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REVIEW ARTICLE

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In vivo kinetic studies to further understand pathogenesis of abnormal lipoprotein metabolism in chronic kidney disease

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Abstract Patients undergoing hemodialysis (HD) have been shown to be at increased risk for cardiovascular disease (CVD) morbidity and mortality which are, at least in part, due to uremic dyslipidemia including increased triglyceride-rich lipoproteins, in particular remnants, decreased high-density lipoprotein (HDL), and increased lipoprotein(a) [Lp(a)]. In vivo kinetic studies using stable isotope revealed that apolipoprotein (apo)A-I, a primary apoprotein constitute of HDL, was catabolized at a faster rate in HD patients, leading to decreased apoA-I, and therefore reduced HDL cholesterol concentrations. Likewise, apoB catabolic rates were significantly lower in intermediate-density lipoprotein (IDL) and low-density lipoprotein (LDL) apoB; the latter is also accompanied by a decreased production rate. In HD patients, IDL apoB levels were elevated, but LDL apoB levels remained within the normal range. Nonetheless, a prolonged residence time for LDL apoB of 2−5 days, made LDL more atherogenic. Atorvastatin completely ameliorated impaired LDL apoB catabolism. With regard to Lp(a) metabolism, both apoB and apo(a) were found to be slowly catabolized, indicating roles of normal kidney function on Lp(a) catabolism. Finally, a compartmental model suggests intracellular, rather than extracellular, assembly of Lp(a). This in vivo kinetic evidence will uncover the underlying mechanism for uremic dyslipidemia and provide strategies to reduce CVD in HD patients.

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Introduction

Patients with end-stage renal disease (ESRD) undergoing hemodialysis (HD) are at increased risk for coronary artery disease (CAD) [1, 2] which is, at least in part, due to lipid abnormalities, typically called uremic dyslipidemia [3]. Uremic dyslipidemia typically represents increased triglyceride (TG) levels, in particular atherogenic remnants, decreased high-density lipoprotein cholesterol (HDL-C), and increased lipoprotein(a) [Lp(a)], with relatively normal or even lower levels of low-density lipoprotein cholesterol (LDL-C). Here, we provide comprehensive data from in vivo kinetic studies using endogenous stable isotope as a tracer in HD patients.

Endogenous stable isotope labeling methodology

Although stable isotope tracer studies have a history of more than a half century, radiotracer studies were the established method for investigation of human dyslipidemia up to late 1980, when a major breakthrough occurred which enabled measurement of low tracer concentrations using quadrupole mass spectrometry. Since then, stable isotope in vivo kinetic studies have been frequently used in humans [4–6].

HDL metabolism: low HDL

Consistent with previous reports, HDL-C and apolipoprotein (apo)A-I, major apoproteins of HDL, were

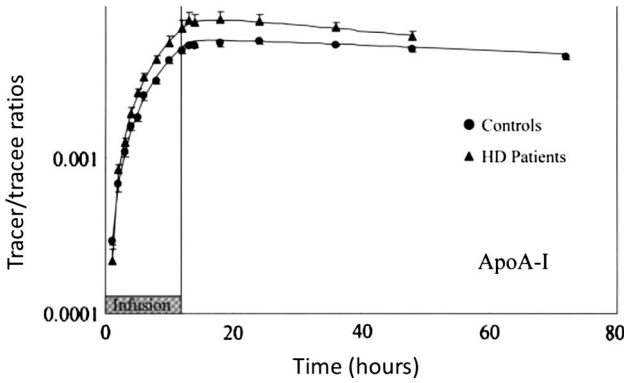

Fig. 1 Tracer/tracee (*T/T*) ratio curves for apoA-I in study subjects. *T/T* ratio curves for apoA-I in the control subjects (*filled circle*) and ESRD-HD patients (*filled triangle*). All data are given as mean ± SEM and are fitted by the a multi-compartmental model using SAAMII

significantly decreased to 32.2 ± 1.9 and 111 ± 7 mg/dl in HD patients compared with controls (44.5 ± 2.4 and 132 ± 4 mg/dl). As shown in Fig. 1, a stable isotope kinetic study [7] revealed that the mean apoA-I fractional catabolic rate (FCR) significantly increased by 59 % to 0.360 ± 0.084 day^{-1} in ESRD-HD patients compared to control subjects of 0.227 ± 0.076 day^{-1} ($p = 0.028$), with production rates unchanged. As a result, the decreased apoA-I levels in ESRD-HD patients were primarily due to the increased rate of catabolism. Although speculative, decreased lecithin–cholesterol acyltransferase and increased cholesteryl ester transfer protein may, at least in part, account for the increased catabolism.

ApoB-containing lipoprotein metabolism: increased intermediate-density lipoprotein (IDL) apoB with normal LDL apoB levels

Despite the fact that total cholesterol, LDL cholesterol, and LDL apoB levels were almost identical in HD patients and controls, an in vivo kinetic study [8] revealed striking abnormalities in IDL apoB and LDL apoB metabolism in HD patients (Fig. 2). IDL apoB FCR was markedly decreased by 70 % (2.87 ± 1.02 vs 8.89 ± 4.94 pools/day, $p = 0.014$) in HD patients, accompanied by a 24 % decrease in production rate (9.05 ± 3.08 vs 11.84 ± 4.42 mg/kg/day, $p = 0.221$), resulting in a 60 % increase in proatherogenic IDL apoB levels in HD patients (6.2 ± 1.8 vs 3.9 ± 2.7 mg/dl). LDL apoB FCR was significantly decreased to 50 % in HD patients compared with controls (0.22 ± 0.12 vs 0.46 ± 0.20 pools/day), which corresponded to a severely prolonged residence time of 4.6 days in HD patients versus 2.2 days in healthy controls. Furthermore, the LDL apoB production rate was

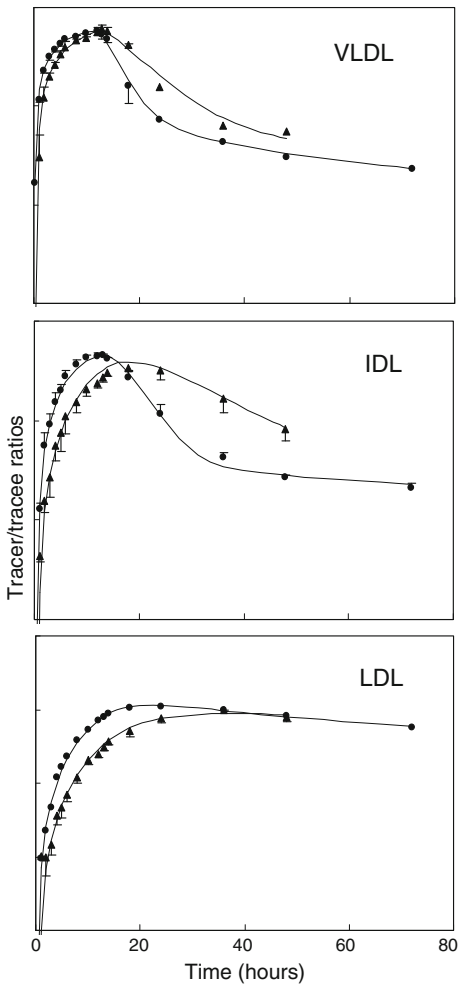

Fig. 2 Tracer/tracee (*T/T*) ratio curves for apoB-100 from VLDL, IDL, and LDL in HD patients (*filled triangle*) and controls (*filled circle*). Data were fitted by multi-compartmental modeling using SAAMII. *Bars* represent standard error of means

significantly decreased in HD patients compared with controls (9.8 ± 4.9 vs 18.4 ± 13.3 mg/kg/day), counteracting the decreased catabolism to keep plasma LDL apoB concentrations within the normal range. In contrast to these changes, very low-density lipoprotein (VLDL) apoB kinetic parameters did not significantly differ in HD patients compared with controls. The decreased catabolism is likely due to the impaired lipolytic cascade in HD patients. Indeed, the relatively normal VLDL levels and kinetic parameters and the corresponding impaired IDL parameters are in good accordance with previous findings of normal lipoprotein lipase masses but significantly decreased activities of hepatic triglyceride lipase in HD patients. With regard to LDL kinetics, this is the first described example of a clinical condition in which reduced synthesis and clearance rates of an atherogenic lipoprotein are masked by normal plasma concentrations. The obtained results therefore demonstrate the need for in vivo kinetic

studies to understand the complex metabolic systems in humans, even in situations where the snap-shot ex vivo values seem to be almost normal. In particular, the observed alterations in lipoprotein metabolism put HD patients at high risk for developing atherosclerotic disease despite their normal cholesterol and LDL cholesterol plasma levels.

We therefore performed the next kinetic study [9] to address the question of whether statin treatment improves LDL kinetics in HD patients. FCRs of VLDL apoB and LDL apoB patients were significantly higher after atorvastatin treatment (7.20 ± 3.08 vs 5.20 ± 2.98 days^{-1}, $p < 0.05$; 0.851 ± 0.772 vs 0.446 ± 0.232 days^{-1}, $p < 0.05$), whereas their concentrations were lower compared with baseline. Accordingly, their residence times in plasma—being the inverse values of FCR—were significantly lower (0.14 vs 0.19 day for VLDL and 1.2 vs 2.2 days for LDL). The production rate was not significantly different. The opposite was observed with IDL apoB. Its production rate was significantly lower, whereas FCRs and concentrations were not significantly different between the two time points. Therefore, we believe this study to be the first to demonstrate a beneficial effect of statin therapy on lipoprotein metabolism in HD patients. The kinetics of atherogenic apoB-containing lipoproteins were improved after administration of low-dose atorvastatin in HD patients. As supported by a recent clinical trial (SHARP) [10], this may translate into beneficial outcomes, depending on the individual risk profile and the progress of atherosclerotic disease.

Lp(a) metabolism: increased Lp(a) levels

Significantly elevated Lp(a) plasma levels have been shown in HD patients. However, due to the lack of knowledge about Lp(a) physiology, namely biosynthesis, assembly, secretion and catabolism, the exact underlying mechanism for the increased Lp(a) in HD patients remains controversial. We therefore investigated the in vivo turnover rates of both protein components from Lp(a), i.e., apo(a) and apoB, in HD patients [8]. As shown in Fig. 3, the FCR of Lp(a)–apo(a) was significantly lower in HD patients compared with controls (0.164 ± 0.114 vs 0.246 ± 0.067 days^{-1}, $p = 0.042$). The same was true for the FCR of Lp(a)–apoB (0.129 ± 0.097 vs 0.299 ± 0.142 days^{-1}, $p = 0.005$). This resulted in a much longer residence time of 8.9 days for Lp(a)–apo(a) and 12.9 days for Lp(a)–apoB in HD patients compared with controls (4.4 and 3.9 days, respectively). The production rates of apo(a) and apoB from Lp(a) did not differ significantly between patients and controls and were even lower for patients when compared with controls with similar Lp(a) plasma concentrations. Overall, this in vivo turnover study showed that the loss of renal function in HD patients causes elevated Lp(a) plasma levels because of decreased clearance but not increased production of Lp(a). Therefore, the prolonged retention time of Lp(a) in HD patients might be an important contribution to the high risk of atherosclerosis in these patients. By utilizing a multicompartmental model, we were able to show that Lp(a) was almost exclusively assembled intracellularly [11].

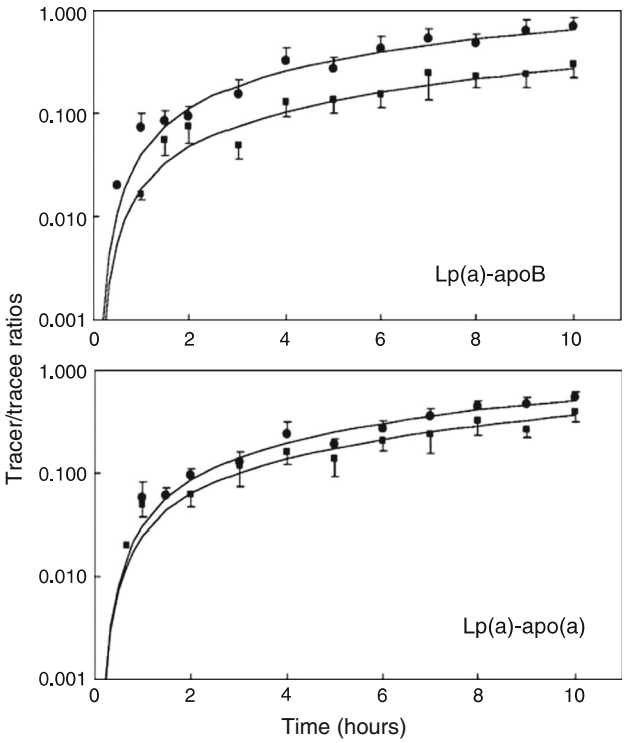

Fig. 3 Tracer/tracee (*T/T*) ratio curves for Lp(a)–apoB (*upper panel*) and Lp(a)–apo(a) (*lower panel*) in HD patients (*filled square*) and control subjects (*filled circle*). Data are given as mean ± SEM and were fitted by the multi-compartmental model using SAAMII

Conflict of interest The authors have declared no competing interest.

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