Title: Obesity in Kidney Transplantation

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Obesity in Kidney Transplantation

Abstract

Kidney transplantation is the preferred modality of renal replacement therapy. Long-term patient- and graft- survival have only improved marginally over the recent decade, mainly due to the development of cardiovascular disease following transplantation. Obesity is a risk factor for cardiovascular disease, and is common pre- and post- transplantation. This article reviews the literature assessing the role of pre- and post- transplant obesity on patient- and graft- survival, discusses the underlying obesity-related mechanisms leading to inferior kidney transplant outcomes, and explores the role of nutritional intervention on improving long-term outcomes of transplantation. While the role of pre-transplant obesity remains uncertain, post-transplant obesity increases the risk of graft failure and mortality. Nutritional

intervention is effective in achieving post-transplant weight loss, but the impact on long-term outcomes has not been established. Future research should focus on conducting nutritional intervention studies aiming to improve long-term outcomes of kidney transplantation.

Keywords

Obesity, Inflammation, Sarcopenia, Kidney, Transplant

Introduction

Kidney transplantation is the preferred modality of renal replacement therapy for many patients with end-stage renal disease (ESRD) [1]. Compared to remaining on transplant waiting list, kidney transplantation improves long-term survival [2], enhances quality of life [3], demonstrates cost benefit [4], and rectifies uraemia and metabolic abnormalities contributing to overall sense of well-being [5]. Despite several advantages following successful transplantation, the corollary of the current shortage of organs is that only a proportion of patients on transplant waiting list proceed to transplantation, with up to 40% dying whilst waiting on dialysis [6]. It is crucial that the best possible use is made of those transplanted kidney (graft), and therefore optimising patient- and graft- survival following transplantation should be a priority in this patient group.

Short-term patient- and graft- survival have substantially improved over the recent decades, with most centres reporting both survival rates at 1 year of greater than 90% [7]. However, long-term success has been difficult to accomplish as evident by the marginal increase in patient- and graft- survival rates over the past 15 years [8]. This phenomenon is multifactorial. Firstly, modification of alloimmunity using immunosuppression has reduced short-term early acute rejection rates [8], but the nephrotoxicity of immunosuppressive medication is known to limit long-term graft survival [9]. Secondly, the use of maintenance immunosuppressive therapy is associated with increased risk of infection and malignancy [10]. Thirdly, cardiovascular disease (CVD) is a well-known long-term complication in kidney transplant recipients (KTRs) [11]. It is both the leading cause of death following transplantation [12] and death with a functioning graft [13].

According to the World Health Organization, overweight is defined as a BMI of 25.0 to 29.9 kg/m^2; and obesity is defined as a BMI of $\geq$ 30.0 kg/m^2 [14]. Prior to transplantation, the role of obesity on long-term patient- and graft survival remains uncertain. However, available evidence suggests that obesity predisposes to delayed graft function with subsequent impact on graft failure [7]. Following transplantation, obesity is strongly associated with reduced long-term patient- and graft survival [7], but it failed to display an independent relationship with CVD risk [15-18]. However, obesity leads to higher prevalence of CVD risk factors including hypertension, dyslipidaemia, diabetes mellitus and insulin resistance, all of which are independently associated with increased risk of graft failure [15-18]. These individual diseases also cluster as part of metabolic syndrome. A recent sub-analysis of the ALERT (Assessment of LEscol in Renal Transplantation) study revealed that metabolic syndrome

was associated with increased risk of graft failure [19]. Obesity is modifiable by nutritional intervention, but the impact of weight loss resulting from these interventions on long-term patient- and graft- survival has not been well-established.

The purposes of this article were to review the relevant literature assessing the role of pre- and post- transplant obesity on patient- and graft- survival, to discuss the potential underlying mechanisms by which obesity induces its detrimental effects leading to inferior kidney transplant outcomes, and to explore the role of nutritional intervention on improving long-term outcomes of kidney transplantation. Finally, this article aims to identify gaps in current literature and recommends potential areas for future research.

Prevalence and impact of obesity prior to transplantation

Overweight and obesity are common at the time of transplantation [20]. Currently, 60% of KTRs are overweight at the time of transplantation, representing a 116% increase from 1987 [20]. Indeed, many transplant centres in the UK and US exclude patients with a BMI greater than 30 or 35 kg/m^2 [21]. A BMI $\geq$ 35 kg/m^2 was the third most common reason to exclude as many as 10% of patients from transplantation [22]. Despite this, the effect of pre-transplant obesity on patient- and graft- survival remains controversial, with several conflicting studies in the literature. *Table 1* summarises the studies examining the impact of pre-transplant obesity on kidney transplant outcomes. In some studies, while pre-transplant obesity had no effect on long-term outcomes, it demonstrated a negative impact upon short-term outcomes including graft failure within the first year post-transplant [23], post-transplant surgical

complications and delayed graft function [24-29]. Despite the lack of relationship between pre-transplant obesity and long-term outcomes in these studies, it is important to note that delayed graft function is associated with reduced long-term graft survival [7,30]. Some studies showed that obesity exerts a negative impact on long-term patient- and graft survival [7,31-36]. In contrast, adverse impact of obesity on both short- and long- term outcomes were seen in some studies [31,33]. Also, a study by Yamamoto et al [35] otherwise demonstrated that while obesity had no effect on short-term graft survival, decreased medium- and long- term graft survival were observed in obese KTRs. Finally, Streja et al showed that obesity was associated with graft loss, but had no effect on mortality [36]. In summary, studies with short-term outcome data have unanimously demonstrated negative impact of pre-transplant obesity whilst studies with long-term outcome data have yielded variable conclusions. Such conflicting results from the latter group of studies may partly stem from large variations in the sample size and follow-up period (2-20 years), with studies of larger sample size and ≥6-year follow-up generally showing an impact.

Impact of body composition prior to transplantation

Given the conflicting data on the effect of pre-transplant obesity on patient- and graft-survival, a recent study explored the effect of body composition on long-term patient- and graft- survival rates. It showed that sarcopenic obesity prior to transplantation was associated with increased mortality and graft failure [36], while sarcopenia in the study was defined as reduced pre-transplant muscle mass represented by lower pre-transplant serum creatinine in patients with BMI $\geq$ 30 kg/m^2.

Impact of weight loss during transplant listing

Whilst the effect of pre-transplant obesity on patient- and graft- survival remains unclear, Schold et al reported that weight loss during transplant listing had no effect on long term outcomes following transplantation including mortality risk and graft loss across the entire BMI spectrum [37]. The same study also highlighted that substantial weight loss pre-transplant was associated with rapid weight gain following transplantation [37]. This finding, together with the observed "obesity paradox" in the dialysis population [38], suggest that weight loss prior to transplantation may not necessarily be beneficial, as mortality risk during transplant listing and following transplantation is not alleviated. However, the authors highlighted that these information needs to be interpreted with caution as data on BMI was taken from the registry and crucial information including the nature of weight change and other aspects of nutritional status is therefore unavailable [37]. Intentional weight loss that is potentially beneficial may be masked by weight loss that is a manifestation of malnutrition or progressive disease [37].

In addition, a retrospective study of the United States Renal Data System (USRDS) registry found that substantial weight loss was achieved with bariatric surgery in a cohort of patients prior to transplant-listing and wait-listed for transplantation [39]. These results were similar to findings from recent studies, which demonstrated that laparoscopic Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy were effective procedures for weight loss and improved candidacy for kidney transplantation [40,41]. However, perioperative complications and

mortality within a 30-day period post bariatric surgery were evident [39,41]. Also, the impact of
intentional weight loss induced by bariatric surgery on short- and long- term patient- and
graft- survival has not yet been examined.

Prevalence and causes of obesity following transplantation

Weight gain following transplantation is very common and occurs in up to 50% of KTRs [42,43],
affecting both obese and non-obese patients [44]. The average weight gain following
transplantation is between 10% and 35% of body weight, with the majority of weight gain
within the first 12 months following transplantation [42,45-47]. Much of the weight gain post-
transplant is attributed to an increase in body fat mass, especially in the abdominal area [48,49].

Excessive weight gain and increased fat mass in KTRs is traditionally attributed to the
immunosuppression treatment protocol post-transplantation. This is due to the well-known
hyperphagic effect of steroids, and its adverse influence on adipocytes, resting energy
expenditure and lipid oxidation, resulting in centripetal obesity i.e. increased fat deposition in
the peritoneum, mediastinum, subcutaneous sites such as face and neck [49]. However, recent
evidence suggests that the effect of steroids on weight gain is controversial. ***Table 2***
summarises the studies showing the impact of steroids on weight gain and body composition.
First of all, an early study by Ratcliffe et al [50] showed that KTRs on steroid withdrawal
therapy achieved a significant reduction in body weight compared to steroid maintenance
therapy. Another study by van den Ham et al [49] indicated that weight gain after the first year
post-transplant was significantly and positively related to cumulative steroid dose. Further

studies by Rogers et al [51] and Woodle et al [52] showed that early steroid withdrawal minimizes weight gain in KTRs. However, contrasting studies proposed that the role of steroid use on post-transplant weight gain is only partial as an increase in body weight was seen in all KTRs regardless of the immunosuppression protocol [42,49,53]. In particular, Elster et al [53] reported no significant difference in weight gain between patients treated with steroid and patients on steroid avoidance therapy, and Johnson et al [42] found no correlation between weight gain and cumulative steroid dose, which in part is similar to findings from van den Ham et al [49] where weight gain in the first year post transplant was related neither to maintenance nor to cumulative steroid dose. Furthermore, a single centre study showed no difference in fat mass between steroid avoidance and steroid maintenance protocols, and no relationship was observed between cumulative steroid dose and body composition [54].

While the effect of immunosuppressive protocol on weight gain and changes in body composition is controversial, other contributing factors for post-transplant weight gain should be considered. Age, gender, ethnicity, pre-transplant BMI, dialysis modality, the occurrence and treatment of rejection, and graft function have all been suggested as significant contributors to weight changes following transplantation [42,45,49]. Importantly, weight gain post transplantation may be largely due to lifting of previous dietary restrictions, improved appetite following the correction of uraemia, and enhanced sense of well-being that occurs with transplantation.

Impact of obesity following transplantation

Irrespective of the contributing factors to post-transplant weight gain, obesity following transplantation is known to adversely affect cardiovascular risk profile and graft function [55]. A recent study by Hoogeveen et al [7] showed that one year following transplant, BMI and BMI increments were both significant risk factors for mortality and graft failure in the long-term. In contrast, Kovesdy et al [56] reported that higher BMI was associated with lower mortality after adjustment for waist circumference, whereas higher waist circumference was associated with higher mortality after adjustment for BMI. The opposite association displayed by BMI and waist circumference highlighted the uncertainty of relying on BMI as a marker of obesity in view of its incapability to distinguish between visceral adiposity, subcutaneous adiposity and muscle mass. Additionally, clinically obese patients with exclusive subcutaneous fat excess were found in a normal metabolic state and demonstrated a limited deposition of fat at visceral sites [57], conferring to reduced metabolic risk. These findings suggest that not only waist circumference appears to be a better prognostic marker for obesity than BMI, visceral adiposity adversely affect kidney transplant outcomes, and increased subcutaneous fat and/or muscle mass may be protective against mortality risk. In addition, recent data from a renal transplant population showed that lower urinary creatinine excretion, a proxy for reduced muscle mass, was associated with increased mortality and graft failure [58].

Obesity-related mechanisms of inferior kidney transplant outcomes

A number of mechanisms associating obesity and inferior transplant outcomes have been proposed, these are summarised in *Figure 1*. Overall, sarcopenic obesity, characterised by

reduced muscle mass coupled with increased fat mass, appears to be the driving force behind these mechanisms.

A link between muscle mass and survival has been suggested, increased muscle mass has been proposed to improve skeletal, respiratory and cardiac muscle function, and consequently improve muscle-based oxidative mechanism leading to increased antioxidant defence [56]. Reduced muscle mass may therefore exerts a negative effect on the proposed mechanism, leading to increased risk of cardiovascular disease, cancer, neurodegenerative disorders, and other chronic conditions [59]. Also, gelsolin produced by the skeletal muscle has been shown to be associated with improved survival in dialysis patients [56]. Although the effect of gelsolin has not been studied in kidney transplantation, the depletion of which may explain the higher mortality risk in KTRs.

Negative metabolic effects of raised BMI and adiposity, particularly visceral adiposity, may explain the increased CVD risk and graft failure observed in KTRs. First of all, the ALERT trial showed that raised BMI was associated with inflammation [60], where inflammatory markers including interleukin-6 (IL-6) and high-sensitivity c-reactive protein (hsCRP) were independently and positively associated with major cardiovascular events and all-cause mortality in KTRs [60]. Specifically, visceral adipose tissue is the most metabolically active system that secretes adipokines (cytokines secreted by adipose tissue), examples include chemerin, IL-6, visfatin, adiponectin, leptin, tumor-necrosis factor-α (TNF-α), and resistin [61]. The role of adipokine has received preliminary attention in kidney transplantation. Kaisar et al found that adiponectin (an adipokine) up-regulates high-density lipoprotein (HDL) and

down-regulates triglycerides in KTRs, a typical profile of dyslipidaemia associated with

obesity [62,57], and confers to increased CVD risk in KTRs[62]. However, Chitalia et al found no

association between adiponectin and CVD risk in kidney transplant population [63].

Nevertheless, adiponectin was shown to correlate inversely with inflammation in KTRs,

characterised by elevated c-reactive protein (CRP) [62]. In addition, elevated levels of visfatin

were found to correlate with inflammation and markers of endothelial damage in KTRs,

including raised levels of hsCRP, prothrombin fragments 1 + 2, and vascular cell adhesion

molecule (VCAM) [64]. Furthermore, raised resistin levels correlated with markers of

inflammation and endothelial dysfunction in KTRs, including elevated levels of hsCRP, IL-6,

thrombomodulin and VCAM [65].

The link between inflammation and mortality in KTRs has been established by Winkelmayer

et al [66]. Inflammation has been proposed to exert its downstream adverse sequelae via the

mediation of vascular damage causing vascular inflammation, which in turn leads to

pathogenesis of atherosclerosis in KTRs [60]. Another suggested mechanism associated with

adiposity is that adipose tissues secretes pro-inflammatory cytokines including TNF-α and

IL-6, which sequentially activates renin-angiotensin-aldosterone pathway, contributing to the

onset and progression of graft damage by sustaining cell growth, inflammation and fibrosis [7].

In addition, the metabolic load of the graft increases as a result of obesity, the graft

consequently adapt by increasing in size and glomerular filtration [7]. The combining effect of

fibrosis and glomerulomegaly are the most common histologic lesions in patients with

obesity-related glomerulopathy, suggesting that these are important pathways leading to graft failure [7].

Obesity intervention strategies

Lifestyle modification and behavioural intervention

Currently, no interventional studies exist to evaluate the effect of pre-transplant obesity management on long-term clinical outcomes of kidney transplantation. It is unsurprising as the effect of pre-transplant obesity on kidney transplant outcomes remains uncertain. In contrast, 4 studies have evaluated the effect of lifestyle interventions on weight management post transplantation, with all studies consistently demonstrated that nutritional interventions were effective in achieving weight loss, as summarised in *Table 3*. It is worth noting that lifestyle intervention incorporating dietary advice led to improved CVD risk factors in KTRs [67-71], but the effect of weight reduction through lifestyle intervention *per se* on kidney transplant outcomes, including "surrogates" such as acute rejection, remains undetermined.

Firstly, Patel et al [72] reported that 4-months of intensive individualised dietary intervention immediately post transplant resulted in significant reduction in body weight and BMI. However, 8 months following cessation of dietary intervention, significant weight gain and increased BMI was observed. These findings suggested that early intensive dietary advice and regular follow-up is effective in controlling weight gain in the first-year following

transplant, and dietary advice should be an important component of post-transplant management. Also, continued dietetic input beyond the early stage may be beneficial for the durability of weight control.

Moreover, Lopes et al [67] showed that the 6 months of American Heart Association (AHA) Step One Diet with individualised diet plan and monthly dietetic review significantly reduced body weight and body fat. This was accompanied by a significant improvement in nutritional intake profile including reductions in calorie, dietary cholesterol, total lipids, saturated fats and monounsaturated fats. Along with this, lipid profile also improved, including decreased total- and low-density lipoprotein (LDL) cholesterol, resulting in reduced CVD risk.

Furthermore, Orazio et al [73] , by using the Transtheoretical Model of Health Behaviour Change to incorporate simple exercise advice and nutrition therapy (Mediterranean-style low glycaemic index diet), produced results that mirrors Lopes et al, where significant weight loss was observed among KTRs with abnormal glucose tolerance. The progress was also complemented with significant improvement in dietary risk factors for CVD including reductions in intakes of energy, total fat and percentage saturated fat. Improvement in other CVD risk factors was also evident, including reductions in triglycerides, total- and LDL-cholesterol. Importantly, patients with >5% weight loss were associated with increased HDL cholesterol.

Conversely, a study by Jezior et al [74] demonstrated that a weight reduction program comprised of 2 sessions with 6 months interval apart failed to achieve an overall weight

reduction. Nevertheless, 27% of patients experienced weight loss following the program. The lack of success could be explained by the nature of this study where no dietary advice was given during the program. At the first visit, patients were only given an evaluation of dietary intake followed by anthropometry assessment and a short description of the negative effects of obesity on post-transplant morbidity. Six months later at the second visit, patients then received dietary advice based on the analysis of the first visit.

In addition to dietetic intervention, increased physical activity level is an important lifestyle modification strategy for weight reduction. Zelle et al [75] reported an association between increased physical activity level and reduced mortality in KTRs independent of waist circumference, muscle mass, triglyceride and insulin levels.

Nutritional intervention vs pharmacological approach

Dietary interventions have shown promising results in weight management when compared with findings from recent prospective controlled trials investigating steroid minimisation as an immunosuppressive strategy. Woodle et al [52] demonstrated that patients on steroid avoidance protocol gained 2.6kg less weight compared to patients on 5mg maintenance steroid therapy. Also, Vincenti et al [76] reported that patients on steroid avoidance protocol gained 1.0kg/m^2 less BMI increment compared to patients on 5-10mg maintenance steroid therapy. These results are rather unremarkable compared to the results from nutritional interventions shown in ***Table 3***. Importantly, both studies [52,76] using steroid minimisation

have shown an increase in acute transplant rejection, which raises concerns over the use of

steroid minimisation as a strategy for weight management.

Alternative strategies to weight management

Generally, weight management has proven to be a difficult challenge, involving calorie

reduction, increased physical activity, and behavioural modification. Increasingly,

pharmacological and surgical options are pursued to tackle the problem. The use of anti-

obesity medications has not been exclusively studied in KTRs. Sibutramine was associated

with hypertension [77], Orlistat interfered with cyclosporine absorption decreasing its

bioavailability [78], and Rimonabant treatment led to increased systemic exposure of

Cyclosporin A as well as psychiatric complications in some patients [79]. Bariatric surgery

yielded substantial weight loss in KTRs [39], and gastric bypass procedure has shown promise

in selected KTRs, leading to reduction in cardiovascular co-morbidity [80].

Future research on obesity in kidney transplantation

Currently, the effect of pre-transplant obesity on patient- and graft- survival remains unclear.

Also, clinical trials demonstrating the effects of intentional pre-transplant weight loss on

subsequent patient- and graft- survival are lacking. Given the well-established contributions

of obesity to increased morbidity and mortality following transplantation, future research in

this area should be channelled towards prospective interventional studies, aiming to evaluate

the impact of pre-transplant intentional weight loss through bariatric surgery, lifestyle modification, and behavioural intervention on short- and long- term outcomes of kidney transplantation.

On the contrary, the adverse effect of obesity following transplantation is well-established. Nutritional intervention studies have shown promising results in achieving weight loss and improving risk factors for CVD, but lacked hard clinical endpoints e.g. risk of graft failure and mortality. Future studies should concentrate on evaluating the effect of weight loss on long-term transplant outcomes. Also, the role of visceral adiposity and its related adipose tissue cytokines have only received preliminary attention in kidney transplantation research. At present, there is a lack of pre-clinical data on this topic, thereby highlighting the need to develop experimental animal models of renal transplant with obesity in parallel to ongoing clinical studies. This will not only aid in dissecting the pathophysiology of obesity in renal transplants, but also paving the way for possible interventional studies in the future. In addition, further clinical research should assess the effect of varying adipokines on inflammation and the associated effects on graft failure and mortality. Similarly, the role of muscle mass in KTRs on long-term transplant outcomes has not been well-investigated.

Conclusion

In summary, obesity is common both at the time of transplantation and following transplantation. While the implication of pre-transplant obesity on kidney transplant outcomes remains unclear, post-transplant obesity is a significant risk factor for graft failure

and mortality. Obesity intervention post-transplantation focusing on nutritional therapy has shown encouraging results in weight management, but the impact on long term outcomes has not been demonstrated. There is now emerging data signifying the relevance and benefit of nutritional intervention in KTRs. It is therefore important that future research should focus on conducting nutritional intervention studies aiming to improve kidney transplant outcomes in this population group.

<u>Practical application</u>

This review article is the first to not only highlight the role of nutritional intervention and the impact of sarcopenia on kidney transplant outcomes, but to illustrate the complex pathophysiology of obesity in this patient population. Future research should focus on conducting prospective studies of nutritional intervention, aiming to evaluate the impact on outcomes of kidney transplantation.

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Table 1: Summary of studies showing the impact of pre-transplant obesity on kidney transplant outcomes

Study	Sample Size	Study Type	Exposure Variable	Outcome Measures	Key Findings	Impact on Kidney Transplant Outcomes
Lynch et al (2009)	869	Retrospective	BMI	▪ Surgical site infection post-transplantation ▪ 3-year graft survival ▪ 3-year patient survival	▪ Prevalence of surgical site infection is higher among obese KTRs. ▪ Obesity had no independent effect on 3-year graft- and patient- survival outcomes.	▪ Impact on short-term outcome ▪ No impact on long-term outcomes
Johnson et al (2002)	493	Retrospective	BMI	▪ Superficial wound breakdown ▪ Complete wound dehiscence ▪ Wound infections ▪ Other post-operative complications ▪ Hospitalization rates ▪ Delayed graft function ▪ Acute rejection episodes ▪ 5-year graft survival ▪ 5-year patient survival	▪ Raised BMI predicts wound breakdown. ▪ BMI does not predict other post-operative complications, hospitalization rates, 5-year graft- and patient- survival.	▪ Impact on short-term outcome ▪ No impact on long-term outcomes
Bennett et al (2004)	173	Retrospective	BMI	▪ Wound infections ▪ Other surgical complications ▪ 3-year graft survival ▪ 3-year patient survival	▪ Patients with BMI>30 kg/m^2 have increased wound infections. ▪ No difference in other surgical complications, 3-year graft- and patient- survival between different BMI categories.	▪ Impact on short-term outcome ▪ No impact on long-term outcomes
Massarweh et al (2005)	193	Retrospective	BMI	▪ Graft-loss (total loss of graft function or patient death with a functioning graft) with mean follow-up time of 24 months ▪ Acute rejection rates ▪ Post-transplant surgical complications	▪ Patients with BMI≥30kg/m^2 had increased incidence of post-transplant surgical complications. ▪ No difference in acute rejection rates, long-term mortality and risk of graft failure between patients with BMI<30kg/m^2 and ≥30kg/m^2.	▪ Impact on short-term outcome ▪ No impact on long-term outcomes
Hoogeveen et al (2011)	1,810	Prospective	BMI	▪ Patient survival in a 20-year follow-up study with median follow-up time of 8.3 years ▪ Graft-survival in a 20-year follow-up study with median follow-up time of 8.3 years	▪ Obesity (BMI>30 kg/m^2) is a risk factor for both patient mortality and graft failure independent of other cardiovascular risk factors. ▪ Obesity (BMI>30 kg/m^2) increased the risk of death and graft failure by 20-40% compared with normal BMI. ▪ A high BMI (>30 kg/m^2) post-transplantation was more strongly related to death and graft failure compared with pre-transplant obesity.	▪ Impact on long-term outcomes
Meier-Kriesche et al (2002)	51,927	Retrospective	BMI	▪ Primary study end-points were graft- and patient-survival for up to 10 years post-transplant. ▪ Secondary study end-points were death censored graft survival, chronic allograft failure, delayed graft function, and acute rejection.	▪ Very high and very low BMI were associated with worse patient- and graft-survival. ▪ Very high and very low BMI were associated with death censored graft failure and chronic allograft failure. ▪ Elevated BMI was associated with increased risk of delayed graft function. ▪ No association between BMI and acute rejection.	▪ Impact on short-term outcome ▪ Impact on long-term outcomes
Sancho et al (2007)	337	Retrospective	BMI	▪ Graft survival with a mean follow-up of 54 months	▪ Compared to normal weight patients (BMI<25kg/m^2), overweight patients (BMI>30kg/m^2) displayed higher incidence of hypertension, left-ventricular	▪ Impact on graft survival ▪ Patient survival was lower in

				▪ Patient survival with a mean follow-up of 54 months ▪ Acute rejection episodes ▪ Post-transplant co-morbidity	hypertrophy, dyslipidemia, acute tubular necrosis, acute rejection episodes, post-transplant diabetes. ▪ No difference in graft survival between BMI categories. ▪ Compared to normal weight patients (BMI<25kg/m^2), patient survival was lower in overweight patients (BMI>30kg/m^2).	overweight patients
Gore et al (2006)	27,377	Retrospective	BMI	▪ Intermediate measures of graft outcome ▪ Overall graft survival for up to 6 years post transplantation	▪ Morbid obesity (BMI≥35kg/m^2) was independently associated with increased risk of delayed graft function, prolonged hospitalization, and acute rejection in the post-operative period. ▪ Morbid obesity (BMI≥35kg/m^2) decreased overall graft survival.	▪ Impact on short-term outcomes. ▪ Impact on long-term outcomes.
Schwarznau et al (2008)	81	Retrospective	BMI	▪ Graft loss within the first year after kidney transplant	▪ Increased BMI was in independent risk factor for graft loss within the first year post transplant	▪ Impact on short-term outcome.
Meier-Kriesche et al (1999)	405	Retrospective	BMI	▪ 7-year graft survival ▪ 7-year patient survival	▪ BMI>25kg/m^2 conferred a 2-fold relative risk of long-term graft loss and patient death. ▪ The 7-year actuarial graft survival was higher among the non-obese KTRs (BMI≤25kg/m^2) compared to the obese KTRs (BMI>25kg/m^2), 88% vs 72%. ▪ The 7-year actuarial patient survival was higher among the non-obese KTRs (BMI≤25kg/m^2) compared to the obese KTRs (BMI>25kg/m^2), 92% vs 81%.	▪ Impact on long-term outcomes.
Howard et al (2001)	833	Retrospective	BMI	▪ 1- and 5- year graft survival ▪ 1- and 5- year patient survival	▪ Higher incidence of delayed graft function was found in overweight KTRs (BMI between 25.0kg/m^2 and 29.9kg/m^2) and obese KTRs (BMI≥30.0kg/m^2). ▪ Higher incidence of post-transplant diabetes mellitus was found in obese KTRs (BMI ≥30.0kg/m^2). ▪ Death with a functioning graft was less common among obese KTRs (BMI ≥ 30.0kg/m^2) compared to normal weight KTRs (BMI between 25.0 kg/m^2 and 29.9kg/m^2) and overweight KTRs (BMI ≥30.0kg/m^2). ▪ No difference in 1-year and 5-year graft- and patient- survival between different BMI categories (<25.0kg/m^2, 25.0-29.9kg/m^2, and ≥30.0kg/m^2).	▪ Impact on short-term outcome. ▪ No impact on long-term outcomes.
Marks et al (2004)	247	Retrospective	BMI	▪ 3-year graft survival ▪ 3-year patient survival ▪ Post-operative complications ▪ Rejection episodes ▪ Length of hospital stay ▪ Readmission rate within the first 6 months post-transplant	▪ No difference in actuarial patient- and graft- survival rate for the first 3 years after transplant between non-obese and morbidly obese KTRs. ▪ Length of hospital stay, number of readmissions within the first 6 months post-transplant, and the number of major wound complications were greater for morbidly obese KTRs compared with non-obese KTRs.	▪ Impact on short-term outcome ▪ No impact on long-term outcomes
Yamamoto et al (2002)	56	Retrospective	BMI	▪ 1-, 3- and 5- year graft survival ▪ 1-, 3- and 5- year patient survival ▪ Delayed graft function ▪ Acute rejection	▪ Obesity (BMI>30kg/m^2) is not a risk factor for delayed graft function, acute rejection, and 1-year graft survival. ▪ Decreased 3-year and 5-year graft survival trend was observed in obese KTRs (BMI>30kg/m^2). ▪ No difference in patient survival between obese and non-obese KTRs at 1-, 2-and 5- year post-transplant.	▪ No impact on short-term outcomes. ▪ Impact on medium- and long-term graft survival ▪ No impact on patient survival in short-, medium, and long-term.
Streja et al	10,090	Retrospective	BMI	▪ Graft survival up to 6 years post-transplant	▪ Up to 6 years post-transplantation, obesity (BMI>30kg/m^2) was not	▪ Impact on long-term graft loss.

(2011)				▪ Patient survival up to 6 years post-transplant	associated with mortality, although it showed a trend towards higher graft loss.	▪ No impact on long term patient survival.

Table 2: Summary of studies showing the impact of steroids on weight gain and body composition

Study	Sample Size	Study Type	Exposure Variable	Study Protocol	Key Findings in relation to Weight Gain and Body Composition
Ratcliffe et al (1996)	100	Randomised controlled trial of steroid withdrawal	Body weight	KTRs were randomised either to reduce prednisolone treatment to zero over 4 months or to maintain their triple immunosuppression unchanged.	▪ Steroid withdrawal was associated with a significant reduction in body weight, whereas slight weight increase was observed in the control group.
van den Ham et al (2003)	123	Longitudinal study with a follow-up period of 5 years	Body weight	KTRs on either steroid- or steroid-free immunosuppression therapy.	▪ Weight gain occurs in all KTRs, no difference in weight gain was found between KTRs on steroid- or steroid-free immunosuppression therapy. ▪ Within the first year post-transplant, increase in body weight was related neither to maintenance- nor cumulative steroid dose. ▪ After the first year post-transplant, cumulative steroid dose was positively related weight gain.
Rogers et al (2005)	301	Prospective study with a follow-up period of 12 months	Body weight	KTRs on either chronic corticosteroid therapy (CCST) or corticosteroid withdrawal (CSWD) within 7-day post-transplant.	▪ Weight gain was significantly higher in KTRs on CCST at 3, 6, and 12 months post-transplant. ▪ Early CSWD minimizes weight gain in KTRs.
Woodle et al (2008)	386	5-year randomised, double-blind, placebo-controlled trial	Body weight	KTS on either early corticosteroid withdrawal (CSWD) or chronic low dose corticosteroid therapy (CCS).	▪ CSWD lead to significantly lower weight gain compared to CCS.
Johnson et al (1993)	115	Retrospective study with an end-point of 5 years post-transplantation	Body Weight	Potential factors (including cumulative steroid dose) influencing post-transplantation weight gain were assessed.	▪ Weight gain did not correlate with cumulative steroid dose.
Elster et al (2008)	95	Retrospective study with 3-year follow-up data	Body Weight BMI	KTRs who received either lymphocyte depletion-based steroid sparing or traditional immunosuppressive therapy that included steroids for maintenance immunosuppression.	▪ Regardless of immunosuppression therapy, BMI and body weight increased post-transplant in all KTRs.
van den Ham (2000)	77	Cross-sectional study	Body composition	KTRs on either 0-, 5-, and 10- mg maintenance steroid therapy.	▪ No significant differences in fat mass, lean body mass, and body fat distribution between KTRs on 0-, 5-, and 10-mg maintenance steroid therapy. ▪ No significant relationships between cumulative steroid dosage and body composition and body fat distribution parameters in KTRs.

Table 3: Comparison between nutritional intervention and steroid minimisation protocols on weight changes

<u>**Study**</u>	<u>**Intervention**</u>	<u>**Magnitude of Weight Changes**</u>
Patel et al (1998)	4-month individualised dietary advice immediately post transplant with regular follow-up compared with no dietary advice and follow-up	Dietetic intervention resulted in 5kg less weight gain compared to no dietetic intervention
Lopes et al (1999)	6-month American Heart Association (AHA) Step One Diet with individualised diet plan and monthly dietetic review	Significant reduction of 3kg
Orazio et al (2011)	Transtheoretical Model of Health Behaviour Change incorporating simple exercise advice and nutrition therapy (Mediterranean-style low glycaemic index diet)	Mean weight reduction not reported, but patients underweight lifestyle intervention resulted in 3.8% weight loss
Jezior et al (2007)	Weight reduction program comprised of 2 sessions with 6 months interval apart	Mean weight unchanged, but 27% of patients enrolled in weight reduction program experienced weight loss
Woodle et al (2008)	Steroid cessation by day 7 post transplantation compared with 5mg steroid maintenance	Steroid cessation resulted in 2.6kg less weight gain compared to 5mg steroid maintenance therapy
Vincenti et al (2008)	Steroid avoidance immunosuppression protocol compared with 5-10mg steroid maintenance therapy	Mean weight reduction not reported, but mean BMI reduction of $1.0kg/m^2$ demonstrated

Figure 1: Obesity-related mechanisms of inferior kidney transplant outcomes