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Causes of dysregulation of lipid metabolism in chronic renal failure

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Abstract

End-stage renal disease (ESRD) is associated with accelerated atherosclerosis and premature death from cardiovascular disease. These events are driven by oxidative stress inflammation and lipid disorders. ESRD-induced lipid abnormalities primarily stem from dysregulation of high-density lipoprotein (HDL) and triglyceride-rich lipoprotein metabolism and oxidative modification of lipoproteins. In this context, production and plasma concentration of Apo-I and Apo-II are reduced, HDL maturation is impaired, HDL composition is altered, HDL anti-oxidant and anti-inflammatory functions are depressed, clearance of triglyceride-rich lipoproteins and their atherogenic remnants is impaired, their composition is altered, and their plasma concentration is elevated in ESRD. The associated defect in HDL maturation is largely caused by acquired lecithin-cholesterol acyltransferase (LCAT) deficiency while its triglyceride enrichment is due to hepatic lipase deficiency. Hyper-triglyceridemia, abnormal composition, and impaired clearance of triglyceride-rich lipoproteins and their remnants are mediated by down-regulation of lipoprotein lipase, hepatic lipase, VLDL receptor, and LDL receptor-related protein (LRP), relative reduction of ApoC-II/ApoC-III ratio, upregulation of acyl-CoA cholesterol acyltransferase (ACAT) and elevated plasma level of cholesterol ester-poor pre-beta HDL. Impaired clearance and accumulation of oxidation-prone VLDL and chylomicron remnants and abnormal LDL composition in the face of oxidative stress and inflammation favors their uptake by macrophages and resident cells in the artery wall. The effect of heightened influx of lipids is compounded by impaired HDL-mediated reverse cholesterol transport leading to foam cell formation which is the central event in atherosclerosis plaque formation and subsequent plaque rupture, thrombosis and tissue damage.

End-stage renal disease (ESRD) is associated with accelerated atherosclerosis and a high incidence of cardiovascular morbidity and mortality [1]. A number of factors contribute to atherosclerosis and cardiovascular disease in ESRD population. Chief among them are oxidative stress, inflammation, hypertension, endothelial dysfunction, insulin resistance, vascular calcification and dyslipidemia [2–9]. The ESRD-induced dyslipidemia is characterized by hyper-triglyceridemia, elevated level of very low density lipoprotein (VLDL), high plasma concentration of lipoprotein remnants, accumulation of oxidized lipids and lipoproteins, low plasma HDL cholesterol concentration and impaired HDL maturation and function [8]. Serum cholesterol and LDL cholesterol values are frequently within or below the normal limits in hemodialysis-treated ESRD patients but are commonly increased in those maintained on peritoneal dialysis modalities. Finally, in ESRD patients low density lipoprotein (LDL) consists of highly atherogenic small-dense particles which contains abnormal levels of residual triglycerides [10,11].

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The ESRD-associated changes of plasma lipid pattern can be significantly altered by dialysis modality, lipid-altering drugs (e.g. statins, fibrates, sevelamer, calcineurin inhibitors, steroids and rapamycin), pre-existing genetic disorders of lipid metabolism, malnutrition and inflammation among other factors. For example, use of the phosphate binding resin, sevelamer, lowers plasma cholesterol by acting as a bile acid sequestrant. Moreover, inflammation, which is a common feature of ESRD, can reduce serum total cholesterol and HDL cholesterol levels. In contrast, chronic peritoneal dialysis which results in substantial losses of proteins in the peritoneal fluid effluent, can cause significant elevation of serum total cholesterol and LDL [10,11] by simulating nephrotic syndrome[12,13].

This article is intended to provide a brief overview of the mechanisms responsible for dysregulation of lipid metabolism in chronic renal failure.

HDL Metabolism in chronic renal failure

In the artery wall, oxidized or otherwise modified lipoproteins are engulfed by macrophages and resident cells via scavenger receptors, a process that can lead to foam cell formation and atherosclerosis. HDL plays a major role in mitigating this process by limiting lipid/lipoprotein oxidation and by retrieving surplus cholesterol from vascular tissue for disposal in the liver, a process commonly known as reverse cholesterol transport (figure 1) [14]. In addition, HDL plays a major role in metabolism of triglyceride-richlipoproteins by serving as an ApoC and ApoE donor to the nascent chylomicrons and VLDL, a process which is vital in metabolism of these triglyceride-rich lipoproteins [15]. Moreover, HDL serves as a potent endogenous inhibitor of inflammation, platelet adhesion, and lipid/lipoprotein oxidation [16].

HDL-mediated removal of surplus lipids from tissue macrophages and resident cells requires attachment of nascent HDL to ATP binding cassette transporter type 1 (ABCA1) or binding of mature HDL to ABCG-1 on the cell membrane [17–19]. Binding of the nascent HDL to ABCA1 triggers active transfer of phospholipids and free cholesterol from adjacent caveolae to the surface of HDL [17]. In addition, HDL binding to ABCG-1 leads to further cholesterol enrichment and maturation of HDL [20]. Free cholesterol reaching the surface of HDL is rapidly esterified by LCAT and sequestered in the core of HDL, allowing maximal uptake of cholesterol by HDL. This process is critical for HDL maturation and efficient HDL-mediated reverse cholesterol transport. Once loaded with cholesterol ester, HDL detaches from ABCA-1/ABCG-1 transporters and travels to the liver. In the liver, HDL forms a reversible bond with the HDL docking receptor, SRB-1, which facilitates simultaneous unloading of its cholesterol ester content, as well as hydrolysis and extraction of its fatty acid cargo by hepatic lipase. This is followed by detachment of the unloaded HDL from SRB-1 and its return to the blood stream for recycling [21]. In addition to SRB1, liver contains an endocytic HDL receptor, beta chain of ATP synthase, which binds and internalizes HDL for degradation [22].

Several factors contribute to reduction of HDL cholesterol and increased proportion of lipid-poor pre-beta HDL, impaired maturation of cholesterol ester-poor to cholesterol ester -rich HDL, and elevated triglyceride content of HDL in this population. The essential steps in HDL metabolism and impact of chronic renal failure or ESRD thereon are briefly described below:

I. Plasma concentration of ApoA-I and ApoA-II is significantly reduced in chronic renal failure [23–24]. Since ApoA-I is the primary protein constituents of HDL, its deficiency can, in part, contribute to the overall reduction of plasma HDL in the ESRD population. Studies performed in experimental animals have shown that the reduction of plasma ApoA-I and ApoA-II in chronic renal failure is due to their diminished gene expression in the liver [24].

II. The primary step in HDL-mediated uptake and removal of surplus cholesterol from the peripheral tissues involves binding of the cholesterol-poor HDL to the ABCA-1 transporter on the cell membrane. HDL binding to ABCA-1 triggers efflux of phospholipid and free cholesterol to the cell surface and from the cell the cell surface to the surface of HDL [17–19]. Potential ABCA-1 deficiency or dysfunction can, therefore, reduce HDL cholesterol and greatly limit HDL maturation as seen in Tangier disease [17–19]. The effect of chronic renal failure on ABCA-1 and ABCG-1 expression is unknown and is currently under investigation in our laboratory. It should be noted that oxidative modification of HDL can interfere with its binding to ABCA-1 transporter [25]. In this context, HDL from patients with end-stage CKD has been recently shown to be pro-oxidant, reflecting its oxidative modification [26]. The CKD-induced oxidative modification of HDL can, therefore, contribute to lipid accumulation in the artery wall by limiting its ability to effectively bind to ABCA-1 transporter in order to mediate reverse cholesterol transport.

III. In addition to the ABCA-1 mediated pathway, which requires HDL binding to the peripheral cells, HDL receives a significant amount of its cholesterol content from albumin, which serves as a carrier of free cholesterol from the peripheral tissues to the freely-floating HDL-3 [27]. Hence, hypoalbuminemia, which is often present in the ESRD and/or CKD patients (due to inflammation, malnutrition or external losses) can potentially contribute to, depressed serum HDL cholesterol.

IV. Plasma LCAT activity and concentration are markedly reduced in ESRD patients [26,28] and hepatic LCAT gene expression is significantly down-regulated of in CKD rats [13,29,30]. Given the critical role of LCAT in HDL maturation and efficient HDL-mediated reverse cholesterol transport, its acquired deficiency must play a major part in the pathogenesis of depressed HDL cholesterol, impaired HDL maturation and atherogenic diathesis in patients with ESRD. In addition to contributing to reduction of HDL cholesterol, impaired HDL maturation and elevated serum levels of cholesterol ester-poor pre-beta HDL particles, LCAT deficiency can accelerate degradation of HDL. This is because, as described below, preferential binding to the endocytic receptor in the liver results in internalization and degradation of immature HDL particles, thereby contributes to reductions of plasma ApoA-1 and total HDL in the ESRD population.

V. After detachment from the binding site in the peripheral tissues the cholesterol ester-rich HDL particles return to circulation to begin a journey to the liver for delivery and disposal of their lipid cargo. While in transit, HDL-2 donates a portion of its cholesterol ester content to VLDL remnant in exchange for triglyceride. This exchange which is mediated by cholesterol ester transfer protein (CETP) plays an important part in cholesterol-enrichment and triglyceride depletion of VLDL remnants, otherwise known as intermediate density lipoprotein (IDL) and their ultimate transformation to LDL. Limited studies conducted in patients with ESRD have found no significant difference in plasma CETP concentration between hemodialysis patients and normal subjects [31–33]. It is of note however that hepatic production and plasma CETP level are significantly elevated in patients with nephrotic proteinuria [34,35]. Since nephrotic syndrome and maintenance peritoneal dialysis are both associated with heavy losses of proteins, ESRD patients receiving chronic peritoneal dialysis might exhibit increased plasma CETP levels.

VI. In addition to its role in hydrolysis and extraction of the residual triglycerides in the IDL, hepatic lipase is essential for hydrolysis and clearance of triglyceride contents of HDL. Chronic renal failure results in marked down-regulation of hepatic lipase in experimental animals with chronic renal failure [36,37,38]. Therefore, triglyceride-

enrichment of HDL in humans and animals with chronic renal disease is largely due to hepatic lipase deficiency.

VII. The final step in HDL-mediated reverse cholesterol/lipid transport involves the delivery and disposal of its lipid cargo in the liver. This process is primarily accomplished via binding of the cholesterol ester-rich mature HDL to SRB-1 which is expressed by heptatocytes and serves as the HDL docking receptor [21]. Binding to this receptor facilitates unloading of cholesterol ester cargo of HDL and hydrolysis of its triglyceride and phospholipid contents by hepatic lipase and the release of the lipid-depleted HDL for recycling. Earlier studies conducted in my laboratory demonstrated significant reduction of SRB-1 protein abundance (despite its normal gene expression) in experimental animals with heavy glomerular proteinuria [39]. In contrast, we found no significant reduction in hepatic tissue SRB-1 abundance in rats with renal insufficiency without heavy proteinuria [24]. By extrapolation, these observations suggest that substantial protein losses via peritoneal dialysate effluent may lead to SRB-1 deficiency in patients maintained on chronic peritoneal dialysis (which simulates nephrotic syndrome in functionally anephric individuals) but not those treated by hemodialysis. The mitochondrial beta chain subunit of ATP synthase has been identified on the plasma membrane of heptatocytes where it serves as an endocytic HDL receptor. Unlike SRB-1, this receptor binds and internalizes ApoA-1 and lipid-poor HDL particles and as such participates in their catabolism [22,40]. The effect, if any of chronic kidney disease on the abundance of this receptor in the liver is currently unknown and is under investigation in our laboratory.

VIII. In addition to its role in reverse cholesterol transport, HDL possesses potent anti oxidant, anti-inflammatory and anti-thrombotic properties which are equally important in protection against atherosclerosis. The latter actions of HDL are mediated by its constituent antioxidant enzymes, paraoxonase and glutathione peroxidase (which can reverse or prevent lipid/lipoprotein peroxidation), LCAT and Apo A-I (which can remove, bind and dispose oxidized phospholipids) and platelet activating factor acetyl hydrolase (which inactivates this pro-thrombotic factor). Recent studies in my laboratories have shown marked reductions of plasma paraoxonase, glutathione peroxidase as well as severe loss of HDL anti-oxidant capacity in ESRD patients maintained on hemodialysis [26]. Thus, diminished plasma HDL level and impaired HDL-mediated reverse cholesterol transport capacity is compounded by its defective anti-oxidant properties, events that contribute to the atherogenic diathesis in ESRD. Systemic inflammation and oxidative stress have been shown to contribute to the reduction of anti-oxidant, anti-inflammatory functions of HDL or conversion of HDL to a pro-oxidant/pro-inflammatory agent [16,41].

Triglyceride and triglyceride-rich lipoprotein metabolism in chronic renal failure

As noted earlier, ESRD results in hyper-triglyceridemia, elevation of VLDL, impaired VLDL and chylomicron clearance as well as increased plasma concentration of IDL and chylomicron remnants and prolonged post-prandial lipemia [8,10,42–45]. This is associated with a relative increase in plasma ApoC-III (a potent inhibitor of lipoprotein lipase) and relative decline in ApoC-II, which is the activator of lipoprotein lipase [8,10,42]. Several factors contribute to hyper-triglyceridemia, elevation of VLDL and accumulation of VLDL and chylomicron remnants in ESRD population. The essential steps in triglyceride and triglyceride-rich lipoprotein metabolism and impact of chronic renal failure or ESRD thereon are briefly described below:

I. Lipid fuel and construction material are transported by VLDL and chylomicron from the liver and intestine, respectively to the muscle for production of energy and to the fat tissue for storage of energy (Figures 2 and 3). After their release in the circulation, nascent VLDL and chylomicrons acquire ApoE and ApoC-II from cholesterol ester-rich mature HDL. This process is critical for subsequent metabolism of VLDL and chylomicrons because Apo E serves as the ligand for binding to lipoprotein lipase and VLDL receptor while ApoC-II serves as activator of lipoprotein lipase. The endothelium-bound lipoprotein lipase in the capillaries that perfuse skeletal muscle, adipose tissue and myocardium, catalyzes hydrolysis of triglyceride contents of VLDL and chylomicrons. This leads to release of over 70% of the fatty acid contents of these particles and uptake of the free fatty acids by myocytes and adipocytes. The substantially lipid-depleted VLDL and chylomicrons are then released to the circulation as IDL and chylomicron remnants where they return the borrowed ApoE and ApoC to the cholesterol ester-poor HDL. HDL-mediated extraction of ApoE and C from the remnant particles is essential for their subsequent clearance by the liver. Thus HDL plays an important role in metabolism of triglycerides and triglyceride-rich lipoproteins by shuttling ApoE and Apo C between nascent and remnant VLDL and chylomicrons.

Earlier studies have demonstrated marked reduction of plasma post-heparin lipolytic activity in ESRD patients and animals with chronic renal failure [8,38,46,47] pointing to diminished pool of endothelium bound lipoprotein lipase. This was widely attributed to lipoprotein lipase depletion caused by recurrent use of heparin for anti-coagulation during regular hemodialysis treatments. However, studies in our laboratory revealed variable down-regulation of lipoprotein lipase gene expression, marked reductions of lipoprotein lipase protein abundance, as well as heparin-releasable and intracellular fractions of this enzyme in skeletal muscle, myocardium and adipose tissue of rats with chronic renal failure induced by 5/6 nephrectomy [48]. These studies further demonstrated the role of elevated parathyroid hormone in downregulation of lipoprotein lipase in these animals [49]. These findings in experimental animals helped to support the earlier observations by Akmal et al [50] in patients with ESRD.

Additional factors contributing to the diminished lipoprotein lipase activity in ESRD include diminished physical activity, reduced ApoC-II to-ApoC-III ratio, low level of cholesterol ester-rich mature HDL (which serves as ApoE and ApoC donor), high level of cholesterol ester-poor pre-beta HDL (which serves as ApoE and ApoC taker), impaired thyroxin (T_4) to-tri-iodothyronin (T_3) conversion and insulin resistance which are constant features of ESRD. In addition, repetitive use of heparin which facilitates detachment of endothelium-bound enzyme and its subsequent removal by LDL receptor-related protein (LRP) in the liver can further aggravate lipoprotein lipase deficiency in patients maintained on hemodialysis [8]. Together these events lead to profound lipoprotein lipase deficiency which plays a large part in the pathogenesis of ESRD-induced hyper-triglyceridemia and impaired VLDL and chylomicron metabolism.

II. Chylomicron remnants and a small fraction of IDL produced as a result of lipolytic action of lipoprotein lipase are removed by liver via binding to a multifunctional receptor, known as LDL receptor related protein (LRP) [51]. Studies conducted in our laboratories have revealed significant downregulation of LRP gene expression and protein abundance in the liver of rats with chronic renal failure [52]. The observed reduction of LRP abundance can, in part, contribute to the high levels of the atherogenic remnants in the CKD population.

III. Under normal condition, great majority of IDL particles are converted to LDL through a series of steps which lead to cholesterol enrichment and extraction of nearly all of their residual triglyceride contents. Conversion of IDL to LDL involves CETP-mediated acquisition of cholesterol esters from HDL in exchange for transfer of triglycerides to HDL, followed by further lipolysis by hepatic lipase. These events lead to formation of cholesterol ester-rich and essentially triglyceride-free LDL. Properly formed LDL is readily cleared by LDL receptor and confers considerably less threat than abnormal oxidation-prone, atherogenic small dense LDL particles containing residual triglycerides. Chronic renal failure has been shown to cause hepatic lipase deficiency [36,38] which as expected results in defective IDL to LDL transformation, elevation of serum IDL, TG-enrichment of LDL and hyper-triglyceridemia.

IV. In addition to lipolytic pathway, a novel pathway has been described for clearance of VLDL via VLDL receptor by adipocytes and myocytes [53]. In a series of studies conducted in our laboratory, we found a marked down-regulation of VLDL receptor gene expression and protein abundance in the skeletal muscle, myocardium and fat tissues of rats with chronic renal insufficiency [54,55]. These findings unraveled an additional mechanism by which chronic renal failure impairs VLDL clearance and thereby raises plasma VLDL and triglyceride levels.

V. The studies cited above clearly point to the central role of impaired clearance of triglyceride-rich lipoproteins in the pathogenesis of ESRD-induced hyper-triglyceridemia. In order to evaluate the potential contribution of triglyceride biosynthesis to the ESRD-induced hypertriglyceridemia, we explored the effect of chronic renal failure on expression of acyl-CoA: diglycerol acyl-transferase (DGAT) which catalyzes the final step in TG synthesis. We found significant downregulation of this enzyme in the liver of rats with chronic renal failure induced by 5/6 nephrectomy [56]. These observations excluded the possible role of heightened triglyceride production capacity as a cause of hyper-triglyceridemia in chronic renal failure. In contrast, animals with heavy glomerular proteinuria were found to exhibit significant upregulation of DGAT in the liver [57]. Since protein losses associated with chronic peritoneal dialysis can simulate nephrotic syndrome in functionally-anephric subjects, increased production capacity may amplify the effect of depressed triglyceride clearance and contribute to the greater hyper-triglyceridemia seen in patients treated with peritoneal dialysis modalities.

Cholesterol and LDL metabolism in chronic renal failure

As mentioned earlier, serum cholesterol and LDL cholesterol concentrations are usually within or below the normal range in hemodialysis-treated ESRD patients but are commonly elevated in individuals maintained on peritoneal dialysis. Moreover, LDL in ESRD patients consists of small and dense particles which contain abnormal levels of residual triglycerides [10,11]. The critical steps in cholesterol and LDL metabolism and impact of chronic renal failure or ESRD thereon are briefly described below:

I. Plasma and tissue cholesterol are derived from dietary intake and endogenous production. The rate-limiting step in cholesterol biosynthesis is catalyzed by HMG-CoA reductase and the rate-limiting enzyme in cholesterol catabolism (conversion to bile acids) is cholesterol 7α-hydroxylase. Earlier studies have demonstrated that chronic renal failure alone without heavy proteinuria does not significantly affect expression or activities of either HMG-CoA reductase or cholesterol 7α-hydroxylase [58]. Conversely, nephrotic proteinuria alone or in combination with renal insufficiency leads to significant upregulation of HMG-CoA reductase gene expression, protein abundance and enzymatic activity [12,13]. This is exemplified by

presence of hypercholesterolemia in patients and animals with concomitant renal insufficiency and heavy proteinuria as well as ESRD patients maintained on chronic peritoneal dialysis in whom losses of protein in the peritoneal dialysate effluent simulates urinary losses in nephrotic syndrome.

II. Cholesterol ester-rich LDL particles are cleared from the circulation by LDL receptor in the liver and peripheral tissues (Figure 2). Earlier studies have shown that hepatic LDL receptor abundance is unchanged in animals with chronic insufficiency before the onset of significant glomerulosclerosis and heavy proteinuria [58] but significantly declines following development of glomerulosclerosis and heavy proteinuria leading to severe hypercholesterolemia [13,59]. Therefore, elevation of serum LDL and total cholesterol in the subpopulation of CKD patients exhibiting heavy proteinuria and ESRD patients maintained on chronic peritoneal dialysis, may be, in part, caused by acquired LDL receptor deficiency.

III. In the liver newly synthesized and imported cholesterol is esterified by acyl-CoA: cholesterol acyltransferase (ACAT) for intracellular storage in cytoplasmic vesicles for packaging and secretion in VLDL. The same enzyme is involved in esterification and storage of cholesterol in macrophages and resident cells culminating in foam cell formation in the vascular and renal tissues. By promoting esterification and intracellular retention of cholesterol, ACAT opposes HDL-mediated reverse cholesterol transport in the peripheral tissues. In a series of studies carried out in our laboratories, we found significant upregulations of ACAT gene expression, protein abundance and enzymatic activity in the liver of rats with chronic renal failure [60]. We subsequently found a marked rise in plasma HDL cholesterol, a significant reduction in non-HDL cholesterol, and decline in triglyceride and reversal of LCAT and LDL receptor deficiencies in response to pharmacological inhibition of ACAT in these animals [61]. These observations illustrate the importance of up-regulation of ACAT in the pathogenesis of lipid disorders in chronic kidney disease.

Biological and therapeutic Implications

The constellation of oxidative stress, inflammation and lipid disorders which are nearly constant features of ESRD is largely responsible for accelerated atherosclerosis and premature death from cardiovascular vascular disease in this population. Impaired clearance and accumulation of oxidation- prone VLDL and chylomicron remnants and abnormal LDL composition in the face of oxidative stress and inflammation favors their uptake by macrophages and resident cells in the artery wall. The effect of heightened influx of lipids is compounded by impaired HDL-mediated reverse cholesterol transport leading to foam cell formation which is the central event in atherosclerosis plaque formation and subsequent plaque rupture, thrombosis and tissue damage. In addition to their impact on plasma lipid profile and atherogenesis, impaired clearance of triglyceride-rich lipoproteins in ESRD has major implication on energy metabolism. This is because impaired lipoprotein lipase activity and VLDL receptor deficiency can limit the availability of lipid fuel for energy production in skeletal muscle and thereby exercise capacity. Similarly, these deficiencies can limit the storage of energy in adipose tissue and contribute to the wasting syndrome.

Since plasma cholesterol is usually normal or reduced in hemodialysis patients, use of cholesterol lowering agents appears to be of little value except in the minority of patients with hyper-cholesterolemia. This supposition is supported by clinical trials of HMG-CoA reductase inhibitors which have yielded negative results in the ESRD populations [62,63]. Instead, the logical treatment should ideally include strategies aim at alleviating inflammation and oxidative stress, enhancing clearance of VLDL, IDL and chylomicron and their remnant as well as restoring HDL metabolism and function. It should be noted that the ideal tools to readily

achieve these objectives remain elusive at this time. None the less dietary modifications, increased physical activity, longer and/or more frequent dialysis treatments, use of ultra-pure dialysates, biocompatible dialyzers, and fistulas instead of catheters or A-V grafts, and refraining from overzealous use of intravenous iron preparations and erythropoiesis stimulating agents represent important steps in the right direction

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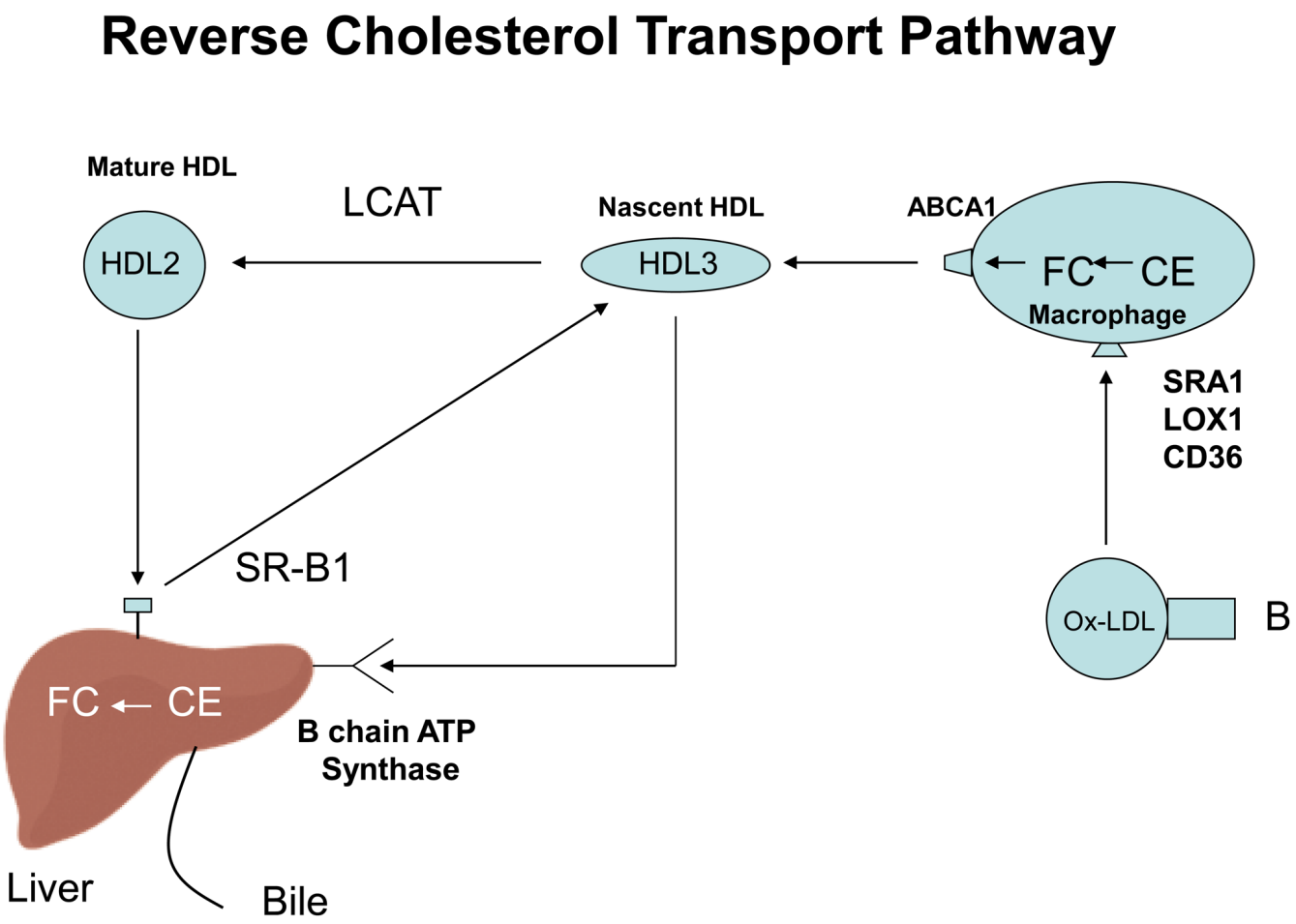

Figure 1.
Diagram of the reverse cholesterol transport pathway depicting oxidized lipoprotein influx via scavenger receptors (SRA-1, LOX-1 and CD 36) and free cholesterol efflux via ABCA-1 transporter in macrophages and resident cells in the artery wall, transfer of free cholesterol from the cell surface to the lipid-poor HDL-3, esterification of free cholesterol and translocation cholesterol ester to the core of HDL, detachment of mature HDL-2 and unloading of its lipid cargo via docking receptor, SRB-1 followed by the release of lipid-depleted HDL for recycling or degradation by the HDL holo-receptor, B chain of ATP synthase.

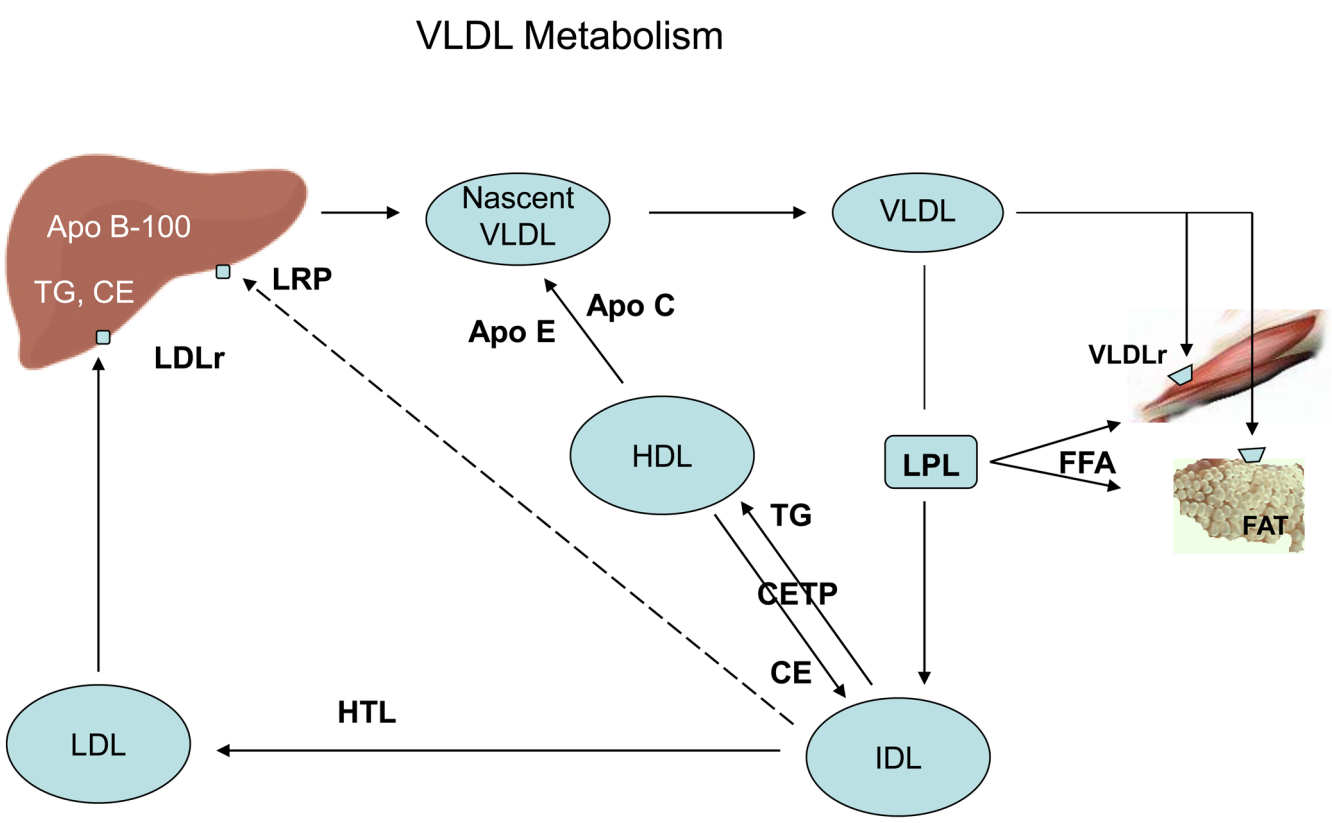

Figure 2.
Diagram illustrating secretion of nascent VLDL by the liver followed by acquisition of ApoE and ApoC from HDL, endocytic removal of VLDL by myocytes/adipocytes via VLDL receptor and their partial delipidation by lipoprotein lipase (LPL) culminating in formation and release of IDL; conversion of the majority of IDL to LDL (via CETP- and hepatic lipase- mediated cholesterol enrichment and triglyceride depletion), uptake of small fraction of IDL via LDL receptor-related protein (LRP) and removal of the bulk of LDL by LDL receptor.

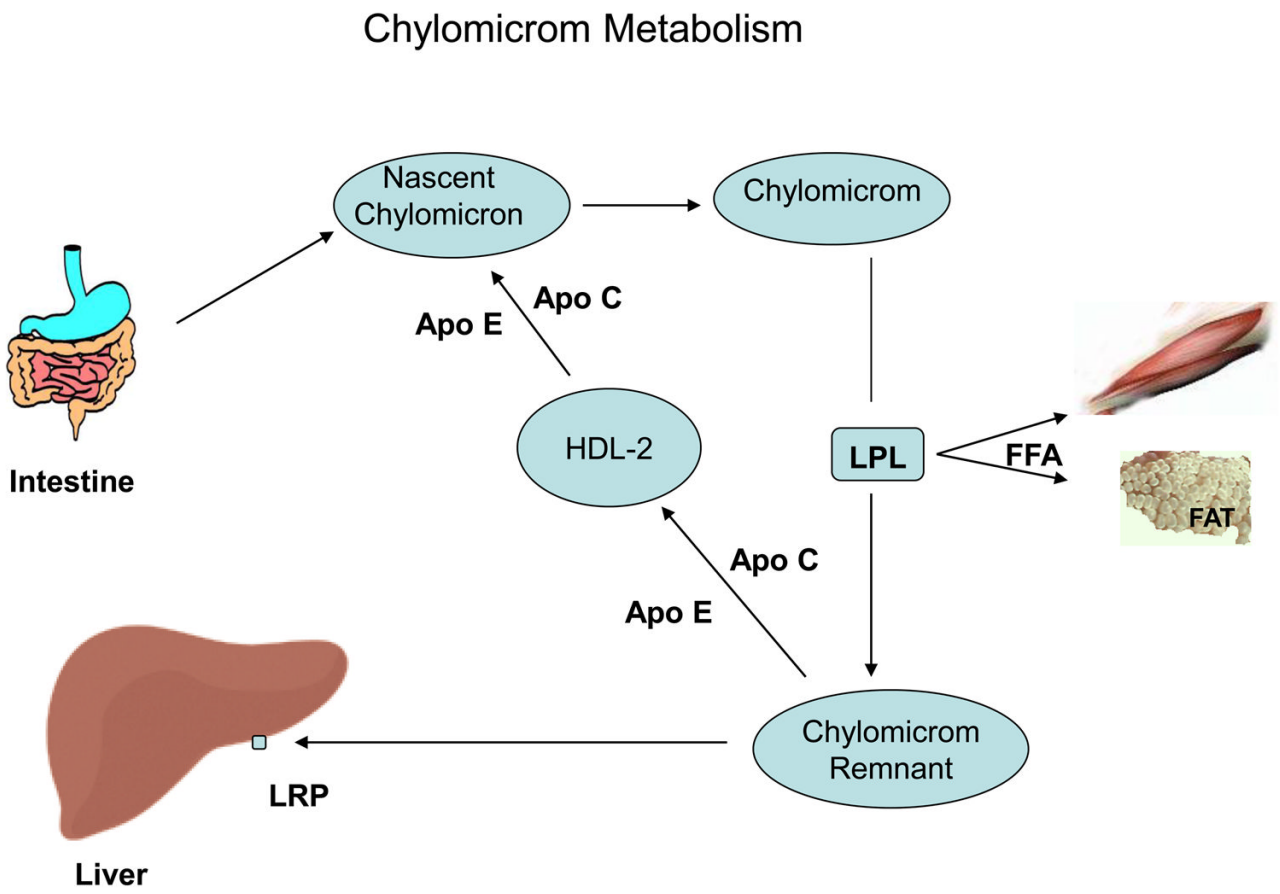

Figure 3.
Diagram depicting secretion of nascent chylomicron by the intestine followed by acquisition of ApoE and ApoC from HDL; partial delipidation of chylomicrons by lipoprotein lipase (LPL) culminating in formation and release of chylomicron remnants and their ultimate removal by LDL receptor-related protein (LRP).