Trends in Transplantation

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Renal transplantatıon and morbid obesity

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Obesity is a worldwide epidemic and public health crisis associated with severe comorbidity leading to end organ dysfunction and poorer transplant outcome [1].

The most common method for defining obesity is based on BMI (i.e., a person's weight [kilograms] divided by the square of his or her height [meters]). The World Health Organization (WHO) considers a BMI between 20 and 25 kg/m² as normal weight, a BMI between 25 and 30 kg/m² as overweight, and a BMI of 30 kg/²as obese. The National Institutes of Health defined morbid obesity as aBMI ≥ 35 kg/m² and severe, obesity related comorbidity as a BMI ≥ 40 kg/m² [2].

Although BMI is easy to calculate and used in many nutritional guidelines, this metric is a poor estimate of fat mass distribution, especially in chronic kidney disease(CKD) which may not be able to differentiate visceral adiposity from muscle mass and non-visceral fat mass. Although waist-hip ratio(WHR)and skin fold thickness are superior to BMI for the correct classification of obesity in CKD in cross-sectional studies, WHR may not be a valid estimate of changes in visceral fat mass over time[3-6].

There areso many comorbid conditions associated with severe obesity that include insulin resistance,diabetes mellitus,increased abdominal fat raises the intra-abdominal pressure and contributes to gastroesophageal reflux, stress urinary incontinence, venous stasis disease, and abdominal hernia in obese patients. Fatty deposits in the liver can progress to nonalcoholic steatohepatitisand excess weight causes joint and back stress that can lead to debilitating joint disease.

Obese patients have impaired pulmonary function, particularly decreased functional residual capacity, and frequently suffer from asthma, obstructive sleep apnea, and obesity hypoventilation syndrome (chronic hypoxemia, hypercarbia, pulmonary hypertension, and polycythemia; Pickwickian syndrome). Other comorbidities include hypertension, dyslipidemia, asthma, and sex hormone dysfunction. Obesity is associated with an increased incidence of uterine, breast, ovarian, prostate, and colon cancer, and of skin infections, urinary tract infections, migraine headaches, depression, and pseudotumor cerebri. The low-grade inflammatory state associated with morbid obesity has been implicated in the development of vascular and coronary artery disease and the hypercoagulable state seen in these patients [7,8].

The American Society of Transplantation recommend a supervised weight loss regimen including a low-calorie diet, behavioral therapy, and a physical activity plan to achieve a goal body mass index (BMI) of less than 30 prior to kidney transplantationand also note that there are insufficient data to suggest which obese patients should be denied a transplant based on their obesity [9].

An analysis of 188 patients Modanlou et al., included patients undergoing weight-reduction surgery both prior to listing and after transplantation demonstrated a 30-day mortality of 3.5% with a further 3.5% dying at 90 days in the post-transplant group [10].

'Obesity paradox' has long been recognized in dialysis with a higher BMI being associated with animproved survival [11].

This phenomenon may be due to the association between sarcopenia (reduced muscle mass) and low BMI. Schold et al., demonstrated that weight loss after transplant listing had no positive impact on post-transplant mortality or graft loss irrespective of BMI at the time of listing [12].

Taken together, the observational data suggest that both a lower BMI and weight loss associated with sarcopenia predicts poor outcomes on dialysis[12].

Obesity impacts many inter-related considerations for transplant practice including candidate selection, outcomes prediction before and after transplant, and waitlist management.

Obese patients transplantation candidates should undergo a thorough cardiac, pulmonary, endocrine and nutritional counselingto minimize medical and surgical complications and improve survival and quality of life[13].

Compared to recipients with BMI ≤ 30, those with obesity defined by BMI >30 had longer operative times, prolonged hospitalizations, higher rates of reintubation, more frequent intensive care unit admissions, and a greater incidence of wound complications[14].

Wound infection is the most common issue encountered in the perioperative period.Decreased oxygen tension and ischemia at the suture line, presence of chronic skin fold infections, and generalized immune impairment, even prior to the immunosuppression medications can lead to this issue[15,16]. Renal transplantation in obese patients has increased risk of surgery including anesthetic problems of airway control and venous access problems, impaired preoperative lung function in approximately one third of obese patients, an increase in cardiac stroke work leading to circulatory problems, thromboembolic,wound complications andtechnical considerations including hemostatic problems andanatomotic function [17-19]. There are also logistical issues such as blood pressure cuff sizing, ultrasound assistance for procedures, diminished quality of some imaging modalities, and capabilities of hospital equipment such as beds and lifts are important considerations [20].

The pulmonary function of obese patients is altered by mechanical

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disability, leading to smaller lung volumes and decreased chest wall compliance[21]. The lack of pain medication can lead to rapid shallow breathing and atelectasis. Incentive spirometry, and continuous positive airway pressure (CPAP) can be used to prevent atelectasis and pneumonia. For thromboembolic risk, anticoagulation with heparin and/or vena caval filters be placed preoperatively in the highest risk patients[21,22].

Outcome differences in obese renal transplant patients were primarily due to a higher mortality resulting from cardiac events. Modlin et al., also stated that, obese patient with a history of cardiac disease should not be transplanted until weight reduction <30 kg/m² [23].

Predisposition to ventricular hypertrophy and increases in blood volume should be considered in fluid management decisions[20]. Sodium intakes are individualized based on fluid retention and blood pressure[24].

Following transplantation, many patients exhibit hypophosphatemia and mild hypercalcemia caused by bone resorption; this is associated with persistent hyperparathyroidism and the effects of steroids on calcium, phosphorous and vitamin D metabolism.Fluid and electrolyte requirements should be evaluated daily. Typically, patients are encouraged to drink 2 L/day, but their overall needs depend on their urine output [25].

Nutritional management of transplant patients will be determined by nutritional status, immunosuppression regimen, presence of infection, function of the transplanted graft, other organ functions, wound healing and metabolic and surgical complications.

Obesity directly impacts transplant outcomes. Meier- Kriesche et al., have shown that patient and graft survival are lower in obese patients (BMI >30). They indicated that, it is specifically related to wound infection and breakdown and is greater when the BMI is >30[26,27].

Whether or not obesity impacts early graft function or long-term outcomes remains unclear.In Yamomoto's study 28 pairs of kidneys were transplanted; one in an obese patient while the other was placed into a nonobese recipient. Graft survival, including delayed graft function, was noted to be similar in the short term but statistically worse for the obese cohort at 7 years and they stated thatchronic allograft nephropathy (CAN) was the primary culprit, rather than cardiovascular factors[28]. Obese patients are considered for transplant because of the obvious survival benefit as compared to the wait listed dialysis patients, despite the poorer outcomes [29].

The number of obese persons is increasing in Turkey[30,31]. In Gurkan et al., studyalthough the complication rate was found to be higher in obese renal transplanted group compared with non obese, the patient and graft survival rates were similar. And the annual mortality rate of obese transplant patients was lower than the annual mortality rate of average dialysis patients reported by the Turkish Society of Nephrology[32].

Grosso et al., retrospectively reviewed 376 renal transplant recipients to evaluate graft and patient survivals between normal and over weight and obese patients at the time of transplantation. Graft loss and was significantly higher and survival was significantly loweramong obese compared with non obese recipients.They indicated that careful patient selection with pretransplantation weight loss is mandatory to reduce the rate of early posttransplantation complications and to improve long term outcomes[33].

ButKandoum et al.'s retrospective study, they showed a significant risk of surgical complications after renal transplantation but they suggested thisnot affect graft survivalbecause any renal transplanted patient needtransplantectomy or return to dialysis[34].

The weight-loss surgery in the kidney disease population is unclear[35].Freeman et al., presented a prospective evaluation of laparoscopic sleeve gastrectomy(LSG) for patients failing to achieve significant weight loss with medical therapy.Over a 25 month period, 52 obese renal transplant candidates with an average preoperative BMI of 43.0 ± 5.4kg/m² underwent LSG.They suggested that LSG is safe, efficaous and superior to medical weight loss management and can increase access to transplantation[36].

Golomb et al., performed8 patients LSG, afterrenal transplantation. The median preoperative BMI 42kg/m²[37].They suggested LSG provided effective weight loss in renal transplant patients without adverse effects on graft function and immunosuppression[37].

Immunosuppression therapy is known to induce metabolic adverse effects, such as protein hypercatabolism, hyperlipidemia, glucose intolerance, hyperkalemia, hypophosphatemia, hypomagnesemia. The nutritional status after transplant is also determined by preexisting medical conditions, such as protein losses, renal osteodystrophy, hyperlipidemia, and cardiovascular disease.

Patients with body mass index (BMI) > 30 kg/m^2 are at risk for steroid induced posttransplant diabetes mellitus[23]. For all renal transplant patients dietary advice should be individualized and include exercise plans and specific goals. The diet should be planned with a moderate energy restriction of about 30% of energy expenditure to reduce body weight in overweight or obese kidney transplant recipients[26].

A combination of several immunosuppressive medications is needed in all transplant recipients to prevent acute andchronic rejection for long-term graft survival. Significant changes in the volume of distribution of drugs occur in obese patients, particularly for lipophilic drugs. When initially dosing lipophilic drugs, the dosages should be based on ideal body weight (IBW) and a percentage of the excess body weight. Altered concentration of plasma binding proteins, differences in regional blood flow, and variable body composition can affect tissue distrubution and transport of drugs into different tissue compartments so the drug doses are unpredictable[38].

Specific dose adjustments could not be made, but recommendations to closely monitor sirolimus and tacrolimus.Mycophenolic acid is metabolized in the gastrointestinal tract, kidney, and liver. Two peak concentration times can be seen when the drug is taken in combination with tacrolimus or sirolimus. The first peak is associated with absorption, whereas the second is thought to be due to enterohepatic circulation of the drug and its metabolites MPA levels can be monitored by area under the curve (AUC) estimation[38].

Conclusion

Obese patients are considered for transplant because of the obvious survival benefit as compared to the wait listed dialysis patients, despite the poorer outcomes[29].

The goal is to selectpatients who likely to have a good outcome. This can be achieved by a multidisciplinary team and a thorough pretransplant evaluation and optimization of the obese patientsmedical comorbidities.

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