

Early renal failure as a cardiovascular disease: Focus on lipoprotein(a) and prothrombotic state

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Abstract

Patients with renal failure are at increased risk of cardiovascular events even at the earliest stages of disease. In addition to many classic cardiovascular risk factors, many conditions that are commonly identified as emerging risk factors might contribute to occurrence of cardiovascular disease. Changes in circulating levels of many of these emerging risk factors have been demonstrated in patients with early stages of renal failure caused by different types of renal disease and have been associated with detection of cardiovascular complications. However, for most of these factors evidence of benefits of correction on cardiovascular outcome is missing. In this article, we comment on the role of lipoprotein(a) and prothrombotic factors as potential contributors to cardiovascular events in patients with early renal failure.

Key words: Early renal failure; Cardiovascular disease; Risk factors; Lipoprotein(a); Prothrombotic state

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Core tip: Cardiovascular disease is the leading cause of morbidity and mortality in patients with chronic renal failure and even patients with moderate impairment of renal function have an increased risk to develop cardiovascular events. Traditional cardiovascular risk factors have a leading role in the pathophysiology of accelerated atherosclerosis of patients with renal failure, but emerging non-traditional factors might also be involved. Evidence of a possible contribution of lipoprotein(a) and prothrombotic state to cardiovascular outcomes of patients with early renal failure is discussed in this editorial.

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INTRODUCTION

Strong epidemiological evidence indicates that subjects with impaired renal function have shorter life-expectancy than subjects with normal renal function^[1]. In subjects with renal failure, cardiovascular events are the leading cause of death and disability^[2,3] and many mechanisms can contribute to increased cardiovascular risk. These mechanisms include, on one hand, conditions that are specific to renal failure, such as reduced hemoglobin and acid-base and electrolyte disturbances and, on the other hand, increased prevalence of classic traditional risk factors for atherosclerosis, such as age, diabetes, hypertension, and dyslipidemia^[4]. In addition to classic cardiovascular risk factors, other conditions that are commonly identified as "emerging" risk factors^[5], have been called into play because they can contribute to cardiovascular events occurring in subjects with relatively low cardiovascular risk as estimated by the current charts^[6,7]. Many of these non-traditional emerging risk factors have been reported to be significantly increased in patients with end-stage renal failure, strongly suggesting a contribution to occurrence of cardiovascular events in these patients^[8,9] (Table 1). It is clear, however, as also previously stated, that subjects with severely impaired renal function have a myriad of additional conditions that contribute to cardiovascular risk and can hide the relevance of some emerging risk factors. Therefore, the weight of these factors on cardiovascular outcomes of renal patients would be more appropriately examined in subjects at the initial stage of renal disease. Noteworthy, some conditions that increase the cardiovascular risk of end-stage renal patients have also been detected in the earliest stages of renal failure and could possibly contribute to cardiovascular outcomes also in patients with mild impairment of renal function^[10]. Here we comment on the evidence supporting the view that early renal failure is a condition associated with high cardiovascular risk and focus on the possible contribution of lipoprotein(a) [Lp(a)] and prothrombotic state to the cardiovascular outcomes of these patients.

EARLY RENAL FAILURE AND CARDIOVASCULAR DISEASE

Evidence obtained in clinical studies demonstrates that the cardiovascular outcome is worse in subjects with initial impairment of renal function as compared to subjects with normal renal function. In a cross-sectional investigation of patients with primary hypertension and different degree of renal function impairment, prevalence of coronary heart, cerebrovascular, and

peripheral artery disease was significantly higher in patients with glomerular filtration rate (GFR) comprised from 30 to 89 mL/min per 1.72 m² than in patients with a GFR of 90 mL/min per 1.72 m² or more^[11]. In a first prospective cohort study with 10-year follow-up, incidence of myocardial and cerebral infarction in patients with GFR between 20 and 50 mL/min per 1.72 m² was three-times higher than in general population^[12]. Patients who had cardiovascular events in this study also had elevated plasma levels of Lp(a), fibrinogen, and homocysteine. A subanalysis of the Hypertension Optimal Treatment study was conducted in hypertensive individuals to estimate the risk of patients with plasma creatinine of 1.7 mg/dL or more to have cardiovascular events or death over a 3.8-year period^[13]. In this analysis, incidence of myocardial infarction and stroke resulted significantly greater in patients with high plasma creatinine levels. Moreover, increased plasma creatinine was associated with a risk of cardiovascular events that was higher than that attributed to other risk factors, including diabetes and previous myocardial infarction. In a post-hoc analysis of the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial, frequency of coronary events and end-stage renal failure was estimated in 3 groups of patients with hypertension who were stratified according to GFR in a 6-year follow-up^[14]. Patients with a GFR < 60 mL/min per 1.72 m² had a six-fold higher probability to have a cardiovascular event than to require dialysis, clearly showing that patients with early renal disease are more likely to have cardiovascular disease than evolve to uremia. Conclusive evidence of a graded association between decreasing GFR and increasing rate of cardiovascular events, however, was reached after publication of two milestone studies that came out in 2004. First, in the Valsartan in Acute Myocardial Infarction Trial (VALIANT) 14527 subjects with myocardial infarction and decreased left ventricular ejection fraction were followed for 2 years^[15]. In patients with a GFR lower than 81 mL/min per 1.72 m² relative risk of death and non-fatal cardiovascular events increased by 10% for each 10 mL/min per 1.72 m² reduction in GFR. Second, in a longitudinal prospective study, Go *et al*^[16] followed more than one million adults who had been included in a health care system to examine the possible association of GFR, as estimated by the MDRD formula, with the risk of death, cardiovascular events and hospitalization. After a follow-up of 2.8 years, mortality progressively increased as the baseline GFR fell below 60 [hazard ratio (HR): 1.2], 45 (HR: 1.8), and 30 (HR: 3.2) mL/min per 1.72 m². Similarly, the HR for nonfatal cardiovascular events was progressively higher with decreasing GFR. Thus, these two important studies together with previous observations obtained in more limited investigation definitely demonstrate that even mild impairment of renal function increases significantly the risk of cardiovascular morbidity and mortality^[17].

Table 1 Classic traditional and emerging non-traditional cardiovascular risk factors in chronic renal failure

Classic traditional cardiovascular risk factors	Emerging non-traditional cardiovascular risk factors
Older age	Proteinuria
Male sex	Left ventricular hypertrophy
Arterial hypertension	Anemia
Diabetes mellitus	Electrolyte abnormalities
Smoking	Acid-base imbalance
Increased LDL-cholesterol	Abnormal calcium/ phosphate metabolism
Decreased HDL-cholesterol	Extracellular fluid overload
Family history of cardiovascular events	Lipoprotein(a) and apolipoprotein(a) isoforms
Physical inactivity	Prothrombotic state
	Homocysteine
	Insulin resistance
	Oxidative stress
	Endothelial dysfunction
	Arterial stiffening

LDL: Low-density lipoprotein; HDL: High-density lipoprotein.

EARLY RENAL FAILURE AND EMERGING NON-TRADITIONAL CARDIOVASCULAR RISK FACTORS

As stated above, a variety of emerging non-traditional cardiovascular risk factors might contribute to increase the cardiovascular risk of patients in the early stages of renal failure (Table 1). Most of these conditions meet three of the requisites needed to define a risk factor, that is biological plausibility as to why it may cause cardiovascular disease, demonstration of a dose-response relationship with decreasing renal function, and demonstration of an independent association with cardiovascular disease and renal failure in observational studies. However, so far none of them has met the fourth and most important requisite, that is demonstration in controlled clinical trials that correction of the risk factor is beneficial for cardiovascular outcomes.

It is well known that some lipoproteins are fundamental to the atherosclerotic process and can increase the impact of renal failure on cardiovascular outcomes. Lp(a) is a heterogeneous low-density lipoprotein that incorporates the highly polymorphic apolipoprotein(a) [apo(a)]^[18]. The *apo(a)* gene is the major gene controlling Lp(a) concentrations^[19] that vary over a broad range and are inversely related to the size of apo(a)^[20]. In 160 hypertensive patients with early impairment of renal function (GFR 30-89 mL/min per 1.72 m²) Lp(a) levels were significantly higher than those of 257 hypertensive patients with normal renal function (GFR 90 mL/min per 1.72 m² or more) and a significant inverse and independent relationship between Lp(a) levels and GFR was reported^[21]. In a further study, it was shown that elevated serum Lp(a) concentrations are not related to the size polymorphism of apo(a) in patients with early renal failure, indicating that in these patients Lp(a) increase can not be ascribed to variations at the

apo(a) gene locus^[22] and strongly suggesting that Lp(a) increase is secondary to impairment of renal function. In this view, one possibility is that the kidney might have a catabolic function on Lp(a) as suggested by detection of degraded apo(a) fragments in urine in an amount that is correlated with GFR^[23]. Furthermore, elevated Lp(a) levels and decreased GFR were significantly associated with increased prevalence of cardiovascular events^[24], suggesting a contribution of this lipoprotein to cardiovascular outcomes in patients with early renal failure. The association of GFR with Lp(a) levels was investigated in the 7675 participants of the Third National Health and Nutrition Survey (NHANES)^[25]. In this population study, a moderate impairment of GFR was associated with greater Lp(a) levels although this association was more prominent in non-Hispanic blacks and Mexican Americans than non-Hispanic whites. Despite this association of elevated Lp(a) levels with early decrease of GFR, other studies demonstrated that this lipoprotein does not contribute to progression of chronic kidney disease^[26]. The mechanisms through which Lp(a) promotes atherosclerosis in patients with or without renal failure are not clearly understood. Proposed mechanisms include and increased Lp(a)-associated cholesterol capture in the arterial intima, inflammatory cell recruitment, and carrying of proinflammatory oxidized phospholipids^[27].

In addition to the proatherogenic properties, prothrombotic effects of Lp(a) due to its structural homology with plasminogen might explain the contribution of this lipoprotein to cardiovascular events^[24]. Also, elevated Lp(a) levels have been found to be frequently associated with hyperhomocysteinemia in patients with pre-dialysis renal failure^[28]. Although an inverse relationship of Lp(a) levels with dietary alcohol^[29] and omega-3 polyunsaturated acid^[30] consumption has been reported and levels of Lp(a) were slightly decreased by use of nicotinic acid^[31] and mipomersen^[32], impact of either dietary or pharmacologic interventions on Lp(a) levels is minimally relevant. Thus, Lp(a) levels are inversely related with renal function and might contribute to cardiovascular outcomes in patients with early impairment of renal function, but lack of treatments that effectively decrease its levels limits this evidence.

Because a prothrombotic state has been demonstrated in patients with end-stage renal disease, research on emerging risk factors potentially contributing to cardiovascular disease in early renal failure has focused on the hemostatic system^[33]. Assessment of the state of activation of the coagulation cascade can be obtained by measurement in plasma of prothrombin fragment 1 + 2 (F1 + 2) that is released when activated factor X converts prothrombin to thrombin, fibrin D-dimer, a breakdown fragment of fibrin, and fibrinogen. In 425 hypertensive patients, 172 of whom had GFR from 30 to 89 mL/min per 1.72 m², we measured hemostatic variables and assessed prevalence of cardiovascular events. After adjustment for confounders, GFR was significantly and inversely correlated with plasma

levels of F1 + 2, D-dimer, and fibrinogen, and for the latter two variables correlation was independent of demographic and anthropometric variables, blood pressure levels, plasma lipids, and urinary protein excretion^[34]. This observation indicated that an activated hemostatic cascade can be detected also in subjects with mild-to-moderate renal failure, possibly leading to a prothrombotic state and increased incidence of atherothrombotic vascular complications. In these patients with early renal failure and activated coagulation system, prevalence of coronary heart disease, cerebrovascular disease, and peripheral arteriopathy was significantly higher than in patients with GFR of 90 mL/min per 1.72 m² or more and cardiovascular disease was independently predicted by both plasma D-dimer and fibrinogen levels. Consistently, in 50 patients with stage 2-3 renal failure plasma fibrinogen was significantly increased possibly contributing to the high cardiovascular morbidity of these patients^[35]. In the 3758 patients with GFR of 20 to 70 mL/min per 1.72 m² of the Chronic Renal Insufficiency Cohort Study, a prothrombotic state was associated with increased prevalence of peripheral artery disease^[36]. In a prospective study of 4029 men aged 60-79 years who were followed for an average period of 6 years, mild-to-moderate renal failure was associated with increased plasma levels of hemostatic markers and caused significantly increased cardiovascular mortality^[37].

Thus, it is clear that changes in coagulation parameters suggesting a prothrombotic state occur early in the course of renal disease and could contribute to increase the cardiovascular risk^[38]. Similar to Lp(a), in the case of hemostatic variables there is no evidence supporting possible benefits on the cardiovascular outcomes of these patients of treatments that may correct the prothrombotic state.

CONCLUSION

Cardiovascular disease is the leading cause of morbidity and mortality in patients with chronic renal failure and even patients in the early stages of renal disease have much greater risk to have cardiovascular disease than to require substitutive treatment with either dialysis or transplantation. It is clear that traditional cardiovascular risk factors play a major role in the pathophysiology of accelerated atherosclerosis typical of renal failure patients, but emerging non-traditional factors might be involved and contribute to cardiovascular disease. For some of these factors, contribution to cardiovascular outcomes might be relevant from the earliest stages of renal failure. However, conclusive evidence should be obtained from intervention trials with correction of these factors and this is currently missing. Therefore, evidence on whether these and other, as yet unidentified, factors contribute to cardiovascular morbidity and mortality in patients with early renal failure is not conclusive and is the subject of ongoing investigation.

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