Nonalcoholic Fatty Liver Disease before Kidney Transplantation Correlates with New Onset Diabetes and Poor Metabolic Outcomes

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Keywords
Nonalcoholic fatty liver disease · Kidney transplant recipients · Metabolic syndrome · New onset diabetes after transplantation · Cardiovascular mortality

Abstract
Introduction: Cardiovascular disease (CVD) is the leading cause of morbidity and mortality after kidney transplantation. Metabolic syndrome is common in renal transplant recipients and is associated with increased CVD risk in those patients. Nonalcoholic fatty liver disease (NAFLD) is considered to be the hepatic manifestation of a multi-system disorder, including CVD and metabolic syndrome. The data about prevalence of NAFLD before kidney transplantation and its consequences following transplantation are scarce.

Methods: A retrospective study of metabolic parameters and sonographic evidence of NAFLD, and an analysis of its metabolic outcomes, was performed in 341 consecutive kidney transplant recipients. Results: One-hundred twenty-four (36.4\%) kidney recipients had NAFLD before transplantation. The risk of NAFLD before kidney transplantation was independently and significantly related to diabetes (OR = 1.8), male gender (OR = 1.4), older age (every year of age increased the risk by 4\%), higher BMI (every increase of 1 kg/m\(^2\) increased the risk by 15\%), and higher triglycerides level. Mean levels of liver enzymes were similar in patients with and without NAFLD. Recipients with NAFLD before transplantation had a higher prevalence of new onset diabetes, even after adjustment to covariables. In addition, they had a higher increase in liver enzymes, triglycerides, and FIB-4 score, as an indication of liver fibrosis, after transplantation. Furthermore, NAFLD pre-transplantation was independently associated with cardiovascular mortality (HR = 4.4) following kidney transplantation. Conclusions: Sonographic evidence of NAFLD before kidney transplantation is associated with significant metabolic outcomes including de novo diabetes and cardiovascular mortality following transplantation and should be included as part of the assessment of kidney transplant candidate.

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Introduction

Cardiovascular disease (CVD) is the leading cause of death and graft loss after kidney transplantation [1–3]. It is well established that all components of metabolic syndrome are highly prevalent in renal transplant recipients and that metabolic syndrome is associated with increased CVD risk in those patients [4–6].

Nonalcoholic fatty liver disease (NAFLD) is caused by an accumulation of fat in the liver in the absence of significant alcohol intake. NAFLD is the most common chronic liver disorder [7, 8], with an estimated prevalence of up to one third in the general adult population in Western countries [9, 10]. It is closely associated with the epidemic of obesity and diabetes and is considered to be the hepatic manifestation of multi-system disorders, including CVD and metabolic syndrome [11–13]. In addition, NAFLD may progress over time to cirrhosis, end-stage liver disease, and hepatocellular carcinoma [8].

Accumulating evidence indicates that the presence and severity of NAFLD is associated with an increased prevalence of chronic kidney disease [14–18]. NAFLD is often seen either prior to transplantation or de novo after transplantation [19], with more robust data in liver transplant recipients [20]. Although in kidney transplant recipients the same might be surmised [21], thus far, the evidence is still lacking regarding the incidence of NAFLD as demonstrated by imaging (abdominal CT scan or ultrasound) before kidney transplantation as well as its consequences following transplantation.

The present study aims to ascertain the prevalence of NAFLD among the kidney transplant candidate, assess the parameters associated with it, and evaluate the metabolic consequences, including new onset diabetes and cardiovascular mortality following transplantation. A better knowledge of metabolic outcomes of this common disorder may be important as part of the pre-transplantation evaluation, for risk assessment and guidance of care following transplantation.

Materials and Methods

Study Design and Population

Included in the study are 341 adult (>18 years old) kidney transplant recipients who underwent transplantation between January 2015 and January 2021 in the Tel Aviv Medical Center, with at least 1 year of follow-up post-transplantation and with an available abdominal imaging, either CT scan or ultrasound, in the 6 months before transplantation. Excluded from the study are recipients with positive serology for hepatitis B or C virus, inflammatory bowel disease, celiac disease, individuals with multiple liver cysts, liver transplant recipients, secondary or primary amyloidosis, individuals with malignancy other than nonmelanomatus skin cancer, pregnant women, and/or individuals with an excessive alcohol consumption (≥30 g/day in men or ≥20 g/day in women). All kidney transplantation candidates underwent a comprehensive evaluation including an interview, physical examination, laboratory tests, and a routine abdominal ultrasound and/or CT scan, according to the local protocols.

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 (CNIs; tacrolimus or cyclosporine), mycophenolate mofetil or mycophenolate sodium, and low-dose prednisone (5 mg/day). According to the patient’s risk stratification for rejection, side effects, or other considerations, the maintenance regimen may be intensified or reduced, including changing doses or suspending specific agent, adding or switching other drugs including mTOR inhibitors (everolimus or sirolimus) or azathioprine.

NAFLD Diagnosis

NAFLD diagnosis was made by an abdominal ultrasound prior to transplantation (up to 3 months before). In 116 patients who did not have an assessment of the degree of liver steatosis in their routine abdominal imaging report, this assessment was done retrospectively by the radiologist who was blinded to the patients clinical and laboratory data. The degree of hepatosteatosis on CT images and US imaging was visually graded according to accepted practice [22–26].

Metabolic Parameters

Diabetes was defined as taking antihyperglycemic medication and/or HbA1C >6.4%. Pre-diabetes was defined as either HbA1C between 5.7 and 6.4% or fasting plasma glucose between 100 and 125 mg/dL, according to the American Diabetes Association (ADA) guidelines [27]. New onset diabetes after transplantation (NODAT) was defined as de novo diabetes that developed after transplantation.

Metabolic syndrome was defined according to NCEP ATP III as 3 or more of the following: blood pressure >130/85 mm Hg (or drug treatment for HTN), pre-diabetes or diabetes, abdominal obesity (waist circumference ≥102 cm for men and ≥88 cm for women), triglycerides (TG) ≥150 mg/dL (or drug treatment for hypertriglyceridemia), high-density lipoprotein <40 mg/dL for women and <50 mg/dL for men (or drug treatment for low high-density lipoprotein) [28]. Glomerular filtration rate was estimated (estimated glomerular filtration rate) using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) creatinine equation, a 4-variable formula [29], and adjusted for body surface area (Mosteller calculation).

HTN was defined as BP >140/90 mm Hg or the use of antihypertensive medications. Body mass index (BMI) was calculated as weight (kilogram) divided by height (meter) squared.

In order to increase the sensitivity of liver function tests among ESKD patients, lower normal values of aminotransferases were defined as aspartate aminotransferase (AST) <24, alanine aminotransferase (ALT) <17 [30, 31]. Normal value of gamma-glutamyl transferase (GGT) was defined, as for the general population, below 42 U/L. Prevalence of liver function tests within those limits as well as normal general limits was also analyzed.
Fatty liver index (FLI) was used for the likelihood of hepatic steatosis and was calculated using the formula: 
\[ \text{FLI} = \frac{(\text{Age} \times \text{AST})}{(\text{platelet count} \times \sqrt{\text{ALT}})}. \]

The result provided from the above equation was interpreted according to two cutoff values: FIB-4 <1.45 indicates low risk of advanced fibrosis; FIB-4 between 1.45 and 3.25 was deemed inconclusive; FIB-4 >3.25 indicates high risk for advanced liver fibrosis [34, 35]. The study was approved by the Institutional Review Board of Tel Aviv Medical Center.

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) for normally distributed variables and as median (interquartile range) for non-normally distributed variables. Continuous variables were compared by using a t test if normally distributed or by the Kruskal Wallis/Mann-Whitney test if non-normally distributed.

Categorical variables were displayed as 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. 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 NAFLD before transplantation and for NODAT, and potential predictors were selected and entered into multivariable logistic regression. Cox proportional-hazards regression was performed to assess all-cause mortality and CVD death, and 95% confidence intervals for the hazard ratios were calculated after adjusting to confounders.

In order to identify which variables are affected by multicollinearity and the strength of the correlation, we calculated variance inflation factors (VIF) and reported VIF above 3. Delta of a specific parameter was defined as the value measured on the last day of follow-up minus the pre-transplantation value.

\( p < 0.05 \) was considered statistically significant for all analyses.
IBM SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, NY, USA), was used for all statistical analyses.

Results

Characteristics of the Study Cohort
124 (36.4%) kidney recipients had NAFLD before transplantation. Two of them had a severe degree of steatosis, 9 had medium degree, and all others mild. Baseline (pre-transplantation) characteristics of the study group according to having NAFLD are shown in Table 1. All recipients were Caucasians, and none of them were treated with azathioprine or cyclosporine.

Kidney recipients with NAFLD before transplantation were significantly older, had a higher prevalence of male sex, a higher BMI, and a higher prevalence of diabetes, metabolic syndrome, and CVDs. As expected, TG were higher in the NAFLD group as well as FLI and FIB-4 scores.

Surprisingly, liver function tests were similar in both groups. Although mean AST and GGT had some trend of being higher in the NAFLD group, there was a similar rate of liver function tests within normal limits in both groups even when the suggested normal limits for ESKD population (AST <24, ALT <17 U/L) were used.

Risk of NAFLD before Transplantation
In a multivariate analysis, after adjustment to covariates significant in univariate analysis, the risk of NAFLD before kidney transplantation was independently and significantly related to diabetes (OR = 1.8), male gender (OR = 1.4), older age (every year of age increased the risk by 4%), higher BMI (every increase of 1 kg/m² increased the risk by 15%), and higher TG level. AST and GGT were not correlated independently with risk of NAFLD (Fig. 1a). When considering FLI instead of parameters included in this calculation (BMI, GGT, serum TG), FLI demonstrated strong and independent association with NAFLD with every one unit of the index increased the risk by almost 6 times (OR = 5.9 (2.1–11.6), \( p < 0.001 \)), Figure 1b. Waist circumference and BMI were highly correlated, with a correlation coefficient (VIF) of 0.87, which indicates a strong multicollinearity, and therefore waist circumference was not included in the analysis.

Post-Transplantation Metabolic Consequences of NAFLD
Table 2 summarizes the metabolic and other laboratory and clinical outcomes following transplantation (on the last day of follow up) of recipients with and without NAFLD before transplant. Recipients with NAFLD before transplantation did not gain more weight compared to recipients without NAFLD, and mean kidney graft function was similar. Nevertheless, they had significantly higher prevalence of NODAT and increase in TG. In addition, recipients with pre-transplant NAFLD had significant increase in liver enzymes and FIB-4 score comparing to recipients without pre-transplant NAFLD.
NAFLD before Transplantation and Risk of New Onset Diabetes

A total of 58 out of 212 (27.3%) recipients, who did not have diabetes before kidney transplantation, had de novo diabetes after transplantation (NODAT). In a multivariate analysis, the risk of NODAT was significantly and independently related to older age, with every year increasing the risk by almost 5%, to a higher BMI at transplantation (every 1 kg/m² increase the risk by 3%), pre-diabetes before transplantation (OR = 1.9), and to NAFLD before transplantation, which increased the risk by 80% (OR = 1.8) (Fig. 2). Maintenance immunosuppression with either low-dose prednisone (5 mg daily) or CNIs was not significantly associated with that risk. When considering FLI before transplantation instead of ultrasonographic evidence of NAFLD, FLI did not reach statistical significance.

Mortality after Transplantation

Thirty-nine recipients died during the follow-up period. In 14 kidney recipients, cause of death was due to...
CVD. After adjustment to significant parameters related to cardiovascular death, including age, diabetes, type of donor, and time on dialysis, NAFLD pre-transplantation was independently associated with CVD mortality, with hazard ratios = 4.4 (Fig. 3). There was no independent correlation of NAFLD before the transplantation and all-cause mortality.

**Discussion**

The term NAFLD is used to cover a spectrum of diseases predominantly characterized by macro vesicular steatosis of the liver, in people who do not consume large amounts of alcohol. The prevailing importance of NAFLD is its link to the metabolic syndrome and its possible role in atherosclerosis.
CVD is the leading cause of morbidity and mortality after kidney transplantation with an incidence among kidney transplant recipients which is much higher than in the general population. This is a consequence of well-known and described risk factors such as pre-transplant CVD, diabetes mellitus, obesity, hypertension, dyslipidemia, reduced kidney function, and albuminuria [36]. Some of these factors may be exacerbated by the use of chronic immunosuppression medications including steroids and CNIs, which are linked to increased risk of diabetes, hypertension, hyperlipidemia, and metabolic syndrome after kidney transplantation [5]. Several findings in our study, which explored the risk NAFLD might pose, are clinically important and might facilitate better decision-making in the evaluation and risk stratification of a potential kidney transplant recipient, as well as guiding possible interventions and treatments following transplantation.

First of all, we found high (36%) prevalence of liver steatosis in kidney transplant recipients. NAFLD is usually an asymptomatic condition, and aminotransferases (AST and ALT) levels, which are used to assess the diagnosis of hepatobiliary disease, are frequently at normal values [37–39] as well as GGT and alkaline phosphatase that may be normal or slightly elevated. In ESKD pa-

### Table 2. Progression of metabolic parameters after transplantation in patients with and without NAFLD before transplantation (mean (SD), unless otherwise stated)

| Variable                      | No NAFLD | NAFLD     | p value |
|-------------------------------|----------|-----------|---------|
| Delta weight, kg              | 5.1 (6.6)| 5.2 (5.8) | 0.74    |
| Delta BMI, kg/m²              | 1.5 (2.1)| 1.7 (1.9) | 0.39    |
| NODAT, n (%)                  | 32 (20.6)| 26 (44.8) | <0.001  |
| Serum creatinine, LDFU, mg/dL | 1.3 (0.6)| 1.4 (0.7) | 0.29    |
| eGFR, mL/min                  | 64 (26)  | 61 (36)   | 0.43    |
| Hemoglobin, LDFU, g/dL        | 13.3 (2.2)| 13.1 (2.2)| 0.26    |
| Platelet count, LDFU, units   | 198 (64) | 189 (61)  | 0.27    |
| ALT, LDFU, U/L                | 25.8 (13)| 25.2 (14)| 0.04    |
| Delta ALT                     | 8.7 (14) | 14.4 (12) | 0.02    |
| AST, LDFU, U/L                | 25 (9.6) | 36.9 (18.1)| 0.03   |
| Delta AST                     | 6.9 (9)  | 16 (18)   | 0.02    |
| GGT, LDFU, U/L                | 39.3 (35)| 60.2 (41)| 0.03    |
| Delta GGT                     | 10 (28)  | 30 (27)   | 0.02    |
| Alkaline phosphatase, LDFU, U/L| 84 (53) | 92 (43)   | 0.18    |
| Serum albumin, LDFU, g/L      | 42.4 (4.5)| 41.8 (4.1)| 0.24    |
| TG, LDFU, mg/dL               | 155.2 (70)| 177 (87)| 0.024   |
| FIB-4, LDFU                   | 1.7 (2)  | 2.6 (3)   | 0.02    |
| Delta FIB-4                   | 0.5 (2)  | 0.9 (2)   | 0.02    |

ALT, alanine transaminase; AST, aspartate aminotransferase; BMI, body mass index; eGFR, estimated glomerular filtration rate; FIB-4, fibrosis-4 score; GGT, gamma-glutamyl transferase; LDFU, last day of follow-up; NAFLD, nonalcoholic fatty liver disease; NODAT, new onset diabetes after transplantation; SD, standard deviation.

**Fig. 2.** Forest plot of multivariable analysis of risk of NODAT in kidney transplant candidates. x = 1 represents similar risk (odds ratio).
patients, the role of liver enzymes in the NAFLD diagnosis is even less valuable as the concentrations of serum aminotransferases in ESKD most commonly fall within the lower end of the range of normal values [40, 41], and serum levels of alkaline phosphatase are elevated due to concurrent renal osteodystrophy [42]. As a result, a liver disease might be underdiagnosed in many kidney transplant candidates. In our study, similar to other reports [19, 43], none of the liver enzymes mentioned above showed any significant differences between individuals with and without hepatic steatosis, which means they cannot guide clinicians in the diagnosis of NAFLD. However, high FLI score and metabolic syndrome-related variables (age, BMI, male gender, diabetes, and serum TG) were significantly associated with NAFLD. As routine abdominal US in kidney transplant recipients does not reliably determine liver steatosis, we suggest use of FLI in this population as a reliable predictor of NAFLD independently of liver enzymes level. Our major finding was that sonographic evidence of NAFLD before kidney transplantation was associated with poor metabolic outcomes, including higher risk for NODAT and CVD mortality.

This independent association of NAFLD and CVD outcomes was demonstrated in general population [44] and in indirect way in some groups of kidney transplant recipients. For example, Mikolasevic et al. [45] showed a correlation between NAFLD and increased level of carotid atherosclerosis, as a marker of CVD. Zelle et al. [46] reported association of elevated GGT and alkaline phosphatase (that may serve as laboratory markers of NAFLD) and cardiovascular mortality in renal transplant recipients.

The mechanism of direct influence of NAFLD on accelerated atherosclerosis and further cardiovascular damage has been explored and was shown to be related to chronic inflammation and endothelial dysfunction [21, 47, 48]. Our findings of significant increased risk of CVD mortality in recipients with pre-transplantation NAFLD, even after adjustments to known CVD risk fac-

![Fig. 3. CVD mortality after kidney transplantation, in recipients with and without NAFLD before transplantation, after adjustment to covariates (p = 0.04).](image)
tors, supports this hypothesis of independent role of NAFLD in CVD acceleration in kidney transplant recipients.

The correlation of NAFLD and risk of diabetes after transplantation is not surprising and was demonstrated in liver transplant recipients [49]. Evidence of this association in kidney transplant recipients is scarce and based on surrogate markers [46, 50]. In our study, diagnosis of NAFLD by imaging before transplantation was correlated with 80% increased risk of NODAT development, even after adjustment to other diabetogenic parameters including BMI and pre-diabetes. Interestingly, despite good correlation between FLI and liver steatosis on imaging before transplantation, FLI failed to demonstrate correlation with NODAT development. This finding, combined with uniformly normal liver enzymes in pre-transplant patients with or without NAFLD, emphasizes the need for specific consideration of hepatic steatosis on pre-transplant abdominal imaging.

Several studies have shown that NAFLD is associated with higher incidence of chronic kidney disease, reduced glomerular filtration rate, and proteinuria in nontransplant individuals [16, 17]. It is clear that these two conditions share risk factors and consequences such as HTN, diabetes mellitus, atherogenic dyslipidemia, obesity, and insulin resistance [51–53]. Mikolasevic et al. [19] reported an association of NAFLD and reduced graft function in kidney recipients. In contrast to that, we could not find a correlation between graft function and NAFLD. Possible explanations may be a relatively short follow-up period post-transplant or a discrepancy in NAFLD diagnosed before transplantation to NAFLD diagnosed after it.

Our study has some limitations: this is a retrospective single-center analysis and is prone to flaws related to this study design. The mean follow-up was less than 5 years post-transplant. It is possible that a longer follow-up post-transplantation might unmask other differences between the groups.

The presence of NAFLD was based on the exclusion of known etiologic factors of liver disease and on imaging findings determined noninvasively and was not confirmed by a liver biopsy, which is considered as the gold standard procedure. Obviously, performing invasive procedures in most individuals with suspected NAFLD was not justified, and therefore, we rely on sonographic diagnosis of NAFLD, as used in routine clinical practice.

The sensitivity and specificity for ultrasound are 85% and 94%, respectively, for detecting ≥20–30% steatosis, when using liver biopsy as the gold standard [53]. The CT scan also performs very well in diagnosing steatosis of 30% or more, with 100% specificity and 82% sensitivity [54, 55]. Therefore, we could analyze the consequences of individuals with NAFLD demonstrated by these techniques. However, the strength of our study is its clinical relevance: we demonstrated a significant association of more convenient and practical imaging tools (abdominal ultrasound or CT scans) with important outcomes post-kidney transplantation. Such a simple and comprehensive measure of liver steatosis which can be evaluated by widely common and noninvasive methods that are routinely used as part of pre-transplantation assessments may provide important information to patients and clinicians.

In conclusion, in accordance with our results, NAFLD should be considered and investigated as a new important risk factor for increased CVD in renal transplant recipients. Further studies are needed to investigate and to confirm these observations. Identifying patients at risk at the time of pre-transplantation 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 Institution (Tel Aviv Sourasky Medical Center) Review Board, approval number TLV-18-0639. Due to the retrospective design of the study, it was approved with the waiver of informed consent.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Ayelet Grupper and Helena Katchman conceived the study; Idan Ben Shabat and Ayelet Grupper contributed to study concept and design and acquisition of data; Aviad Rabinowich reviewed the abdominal ultrasound of transplant recipients; Doron Schwartz, Idit F. Schwartz, Yaacov Goykhman, Orit Kliuk Ben-Bassat, Roni Baruch, Roie Tzadok, Moshe Shashar, and Keren Cohen-Hagai contributed to interpretation of data and performed the
data collection; Idan Ben Shabat, Idit F. Schwartz and Doron Schwartz, and Aviad Rabinovich contributed to drafting of the manuscript; and all authors critically reviewed the manuscript and approved it.

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Data Availability Statement

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