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ORIGINAL ARTICLE

Low levels of high-density lipoprotein cholesterol: an independent risk factor for late adverse cardiovascular events in renal transplant recipients

Kulpreet Barn,[1] Mark Laftavi,[2] Drew Pierce,[2] Chin Ying,[3] William E. Boden[1] and Oleh Pankewycz[2]

1 Department of Medicine, State University of New York, University at Buffalo, Buffalo General Hospital, Kaleida Health, Buffalo, NY, USA
2 Department of Surgery, State University of New York, University at Buffalo, Buffalo General Hospital, Kaleida Health, Buffalo, NY, USA
3 Department of Biostatistics, Social and Preventative Medicine, State University of New York, University at Buffalo, Buffalo, NY, USA

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Correspondence
Oleh Pankewycz MD, Division of Transplantation, Department of Surgery, State University of New York (SUNY) at Buffalo, Buffalo General Hospital, 100 High Street, Buffalo, NY 14203, USA. Tel.: +1 716 859 1345; fax: +1 716 859 4631; e-mail: op3@buffalo.edu

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Summary

Long-term kidney transplant graft and patient survival is often limited by cardiovascular (CV) disease. Risk factors for CV disease such as diabetes, hypertension and elevated low-density lipoprotein levels are well documented; however, the impact of low levels of high-density lipoprotein (HDL) has not been defined. We performed a retrospective chart review of 324 consecutive renal transplant recipients from 2001 to 2007 to correlate baseline HDL levels with major adverse cardiovascular events (MACEs) defined as a composite of new onset CV illness, cerebral vascular events and peripheral vascular disease. A total of 92 MACEs occurred over a total of 1913 patient years of follow-up. Low HDL cholesterol levels were noted in 58.3% of patients. Compared with those with normal HDL levels, a greater percentage of patients with low HDL levels had post-transplant MACEs (20% vs. 60% respectively) and experienced an increased rate of all cause mortality. Sixty-two percent of all MACEs occurred in patients with low HDL levels. In the low HDL group, the odds ratio for experiencing a MACE was 1.92. Therefore, HDL cholesterol may provide an important new therapeutic target to prevent vascular morbidity and mortality following renal transplantation.

Introduction

Renal disease is a growing major health-care problem in the United States (US) and worldwide [1,2]. Given the increased prevalence of hypertension and diabetes in the United States both the population of patients with end-stage renal disease (ESRD) and transplant programs to treat ESRD are increasing at the rate of 8% and 4% respectively accounting for an increasingly larger share of the US medical budget [2–4]. Because renal transplantation provides better patient survival and quality of life at a lower overall cost when compared with dialysis, this approach has now become the treatment of choice for ESRD patients [5].

Recent improvements in the immediate and near term medical management of transplant recipients have resulted in 1-year graft and patient survival rates in excess of 90% for both deceased and living donor kidney recipients [6]. By contrast, however, long-term graft and patient survival rates have not kept pace with these early improvements and remain the most important barriers to successful long-term outcomes following renal transplantation [3,7].

One of the major causes of late graft loss is patient death with function [3]. Cardiovascular disease (CVD) is now the primary cause of patient death following renal transplantation and accounts for a third of all graft losses [3]. Typical clinical risk factors for post-transplant CVD contribute to morbidity and mortality and current clinical practice guidelines to prevent these modifiable factors are well-recognized [8,9]. In terms of dyslipidemia, current practice guidelines focus principally on using statin

therapy to control low-density lipoprotein (LDL) levels [10,11]. However, the fundamental dyslipidemia associated with diabetes, obesity and metabolic syndrome is not only elevated LDL cholesterol (LDL-C), but also low levels of high-density lipoprotein cholesterol (HDL-C) and elevated triglyceride (TG) levels. Accordingly, there is a paucity of data regarding the role of low LDL levels and the risk of developing major adverse cardiovascular events (MACEs) in postrenal transplant patients.

In the general population, low HDL-C levels inversely correlate with CVD and increase cardiovascular mortality [12,13]. However, in the renal transplant population, a low HDL-C level has not been shown to be an independent risk factor for MACE. If this could be established, it would offer a new therapeutic target, that of raising low levels of HDL-C, as a means to improve clinical outcomes in the post-transplant population. The purpose of this study was to examine the correlation between low HDL-C levels and MACEs in renal transplant patients and specifically to examine the correlation between low HDL-C levels and cardiovascular morbidity and mortality.

Methods

Study design and patient selection

This retrospective study was conducted at Buffalo General Hospital (BGH), Kaleida Health systems with approval from the Institutional Review Board of SUNY, University at Buffalo. All patients who received a kidney transplant between the years 2001 to 2007 were identified for extensive chart review. Initially, 400 transplant recipients qualified for the study. All transplant recipients were followed in a single transplant clinic at BGH and their care was directed by one transplant team. Following transplantation, patients are seen exclusively by the transplant team at least monthly for the first year. Patients are admitted only to BGH for the first six post-transplant months. Afterwards, the transplant team is notified of all subsequent medical or surgical complications for coordination of care and immunosuppressive therapy. All patients are seen at least twice per year after the first year post-transplant. Comprehensive medical records for all patients were maintained within the single transplant center. By analyzing hospital electronic records and medical charts as well as transplant clinic records, patient demographics, lipid profiles, duration of dialysis, statin use, immunosuppressive therapy, presence of diabetes and hypertension and subsequent MACEs were obtained. To verify the accuracy of the data, chart review was performed by two investigators (KB and DP). Seventy six patients had incomplete records or were lost to follow-up, leaving 324 evaluable patients included in this study. Average time of follow-up after transplantation was 3.9 years (range 1–7 years).

All patients received induction immunosuppressive therapy with either anti-thymocyte globulin (Thymoglobulin, $n = 253$; Genzyme, Boston, MA, USA) or anti-interleukin 2 receptor antibody (Simulect, $n = 71$; Novartis, Basel, Switzerland). Most patients received triple maintenance immunosuppression consisting of a calcineurin inhibitor ($n = 194$) or sirolimus ($n = 130$) together with mycophenolate and low dose steroids consisting of 5 mg/day of prednisone by day 30 post-transplant. In 34 patients, steroids were withdrawn 7 days post-transplant.

Study definitions

Fasting lipid profiles were documented at least once and on average 2.48 times per transplant recipient. Because this study was by design a retrospective assessment of post-transplant lipid values, we did not systematically assess pretransplant lipid parameters in this population. All lipid measurements were performed in a fasting state after transplantation. The average time to lipid measurement was 30.8 ± 45.1 weeks after transplantation. For patients with greater than one lipid study, the average was used in this analysis. TG levels, LDL, HDL were recorded separately and analyzed using multivariate and univariate analysis. High LDL levels were considered as being >100 mg/dl. Low HDL cholesterol (HDL-C) levels were defined as being <40 mg/dl for men and <50 mg/dl for women. TG levels were considered high if >150 mg/dl.

Patients were labeled as having metabolic syndrome if they had three of the following five risk factors: body mass index at the time of transplant evaluation of >30 kg/m^2, TG level >150, gender-based HDL levels less than the upper limits listed above, diabetes and hypertension. Pre-existing cardiovascular burden was defined as having a medical history of acute myocardial infarction, coronary artery disease with stent or bypass grafting, cerebral vascular event (CVA) with transient or permanent neurological impairment or peripheral artery disease (PAD) with amputation, bypass grafting or stenting. Diabetes was defined as requiring insulin or oral hypoglycemic therapy. Hypertension was defined as a blood pressure of >140/90 or usage of antihypertensive therapy.

Clinical events

Patient records were reviewed for the development of MACEs defined as (i) cardiovascular events comprised recent myocardial infarction, new onset atrial or ventricular arrhythmia, congestive heart failure or coronary artery bypass or stenting; (ii) peripheral vascular events which included Doppler indices indicating worsening PAD, new

onset nonhealing leg ulcerations or infections, need for femoral bypass grafting or stenting; and (iii) cerebral vascular events including CVA or transient neurologic ischemic event. Atherosclerosis-related MACEs were defined as the sum of all three forms of vascular related clinical adverse events.

Statistics

Univariate analysis was performed by two tailed student's *t*-test and ANOVA to analyze parametric data. Nonparametric data were analyzed using chi-square. An analysis for independent risk factors for adverse atherosclerotic events was performed using a backward elimination logistic regression model using a significance level of 0.05 to retain. In addition, the odds ratio of MACEs for low HDL-C (HDL-C < 40 mg/dl for men and <50 for women) to normal HDL-C was calculated. The relationship between MACEs and LDL to HDL cholesterol ratios was analyzed by quartiles using the Fisher exact test and confirmed by logistic regression analysis. All analyses were performed with SAS version 9.1.3 (SAS Institute Inc, Cary, NC, USA). Kaplan–Meier curves were generated using XLStat (Addinsoft, New York, NY, USA).

Results

Atherosclerosis-related major adverse clinical events

Of the 324 patients in this review, 92 (28%) transplant recipients experienced a significant MACE (Table 1). By univariate analysis, significant risk factors for developing a MACE included a history of diabetes, receipt of a deceased donor organ transplant, the presence of previous CV disease, the presence of the metabolic syndrome, a high LDL-C, and a low HDL-C. By multivariate analysis, low HDL-C levels remained significantly associated with higher atherosclerosis-related MACEs ($P < 0.05$). Having a low HDL-C increased the odds of experiencing a MACE by approximately two fold (OR: 1.92, 95% CI: 1.15–3.20). Thus, low HDL-C was a significant risk factor for developing a MACE either independently or in association with the presence of the metabolic syndrome. MACEs were evenly divided amongst patients with LDL/HDL ratios of <1.5 (21.7%), 1.5–2.0 (15.2%), 2.0–2.5 (23.9%) and >2.5 (39.1%) ($P = 0.41$).

Hypertension was very common in our population and was equally distributed between the two groups. Smoking was infrequent in the study population and did not discriminate between the two groups. The use of statin therapy was almost universal and was equal in both groups. Despite widespread statin therapy, a low LDL-C level remained significantly associated with having fewer adverse atherosclerosis-related MACEs.

Table 1. Univariate analysis of risk factors for major adverse cardiovascular events.

	Patients with atherosclerotic event ($n = 92$)	Patients without atherosclerotic event ($n = 232$)	*P*-value
Recipient age (years)	53 ± 11.8	49 ± 13.2	0.17
Diabetes	52%	24%	<0.001
Male	58%	59%	0.81
Hypertension	67%	66%	0.86
Sirolimus therapy	28%	35%	0.22
Statin therapy	76%	71%	0.32
Living donor	11%	23%	0.01
Smoking	15%	11%	0.26
Creatinine < 1.2 at 1 year	34%	41%	0.09
Low HDL-C (M < 40, F < 50)	69%	54%	0.01
Low LDL-C	28%	42%	0.01
Pre-existing CV burden	56%	36%	0.008
Elevated TG	54%	43%	0.08
BMI > 30	28%	31%	0.57
Metabolic syndrome	44%	27%	0.003

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CV, cardiovascular; TG, triglyceride; BMI, body mass index.

Subgroup analysis of low HDL-C risk

Low HDL-C was very common amongst our patient population with 58.3% of our transplant recipients having an HDL-C that was lower than normal (Table 2). When analyzed for individual vascular complications, having a low HDL-C was significantly associated with adverse peripheral vascular events and total cardiovascular events. When cardiovascular events were limited to those related to coronary artery disease such as myocardial infarction, again a low HDL-C was found to be a significant predisposing risk factor. The incidence of cerebral vascular disease was very low in our population and could not be correlated with HDL-C levels. A low HDL-C level was associated with having more than one MACE as well as all cause mortality.

MACE-free survival

Survival free of MACE in patients with low HDL-C was lower when compared with patients who had normal levels of HDL-C ($P < 0.05$). Kaplan–Meier analysis demonstrated that patients with low levels of HDL-C began experiencing atherosclerosis-related MACEs more frequently beginning early after transplantation (Fig. 1). By 7 years post-transplantation, it was estimated that up to 54% of patients with low HDL-C will have experienced a MACE compared with 30% of patients with normal levels of HDL-C.

Table 2. Subgroup analysis of risk factors for adverse vascular events.

Adverse events	Low HDL-C (n = 186)	Normal HDL-C (n = 138)	Odds ratio	P-value
Peripheral vascular events	27 (14.5%)	10 (7.2%)	2.17	0.04
Cardiovascular event	38 (20.4%)	16 (11.5%)	2.03	0.03
Cerebral vascular event	5 (2.6%)	2 (1.4%)	1.87	0.44
Coronary artery disease (AMI, CABG, angina, PCI)	30 (16.5%)	12 (8.7%)	1.96	0.04
Multiple events	29 (15.5%)	10 (7.2%)	2.36	0.02
All cause mortality	20 (10.7%)	6 (4.3%)	2.65	0.03

HDL-C, high-density lipoprotein cholesterol; AMI, acute myocardial infarction; CABG, coronary artery bypass graft; PCI, percutaneous coronary artery intervention stenting.

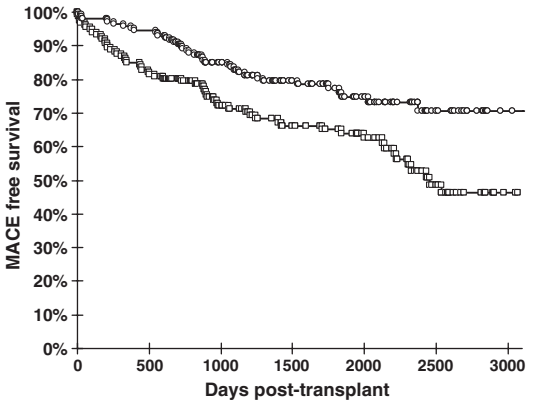

Figure 1 Kaplan–Meier curves of major adverse cardiovascular events (MACEs) free survival after renal transplantation. MACE-free survival after renal transplants was subjected to Kaplan–Meier analysis comparing patients with normal high-density lipoprotein (HDL) levels (open circles) to those with low HDL levels (open squares). Patients with low HDL cholesterol levels had a lower event-free survival at all time points after transplantation ($P < 0.05$).

Discussion

Post-transplant CVD is becoming an increasingly important clinical challenge in patient management [3]. As the population with ESRD requiring transplantation ages and suffers from a greater number of comorbid clinical conditions, the prevention and treatment of progressive vascular disease are becoming a vital priority in transplant recipients [3]. Moreover, following renal transplantation, patients are subject to the added risk of immunosuppressive therapy which may increase the propensity of developing atherosclerosis-related risk factors such as diabetes, hypertension and dyslipidemia [14]. This constellation of adverse vascular factors now forms the basis of a major cause of graft loss, namely, death with functioning allograft [3]. Therefore, devising means to improve cardiovascular risk, morbidity and mortality in this doubly at-risk population is imperative.

Modifiable factors such as diabetes, hypertension, dyslipidemia and smoking have already been well established in the general population and in renal transplant recipients [8]. Primary and secondary prevention of cardiovascular risk factors such as elevated LDL-C have been shown to improve long-term cardiovascular mortality in the general and transplant populations [11]. In addition to confirming that traditional risk factors for developing post-transplant atherosclerosis-related complications such as diabetes, metabolic syndrome, LDL-C and deceased donor kidney transplant, our study now shows that low levels of HDL-C are associated with a significantly increased risk for MACEs following transplantation. Most significantly, low HDL-C was found to be a risk factor for all cause post-transplant mortality.

Previously, the risk conferred by low levels of HDL-C in transplant recipients was considered as a component of the metabolic syndrome [15,16]. By contrast, this study highlights the independent risk of a low HDL-C in transplant recipients. In the general population, low HDL-C levels are associated with increased cardiovascular risk [12,13,17]. Even in statin treated patients with LDL-C levels <70 mg/dl, low HDL-C remains predictive of cardiovascular events [13]. Normal to elevated levels of HDL-C has been implicated as an anti-atherogenic lipid through its mechanism of reverse cholesterol transfer. However, HDL-C may modulate several additional beneficial mechanisms on vascular disease including anti-inflammatory, antioxidative, antithrombotic effects as well as promoting nitric oxide production [18–20]. Thus, raising low levels of HDL-C may be an attractive target molecule for the prevention of CVD. To date, there has been a paucity of clinical trials aimed at increasing HDL-C and lowering clinical events. This may be caused by a combination of factors not related to HDL-C such as inherent toxicity of the drugs used, drug intolerance or ineffective increases in HDL-C [21,22]. The VA-HIT trial evaluated the long-term efficacy of gemfibrozil in 2539 male veterans with established coronary heart disease, normal LDL-C levels, and abnormally low HDL-C levels (mean: 32 mg/dl at

baseline) during a 5.1-year follow-up. Treatment with gemfibrozil raised HDL-C only 2 mg/dl (to a mean 34 mg/dl), yet this was associated with a significant 27% relative risk reduction in the composite outcome of death, MI or stroke, when compared with placebo [23]. Newer formulations of niacin and novel agents targeting cholesterol ester transfer protein are being developed to overcome these challenges and may prove to be more effective in raising low levels of HDL-C and decreasing long-term clinical events [24,25]. A large-scale, NIH-funded randomized clinical trial comparing extended-release niacin combined with simvastatin versus simvastatin monotherapy on long-term clinical outcomes in 3300 patients with low levels of HDL-C and established vascular disease is nearing completion of patient accrual, but follow-up is not scheduled to be completed until late 2011.

There are several limitations to this study. Given the retrospective nature of this analysis, no systematic assessments of lipid values were made. The absence of an apparent relationship between LDL-C and HDL-C ratios and MACEs may have been attributed to the small number of patients who developed an adverse clinical event during follow-up and the high rate of statin usage during the period of observation. Moreover, this is a single center study with a relatively small patient population and a limited number of lipid studies. However, the strength of this study lies in the completeness of data capture in a well defined and managed population. Prospective well-designed studies in a larger number of patients will be needed to confirm these findings.

Nevertheless, our observation that low HDL-C contributes significantly to atherosclerotic disease in transplant recipients suggests that HDL-C directed therapy may be beneficial in this selected group. Given the extraordinary rate of vascular disease progression in the renal transplant population, efforts to increase HDL-C may have an important therapeutic role in this challenging and high-risk group of patients. Studies are being contemplated to test the efficacy, tolerability and toxicity of novel niacin preparations in transplant recipients.

Authorship

KB, OP, WEB and ML: designed and conducted the research project. KB: collected and analyzed the data. CY: analyzed the data and contributed to writing the paper. KB, OP, ML and WEB: wrote the paper. DP: collected and helped analyze the data.

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