Presence of Sarcopenia before Kidney Transplantation Is Associated with Poor Outcomes

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Keywords
Sarcopenia · End-stage kidney disease · Computed tomography · Muscle loss · Kidney transplantation

Abstract

Introduction: Kidney transplantation is the treatment of choice for patients with renal failure. It is crucial to select which patients may benefit from renal transplantation and which are at high risk for post-transplant complications. Sarcopenia is associated with poor outcome in various conditions, including in chronic kidney disease patients. The gold standard for measuring sarcopenia is computed tomography (CT) imaging to estimate muscle mass and quality since it is objective, reproducible, and reflects the overall health condition. The data regarding those measurements among kidney transplant recipients are limited, therefore we aimed to describe it in patients before kidney transplantation, assess the parameters associated with sarcopenia, and evaluate the clinical significance of those markers on outcomes following transplantation. Methods: We retrospectively analyzed 183 kidney transplant recipients who had a CT scan 90 days prior to transplant. Sarcopenia was assessed by measuring the cross-sectional area (CSA) and mean muscle density of the psoas muscle at the third and fourth lumbar vertebrae levels and paravertebral muscles at the 12th thoracic vertebra level. Results: There was a strong linear correlation between muscle size measured as CSA of the psoas muscle at the L3 and L4 vertebral body level and the CSA of the paravertebral muscles at the D12 vertebra level, and a moderate correlation to muscle density at those levels. Age was independently associated with risk of sarcopenia, defined as psoas CSA in the lowest tertile, with every year of age increasing the risk by 5%. CSA at the L3 level had a significant independent association with post kidney transplantation mortality, with an adjusted hazard ratio of 0.86 per cm\textsuperscript{2}. There was a significantly longer hospitalization period postoperation in kidney recipients in the lower tertile of psoas CSA and density. Conclusions: Sarcopenia as measured by psoas CSA is associated with poor short- and long-term outcomes following kidney transplantation and should be included as part of the assessment of kidney transplantation candidates.

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Introduction

Kidney transplantation is the treatment of choice for most patients with end-stage renal disease (ESRD). It improves quality of life and life expectancy and has a lower financial burden on the healthcare system in comparison to dialysis [1, 2].

Every year, a growing number of older patients are candidates for enrollment on the kidney transplant waiting list [3]. Given the limited number of organs available for transplant, it is crucial to select which patients will benefit most from renal transplantation and which are at higher risk for post-transplant complications.

Sarcopenia is defined as the progressive and generalized loss of skeletal muscle mass and strength, resulting in an increased risk of poor quality of life and death [4]. Sarcopenia has been traditionally defined as an aging process, but may be accelerated by chronic illness and malnutrition [5]. Sarcopenic patients are often frail and have increased disabilities and comorbidities. The combination of these qualities often results in inferior health outcomes.

Sarcopenia has been well-studied in patients undergoing liver transplantation [6–10], major surgeries [11–15], and cancer [16] and found to be associated with poor outcome. There is emerging evidence that sarcopenia is related with mortality in chronic kidney disease patients [17, 18] and with a higher waitlist, mortality in kidney transplant candidates [19]. The presence of low muscle mass at the time of kidney transplant has also been associated with increased mortality, graft failure, and postoperative complications [20–22].

While multiple modalities have been used to diagnose and measure sarcopenia, the current gold standard is to use computed tomography (CT) and/or magnetic resonance imaging (MRI) to estimate muscle mass and quality as determined by muscle density or mean muscle attenuation (MA) and intramuscular fat infiltration [4, 23]. These imaging modalities are preferred as they provide higher accuracy in quantifying muscle and fat as compared to other methods such as dual-energy X-ray absorptiometry or bio impedance analysis [24]. The psoas muscle is a good indicator of sarcopenia since it is susceptible to changes among chronically ill patients, but not in acute illness [23].

In most studies, muscle volume and density were measured in a semiautomated fashion by manually outlining the borders of the muscles and analyzing them with various software [25]. Most used semiautomated algorithms are programmed into MATLAB software. The most common muscle measured was the psoas muscle at the level of L3. Some studies measured muscle mass at multiple paravertebral levels. The masseter muscle mass was also measured in some studies [26] (as it is included in CT of the brain which is performed routinely in many patients). We chose to measure the psoas muscle at the L3 and L4 levels and the paravertebral muscles at D12 (since the paravertebral muscles at the level of D12 are included in both chest and abdominal CT scans).

Measurements of sarcopenia by CT may be particularly attractive to transplant clinicians and policymakers as they are both objective and reproducible. Furthermore, measures of muscle mass likely do not reflect acute severity of illness, but are rather indicators of overall health.

The data about short- and long-term effects of sarcopenia as measured by preoperative CT scans on kidney transplant candidates are scarce. Therefore, the present study aimed to describe muscle mass and quality in ESRD patients before kidney transplantation in abdominal CT performed perioperatively, assess the parameters associated with sarcopenia, and evaluate the clinical significance of those markers on the outcomes after transplantation.

Methods

Patients

The study includes all adult kidney transplant recipients who underwent kidney transplantation between January 2015 and January 2021 in our institution, who had an available abdominal non-contrast CT scan within 90 days preceding their transplantation. In our center, the induction immunosuppression therapy consists of antithymocyte globulin or basiliximab, according to patients’ risk of rejection, in addition to methylprednisolone intravenously. We use a maintenance regimen consisting of triple immunosuppression therapy including calcineurin inhibitors; tacrolimus or cyclosporin, mycophenolate mofetil or mycophenolate sodium, and low dose prednisone (5 mg/day). According to the patients’ risk stratification for rejection, side effects or other considerations, the maintenance regimen may be changed by the attending nephrologist.

Clinical and epidemiological data were obtained from the medical charts, including age, sex, race, body mass index (BMI), cause of kidney failure, presence of comorbidities (diabetes and cardiovascular disease [CVD]), time on dialysis prior to transplantation, donor type (deceased or living), induction and maintenance immunosuppression, days of admission after the transplantation, graft failure (defined as need for chronic dialysis or retransplant), and death, as well as laboratory data including blood count, liver function tests, and serum albumin before transplantation. BMI was defined as weight in kilograms divided by height in square meters.
CT Image Acquisition and Analysis

Abdominal CT scans, which were performed on modern generation multidetector CT scanners as part of pretransplant evaluation or for routine diagnostic purposes, were used to quantify skeletal muscle area and MA. CT images performed within 90 days of transplantation were deemed to represent skeletal muscle status at the time of transplantation.

Two experienced staff body radiologists (I.D. and H.Y.), who were blinded to patients’ data, retrospectively evaluated the CT scans of these patients. Lean core muscle area using the psoas muscle was determined from preoperative abdominal CT. The cross-sectional area (CSA) as well as the density measured as mean MA of the right and left psoas muscle were measured at the L3 and L4 levels, and paravertebral muscles at the D12 level. This was accomplished by first identifying individual vertebral levels on the patient’s CT scan in the sagittal reconstruction. The individual transverse imaging slice at the inferior border of L3, L4, and D12 was then used to outline the region of each muscle using a free-hand region of interest tool on the PACS system. The areas of the enclosed muscle regions were then computed and summed to generate the total CSA of the psoas and paravertebral muscles. In order to account for fatty infiltration, the average density in Hounsfield units of the outlined muscle region was also measured.

Total muscle area was calculated as the sum of the right and left CSA of the muscle at the relevant level. The psoas index (PI) was measured by the total psoas muscle area and normalizing it by the square of the height: PI = (Right CSA psoas + Left CSA psoas)/height² in cm²/m² [27]. MA was measured as the Hounsfield Unit average calculation (threshold range for skeletal muscle segmentation was between −29 and +150 Hounsfield Unit) and was expressed as the mean of right and left muscles at the relevant level.

Statistical Analysis

Continuous variables were first tested for normal distribution using the Kolmogorov-Smirnov test and Q-Q plots and were summarized and displayed as mean (standard deviation [SD]) for normally distributed variables and as median (interquartile range [IQR]) for non-normally distributed variables. Categorical variables were displayed as the number of patients and the percentage in each group. For all categorical variables, the χ² statistic was used to assess the statistical significance between groups. Continuous variables were compared by using a t test if normally distributed or by Kruskal Wallis/Mann-Whitney test if non-normally distributed. Correlation between continuous parameters was calculated by Pearson’s correlation coefficient.

Univariable logistic regression analysis with relevant parameters was performed to identify significant predictors of low muscle CSA, and potential predictors were selected and entered into multivariable logistic regression. Cox proportional-hazards regression was performed to death and graft loss and 95% confidence intervals for the hazard ratios were calculated after adjusting to confounders.

Results

247 patients underwent kidney transplantation between January 2015 and January 2021. Among them, 183 (74%) had a CT scan performed within 90 days of transplant and were included in the study. Among the 64 recipients excluded, 44 of them did not have any CT in the 12 months prior to transplantation, and the other 20 had a CT scan 3–12 months prior to transplantation. Recipients excluded from the study were younger (median age at transplantation was 56 years [IQR 42–66 years] vs. 54 [IQR 41–59 years], p = 0.03 for recipients included and excluded from the study, respectively); had a lower dialysis vintage (12 [3–18] vs. 10 [0–15] months, p = 0.04); had a higher prevalence of living donors (72 vs. 56.2%, p = 0.04), and had a lower prevalence of diabetic kidney disease or nephrosclerosis as primary kidney disease (50.3 vs. 36% p = 0.05, for recipients included and excluded from the study, respectively). One patient was of Ethiopian origin, and all the rest were Caucasians.

Cross-Sectional Area and Density before Transplantation

Mean total muscle CSAs were significantly different for males and females, both for psoas muscles at the L3 and L4 levels, as well as paravertebral muscles at the D12 level (10.5 ± 3.3 vs. 17.5 ± 4.4 cm² TPA at L3; 15.5 ± 3.9 vs. 25.4 ± 5.7 cm²; 21.9 ± 4.9 vs. 33 ± 7.1 cm² for females and males, respectively; p < 0.05 for all), and were normally distributed for both men and women. However, mean muscle (psoas and paravertebral) densities were similar in both genders.

Older age was inversely correlated with MA (r = −0.44, p < 0.001) and with CSA for both males (r = −0.20, p = 0.05) and females (r = −0.32, p = 0.03). Total psoas CSA at L3 was positively correlated with body weight (r = 0.46, p < 0.001) and BMI (r = 0.25, p = 0.02), whereas the density of the psoas was negatively correlated with body weight (r = −0.22, p = 0.01) and BMI (r = −0.27, p = 0.03).

Table 1 summarizes the baseline characteristics for the study cohort stratified by tertiles of psoas CSA in L3. Tertiles were defined separately for males and females. Patients in the lowest tertile were significantly older, had a lower BMI, had a longer dialysis vintage before transplantation for a longer period, had a higher prevalence of CVD, and were less likely to have a living kidney donor. We further analyzed the risk of sarcopenia before transplantation, defined as psoas CSA in the lowest tertile. Af-
ter adjustment to covariates, age was the only parameter independently correlated with sarcopenia, with every year of age increasing the risk by 5% (Table 2).

**Correlation of Cross-Sectional Muscle Area, Muscle Index, and MA**

There was a strong linear correlation between muscle size measured as CSA of psoas at the L3 and L4 levels ($r = 0.93, p < 0.001$) and CSA of paravertebral muscles at the D12 level ($r = 0.64, p < 0.001$) and PI ($r = 0.97, p < 0.001$). In addition, there was a significant correlation, however milder, between MA at those measured points and CSA ($r = 0.18 \, p = 0.05; \, r = 0.25 \, p = 0.004; \text{and } r = 0.21, \, p = 0.01$, for psoas CSA at L3 and psoas mean MA at L3, L4, and paravertebral at D12, respectively).

**Clinical Significance of Sarcopenia following Kidney Transplantation**

Mortality Post Kidney Transplantation

Twelve kidney recipients died during the follow-up period (4 due to CVD, 1 due to cancer, 7 due to infection). None of the excluded recipients died during the follow-up period, and after adjustment to confounders including age, dialysis vintage, type of primary kidney disease (nephrosclerosis or diabetic kidney disease vs. other diagnosis), and type of donor, the survival rates were similar between included and excluded participants. CSA at L3 level had a significant independent association with post kidney transplantation mortality, with an adjusted hazard ratio of 0.86 per cm$^2$, indicating a 14% reduction in risk of mortality for every 1 cm$^2$ in-
crease in total psoas CSA before transplant, after adjustment to age, BMI before transplantation, dialysis vintage, diabetes mellitus before transplantation, and type of donor (Table 3).

Figure 1 shows patient survival in the different tertiles of psoas CSA, adjusted to these covariates. The mortality rate after kidney transplantation was inversely associated with CSA tertiles ($p = 0.04$). However, MA was not significantly associated with mortality after adjusting to covariates. In addition, death-censored graft survival was not correlated independently with muscle size or density.

#### Discussion

Sarcopenia can be accelerated in chronic medical illness, and its presence is a marker for poor outcome in various clinical conditions [5]. In addition, it is a frequent finding in ESRD patients, in whom muscle loss occurs at a younger age, and more markedly, in comparison to age-matched controls [28].

In a recent study by Dienemann et al. [29], muscle mass and strength were improved after kidney transplan-
tools which makes it a useful and convenient parameter to use. The European Working Group on Sarcopenia in Older People [4] published a framework for diagnosis of sarcopenia, including a clinical questionnaire, muscle strength test, muscle quantity or quality test, and a physical performance test. Currently, there are several modalities to measure muscle quantity and quality, such as appendicular skeletal muscle mass (measured through dual-energy X-ray absorptiometry), bioelectrical impedance analysis, and specific muscle CSA or volume that can be measured through CT or MRI [25].

MRI and CT are considered the gold standard for non-invasive assessment of muscle quantity and mass [34], and CT is the imaging modality used in most studies analyzing outcomes of sarcopenia, with total psoas muscle CSA at the level of L3 and L4 being the dominant method. In our cohort, the correlation of CSA and mean MA was significant albeit milder. However, MA was not independently correlated with mortality following transplantation, although MA was found as a predictor of outcome in cancer patients and transplantation [11, 35]. A possible explanation might be that in kidney recipients, the mortality rate is influenced by multiple factors confounding the effect of MA itself. Aging is associated with sarcopenia [5]. Similar to our findings, older age was consistently associated with sarcopenia measured in various methods [36–39], highlighting its importance in ESRD patients as well as in other populations.

We demonstrated a significant correlation of a more convenient and practical imaging tool, measurements of psoas CSA at L3 level, as a predictor of mortality and length of admission. Such a simple yet objective and comprehensive measure of overall burden of disease, such as sarcopenia, which can be evaluated by a widely available CT that is routinely done as part of pretransplantation assessments, may provide important information to patients and clinicians.

In addition, it could mark patients seen at pretransplant clinic for highly targeted nutritional and physical therapy interventions, or other novel treatment pathways in an effort to avoid poor outcomes. Further studies are required to assess efficacy of such interventions, as well as establishment of a robust radiologic threshold value for defining sarcopenia in kidney transplant recipients.

Our study has some limitations. The first one is specific to a single-center retrospective study. In addition, we excluded patients who did not have CT imaging within 90 days prior to surgery, which may have resulted in a selection bias. However, most recipients in the relevant period of time (75%) were included, and after adjustment to significant confounders, the mortality rate was similar.
between included and excluded participants. In addition, alternative measurements of sarcopenia were not available as sarcopenia assessment was not part of the routine pretransplant evaluation. Since there is no consensus on threshold of sarcopenia definition in this population, we defined the lowest tertile in our cohort as such, as was done in numerous previous studies [25]. Another limitation is the manual muscle area captured by the aforementioned free-hand region of interest. Although possibly even more accurate than automated programs, it can change per radiologist measuring.

In conclusion, sarcopenia as measured by psoas CSA is associated with poor short- and long-term outcomes following kidney transplantation and should be included as part of the assessment of kidney transplantation candidates. Identifying sarcopenic patients at the time of pretransplantation evaluation will enable early interventions, as well as risk stratification, prior to transplantation.

Statement of Ethics

This study protocol was reviewed and approved by the local Ethical Institutional Review Board, approval number TLV-18-0639. Due to the retrospective design of the study, it was approved with waiver of informed consent.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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None to declare.

Author Contributions

Grupper, A. and Druckmann, I. conceived the study; Yashar, H., Grupper, A., and Druckmann, I. contributed to study concept and design and acquisition of data; Yashar, H. and Druckmann, I. reviewed the CT scans of transplant recipients; Schwartz, D., Schwartz, I.F., Goykman, Y., Kliuk Ben-Bassat, O., Baruch, B., Tzadok, R., Shashar, M., and Cohen-Hagai, K. contributed to interpretation of data and performed the data collection; Schwartz, I.F. and Schwartz, D., Shashar, M., and Yashar, H. contributed to drafting of the manuscript; all authors critically reviewed the manuscript and approved it.

Data Availability Statement

All data analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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