

# Lipoprotein metabolism in chronic renal insufficiency

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**Abstract** Chronic renal insufficiency (CRI) is associated with a characteristic dyslipidemia. Findings in children with CRI largely parallel those in adults. Moderate hypertriglyceridemia, increased triglyceride-rich lipoproteins (TRL) and reduced high-density lipoproteins (HDL) are the most usual findings, whereas total and low-density lipoprotein cholesterol (LDL-C) remain normal or modestly increased. Qualitative abnormalities in lipoproteins are common, including small dense LDL, oxidized LDL, and cholesterol-enriched TRL. Measures of lipoprotein lipase and hepatic lipase activity are reduced, and concentrations of apolipoprotein C-III are markedly elevated. Still an active area of research, major pathophysiological mechanisms leading to the dyslipidemia of CRI include insulin resistance and nonnephrotic proteinuria. Sources of variability in the severity of this dyslipidemia include the degree of renal impairment and the modality of dialysis. The benefits of maintaining normal body weight and physical activity extend to those with CRI. In addition to multiple hypolipidemic pharmaceuticals, fish oils are also effective as a triglyceride-lowering agent, and the phosphorous binding agent sevelamer also lowers LDL-C. Emerging classes of hypolipidemic agents and drugs affecting sensitivity to insulin may impact future treatment. Unfortunately, cardiovascular benefit has not been convincingly demonstrated by any trial designed to study adults or children with renal

disease. Therefore, it is not possible at this time to endorse general recommendations for the use of any agent to treat dyslipidemia in children with chronic kidney disease.

**Keywords** Chronic kidney disease · Lipid disorders · Cardiovascular disease · High-density-lipoprotein metabolism · Cholesterol metabolism · Triglyceride · Children

## Abbreviations

AAP	American Academy of Pediatrics
ADPKD	Autosomal dominant polycystic kidney disease
AHA	American Heart Association
Apo	apoproteins (apolipoproteins)
ASCVD	atherosclerotic cardiovascular disease
ATGL	adipose triglyceride lipase
CE	esterified cholesterol (cholesteryl esters)
CETP	cholesteryl ester transfer protein
CKD	chronic kidney disease
CRI	chronic renal insufficiency
DHA	docosahexaenoic acid
EPA	eicosapentaenoic acid
ESRD	end-stage renal disease
FFA	free fatty acids (nonesterified fatty acids)
FSGS	focal and segmental glomerulosclerosis
GFR	glomerular filtration rate
HDL	high-density lipoproteins
HDL-C	HDL cholesterol (cholesterol content of HDL)
HL	hepatic lipase
HSL	hormone-sensitive lipase
HSPG	heparan sulfate proteoglycans
IgAN	immunoglobulin A nephropathy
IDL	intermediate-density lipoproteins
IR	insulin resistance
KDOQI	National Kidney Foundation Kidney Disease Outcomes Quality Initiative

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LCAT	lecithin-cholesterol acyltransferase
LDL	low-density lipoproteins
LDL-R	LDL receptor
LPL	lipoprotein lipase
LRP	LDL-receptor-related protein
NKF	National Kidney Foundation
PL	phospholipids
PLTP	phospholipid transfer protein
PON	paraoxonase
PPAR	peroxisome-proliferator-activated nuclear receptors
SNP	single nucleotide polymorphisms
Statin	3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitor
TG	triglyceride
TRL	triglyceride-rich lipoproteins [chylomicrons, very-low-density lipoproteins (VLDL) and their remnants]
VLDL	very-low-density lipoproteins

## Introduction

Chronic renal insufficiency (CRI) leads to marked alterations in lipoprotein metabolism. Inasmuch as dyslipidemia is a well-established risk factor for atherosclerosis, study of the pathophysiology underlying these alterations and of potential methods of ameliorating them is of great interest. Adults with chronic kidney disease (CKD) suffer a high burden of atherosclerotic cardiovascular disease (ASCVD) [1–4]. Whereas clear functional, morphological, and outcome-related evidence of accelerated ASCVD is found in children with end-stage renal disease (ESRD) [5–11] and young adult survivors of childhood ESRD [12–15], evidence of ASCVD in milder childhood CKD is lacking. Nonetheless, it is well known that in the general population, subclinical atherosclerosis begins in childhood [16], and it is very likely that this process is accelerated in children with CKD [17]. The latter presumption is accepted to the extent that the National Kidney Foundation (NKF) has issued guidelines of care relating to dyslipidemia in individuals with CKD, including youth from the onset of puberty [1]. Though outside the scope of this review, there is accumulating information that in addition to atherosclerosis, dyslipidemia contributes to the initiation and progression of CKD itself. This process is incompletely understood but may involve, among other factors, adverse effects on mesangial cells and injury to the renal endothelium and podocytes induced directly by lipoproteins, particularly via lipid mediators of oxidative stress [18–20].

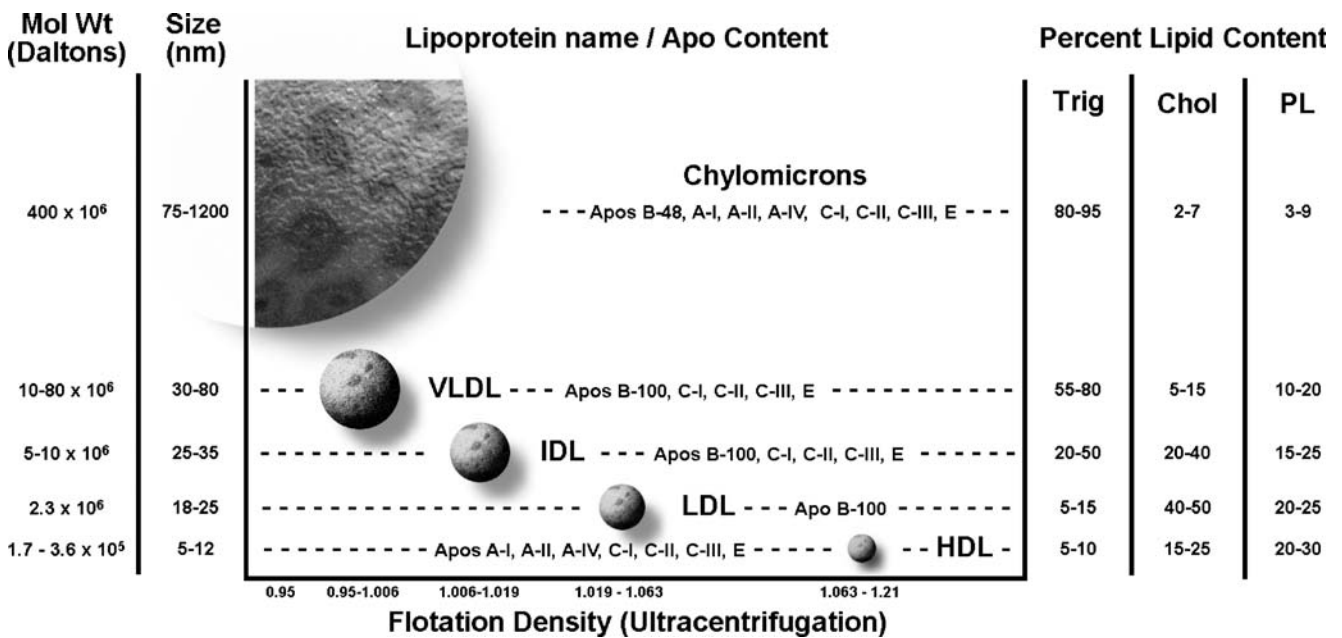
CRI, defined as a significant and sustained reduction in glomerular filtration rate (GFR), results from a variety of conditions and is accompanied by a spectrum of shared

comorbidities. The term CRI is convenient to this review because it focuses on the effects of decreased GFR, excluding consideration of specific renal diseases such as nephrotic syndrome or diabetic nephropathy. The broader term of CKD is used in this review when discussion turns to literature in which that term was used. Nonnephrotic proteinuria, overweight, malnutrition, and intrinsic or genetic differences in individual metabolism are significant sources of variation in expression of dyslipidemia among the population with CRI. Nonetheless, as GFR declines, regardless of cause, a certain shared pattern of dyslipidemia emerges. This is the subject of this review, which will focus on abnormalities of lipoprotein metabolism that are commonly encountered among individuals with CRI, the mechanisms thought to account for their occurrence, and strategies for treatment. It is necessary to begin with an overview of normal lipoprotein metabolism.

## Lipoprotein nomenclature, function, and characteristic findings in CRI

Lipoproteins are a family of structurally similar particles with surprisingly variable composition and function. Major classes of lipoproteins have been categorized by their physical or chemical properties, most commonly by their density and flotation characteristics when separated by ultracentrifugation [21]. These include chylomicrons, very-low-density lipoproteins (VLDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL). Nonetheless, lipoproteins are polydisperse, demonstrating a continuum of composition, size, density, electrophoretic mobility, associated proteins [apoproteins(apo)] and other characteristics by which they may be measured (Fig. 1) [21–23].

The intestine and liver are the primary sites of lipoprotein synthesis. The major and most basic role of lipoproteins is to transport water-insoluble lipids from dietary and endogenous sources to sites of storage and utilization and between sites of tissue storage and utilization. The main lipid cargo of these particles consists of triglycerides (TG), free cholesterol, esterified cholesterol (CE), and phospholipids (PL). The free and CE, as well as PL, are the key structural elements required for the formation and maintenance of cellular and subcellular membranes that allow, through compartmentalization, complexity of biochemical function from the microscopic to macroscopic scale. Lipids, particularly TG, also serve as a principal metabolic source of fuel for all tissues, and the regulated pathways of lipoprotein physiology link the nutritional environment to the metabolic demands of the body. Lipoproteins are also involved in distribution of a number of lipid-soluble hormones and metabolites. It is important to note that, in contrast, the principal carrier of circulating free



**Fig. 1** The most common classification of lipoproteins is based on flotation density/ultracentrifugation. The physical properties of the major lipoprotein classes are shown. Other common classification

systems include differentiation by apolipoprotein content or electrophoresis. No single system captures the diversity of lipoprotein properties

fatty acids (FFA) is albumin, usually transporting FFA released from hydrolysis of TG in adipose stores for eventual hepatic uptake [24].

Major regulation of lipoprotein physiology is accomplished through the specific activities of apo. In addition to their structural role in lipoproteins, the apo accomplish this regulation as activators or inhibitors of enzymatic actions or as ligands for various receptors. Mutations and polymorphisms in the genes encoding apo or proteins with which they interact result in alterations of lipoprotein physiology and in human disease [25].

CRI produces a characteristic effect on the major lipoprotein fractions that can be summarized as increased VLDL and chylomicron remnants with increased total TG, and decreased HDL-cholesterol (HDL-C) with nearly normal total and LDL-C (Table 1) [1, 26]. Sometimes referred to as atherogenic dyslipidemia, this pattern is considered dyslipidemic precisely because it is associated with increased risk of ASCVD [27–29]. Similar findings are apparent from studies in children with CRI, though the data is more limited (Table 2) [30–47]. Characteristic changes in selected apo, enzymes,

and regulatory molecules resulting from CRI are shown in Table 3 [26, 30–32, 36, 44–75]. Where multiple studies are consistent, one tends to presume the data are more reliable; on the other hand, discrepancies among studies are likely to result from numerous confounding variables including differences in population characteristics, sample size, and measurement techniques among others. In particular, peritoneal dialysis patients tend to exhibit hypercholesterolemia relative to pre-dialysis or hemodialysis patients.

Postprandial lipoproteins and effects of CRI

Intestinal lipoproteins distribute dietary lipid in the postprandial state. All apoB-48 and a proportion of apoA-I and apoA-II is produced by the intestine [21, 76]. Whereas lipoproteins are not commonly assessed in the postprandial state, this period was recognized many years ago to be of key importance in atherogenesis [77], and more recent work has solidified the assertion that alimentary lipoproteins directly and indirectly participate in vessel pathology [78–84].

**Table 1** Characteristic dyslipidemia of chronic renal insufficiency

	TG	TC	HDL-C	Non-HDL-C	LDL-C	VLDL-C	Lp(a)
CRI	↑	↔	↓	↑	↔	↑	↑
HD	↑	↔	↓	↑	↔	↑	↑
PD	↑	↔,↑	↓	↑	↔,↑	↑	↑

Data from references [1, 26]

CRI chronic renal insufficiency, HD hemodialysis, PD peritoneal dialysis, TG triglycerides, TC total cholesterol, HDL-C high-density-lipoprotein cholesterol, LDL-C low-density-lipoprotein cholesterol, VLDL-C very-low-density-lipoprotein cholesterol, Lp(a) lipoprotein (a)

**Table 2** Dyslipidemia in pediatric chronic renal insufficiency and end-stage renal disease

	Study	N	TG	TC	HDL-C	LDL-C	VLDL-C
CRI	Querfeld et al. [30]	20	↑ 2-fold	↑ 25%	↓ 15%	↑ 25%	↑ 2-fold
	Papadopoulou et al. [34]	9	↑ 2-fold	Normal	↓ 35%	Normal	Normal
	Zacchello et al. [37]	25	↑ up to 2.5-fold	Normal	↓ up to 30%		
	Muller et al. [39]	10	↑ 2-fold	↑ 30%			
	Berger et al. [40]	21	<sup>a</sup> ↑ in 27%	<sup>a</sup> ↑ in 12%			
	Asayama et al. [44]	18	↑ up to 4-fold	↑ up to 50%	↓ up to 30%		
HD	Querfeld et al. [30]	10	↑ 1.5-fold	Normal	↓ 30%	Normal	↑ 2-fold
	Gambert et al. [33]	9	↑ ~4-fold	↑ ~30%	Normal	Normal	↑ ~4-fold
	Papadopoulou et al. [34]	8	↑ 2.5-fold	Normal	↓ 35%	Normal	↑ 2-fold
	El Bishti et al. [35]	16	↑ 2.5-fold	↑ 40%			
	Ohta & Matsuda [36]	15	↑ 3-fold	↓ 15%	↓ 50%		
	Zacchello et al. [37]	10	↑ 2.5-fold	Normal	↓ 20%		
	Muller et al. [39]	12	Normal	↑ 15%			
	Berger et al. [40]	11	<sup>a</sup> ↑ in 65%	<sup>a</sup> ↑ in 4%			
	Van Gool et al. [42]	10	↑ 2.5-fold	Normal	↓ 25%	Normal	
	Asayama et al. [44]	9	↑ 4-fold	Normal	↓ 50%		
	Cengiz et al. [46]	27	↑ 2-fold	Normal	↓ 25%		
	Querfeld et al. [30]	16	↑ 1.5-fold	↑ 40%	↓ 15%	↑ 50%	↑ 2-fold
	Asayama et al. [31]	27	↑ 3-fold	↑ 40%	↓ 15%		
	Kosan et al. [32]	20	↑ 2-fold	↑ 45%	Normal		
PD	Querfeld et al. [38]	68	↑ > 2-fold	↑ 10–20%			
	Muller et al. [39]	24	↑ 2.5-fold	↑ 45%			
	Berger et al. [40]	17	<sup>a</sup> ↑ in 70%	<sup>a</sup> ↑ in 24%			
	Broyer et al. [41]	15	↑ up to 4-fold	↑ 60%			
	Scolnik et al. [43]	53	<sup>a</sup> ↑ in 82–100%	<sup>a</sup> ↑ in 75–100%	<sup>a</sup> ↓ in 26%		
	Bakkaloglu et al. [45]	18	↑ 2.5-fold	↑ 15%	↓ 25%		
	Ohta et al. [47]	13	↑ 2-fold	↑ 20%			

Rounded to nearest 0.5-fold change or 5% change (approximated when tabular data was not available).

LDL-C and VLDL-C only given if study measured directly

CRI chronic renal insufficiency, HD hemodialysis, PD peritoneal dialysis, N number of patients in study, TG triglycerides, TC total cholesterol, HDL-C high-density-lipoprotein cholesterol, LDL-C low-density-lipoprotein cholesterol, VLDL-C very-low-density-lipoprotein cholesterol

<sup>a</sup> Percentage of subjects in the study with abnormal values, not the lipid values themselves

Dietary lipid is absorbed by enterocytes, which then esterify them to form TG and CE. These become the inner hydrophobic core of nascent chylomicrons, which are assembled through the coordinated activity of microsomal triglyceride transfer protein and apoB-48 [85–87]. The unilamellar surface of chylomicrons, as with all lipoproteins, contains amphipathic PL, a limited amount of free cholesterol, and apo. Each chylomicron contains a single non-exchangeable molecule of apoB-48, which can be considered its defining apo, though these particles also carry apoA-I, apoA-II, and apoA-IV [21]. Unlike the majority of absorbed nutrients, which pass from the gut into the portal venous system for first-pass liver metabolism, the TG-loaded nascent chylomicrons are secreted into the intestinal lymph (chyle), flowing first to the cardiopulmonary circuit via the thoracic duct and great veins and only later to the systemic circuit, including the liver [88]. Of note, short- and medium-chain fatty acids are excluded from the chylomicron pathway, following the portal route instead [89]. In the lymph system and bloodstream, chylomicrons mature by

acquiring apoC-II, C-III [90–93], and apoE [94–97] from HDL already present in the circulation [98].

Chylomicron catabolism begins at the endothelial surface of extrahepatic (peripheral) tissue beds by the action of lipoprotein lipase (LPL). Fatty acids liberated from the particle by LPL are absorbed by the target tissues, beginning with the heart and lungs then muscle and adipose in the systemic circulation [88]. The efficiency of LPL depends on the particle's relative abundance of apoC-II and apoC-III, which activate and inhibit LPL, respectively [99–106]. In fact, as core TG is removed by the action of LPL, the particle diminishes in size, and surface apoA and apoC proteins are progressively shed. The so-called chylomicron remnant particle is finally released by LPL with its core relatively enriched in CE compared with TG. Additional cholesterol enrichment is accomplished by the action of cholesteryl ester transfer protein (CETP), which exchanges TG and CE between TRL (of either intestinal or hepatic origin) and more cholesterol-rich HDL or mature LDL [107]. Whereas some remnants appear to be taken up completely

**Table 3** Characteristic effects of chronic renal insufficiency (CRI) on apoproteins (apo), enzymes, and regulatory molecules

Protein	Selected studies in adults with CKD	Studies in children with CKD	Function/comments
ApoB	↑ CRI, HD, PD [51, 53–56, 68] ↔ CRI, HD [48, 50, 51, 54, 57, 64, 73] ↓ HD [61]	↑ CRI, HD, PD [30–32, 45] ↔ HD [42] ↓ HD [36]	Fixed 1:1 ratio of molecules per lipoprotein Level reflects number of lipoprotein particles
ApoE	↑ CRI, HD, PD [52–55, 61, 64, 68] ↔ CRI, HD [52, 53, 56, 57]	↓ PD [47]	A ligand for the LDL-R, LRP, and VLDL-R May reflect prolonged TRL circulation
ApoA-I	↓ CRI, HD, PD [50–56, 64, 73, 74] ↔ CRI, PD [48, 55, 57, 68, 73]	↔ CRI, PD, HD [30–32, 42, 47]	Consistent with low HDL, activates LCAT Transcription induced by PPARα
ApoC-II	↑ HD [61]	↓ HD [30, 36]	Freely filtered by the glomerulus
ApoC-III	↑ CRI, HD [52, 53] ↔ CRI, HD [48, 52, 64]	↑ HD, PD [36, 47]	Activates LPL
Lp(a)	↑↑ CRI, HD, PD [48, 49, 52–57, 64]	↑↑ HD, PD [36, 47]	Inhibits LPL, slows TRL catabolism Transcription inhibited by PPARα
Lp(a)	↑ CRI, HD, PD [50, 51, 60, 68, 73] ↔ CRI [73]	↑ CRI, HD, PD [30, 45, 46] ↔ HD [42]	Largely unknown Role in fibrinolysis, prothrombotic ? Growth hormone effect -mixed data [69, 70]
Lipase activity	↓ CRI, HD, PD [26, 55, 58, 59]	↓ CRI, HD, PD [44, 47]	Associated with increased ApoC-III Released from endothelium by IV heparin LPL transcription is induced by PPARα
LCAT	↓ HD [64, 65]		Esterifies cholesterol to CE Enables CE transfer to particle core Necessary to form HDL
CETP	↓ HD [64, 66]	↑ PD [31]	Exchanges TG for CE between lipoproteins; activity generally lowers HDL levels
PON	↓ CRI, HD, PD [63, 67, 71–75] ↔ CRI [73]	↓ PD [62]	HDL-associated esterase, antioxidant activity PON/HDL or PON/apoA-I normal in some reports
	↑ PD [68]		

*Lp(a)* lipoprotein (a), *CKD* chronic kidney disease, *HD* hemodialysis, *PD* peritoneal dialysis, *LDL-R* low-density-lipoprotein receptor, *LRP* LDL-R-related protein, *VLDL-R* very-low-density-lipoprotein receptor, *TRL* triglyceride-rich lipoproteins, *HDL* high-density lipoproteins, *LCAT* lecithin-cholesterol acyltransferase, *PPAR* peroxisome-proliferator-activated receptors, *LPL* lipoprotein lipase, *IV* intravenous, *CETP* cholesteryl ester transfer protein, *TG* triglyceride, *CE* cholesteryl esters, *PON* paraoxonase

by peripheral tissues [88], the major catabolism continues with their circulation to the hepatic sinusoids, where their reduced size allows them to pass into the space of Disse. In this extracellular space, remnants encounter a complex network of heparan sulfate proteoglycans (HSPG) that capture them, facilitating their further depletion of lipid by HSPG-bound hepatic lipase (HL) [108]. With apoE available via rapid exchange from HDL [94–97] and high local concentrations of apoE, remnants accumulate this apo, which serves as a ligand for both the LDL receptor (LDL-R) and LDL-R-related protein (LRP) [108]. Finally, the interactions amongst apoE, LPL, HL, and HSPG lead to binding and endocytosis by one or the other of those receptors [108]. This marks the end of the postprandial phase of lipoprotein metabolism.

Studies of postprandial lipoprotein metabolism in the setting of CKD are very limited. Whereas there is no widespread indication from clinical practice of a significant alteration in intestinal fat absorption [109], this may in fact occur [110, 111]. Regardless, in studies of patients with CRI, there is a greater rise and an abnormally prolonged

increase in circulating triglycerides postprandially [112, 113]. Impaired clearance of chylomicron remnants accounts for some of this finding [114, 115]. However, as chylomicrons out-compete hepatic TRL, vying for LPL binding and lipolysis, the postprandial rise in circulating TG is actually borne to a major extent by TRL of hepatic origin [116]. Because of this, the mechanisms of increased postprandial TG involve both chylomicron metabolism and the metabolism of the hepatically derived TRL [117]. These mechanisms are discussed together below.

#### Hepatic lipoproteins and effects of CRI

Hepatically derived lipoproteins occupy the central role in the redistribution of internal stores of lipid and of newly synthesized lipid, particularly in the fasting state. The liver produces all apoB-100, apoE, most apoC-II, and apoC-III, and a significant proportion of apoA-I and apoA-II [21]. Moreover, hepatic tissues express receptors for all of the lipoprotein classes, reflecting its central role in metabolism. Lipoproteins of hepatic origin, as measured in fasting blood

samples, are routinely used to assess risk of atherosclerotic disease [29]. In the common classification of lipoproteins, the liver synthesizes two major types: HDL and VLDL. These types are quite divergent in structure, function, and impact on health.

*ApoB-100 lipoprotein family: lipid transport from the liver to peripheral tissues*

VLDL are triglyceride-rich lipoproteins that are smaller but otherwise similar in structure to chylomicrons. As with chylomicrons, microsomal triglyceride transfer protein is required for VLDL production, and its absence results in abetalipoproteinemia [118]. VLDL differ from chylomicrons in that their defining apolipoprotein is apoB-100 rather than apoB-48. The apoB gene (*APOB*) is the same, but the intestinal transcript (48% of the length of the full hepatic transcript) lacks the LDL-R binding region, foretelling the divergence in the ultimate catabolic fates between chylomicron and VLDL remnants. VLDL, the parent apoB-100 lipoprotein, and its remnants are predominant not only in the fasting state, but even following meals, they are considerably more numerous than chylomicrons [116]. A variety of rare mutations in *APOB* causes familial hypobetalipoproteinemia, clinically similar to abetalipoproteinemia [119].

Focused research has shown that both co- and posttranscriptional and posttranslational degradation of apoB-100 are the major regulatory mechanisms determining the rate of VLDL production [85]. ApoB-100 degradation and, therefore, net secretion of VLDL, is determined principally by the availability of TG, which drives production [120]. In general, the supply of hepatic TG is a function of (1) the delivery of fatty acids resulting from lipolysis of adipose stores, (2) the rate of hepatic fatty acid synthesis, and (3) how much triglyceride is delivered to the liver by remnants of VLDL and chylomicrons [27]. The importance of the last source depends on the efficiency of TG uptake from VLDL and chylomicrons in adipose and muscle, as any leftover lipid remains in the remnant particle [98, 120]. As discussed below, each of these three factors is affected by CRI.

VLDL and its remnants are initially catabolized like chylomicron remnants. VLDL are engaged by LPL in adipose and muscle tissue beds and then by HL in the space of Disse within the hepatic sinusoids [23, 116]. Some remnants of VLDL are removed from the circulation by hepatic endocytosis mediated by several potential binding interactions, including either apoE or apoB-100 in the particle and the LDL-R, via nonspecific proteoglycan binding and, to a small extent, the VLDL receptor [108, 121–123]. Unlike chylomicrons, the LRP does not appear to participate significantly in the hepatic clearance of apoB-100 containing lipoproteins, at least in mice [124]. Whether this difference in hepatic receptor clearance generally holds true has not been clearly

distinguished [125, 126], although it has been shown that LRP can mediate uptake of aggregated LDL in human endothelial cells [127] and lipoprotein (a) [Lp(a)] in human fibroblast cells [128].

*LDL form in the circulation*

As introduced previously, VLDL catabolism diverges from that of chylomicrons in that about half of VLDL remnants, particularly the smaller ones, remain in the circulation for prolonged periods and are destined to become LDL [21, 123]. This occurs as the remnants are progressively depleted of TG and enriched in CE, increasing in density to intermediate-density (IDL) and finally mature LDL. In the process, the particle sheds essentially all apo except its single apoB-100 moiety [21]. This modeling is accomplished not only by the major lipases but also through the action of CETP, previously described [23]. LDL carries 60–70% of circulating cholesterol and is perhaps the most epidemiologically relevant lipoprotein related to atherogenesis [29]. LDL are cleared from the circulation by the liver via the LDL-R, a well-described process that is defective in familial hypercholesterolemia due to mutation of the LDL-R [129] and in familial ligand-defective apoB-100 (also leading to hypercholesterolemia) due to mutation precisely within the LDL-R binding region of *APOB* [119].

*ApoB-100 lipoproteins and CRI*

There is considerable evidence that the concentration of TRL, including IDL and VLDL, is increased among individuals with CRI [26, 130, 131]. This relative hypertriglyceridemia also manifests within individual lipoprotein classes: the ratio of TG to CE is higher in LDL and HDL and lower in VLDL and IDL [48, 59, 61, 132]. These changes are consistent with a scenario common to all hypertriglyceridemic states: a pathological increase in TRL is followed by the CETP-mediated transfer of the TG from this expanded pool of substrate into HDL and LDL in exchange for CE [133]. These changes in composition lead to important effects in both LDL and HDL (discussed below) and may therefore be considered the “root” of the dyslipidemia of CRI. Much interest, therefore, has focused on the mechanisms leading to the observed increase in TRL.

Patients with CRI usually demonstrate levels of total cholesterol and LDL-C that are similar or slightly less than that of the general population, except for those undergoing chronic peritoneal dialysis in whom these levels are usually elevated [26, 130, 131]. It is likely that many reports have actually overestimated LDL-C and underestimated VLDL-C, as the Friedewald equation [134] used for that purpose is somewhat inaccurate in the setting of CRI (even when the total TG level is less than 400 mg/dl) [135]. Sequential

ultracentrifugation remains the gold standard for precise measurement of the density fractions. Regardless, despite normal or low concentrations of LDL-C, the LDL particles themselves are small and more dense than normal [59, 136, 137] because of increased VLDL precursors and TG/CE exchange followed by TG lipolysis [123]. As small dense LDL are prone to oxidation, and as oxidative stress is increased in CRI, levels of oxidized LDL are increased [138–140]. Small dense LDL and oxidized LDL are both atherogenic [141, 142].

Measurement of total apoB or the apoB content of individual lipoprotein classes provides information about the number of lipoprotein particles, because each of the apoB lipoproteins contains only one apoB molecule. Most people with CRI have increased or normal levels of apoB [48, 50, 51, 53–57, 143]. When considered along with the elevated total TG and normal or low total cholesterol, one again concludes that CRI leads to increased concentrations of apoB-containing TRL.

#### *HDL: reverse cholesterol transport*

The apolipoprotein composition of HDL is principally apoA-I (70%) and apoA-II [107]. Besides a host of other apos (including apoC-II, apoC-III, and apoE), HDL carry a work crew of proteins that are active in its own remodeling and in the modification of other lipoproteins, including lecithin-cholesterol acyltransferase (LCAT), CETP, and paraoxonase (PON) [107, 144, 145]. Whereas levels of apoA-I correlate with HDL levels, apoA-I, unlike apoB, transfers readily between lipoprotein particles, and the number of molecules per HDL particle is not fixed [21, 107]. There is strong epidemiologic evidence that HDL exerts a protective effect against atherosclerosis independent of the effect of LDL [29].

The origin of HDL, the subject of an excellent recent review [146], also differs from that of apoB lipoproteins in that the particles are not formed intracellularly. Instead, lipid-poor apoA-I is secreted by the intestines (where it integrates into chylomicrons) and the liver [107, 146]. The small, lipid-poor complexes of freshly secreted hepatic apoA-I and PL become HDL as they swell by adding more PL for the surface and neutral lipids for the core [107, 146]. Phospholipid is moved from TRL during their lipolysis to HDL by phospholipid transfer protein (PLTP) [107]. The HDL core, in particular, grows via the sequential and complementary actions of the ABC transporters A1 (ABCA1) and G1 (ABCG1), which transfer free cholesterol from cell membranes. Those transfers are followed by the esterification of free cholesterol by LCAT and incorporation of the resulting CE into the neutral lipid core [107, 146]. Defective ABCA1 leads to Tangier disease and defective LCAT to “fish-eye” disease or familial LCAT deficiency (associated with severe renal disease secondary to glomer-

ular lipid deposition) [25, 147, 148]. ABCA1 and ABCG1, regulated via LXR nuclear receptors in response to oxysterol ligands, are of key importance in protection from atherosclerosis through their ability to promote cholesterol efflux from lipid-laden macrophages (foam cells) [149–151]. As previously mentioned, HDL is significantly modified in the circulation by its acquisition of TG from TRL in exchange for CE, as mediated by CETP [107, 145, 146]. HDL also serves as a reservoir for apoC [91–93] and apoE [94–97] proteins that are readily transferred to and from chylomicrons during the ebb and flow of postprandial lipemia.

HDL catabolism may be understood by following the paths of its individual components. Cholesteryl esters are selectively removed through interaction with the scavenger receptor class B type I (SR-B1), also called HDL receptor, although it also binds VLDL and LDL [146]. Not surprisingly, SR-B1 is expressed in sites of cholesterol utilization, principally the liver and steroidogenic organs; in particular, it is the liver where HDL completes its delivery function in the “reverse” cholesterol transport pathway [146]. The fate of apoA-I lies elsewhere. When lipases act on HDL to remove core TG and surface PL, the particle shrinks and free apoA-I is shed; this process is enhanced in the setting of hypertriglyceridemia [133]. Free apoA-I is filtered at the glomerulus and, subsequently, via interactions with the megalin/cubulin complex, it is taken up by the proximal tubular epithelium and completely degraded within endocytosed lysosomes [152–154].

#### *HDL, apoA-I and CRI*

In patients with CRI, HDL and apoA-I levels are nearly universally found to be significantly decreased [26, 48, 50–57, 61]. As discussed previously, elevation of TRL is likely the basic dyslipidemic force in CRI. This induces transfer of excess TG into HDL particles, increasing their susceptibility to serve as substrate for hepatic lipase and shed free apoA-I, which is lost to glomerular filtration and renal catabolism. Because free apoA-I levels are inversely related to the GFR, the route of their clearance [155, 156], the fact that free apoA-I is markedly increased in CRI despite low total apoA-I is consistent with increased loss from HDL during lipolysis, reduced renal clearance, or both. More definitive metabolic turnover studies in individuals with CRI have demonstrated increased rates of apoA-I catabolism without change in production rate [157, 158]. Nonetheless, other mechanisms may also contribute to low HDL levels, such as decreased LCAT activity [64, 65].

#### *Lipoproteins and genetics*

Genetic variability is a source of significant variability in lipoprotein metabolism. While a full discussion is outside

the scope of this review, some relevant observations should be discussed. The three *APOE* alleles have a well-established effect on the lipoprotein profile [159]. The effect of these common *APOE* allelic variations on renal disease itself is not clear, but certain rare mutations of the gene encoding apoE lead to lipoprotein glomerulopathy [160]. Single nucleotide polymorphisms (SNPs) associated with *LIPC* (hepatic lipase) are clearly linked to differing lipolytic activities of that enzyme [161]. The gene cluster *APOA5/APOC3/APOA4/APOA1* is notable for multiple SNPs that may influence the lipid profile. Due to extensive linkage disequilibrium, these SNPs cluster into two conserved haplotype blocks, one containing *APOA5* and the other containing the rest of the genes [162]. In particular, SNPs involving *APOC3* and *APOA5* appear to affect the TG level [162, 163]. SNPs associated with *LPL* [164] and *ABCA1* [165] have also been noted to influence the lipoprotein profile.

### Mechanisms leading to increased TRL in CRI

As the root abnormality of dyslipidemia in CRI, factors leading to increased TRL have been the subject of several investigations. The major deficit appears to be impaired lipolysis of TRL due to decreased activity of the major lipases, LPL and HL [58, 166–168]. Indeed, kinetic studies of lipoprotein turnover among adults with CRI/ESRD support this idea [169–174], with some finding additional evidence of a slight increase in VLDL synthesis [171, 175].

An important association is the consistent finding of increased concentrations of apoC-III among individuals with CRI (Table 2) [48, 49, 52, 53, 57]. ApoC-III has been implicated as a mediator of increased plasma TG in several studies; for instance, apoC-III modulates in vitro binding of lipoprotein to cell receptors [176, 177] and proteoglycans [178] and, when present in excess, decreases TG lipolysis [99, 100, 179]. Thus, transgenic mice expressing high levels of apoC-III develop hypertriglyceridemia [106, 176], whereas apoC-III knockout mice are resistant to postprandial hypertriglyceridemia [102]. Two sisters deficient in apoC-III and apoA-I provided evidence that apoC-III inhibits LPL in humans, with low TG levels and accelerated VLDL catabolism [180]. Finally, elevated apoC-III is usually associated with elevated TG levels in humans [181].

Although data is limited, CETP is decreased at least in some adult patients with ESRD [64, 66] and increased in one study of children [31] (Table 3). Decreased CETP would be expected to increase HDL, which is clearly not the case in most individuals with CRI. Moreover, in a group of patients with CRI studied by Kimura et al. [66], higher CETP levels were associated with less ASCVD, an effect that persisted after adjustment for HDL levels and when analysis was limited only to patients with higher HDL. Although CETP

activity was not assessed in this study, it remains a somewhat paradoxical result, as lower CETP activity is generally considered protective against ASCVD so long as HDL levels are actually increased [182]. It is intriguing, therefore, that Hayek et al. [183] also found CETP to be antiatherogenic in transgenic mice overexpressing human apoC-III, and suggests further study of this phenomenon is required.

### Insulin resistance accompanies CRI

A complete discussion of dyslipidemia related to CRI must include insulin resistance (IR), a long-recognized [184–187] and extremely consistent aspect of renal insufficiency, most likely secondary to a post(insulin)receptor defect [188, 189]. To their credit, scientists first describing uremic dyslipidemia correctly theorized much of the pathophysiology described over the following 40 years, including the presumed contribution of IR [166, 190, 191]. In the general population, IR usually occurs as one part of a cluster of findings, including obesity, dyslipidemia, hypertension, and hypercoagulability [192]. This clustering can become evident during childhood [193]. Interestingly, the pattern of dyslipidemia associated with IR is remarkably similar to that found in patients with CRI [120, 194]. In addition, many individuals with uremia demonstrate a decreased insulin secretory response [195–197]. It is well-recognized that insulin regulates LPL in a tissue-specific manner, increasing its activity in adipose and decreasing it in muscle [198–200]. Thus, abnormalities of both insulin secretion and sensitivity may have significant roles in the development of disordered lipid metabolism in uremia.

Together, IR and impaired lipolysis of remnant lipoproteins offer a nearly complete schema to explain the observed dyslipidemia of CRI. Remnants and other TRL are elevated primarily because of poor lipolysis. When present, the slight increase in VLDL production probably results from increased hepatic TG supply. Increased levels of TRL provide increased TG to the liver, as they are finally internalized by various cell-surface receptors. In addition, hepatic TG stores are augmented by IR [120], which leads to increased hepatic fatty acid synthesis and also increases FFA flux from body fat. This last phenomenon may result from several factors. As the scaffold for TG, glucose-derived glycerol is required to “trap” FFA within the adipocyte, and reduced insulin-mediated glucose uptake may limit the supply of glycerol [120]. In regard to efflux of FFA from adipose, two major intracellular lipases are relevant: the recently discovered adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL) [201]. ATGL hydrolyzes the first fatty acid from stored TG [202], and without ATGL, fat stores cannot be utilized for energy [203]. Although the regulation of ATGL has not yet been elucidated, the inhibition of HSL activity by insulin is a well-known phenomenon that plays a

key role in energy balance. Thus, IR is associated with impaired down-regulation of diacylglycerol hydrolysis by HSL, eventually leading to excessive FFA liberation from adipose [204]. An intriguing link between IR and the dyslipidemia of CRI is knowledge of an insulin response element that may directly or indirectly via *FOXO1* modulate apoC-III gene expression [205–208]; however, the actual importance of this finding remains to be seen.

**Proteinuria: a hidden variable in plain sight?**

The hyperlipidemia of nephrotic syndrome is clinically obvious [209]. However, there is plentiful evidence that nonnephrotic (microscopic) proteinuria also affects lipoprotein physiology. Diabetic and hypertensive patients with either microalbuminuria or macroalbuminuria have higher rates of dyslipidemia than their counterparts with normoalbuminuria [210]. Noting that the prevalence of microalbuminuria is very low among healthy individuals [211], large population-based studies demonstrate an association between microalbuminuria and dyslipidemia and with other components of the metabolic syndrome [212, 213].

Because CRI is commonly associated with nonnephrotic proteinuria, it complicates the study of dyslipidemia. To put this in perspective, epidemiological data show that diabetes, hypertension, focal and segmental glomerulosclerosis (FSGS), and autosomal dominant polycystic kidney disease (ADPKD) accounted for 70% of all ESRD cases in the United States during 2000–2004, while nonspecific glomerulonephritis accounted for about another 14%. Of these conditions, nonnephrotic proteinuria is particularly evident in FSGS [214] and diabetic nephropathy [215] and is common in hypertensive CKD [216] and in ADPKD [217]. Thus, it is probably the case that few patients (if any) with CRI *do not* have nonnephrotic proteinuria. That being the case, it is apt to consider proteinuria a mediator of uremic dyslipidemia and not clinically relevant to attempt to statistically “control” for its effect. Interestingly, the adverse effects of low-grade proteinuria on lipids and ASCVD among individuals *without* overt renal disease are becoming better recognized [218, 219] indicating that the magnitude and mechanisms of the dyslipidemic effect of proteinuria should continue to be a focus of study [220].

## Treatment

It is notable that evidence associating increased total or LDL cholesterol to ASCVD in patients with CRI has not only been lacking but, in fact, low cholesterol was associated with higher mortality in the setting of ESRD (mainly hemodialysis, reviewed recently by Kopple [221]). The cholesterol-reducing effects of high rates of malnutrition and inflammation in this

population obscures the epidemiological but perhaps not the pathophysiological relationship to ASCVD, which Liu et al. uncovered by adjusting for these factors [222]. Even with these epidemiological observations in mind, we continue to lack solid evidence of the benefit of treating dyslipidemia in persons with CKD.

Unfortunately, studies examining the effect of lipid reduction have largely excluded patients with renal disease. Nevertheless, analysis of very large prevention trials using 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors (statins) have allowed limited analysis of subsets with CKD and have generally shown benefit from treatment. Examples of such subset analysis come from the Treatment to New Thresholds (TNT) study [223], the Medical Research Council/British Heart Foundation (MRC/BHF) Heart Protection Study (HPS) study [224], and a combined analysis of the Cholesterol and Recurrent Events (CARE) and West of Scotland Coronary Prevention Study (WOSCOPS) and Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) studies [225]. In contrast, no benefit was noted among diabetic patients with renal insufficiency in the “4D trial” (Deutsche Diabetes Dialyse Studie), possibly because of a high degree of preexisting vascular disease [226]. Likewise, Isbel et al. carried out a randomized controlled trial (RCT) among 200 advanced CKD patients that compared standard care to meticulous (and successful) treatment of multiple cardiovascular risk factors, including statin treatment, but found no differences in outcome measures over a 2-year period [227]. Following pilot investigation [228], and now with enrollment complete, the large, ongoing Study of Heart and Renal Protection (SHARP) will address the issue of treatment of dyslipidemia in patients with CKD directly.

The NKF guidelines on dyslipidemia in patients with CKD, acknowledging there is no proof of benefit of treating high LDL cholesterol from randomized trials among adults or children, has nevertheless recommended treatment for such patients, using statins if necessary: the NKF LDL-C goals in adults is 100 mg/dl or less, and 130 mg/dl or less in children who have entered puberty; statins are not recommended for prepubertal children [1]. Recently, the American Heart Association (AHA) and American Academy of Pediatrics (AAP) endorsed a similar treatment algorithm, citing the NKF report as well as voicing the opinion that conclusive evidence of treatment benefit in children is unlikely to be achieved quickly. The AHA/AAP LDL-C treatment goals for children with ESRD/CKD are 100 mg/dl or less, also calling for statins if required [229]. Both sets of guidelines parallel the ATP III guidelines for adults at high risk of ASCVD [29] and presumably would call for statin use in some children for many years.

The authors of the present review, citing the current lack of conclusive data of the benefit of statin treatment even among

adults with CKD suggest that these recommendations for the treatment of children stray too far from evidence-based medicine founded upon risk–benefit analysis. We believe, therefore, that practitioners should view these algorithms with skepticism, and those who follow them should proceed with caution. Development of precise, noninvasive methods of detection and quantification of early atherosclerosis in multiple arterial beds, such as black-blood magnetic resonance imaging (MRI) [230], presents the opportunity to study this issue directly and allow treatment decisions about prolonged statin use to be based on individual ASCVD assessment of children with CKD. It must be noted that the majority of information about statin use in children with or without CKD is based only on short-term data [231]. Even in adults, use of statins in CKD may be complicated by myopathy and requires knowledge of renal dosing requirements with close attention to interaction with other agents that might affect pharmacokinetics [1].

Fibrates, activators of alpha-type peroxisome proliferator-activated nuclear receptors (PPAR $\alpha$ ), effectively lower TG levels. Their multiple effects would appear to be a perfect fit for the dyslipidemia of CRI, which they have been shown to ameliorate [232–234]. These include increased production of apoA-I, apoA-II, and LPL, with decreased production of apoC-III and induction of hepatic fatty acid oxidation [235]. Fibrates may be used in adult individuals with CRI and very high TG levels (>500 mg/dl). The NKF Kidney Disease Outcomes Quality Initiative (KDOQI™) guidelines on managing dyslipidemia in adults with CKD favor gemfibrozil because it is unique among fibrates in not requiring dose adjustment for decreased GFR [1] as its pharmacokinetics are not altered in that setting [236]. Increased creatinine is a possible side effect of all the fibrates, and patients should also be monitored for alterations in hepatic function and rhabdomyolysis. Homocysteine elevation is a side effect of uncertain significance associated with all the fibrates [237, 238]. This agent has not been investigated in children and cannot be recommended for them.

The n-3 fatty acids (eicosapentaenoic and docosahexaenoic acids, EPA and DHA) found in fish oils reduce VLDL production [239–241] and are used therapeutically in patients with hypertriglyceridemia [242–244]. Therefore, fish oils may improve dyslipidemia in patients with CRI. Fish oil treatment to decrease progression of IgA nephropathy (IgAN) has been tested in a few in randomized controlled trials [245]. One such trial involved 106 patients (55 treated with fish oil) with mild CRI and modest hypertriglyceridemia (TG~200 mg/dl); despite a positive renal effect of treatment, there was no difference from placebo in regard to lipid levels during the 2 years of treatment [246, 247]. Another study compared doses of fish oil in a similar group of patients with IgAN, producing changes at 12 but not 24 months of treatment: a decline in

TG in the low-dose group and a decline in HDL and LDL in the high-dose group [248]. Other studies have generally been short term. Fish oil supplementation in dialysis patients produced significant improvement of the lipid profile in most [249–252], but not all [253], studies. In a study of patients with intermediate CRI, fish oil induced a 21% reduction in total TG [254]. Fish oil was shown to reduce hypertriglyceridemia in one small group of children with ESRD [255]. Besides their effect on lipids, fish oils may have other beneficial effects on vascular health; it should be noted, however, that they may prolong bleeding time, and patients with CRI should be probably be more cautious than the general population regarding certain fish that are more likely to be contaminated with heavy metals [256–258]. Overall, they probably offer benefit to patients with CRI [259]. It is relevant to note that a recent study found that dialysis patients consumed less fish than did healthy individuals and consequently had less tissue EPA and DHA stores [260].

There are many known treatments for dyslipidemia that are outside the scope of this review except for brief mention. General nutritional guidelines on fat consumption, including lowering total, saturated, and trans fats as well as limiting cholesterol should be coordinated with guidelines suitable for patients with CRI to the extent possible. Obesity should be addressed if present, and treatment of malnutrition related to CRI is essential [261]. Indeed, meeting the nutritional requirements to maintain growth is a cornerstone of pediatric medicine, and intensive intervention for growth-impaired children with CRI is often indicated [262]. Whereas at least one study found tube feeding did not worsen dyslipidemia [263], children with poor growth or malnutrition probably require such intervention, even if lipid levels are affected. The benefit of exercise is known to extend even to ESRD [264]. Sevelamer, in clinical use as a phosphorous binder, also effectively binds bile acids [265] and therefore has a cholesterol-lowering effect, as demonstrated by a 27% reduction in a recent study of children with severe CRI [266]. Other intestinal binding agents include the classic bile acid binding resins as well as plant stanols and sterols. The newer agent, ezetimibe, blocks cholesterol absorption. Treatments known to reduce proteinuria may improve the lipid profile. The class of PPAR $\gamma$  agonists, which improve IR and have renoprotective effects among diabetic patients [267], are agents likely to be the focus of study in patients with nondiabetic CRI. Likewise, agents from the new class of CETP inhibitors, torcetrapib and JTT-705 [268, 269], are nearing the end of their development, and although an expected increase in HDL levels should theoretically be beneficial for patients with CRI, caution is required in light of the murine model, with overexpression of both CETP and apoC-III [183], and the study of Kimura et al. [66] that

both found benefit of higher CETP. Indeed, development of torcetrapib was recently discontinued due to significant safety concerns during very late clinical testing [270], so the future of this class of agent is not clear. Carnitine improved dyslipidemia in a study of pediatric CRI [32], as did some elements of standard care, including vitamin D treatment and correction of anemia and acidosis [271–273].

## Summary

Dyslipidemia is an important risk factor for cardiovascular disease and a likely mediator of CKD progression. Dyslipidemia in CRI manifests principally as increased TG and decreased HDL, with nearly normal total cholesterol. Chylomicron and VLDL remnants have prolonged circulation and are found in increased levels among patients with CRI. HDL and its principal apolipoprotein, apoA-I, are reduced, probably as a consequence of elevated TRL. Insulin resistance, increased apoC-III, and impaired lipolysis are significant pathophysiological factors in this process, and nonnephrotic proteinuria is an indelible presence in this scenario. Statins, fish oil, fibrates, and agents reducing the intestinal absorption of cholesterol are examples of existing treatments that have normalizing effects on the lipid profile in CRI. Though data from some large, non-CKD-oriented trials of statins suggested reduced risk of ASCVD, others did not. Therefore, one must be cautious in drawing conclusions from these studies. With results from ongoing trials among individuals with CRI anticipated soon, more definitive recommendations should emerge, at least for adult patients. Development of pharmaceutical agents with novel activity on pathways central to the development of dyslipidemia in CRI offer exciting directions for future investigation.

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