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Renal Lipoprotein (a) Metabolism

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ABSTRACT

The kidney plays a central role in lipoprotein(a) catabolism, acting as a "cemetery for lipoprotein(a)" through uptake, fragmentation, and excretion. Direct human evidence comes from Kronenberg et al., who found significant arteriovenous differences in lipoprotein(a) levels between the aorta and renal vein, demonstrating active renal uptake. Clinical evidence from renal replacement therapy further supports this role: lipoprotein(a) levels decrease rapidly after kidney transplantation but remain unchanged with hemodialysis, indicating that functioning renal tissue, not filtration, drives lipoprotein(a) metabolism. Animal studies by Reblin et al. provided mechanistic insights, showing rapid clearance of injected human lipoprotein(a) in rats, with apolipoprotein(a) localized in proximal tubular cells and fragments detected in urine. This supports the idea that the kidney fragments lipoprotein(a) before excretion. Kostner & Kostner proposed a model where circulating lipoprotein(a) undergoes proteolytic cleavage in the kidney, producing apolipoprotein(a) fragments that may themselves be biologically active and contribute to lipoprotein(a)'s atherogenicity. Clinical observations confirm that chronic kidney disease alters lipoprotein(a) metabolism. Patients with proteinuria or amyloidosis show elevated lipoprotein(a), often correlating with urinary albumin excretion, highlighting the kidney's regulatory role. The mechanism of elevation varies by disease: in proteinuria and peritoneal dialysis, hepatic synthesis is upregulated, while in hemodialysis, impaired catabolism predominates. These abnormalities likely amplify the already high cardiovascular risk in chronic kidney disease, particularly in individuals with genetically determined small apolipoprotein(a) isoforms. Despite advances, the precise site and mechanisms of lipoprotein(a) clearance remain unclear. However, the consensus is that reduced clearance, not increased production, drives lipoprotein(a) accumulation in kidney disease. Understanding renal processing of lipoprotein(a) may provide therapeutic opportunities, with future strategies aiming to inhibit lipoprotein(a) assembly or enhance apolipoprotein(a) fragmentation to mitigate cardiovascular risk.

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Abbreviations

Lp(a): Lipoprotein(a)
Apo(a): Apolipoprotein(a)

Introduction

The kidney plays a central and multifaceted role in lipoprotein(a) (Lp(a)) catabolism through complex mechanisms involving uptake, fragmentation, and excretion, representing what researchers have termed a "cemetery for Lp(a)."

Direct Evidence for Renal Lp(a) Metabolism

The most compelling direct evidence comes from Kronenberg et al., who measured Lp(a) concentrations simultaneously in the ascending aorta and renal vein of 100 patients undergoing coronary angiography or angioplasty. They found significant arteriovenous differences even after correcting for hemoconcentration (20.1 ± 21.6 mg/dL versus 18.7 ± 20.3 mg/dL, $P < 0.001$), corresponding to a mean arteriovenous difference of -1.4 mg/dL or -9% of the arterial concentration. This study demonstrated for the first time that substantial amounts of this atherogenic lipoprotein are actively taken up by the human kidney, though the underlying mechanisms remained unknown at the time [1].

Clinical Evidence from Renal Replacement Therapy

Rosas et al. provided crucial clinical evidence through a prospective study of patients initiating hemodialysis or receiving renal transplants. In transplant recipients, Lp(a) levels decreased rapidly and dramatically - mean levels at two weeks were 35.3% lower than prior to transplantation. Each reduction of 50% in creatinine was associated with a 10.6% reduction in Lp(a) ($p < 0.001$) [2]. Importantly, there was no significant change in Lp(a) after initiation of hemodialysis, suggesting that functioning renal tissue, rather than simple filtration, is responsible for Lp(a) catabolism. This rapid decrease after transplantation provides strong support for a metabolic role of the kidney in Lp(a) catabolism and suggests that the increase in Lp(a) seen in chronic kidney disease results from loss of functioning renal tissue.

Mechanistic Insights from Animal Studies

Reblin et al. established a heterologous rat model to study renal catabolism of human Lp(a), providing detailed mechanistic insights. Pure human Lp(a) injected into Wistar rats was cleared from circulation with a half-life of 14.5 hours. Strong intracellular immunostaining for apolipoprotein(a) (apo(a)) was observed in the cytoplasm of proximal tubular cells after 4, 8, and 24 hours. Notably, apolipoprotein B was colocalized with glomerular apo(a) for 1 to 8 hours after injection, but renal capillaries and tubules remained negative for apoB [3]. During all urine collection

periods, apo(a) fragments with molecular weights of 50 to 160 kD were detected in the urine, demonstrating that the kidney plays a major role in fragmentation of Lp(a).

Fragmentation and Excretion Mechanisms

Kostner & Kostner proposed a detailed model of renal Lp(a) processing: circulating Lp(a) interacts specifically with kidney cells, causing cleavage of 2/3 to 3/4 of the N-terminal part of apo(a) by a collagenase-type protease. Part of these apo(a) fragments are found as excretory products in urine, but there are indications that they represent the biologically active form of apo(a) and may be responsible for the atherogenicity of Lp(a) [4]. The kidney is specifically identified as the site of apo(a) fragment excretion, though the uptake and clearance sites of intact Lp(a) remain poorly delineated [5].

Clinical Implications in Kidney Disease

Patients with chronic kidney disease exhibit major disturbances in Lp(a) metabolism, with concentrations influenced by both glomerular filtration rate and the amount of proteinuria [6]. Karádi demonstrated that patients with different degrees of heavy proteinuria and normal renal function show high serum levels of Lp(a), with a direct correlation between urinary albumin secretion and serum Lp(a) levels, suggesting a regulatory role of the kidney. In patients with primary amyloidosis, extremely elevated Lp(a) levels were found that surpassed the quantity of urinary albumin secretion, suggesting direct involvement of renal tissue in Lp(a) catabolism [7].

The Mechanism Varies by Disease Type

In patients with heavy proteinuria or protein loss due to peritoneal dialysis, enhanced protein synthesis in the liver affects Lp(a) generation, while in hemodialysis patients, a catabolic block is responsible for elevation [6]. These elevated concentrations likely contribute to the tremendous cardiovascular risk in patients with kidney disease, particularly given that genetically determined small apo(a) isoforms are associated with increased risk for cardiovascular events and total mortality.

Current Understanding and Future Directions

Despite mounting evidence, Albers et al. noted that while numerous studies suggest a role of the kidney in Lp(a) catabolism, direct evidence was still developing [8]. The field has progressed significantly, with studies demonstrating that marked elevation of Lp(a) in hemodialysis patients results from decreased Lp(a) clearance rather than increased production, consistent with the notion that the kidney degrades Lp(a) [9]. However, the major site and mode of Lp(a) clearance remain unidentified, and the metabolism of this enigmatic lipoprotein still remains poorly understood [10].

The kidney's role in Lp(a) metabolism represents a critical area for therapeutic intervention, as strategies for reducing this atherogenic lipoprotein should aim at interfering with either the assembly of Lp(a) or the stimulation of apo(a) fragmentation [4]. Understanding these renal mechanisms may be key to developing treatments for the elevated cardiovascular risk associated with high Lp(a) levels.

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None.

Conflicts of Interest

No conflict of interest.

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