Moreover, increased numbers of mast cells and natural killer T-cells have been observed in adipose tissue, contributing to local inflammation[31,32]. In addition, there is a marked proliferation of CD4+ T-cells and, particularly noteworthy, a decline in the number of T regulatory cells (T_{reg}). Both findings represent a shift towards a Th1-type immune response[33,34]. It can thus be postulated that the proinflammatory response subsequent to obesity may impact both innate and adaptive immune responses following organ transplantation. Although not proven at this point, chronic low-grade inflammation may result in a significant activation of immune cells, their ligands, and receptors, releasing proinflammatory cytokines and accelerating alloimmune responses.

Mediators linking obesity and immune responses

As adipose tissue is considered an endocrine organ, several secreted products from adipocytes have been characterized. Besides the production of proinflammatory cytokines, adipocytes have also the capacity to produce further soluble factors, so-called adipocytokines. These molecules provide an important link between obesity, insulin resistance, and chronic inflammation[35]. Adiponectin and leptin are the most abundantly produced adipocytokines. Both play specific roles in immune responses and have been shown to have a significant impact on allograft survival in animal transplant models.

Adiponectin is mainly associated with anti-inflammatory capacities through the inhibition of TNF-α induced adhesion molecules. Furthermore, adiponectin also induces the production of IL-10 and IL-1 receptor antagonist, both skewing immune responses towards a Th2 profile[36,37]. Of relevance for organ transplantation, grafts in adiponectin-deficient mice were more rapidly rejected[38]. Furthermore, a prospective study, which monitored metabolic factors in obese kidney graft recipients (BMI > 30), revealed a significant increase of adiponectin levels in patients successfully achieving a weight reduction based on dietary intervention and steroid withdrawal[39].

In contrast to adiponectin, leptin has predominantly proinflammatory characteristics. Leptin receptors are expressed on several cell types of innate and adaptive immunity[40]. Leptin increases the production of proinflammatory cytokines such as TNF-α, IL-6, and IL-12, all resulting in a Th1-dominated immune response[41].

Of note, leptin-deficient mice have increased numbers of T_{reg}[42]. Recently, leptin has also been shown to affect allograft survival in a murine skin transplant model. Survival of allogeneic skin transplants was prolonged in obese leptin-deficient (Lep$^{ob/ob}$) mice, while T_{reg} frequencies had increased and a shift towards a Th2 profile was observed[43].

Outcome optimization: the immunological impact of weight loss

While obesity has been linked to inferior outcomes following renal transplantation in most clinical reports, there is also evidence that obesity may have both protective and detrimental consequences on transplant outcome. This phenomenon, known as the "obesity paradox", has recently also been confirmed in patients undergoing non-bariatric general surgery[44]. Thus, the question arises how to reverse the detrimental effects of obesity and how to shift the inflammatory network towards protective conditions. Intended weight loss appears to be a simple option, although catabolic conditions and their detrimental effects on chronic illnesses require close monitoring. At the same time, weight loss has also been shown to have beneficial immunological consequences, mainly mediated by adipocytokines. These effects seem to be reproducible by bariatric surgery, suggesting a potential beneficial impact on transplant outcomes.
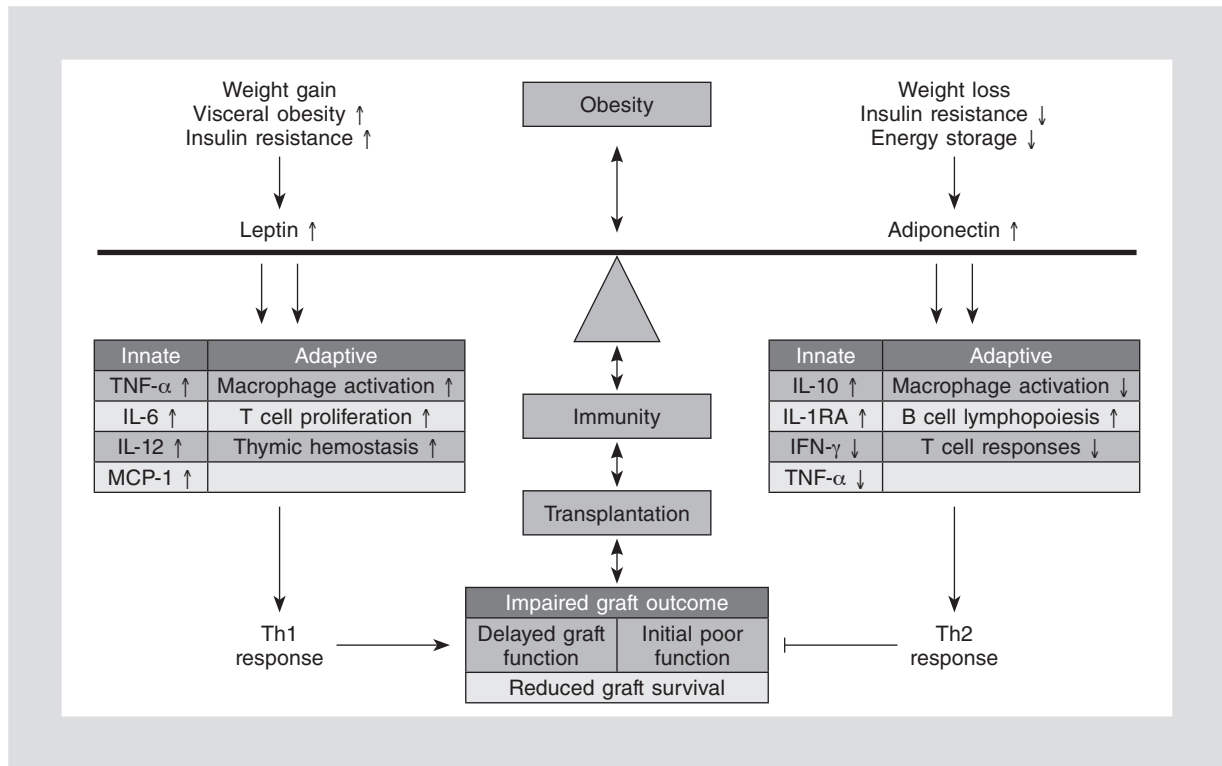
Adipocytokines and transplant outcome

A prospective study monitoring metabolic factors in obese kidney graft recipients (BMI > 30) revealed a significant increase of adiponectin in parallel to significant decreases of leptin levels in patients achieving weight loss[39]. Furthermore, leptin deficiency resulted in a prolonged graft survival linked to a shift towards Th2 conditions[43]. These exciting data

suggest that adipocytokines might be key mediators in orchestrating the inflammatory network of obesity (Fig. 1). Whether monitoring of leptin and adiponectin levels may help predicting individual risk profiles in obese transplant candidates or recipients remains to be elucidated. Of note, a significant decrease of serum leptin levels and improvement of insulin resistance have also been reported following bariatric surgery[45,46]. Although there are only few studies on safety and efficacy of bariatric surgery in renal transplant candidates or recipients, therapeutic approaches in obese transplant candidates may include bariatric surgery and its inherent metabolic and immunological consequences.

Bariatric surgery in transplant candidates and recipients

A retrospective analysis of the USRDS database reported on outcomes of obese kidney transplant candidates and obese graft recipients undergoing bariatric surgery. This study revealed slightly increased perioperative mortality compared to individuals undergoing bariatric surgery without kidney disease[47]. A small-volume, single-center analysis in wait-listed patients and recipients showed no increase in perioperative mortality or graft loss while demonstrating mean excess body weight loss (EBWL) of almost 70% by one year[48]. Another single-center study showed that laparoscopic bariatric surgery in morbidly obese patients with end-stage renal disease (ESRD) awaiting transplantation could be performed without perioperative mortality. Mean EBWL > 60% was achieved by nine months and all patients reached the institution's BMI limit for listing[49].

However, case reports have also documented acute rejections subsequent to bariatric surgery[47], potentially linked to a modified resorption and metabolism of immunosuppressants following gastric bypass surgery[50]. An increase in dose requirement following

Figure 1. *Characteristics of the inflammatory network linking obesity, immunity, and transplantation. Perturbation and dysbalance of energy hemostasis lead to an increased production of adipocytokines favoring either leptin or adiponectin, depending on the underlying metabolic changes. Both adipocytokines have a significant impact on innate and adaptive immune responses resulting in Th1 or Th2 responses. TNF: tumor necrosis factor; IL: interleukin; MCP: monocyte chemotactic protein; IFN: interferon; RA: receptor antagonist.*

bariatric surgery with malabsorptive components has been reported for most frequently used immunosuppressive drugs, emphasizing the need for meticulous drug monitoring in transplanted patients following bariatric surgery[51]. The risk of interference with immunosuppressants may be minimized in solely restrictive bariatric surgery procedures. Several cases of laparoscopic adjustable gastric banding (LAGB) have been reported in waitlisted and transplanted patients. Of note, significant major complications and high surgical revision rates after LAGB have been reported[52,53]. Laparoscopic sleeve gastrectomy (LSG) has once been used as a bridge to definitive surgery in high-risk patients, but has recently also been proposed as a stand-alone procedure in high-risk individuals such as patients suffering from hepatic cirrhosis[54]. Although data on LSG in patients with ESRD or renal transplant candidates remain limited,

results are encouraging for both outcomes and management of immunosuppressants[55-57].

Conclusion

Obesity has been conceptualized as a state of chronic low-grade inflammation in the recent past. The relevance of this concept for organ transplantation will need to be probed in more detail moving forward. Exciting data provide evidence for an inflammatory network orchestrated by adipose tissue, chemokines, and adipocytokines affecting innate and adaptive immunity. Increased immunogenicity and impaired outcomes following solid-organ transplantation may reflect crosstalks between metabolism, inflammation, and immune responses.

Most clinical reports document inferior outcomes and higher complication rates in

obese recipients following kidney transplantation. In an approach to better predict the individual risk profile in obese transplant candidates and recipients, waist circumference or waist-to-hip ratio may more appropriately reflect the risk of obesity. Moreover, clinical and experimental studies will need to distinguish between consequences of obesity *per se* and associated risk factors.

Metabolic changes following bariatric surgery or weight loss may have profound effects on the inflammatory network related to obesity and may improve transplant outcomes. Solely restrictive bariatric procedures with limited risk of interference with immunosuppressive therapy may be beneficial in selected transplant recipients.

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