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INVITED COMMENTARY

Invited commentary on low high-density lipoprotein is a risk for vascular disease

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Cardiovascular disease (CVD) remains the leading cause of death after kidney transplantation, with a mortality rate of close to 5 per 1000 patient-year, accounting for 30–50% of deaths with functioning graft [1,2]. Although transplantation significantly improves the risk of CV death in patients with end-stage renal disease (ESRD) [3], this risk still remains high; it is 50-fold higher than that prevailing in general population in younger patients. This is to some extent attributable to pre-existing CVD, inherited from pretransplant period, including left ventricular hypertrophy (LVH), coronary artery disease (CAD), arteriosclerosis and vascular calcification. Moreover, traditional risk factors for CVD, including renal dysfunction, hypertension, dyslipidemia, diabetes, and obesity either persist or develop *de novo* after transplantation. However, these risk factors do not completely explain the large discrepancy in the rate of CV events in this patient population. Therefore, a number of nontraditional risk factors have been incriminated. Examples of the suggested risk factors include anemia, hyperhomocysteinemia, lupus anticoagulant antibodies, proteinuria, oxidative stress, systemic inflammation, advanced glycosylation end-products (AGEs), and osteoprotegerin [4–7].

Dyslipidemia is a common metabolic complication after transplantation, present in more than 50–60% of the patients [8,9]. Immunosuppressive agents, diabetes, and obesity generally are associated with worsening of lipid abnormalities. The typical profile is that of elevated low-density lipoprotein cholesterol (LDL-C) and triglyceride levels and reduced high-density lipoprotein cholesterol (HDL-C). Evidence suggests that treatment of high LDL-C is associated with improved CV outcomes. In the Assessment of Lescol in Renal Transplantation (ALERT) trial 2102 transplant recipients with total cholesterol 154–347 mg/dl (4.0 to 9.0 mM) were randomized to receive fluvastatin 40 to 80 mg daily or placebo [10]. After 5 years of follow-up, fluvastatin therapy was associated with a significant (35%) reduction in the incidence of myocardial infarction (MI) and cardiac death [11]. Although the 13% reduction in the primary outcome of major adverse cardiac events (MACE; MI, death, or coronary intervention) was not statistically significant in the study period, with a 2-year extension, there was 21% reduction in the risk of MACE [12]. However, these encouraging results do not obviate the need for exploring the role of other lipid components as potential risk factors that could be therapeutic targets.

High-density lipoprotein cholesterol is a strong candidate target, as it has been recognized as an antiatherogenic lipoprotein. The protective effects of HDL are multi-faceted and include reverse cholesterol transport, antithrombotic, antioxidative, and anti-inflammatory effects, promotion of nitric oxide synthesis and release, and protecting and regulating endothelial cell phenotype [13–18]. Reverse cholesterol transport from macrophages in the atherosclerotic plaque and modulation of their pro-inflammatory phenotype may be among important antiatherogenic properties of HDL [13–15]. Current data

regarding the association of HDL-C with CVD following transplantation is insufficient and inconclusive. In a study of 706 renal transplants, Kasiske *et al.*, found HDL-C as the best predictor of ischemic heart disease (HR: 0.8 for each 10 mg/dl) [19]. However, Aker *et al.* did not find an independent association between HDL-C and CVD [20]. More recently, *post hoc* analysis of ALERT trial data showed that LDL/HDL ratio was an independent risk factor for major adverse cardiac events (MACE) only in women [21]. In cardiac transplant recipients, low levels of HDL-C have been associated with positive vascular remodeling, as evidenced by increased brachial artery diameter.

In this issue of the journal, Barn *et al.* have reported the results of a retrospective, single-center cohort study on the association of HDL-C and MACE, defined as any cardiac, peripheral vascular, or cerebrovascular ischemic event, congestive heart failure or arrhythmia, in 324 renal transplant recipients. The patients had at least one lipid profile tested, on average 31 weeks post-transplant and were followed for a mean of 3.9 years. Among this cohort, they observed low HDL-C levels (defined as <40 mg/dl in men and <50 mg/dl in women) in 58.3% of the patients. Twenty-eight percent experienced a MACE, with estimated 7-year rate of 54% with low HDL-C and 30% with normal levels. After adjustment for diabetes, deceased donor organ, previous CVD, and high LDL-C, low HDL-C was associated with 92% increase in the risk of experiencing a MACE (95% CI:15–220%). In this cohort, MACE risk was not significantly related to LDL/HDL ratio. This study provides valuable information regarding the adverse effects of low HDL-C in kidney transplant recipients. However, there are a number of limitations that call for cautious interpretation of the results. Some of the patients had only one HDL-C value, and for the rest average of few values was used as the predictor variable and the measurements were made over a wide range of periods after transplantation. Changes in HDL-C along with other important factors over time including LDL-C, smoking status, weight change, new onset diabetes, glycemic control, lifestyle parameters, immunosuppressive drugs, blood pressure control, antihypertensive agents, and others have not been accounted for.

However, the results of this study provide further support for the role of HDL-C in transplant outcomes and call for further prospective investigations to better evaluate its link with CVD as the major cause of death and graft loss.

The antiatherogenic properties of HDL-C make it a target for pharmacologic intervention. The results of Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) showed 11% reduction in risk of coronary heart disease with each 5 mg/dl (0.13 mM) increase in HDL-C. However, atheroprotective effects of HDL particles may not be shared similarly among its different subpopulations, and this may explain why HDL may not have played a significant role in the gemfibrozil-mediated CVD risk in this trial [22]. In ILLUSTRATE trial, 24 months of treatment with torcetrapib, a potent cholesteryl ester transfer protein (CETP) inhibitor, increased HDL-C levels by 60% and lowered LDL-C by 20%. However, this favorable change in lipid profile was not associated with significant improvement in progression of coronary atherosclerosis evidenced by percent atheroma volume change. However, torcetrapib-treated patients in the highest quartile of HDL-C change showed the least progression compared with the lowest quartile, and showed significant regression of percent atheroma [23]. Niacin use is associated with increase in HDL-C, and several studies are currently examining its impact on different CV outcomes.

Considering the paucity of strong data regarding the association of HDL-C with CVD after transplantation, and lack of data supporting use of HDL-C elevating agents, even in general population, there is a great need for properly designed studies to convincingly demonstrate the deleterious impact of low HDL-C, or its subtypes, on CV outcomes post-transplant, which will open the door for investigation of therapeutic interventions. Until further evidence is available, following the recommendations of the NKF Working Group on the management of dyslipidemia in kidney transplant recipients is advisable.

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