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BRIEF REPORT

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Postoperative association between impaired renal function and vascular dysfunction in liver transplant recipients

To the editor,

Liver transplantation (LT) recipients have an increased risk of developing cardiovascular disease (CVD), but the physiological mechanisms driving this risk are not yet fully understood. A decline in renal function after transplant may be an important contributor to the development of CVD among these patients. In this regard, a recent article published in *Liver Transplantation* by Hassouneh et al. demonstrated that estimated glomerular filtration rate (eGFR) 6 months following LT was a strong predictor of future atherosclerotic events and that the addition of eGFR to the Framingham Risk Score improved CVD risk stratification among LT recipients.[1] Vascular dysfunction characterized by endothelial dysfunction and arterial stiffness have previously been documented as the initial pathophysiological events in the development of atherosclerosis and are common characteristics observed with declining renal function.[2] Renal function decline after LT may lead to endothelial dysfunction and arterial stiffness, which may accelerate the development of atherosclerotic CVD. The association between altered renal function and vascular dysfunction after LT has not yet been investigated. Therefore, following the work of Hassouneh et al., we performed a series of physiology-based assessments to ascertain if vascular dysfunction may be a potential therapeutic target to mitigate CVD risk in patients with renal dysfunction following LT.

PATIENTS AND METHODS

A total of 29 LT patients (12 men and 17 women; median age, 57 years [interquartile range, IQR, 52–64 years]; eGFR, 49 ml/min/1.73 m^2 [IQR, 43–73 ml/min/1.73 m^2]) were investigated. All study procedures were approved by the Institutional Review Board of Virginia Commonwealth University and conformed with the Declaration of Helsinki. Participants provided written informed consent. Prior to vascular testing, patients were instructed to refrain from using tobacco products or ingesting caffeine for at least 12 h, avoid exercise for at least 24 h, fast for at least 4 h, and withhold all morning medications. A blood draw for routine clinical laboratory tests, including creatinine levels, was obtained by venipuncture. The

TABLE 1 Participant characteristics (n = 29)

Demographics	Median (IQR) or *n*
Age, years	57 (52–64)
Sex, male/female	12/17
Race, Black/White	7/22
Time from transplant, days	767 (328–2705)
Etiology of cirrhosis	
Nonalcoholic steatohepatitis	12
Alcohol	6
Hepatitis C	6
Primary sclerosing cholangitis	3
Other	2
Pretransplant prevalence of comorbid conditions	
Hypertension	11
Dyslipidemia	7
Type 2 diabetes mellitus	4
Posttransplant prevalence of comorbid conditions	
Hypertension	27
Dyslipidemia	14
Type 2 diabetes mellitus	9
Calcineurin inhibitor immunosuppressant regimen	
Tacrolimus	26
Cyclosporine	4

Abbreviation: IQR, interquartile range.

Abbreviations: CIMT, carotid intima-media thickness; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; FMD_{BA}, flow-mediated dilation of the brachial artery; IQR, interquartile range; LT, liver transplantation.

eGFR was calculated with the 2021 Chronic Kidney Disease Epidemiology Collaboration equation, estimating kidney function without a race variable. Conduit artery endothelial function was assessed via flow-mediated dilation of the brachial artery (FMD_{BA}). Images of the brachial artery were obtained with duplex ultrasound (Logic e, GE Healthcare) and analyzed offline with edge detection software (Cardiovascular Suite, Quippu). This technique is an established in vivo bioassay of nitric oxide production and therefore an ideal marker of vascular endothelial function, the initial pathophysiologic step in the development of atherosclerosis.[3] B-mode ultrasound images of the carotid artery were combined with central aortic pressure waveforms acquired by applanation tonometry (Sphygmocor CPVH, Atcor Medical) to obtain carotid intima-media thickness (CIMT), distension, distensibility, compliance, and stiffness (Cardiovascular Suite, Quippu). These ultrasound-derived parameters of carotid artery structure and function are established independent predictors of atherosclerotic vascular events. Central arterial hemodynamics were derived from radial waveforms with the generalized transfer function and wave separation analysis using a modified triangular flow waveform to obtain central aortic pulse pressure, reflection magnitude, and augmentation index.[4] Central aortic pressures are better predictors of CVD compared with brachial pressures.[4] Furthermore, the central hemodynamics assessed herein provide an indicator of left ventricular pulsatile load, establishing potential vascular contributions to heart failure, a commonly reported CVD in LT recipients and individuals with impaired renal function.[4] All statistical analyses were conducted using SPSS (IBM Corp.). Variables were compared between patients with an eGFR <60 and >60 ml/min/1.73 m^2 using Mann–Whitney U tests. Correlations were assessed using the two-tailed Spearman ρ. Data are reported as median (IQR).

RESULTS

Participant characteristics are summarized in Table 1. Serum creatinine levels (median, 1.35 mg/dl [IQR, 1.10–1.68 mg/dl]) were negatively associated with vascular endothelial function via FMD_{BA} (median, 4.81% [IQR, 3.70%–6.28%]; $r = -0.4$; $p \leq 0.001$). eGFR (median, 49 ml/min/1.73 m^2 [IQR, 43–73 ml/min/1.73 m^2]) was positively associated with carotid compliance (median, 1.07 $10^{-6}{\cdot}m^2 \cdot kPa^{-1}$ [IQR, 0.65–1.53 $10^{-6}{\cdot}m^2 \cdot kPa^{-1}$]; $r = 0.4$; $p = 0.02$). eGFR

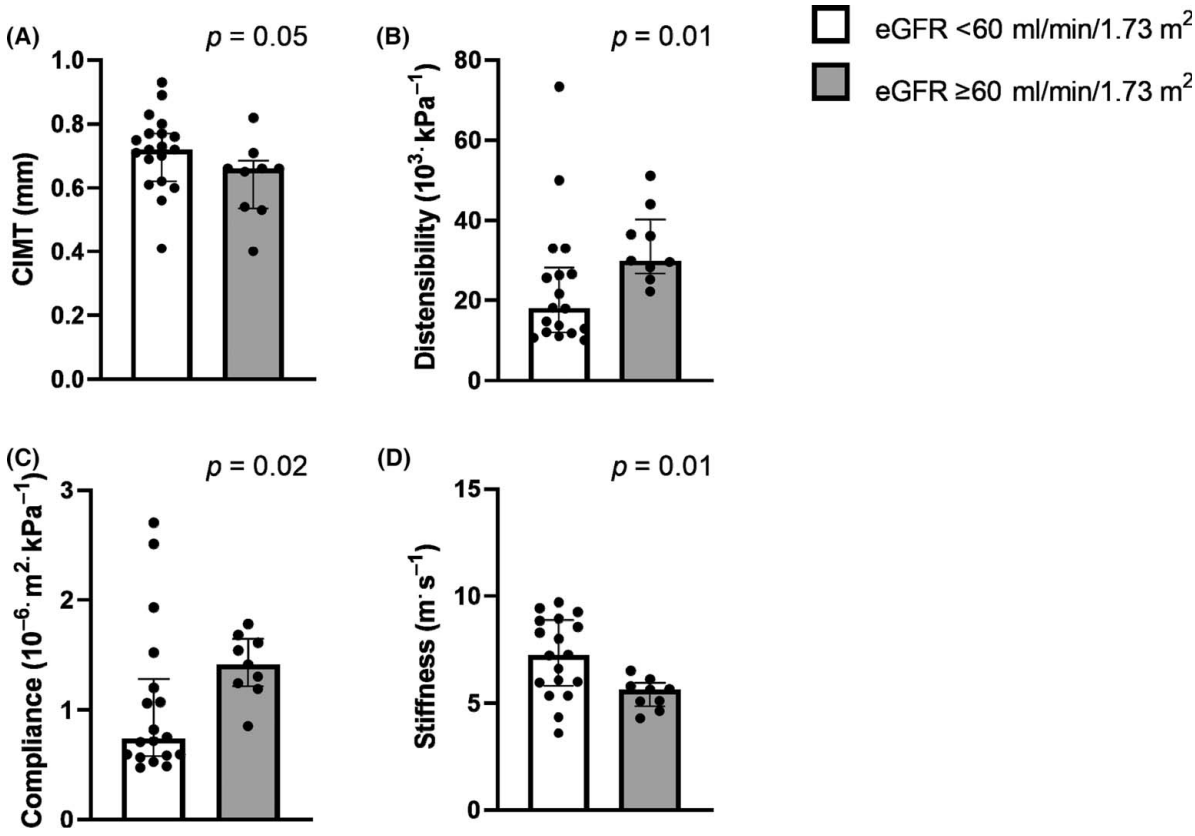

FIGURE 1 Differences in carotid artery structure and stiffness according to eGFR. (A) Patients with an eGFR < 60 ml/min/1.73 m^2 had greater CIMT, (B) lower carotid distensibility, (C) lower carotid compliance, and (D) higher carotid stiffness compared with patients with an eGFR ≥ 60 ml/min/1.73 m^2.

was negatively associated with carotid stiffness (median, 6.07 m · s^{-1} [IQR, 5.35–8.15 m · s^{-1}]; $r = -0.5$; $p = 0.008$), central pulse pressure (median, 45 mm Hg [IQR, 37–54 mm Hg]; $r = -0.35$; $p = 0.02$), reflection magnitude (median, 69% [60%–78%]; $r = -0.36$; $p = 0.03$), and augmentation index (median, 27% [IQR, 21%–32%]; $r = -0.4$; $p = 0.03$). Patients with an eGFR <60 ml/min/1.73 m^2 had worse markers of carotid artery structure and stiffness (Figure 1), including CIMT (eGFR >60 vs. <60 ml/min/1.73 m^2; medians, 0.66 mm [IQR, 0.54–0.66 mm] vs. 0.71 mm [IQR, 0.62–0.76 mm]; $p = 0.05$), distensibility (medians, 29.82 10^3 · kPa^{-1} [IQR, 28.14–36.56 10^3 · kPa^{-1}] vs. 25.62 10^3 · kPa^{-1} [IQR, 14.20–33.02 10^3 · kPa^{-1}]; $p = 0.01$), compliance (medians, 1.41 10^{-6} · m^2 · kPa^{-1} [IQR, 1.24–1.61 10^{-6} · m^2 · kPa^{-1}] vs. 1.07 10^{-6} · m^2 · kPa^{-1} [IQR, 0.65–1.53 10^{-6} · m^2 · kPa^{-1}]; $p = 0.02$), and stiffness (medians, 5.63 m · s^{-1} [IQR, 5.08–5.79 m · s^{-1}] vs. 6.07 m · s^{-1} [IQR, 5.35–8.15 m · s^{-1}]; $p = 0.01$).

DISCUSSION

Our findings demonstrate that LT patients with impaired renal function have worse vascular endothelial function and increased arterial stiffness. It was recently demonstrated that renal dysfunction is a predictor of CVD in LT recipients, independent of peri- and postoperative traditional CVD risk factors.[1] The current findings suggest that vascular dysfunction may be one potential mechanism explaining this relationship. Although vascular dysfunction is expected in the setting of renal dysfunction, the etiology of renal dysfunction may be unique among LT recipients compared with the general population. In this respect, it has been speculated that aberrant changes in cardiometabolic risk factors such as increased weight gain after LT in combination with immunosuppressant therapy can act synergistically to impair renal function and accelerate vascular dysfunction and the subsequent development of CVD.[1,5] It is also plausible that vascular endothelial dysfunction and increases in arterial stiffness may exacerbate renal function declines as a result of renal hypoxia and organ damage from excess pulsatility, respectively. Our findings suggest that vascular dysfunction may be an attractive therapeutic target to mitigate CVD in LT patients with abnormal renal function. However, future research should aim to confirm the accuracy and ability of these indexes of vascular function to predict CVD outcomes after transplant in relation to renal dysfunction. Contributing to this framework of evidence may have clinical implications for renal and vascular consequences of LT and the associated cardiovascular implications. In this regard, the development of therapeutic strategies aimed at improving vascular function may hold promise for reducing CVD risk in LT patients with impaired renal function.

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CONFLICT OF INTEREST

Nothing to report.

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