Dyslipidemia of the Metabolic Syndrome

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The three major components of dyslipidemia associated with the metabolic syndrome are increased fasting and postprandial triglyceride-rich lipoproteins (TRLs), decreased high-density lipoprotein (HDL), and increased small, dense low-density lipoprotein (LDL) particles. Insulin resistance and compensatory hyperinsulinemia lead to overproduction of very low-density lipoprotein particles. A relative deficiency of lipoprotein lipase, an insulin-sensitive enzyme, is partly responsible for the decreased clearance of fasting and postprandial TRLs, and the decreased production of HDL particles. The resulting increased concentration of cholesteryl ester-rich fasting and postprandial TRLs is the central lipoprotein abnormality of the metabolic syndrome. The increase of small, dense LDL particles, and decrease of large, buoyant HDL particles are consequential events. All these lipoprotein defects contribute largely to the increased cardiovascular disease risk in individuals with insulin resistance. Peroxisome proliferator-activated receptor (PPAR)α, PPARγ, and PPARδ agonists seem to improve dyslipidemia of the metabolic syndrome by regulating the expression of important genes involved in the deranged lipoprotein metabolism associated with insulin resistance.

Introduction

The metabolic syndrome is characterized by a constellation of abnormalities that represent major risk factors for both type 2 diabetes mellitus and cardiovascular disease (CVD). The resistance to insulin-mediated glucose disposal and compensatory hyperinsulinemia are central to both the metabolic syndrome and diabetes, and seem to be responsible for most, if not all, of the associated abnormalities. Atherogenic dyslipidemia is an important component of the cluster of abnormalities characteristic of the metabolic syndrome, which also consists of abdominal obesity, insulin resistance (with or without glucose tolerance), raised blood pressure, and prothrombotic and proinflammatory states (Table 1) [1]. There are three major components of dyslipidemia that occur in insulin resistance: increased fasting and postprandial triglyceride-rich lipoproteins (TRLs), decreased high-density lipoprotein (HDL), and increased small, dense low-density lipoprotein (LDL) particles. Because the metabolism of all lipoproteins is highly interrelated (Fig. 1), it is likely that a common fundamental metabolic defect explains all of the lipoprotein changes in the dyslipidemia of insulin resistance. It is indeed rare that they are found separately in insulin-resistant individuals.

Population-based studies have universally and consistently found positive associations of measures of insulin resistance with plasma total or very low-density lipoprotein (VLDL) triglyceride, and negative associations with HDL cholesterol concentration. These associations have remained significant when adjusted for main covariates such as obesity, age, smoking and physical activity, and appear to be consistent in both sexes and among various populations, such as white subjects (Framingham Heart Study [2], Paris Prospective Study [3], Quebec Cardiovascular Study [4]), blacks (CARDIA [5]), Hispanics (San Antonio Heart Study [6]), Asians [7], and American Indians (Pima Indians [8], Strong Heart Study [9]).

Pathogenesis

Elevated fasting triglycerides

The hepatic overproduction of VLDL appears to be the primary and crucial defect accompanying insulin resistance and compensatory hyperinsulinemia (Fig. 2). Inability to suppress hepatic glucose production, impaired muscle glucose uptake and oxidation, and inability to suppress release of nonesterified fatty acids (NEFA) from adipose tissue are the most important consequences of insulin resistance in liver, muscle, and adipose tissue, respectively. These events give rise to increased NEFA and glucose flux to the liver, an important regulator of hepatic VLDL production [10].

Another key site in the regulation of VLDL secretion is the rate of apolipoprotein (apo) B-100 degradation. Newly synthesized apo B-100 remains associated with the rough endoplasmic reticulum, and is degraded by the ubiquitin/proteasome system, or is translocated into the lumen and incorporated into lipid poor VLDL precursors. Next, the lumenal apo B-100 either is degraded or advances, acquiring the remaining VLDL lipids in the smooth endoplasmic

Table 1. The metabolic syndrome according to Adult Treatment Panel III

Risk factor	Defining level
Abdominal obesity (waist circumference)	
Men	> 102 cm
Women	> 88 cm
Triglycerides	≥ 150 mg/dL
HDL cholesterol	
Men	< 40 mg/dL
Women	< 50 mg/dL
Blood pressure	≥ 130 / > 85 mm Hg
Fasting glucose	≥ 110 mg/dL

HDL—high-density lipoprotein.
(*Adapted from* Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults [1].)

reticulum/cis-Golgi. Apo B-100 is stabilized and protected from degradation by the heat shock protein 70 (HSP-70). Lipids and microsomal triglyceride protein (MTP), a heterodimeric lipid transfer protein that is required for the assembly of apo B-containing lipoproteins, play a major role in the translocation of apo B-100. If it does not occur, then the apo B-100 is degraded. Insulin seems to be an important factor in the intracellular degradation of freshly translated apo B-100. Therefore, in the insulin-resistant state there is inability to suppress apo B-100 degradation, and a consequent imbalance between secretion and degradation in favor of the former [11].

However, hepatic VLDL-apo B overproduction in the fructose-fed hamster, a novel animal model of insulin resistance, appears to result from both increased intracellular stability of nascent apo B and enhanced expression of MTP [12••]. In fact, insulin also negatively regulates MTP gene expression, resulting in a decrease of MTP transcription, even though sustained changes in MTP mRNA levels would be required to affect MTP protein levels in humans [13,14••]. In addition, neither MTP nor newly synthesized triglycerides seem necessary for the later stages of apo B-100–lipoprotein assembly and secretion in either HepG2 or McA-RH7777 cells [15••]. Therefore, the end result in insulin resistance states is an increased assembly and secretion of VLDL.

Very low-density lipoprotein particles have been shown to increase plasminogen activator inhibitor type 1 (PAI-1) biosynthesis in endothelial cells by inducing transcription of the PAI-1 gene promoter. Similarly, VLDL increase PAI-1 synthesis by stabilizing PAI-1 mRNA transcripts. The induction of PAI-1 by VLDL particles is dependent on the interaction of the lipoprotein with the LDL receptor (LDLR), and correlates with intracellular triglyceride accumulation. VLDL-induced PAI-1 biosynthesis results from a principal signaling pathway involving protein kinase C-mediated mitogen-activated protein kinase activation [16]. The concurrent compensatory hyperinsulinemia of the metabolic syndrome contributes to the increase of PAI-1 levels in this condition, because insulin has also been shown to increase PAI-1 gene transcription through interaction with its receptor [17•]. Insulin is a stimulator of lipoprotein lipase (LPL) activity, by increasing LPL mRNA, and therefore enhancing its rate of synthesis. LPL activity in skeletal muscle of insulin-resistant subjects has been shown to be lower, suggesting a defective insulin regulation of LPL. Therefore, the decreased LPL activity and mass in insulin resistance slow down the normal lipoprotein metabolic cascade, resulting in decreased clearance of VLDL [18,19].

Very low-density lipoproteins are mainly cleared from circulation by the LDLR, also referred to as the apo B/E receptor. The transcription of the LDLR gene is regulated by intracellular cholesterol concentration, hormones, and growth factors. Sterol regulatory element-binding protein-1 is selectively involved in the signal transduction pathway of insulin and insulin-like growth factor-I (IGF-I) leading to LDLR gene activation [20]. Insulin resistance may also impair LDLR activity, thus contributing to the delayed VLDL particle clearance accompanying this condition.

Insulin acutely suppresses the total production rate of VLDL particles by primarily decreasing the production of large, VLDL1 (Sf 60-400), without affecting that of small TRLs, VLDL2 (Sf20-60) [21]. This effect seems to be independent of the availability of NEFA [22]. In type 2 diabetes insulin appears unable to inhibit acutely the release of VLDL1 from the liver, despite efficient suppression of serum NEFA [23]. However, the decrease in circulating VLDL particles following acute insulin action in insulin sensitive individuals appears to be the result not only of a decreased hepatic production [24], but also an increased clearance.

Elevated postprandial lipemia

Less is known about the mechanisms responsible for the association of insulin resistance with increased postprandial lipemia. During the postprandial state, dietary fatty acids are transported from the intestine to peripheral tissues as chylomicron triglycerides. In the capillary beds of peripheral tissues, chylomicron triglycerides are lipolyzed by LPL, allowing the delivery of NEFA to cells and resulting in production of smaller, cholesteryl ester-enriched chylomicron remnants. These particles are rapidly removed from the blood primarily by the liver through two receptors, LDLR and LDLR-related protein (LRP), acting in association with heparan sulfate proteoglycans (HSPGs) and/or hepatic lipase (HL) [25•].

Some investigators have examined the relation between postprandial lipemia and insulin resistance, plasma glucose, and insulin response to a meal in healthy nondiabetic subjects [26]. Postprandial triglyceride levels, as an indirect measure of chylomicron remnant particles, were found to be significantly related to insulin action. A significant relation of triglyceride levels to postheparin

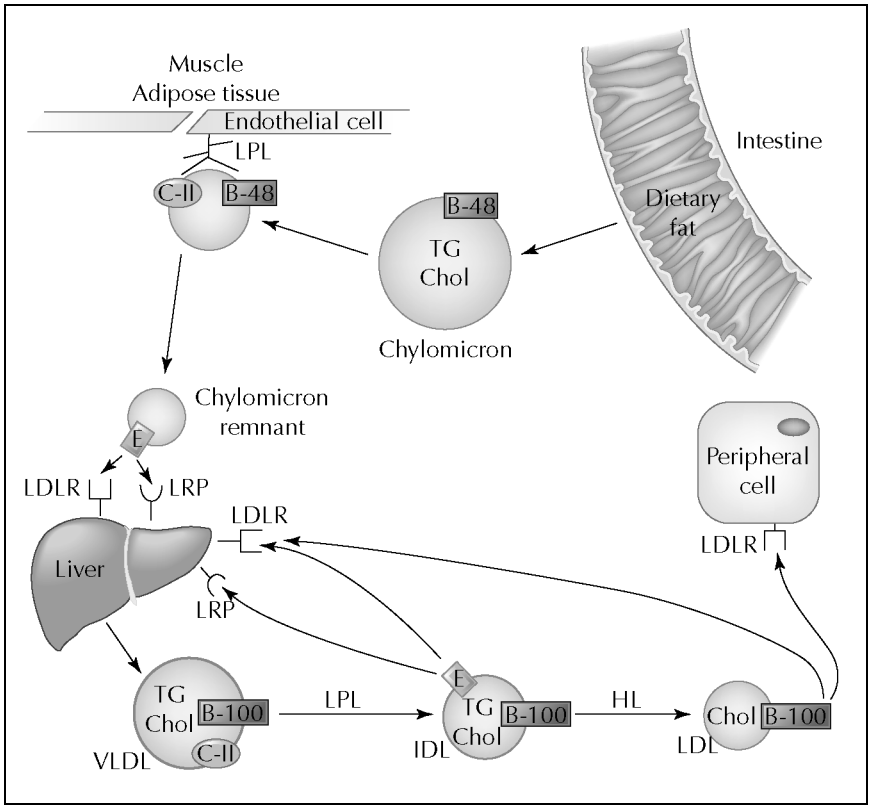

Figure 1. Metabolism of fasting and postprandial TRLs. The role of apolipoprotein (apo) C-II is LPL activation, whereas apo E is fundamental for TRL clearance. Chol—cholesterol; IDL—intermediate-density lipoprotein; LDLR—low-density lipoprotein receptor; LRP—LDLR-related protein; TG—triglyceride; TRL—triglyceride-rich lipoprotein; VLDL—very low-density lipoprotein.

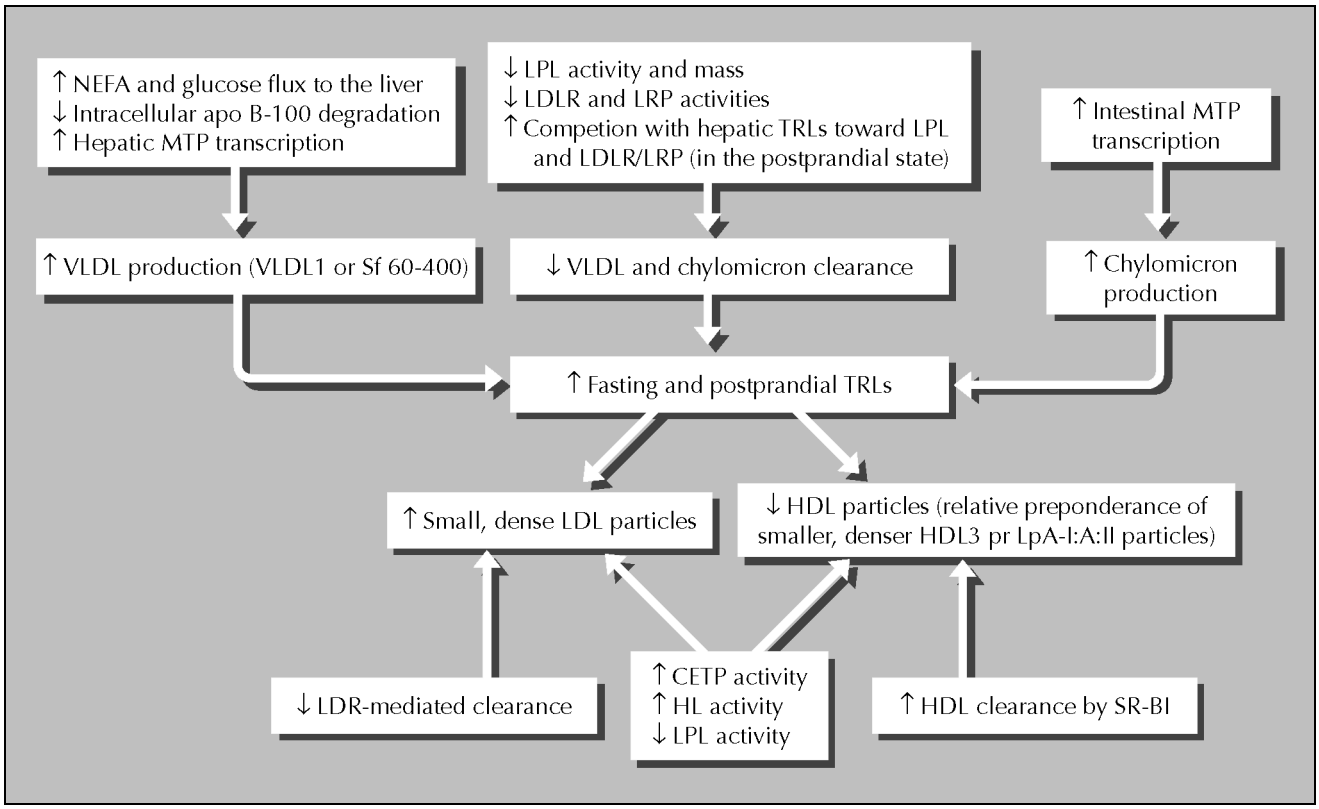

Figure 2. Pathogenesis of dyslipidemia in the metabolic syndrome. Central role of fasting and postprandial TRLs. CETP— cholesteryl ester transfer protein; HDL—high-density lipoprotein; HL—hepatic lipase; LDLR— low-density lipoprotein receptor; LRP—LDLR-related protein; Lp—lipoprotein; NEFA— nonesterified fatty acids; MTP— microsomal triglyceride protein; SR-BI—Scavenger receptor BI; TRL—triglyceride-rich lipoprotein; VLDL—very low-density lipoprotein.

plasma LPL activity was also demonstrated. Because LPL is an insulin-sensitive enzyme, which is suppressed in insulin resistant individuals, its deficiency might contribute to the abnormal levels of remnant particles in insulin resistance.

The relation of fasting insulin concentrations to postprandial lipoproteins has also been evaluated in a population-based study of healthy middle-aged men with apo E3/3 genotype [27]. Aside from postprandial triglycerides, postprandial TRL apo B-48 and apo B-100 concentrations were also determined, as a measure of chylomicron and VLDL remnant particle concentrations. Fasting plasma insulin was associated with the triglyceride response to the test meal, independent of obesity measures, blood glucose, and fasting triglyceride concentrations. Exaggerated and prolonged postprandial lipemia in subjects in the upper quartile of the plasma insulin distribution was largely accounted for by large TRLs (Sf > 60). However, insulin relations to large postprandial TRLs exclusively reflected the association between plasma insulin and the fasting plasma concentrations of these lipoprotein species. On the other hand, plasma insulin and late postprandial plasma concentrations of small TRLs (Sf 20–60) were related independent of insulin influences on fasting concentrations. Indeed, this slow removal of chylomicron remnants is a common observation in insulin-resistant individuals. This study concluded that the degree of insulin sensitivity is a major determinant of postprandial lipemia, and supports the hypothesis that the preferential clearance of chylomicron triglycerides by LPL leads to accumulation of hepatogenous VLDL during the alimentary period [28]. Because postprandial particles may play an important role in the pathogenesis of CVD, the increased postprandial lipemia in insulin resistance may contribute to increased CVD risk [29].

Insulin does not seem to influence LRP mRNA and protein expression acutely, although it stimulates recycling of LRP from an endosomal pool to the plasma membrane, thus increasing the cell surface presentation of LRP [30,31]. The diminished insulin action on both receptors, LDLR and LRP, could theoretically contribute to the increased postprandial lipemia of the metabolic syndrome, even though this process is far from saturable in normal functioning receptors.

It is not clear yet if an overproduction of intestinal TRLs (chylomicrons) has a role in the postprandial lipemia of diabetes in humans. Animal studies (obese Zucker rats, and diabetic New Zealand white rabbits) have shown a higher secretion of lymph chylomicron particles in the insulin-resistant animals compared with controls (lean rats and nondiabetic rabbits) [32,33]. These animal studies suggest that intestinal MTP could play some role in the postprandial dyslipidemia of diabetes in humans.

Increased small, dense low-density lipoprotein particles

Elevated LDL cholesterol is not a characteristic of the dyslipidemia of insulin resistance. In the insulin-resistant state, the composition and distribution of LDL particles are altered, resulting in a preponderance of small, dense LDL. The LDL particle is characterized by a core consisting primarily of cholesteryl ester surrounded by apo B-100. In insulin resistance, the lipid content of the core changes because cholesteryl ester decreases and triglyceride increases relatively, leading to a decreased number of cholesterol molecules per apo B-100 (or LDL) particle. Fasting triglyceride and small, dense LDL concentration are positively correlated, because the formation of small, dense LDL depends largely on the metabolism of VLDL particles. In insulin-resistant states, the increased concentration and delayed clearance of VLDL particles induce an increased exchange between cholesteryl esters in LDL and triglycerides in VLDL, mediated by cholesteryl ester transfer protein (CETP). This exchange produces LDL particles enriched in triglycerides, which are rapidly lipolyzed by HL, leaving smaller, denser LDL particles. The activities of both CETP and HL appear to be increased in the metabolic syndrome. This exchange process also leads to highly atherogenic cholesteryl ester-enriched VLDL particles. Small, dense LDL particles seem to be more prone to modifications, such as oxidation and glycation (increased in the presence of high glucose levels), which could lead to increased production of antibodies against the modified apo B-100 and formation of immunocomplexes. All these modifications might result in a decreased LDLR-mediated clearance of small, dense LDL particles [34], which could contribute to their elevated plasma levels in the insulin-resistance syndrome, and particularly in uncontrolled type 2 diabetes. The modified LDL is mostly taken up by macrophage scavenger receptors, rather than the normal LDLR pathway, thus inducing atherosclerosis. The association between LDL subclass patterns and plasma insulin, as a measure of insulin resistance, has been demonstrated in many population-based studies, even independently of plasma triglycerides and HDL cholesterol [35•,36].

Lipoprotein [Lp](a) is a cholesterol ester-rich, LDL-like lipoprotein containing the characteristic apo(a), which is coded by one of the most polymorphic genes known in humans. Therefore, plasma concentrations of Lp(a) vary enormously between individuals and considerably across populations, and are determined by synthesis and not by degradation. Both transcriptional and post-translational mechanisms have been identified as regulating Lp(a) production. Assembly of Lp(a) seems to occur extracellularly from newly synthesized apo(a) and circulating LDL, even though in-vivo kinetic studies have revealed the possibility of an intracellular assembly. Lp(a) assembly involves multiple interactions between apo(a) and apo B-100 of LDL, as well as a disulfide linkage of two free cysteine residues on both proteins. Lp(a) is thought to facilitate the atherosclerotic process, because it has been found in atherosclerotic lesions.

Data on the role of Lp(a) in diabetes are still conflicting, even though a large, population-based study has failed

to show elevated Lp(a) levels in type 2 diabetes. In this study, part of the San Antonio Heart Study [37], 260 patients with type 2 diabetes and 366 nondiabetic subjects had similar Lp(a) concentrations. A recent study in American Indians has actually demonstrated that diabetic participants had significantly lower Lp(a) levels than nondiabetic participants for both sexes [38]. This study has also shown a lower concentration of Lp(a) in American Indians (almost half of that in whites and one sixth in blacks), and a high correlation of Lp(a) concentration with Indian heritage, confirming the concept that Lp(a) concentration is in large part genetically determined.

Decreased high-density lipoprotein cholesterol

High-density lipoprotein particles are the smallest lipoprotein particles, with cholesterol ester in the central core and a variety of apolipoproteins that govern their metabolism. Although the mechanisms that regulate HDL are not completely understood, the atherogenic potential of low HDL levels is well known. Several mechanisms can contribute to the decreased HDL in insulin resistance, and as in the formation of small, dense LDL particles, TRL metabolism plays an important role. Most studies of lipoproteins have shown an inverse relationship between VLDL triglycerides and HDL cholesterol. Impaired TRL lipolysis leads to reduced HDL concentration, by decreasing the transfer of apolipoproteins and phospholipids from TRL to the HDL compartment. In addition, the delayed clearance of TRLs facilitates the CETP-mediated exchange between cholesterol esters in HDL and triglycerides in VLDL. The increased activity of HL in insulin-resistant states produces smaller HDL particles and facilitates HDL clearance. An increased clearance of HDL particles might also occur in poorly controlled type 2 diabetes, following the increased glycation of the major apolipoprotein of HDL, apo A-I. Finally, insulin could also have a direct effect on the production of apo A-I or hepatic secretion of nascent HDL. Therefore, in insulin resistance there is a substantial decrease of HDL particles, especially the larger HDL_2 (compared with the smaller HDL_3) and HDL containing mostly apo A-I (referred to as LpA-I particles). The LpA-I particles are more effective than LpA-I:A-II particles in the reverse cholesterol process, and therefore are considered more antiatherogenic. The function of the other major apolipoprotein of HDL, apo A-II, is not clear yet. Recent data have suggested a possible role of apo A-II in visceral fat accumulation, even though no direct relationship with insulin resistance has been demonstrated in humans [39••]. However, studies on knockout and transgenic human apo A-II mice have shown a clear role of this apolipoprotein in insulin sensitivity.

Role of Peroxisome Proliferator-activated Receptors Activation

Peroxisome proliferator-activated receptors (PPARs) are transcription factors that act as dietary lipid sensors regulating fatty acid, carbohydrate, and lipid metabolism (Table 2). PPARs regulate gene expression upon heterodimerization with the retinoid X receptor (RXR) and subsequent binding to PPAR-response elements (PPREs), which are located in the promoter region of target genes. The hypolipidemic effects of the fibrates and the antidiabetic effects of the thiazolidinediones (TZDs) in humans are known, and due to activation of PPARα and PPARγ subtypes, respectively.

Peroxisome proliferator-activated receptor-α is predominantly expressed in liver, kidney, heart, and skeletal muscle, where it controls fatty acid catabolism [40••]. Fibrates efficiently lower plasma concentrations of cholesterol and triglycerides, and increase HDL-cholesterol levels. PPARα enhances the transcription of apo A-I and apo A-II, thereby increasing HDL production. Fibrates lower triglyceride levels as a result of enhanced lipolysis, by increasing LPL and reducing apo C-III gene expression, induction of fatty acid uptake and catabolism, and reduced fatty acid synthesis and VLDL production by the liver. Moreover, fibrates increase the removal of LDL particles by modifying LDL composition, which increases the affinity of LDL for the LDLR.

Peroxisome proliferator-activated receptor-γ is highly expressed in brown and white adipose tissue and the intestine, and triggers cellular differentiation, promotes lipid storage, and modulates the action of insulin. TZDs exert mainly hypotriglyceridemic actions, even though activation of PPARγ by TZDs in macrophages also induces ATP-binding cassette A1 (ABCA1) transporter expression to promote reverse cholesterol transport [41]. TZDs exert hypotriglyceridemic effects by increasing lipolysis and clearance of TRLs in adipose tissue. The lipolytic action of PPAR agonists may also contribute to increased HDL levels. Finally, both PPARα and PPARγ are expressed in macrophages and foam cells that are resident in atherosclerotic lesions, where they exert anti-inflammatory activities. New treatment approaches with molecules having both PPARα and PPARγ activities are now being investigated.

Peroxisome proliferator-activated receptor-δ, another member of the PPAR family, is ubiquitously expressed and controls brain lipid metabolism and fatty acid-induced adipogenesis and preadipocyte proliferation. The function of PPARδ subtype is less known, even though recent data suggest a role in reverse cholesterol transport. PPARδ seems to increase the expression of the ABCA1 in macrophages, thus inducing apo A-I specific cholesterol efflux. When a PPARδ ligand was given to insulin-resistant middle-aged obese rhesus monkeys, it produced a significant dose-dependent increase in serum HDL cholesterol, and a decrease in small, dense LDL, fasting triglycerides, and fasting insulin concentrations [42••]. Interestingly, PPARδ also increases HDL cholesterol plasma concentrations in insulin-resistant mice. Studies in humans are underway.

Table 2. Role of PPARs in regulating the expression of genes involved in lipoprotein metabolism

PPARα	PPARγ	PPARδ	Effect
↑Apo A-I ↑Apo A-II ↑SR-BI	↑ABCA1	ABCA1	↑reverse cholesterol transport (↑HDL cholesterol)
↑LPL	↑LPL		↑clearance of fasting and postprandial lipoproteins (↓fasting and postprandial triglycerides)
↓Apo C-III			↓small, dense LDL (↑LDL clearance through LDLR) ↑reverse cholesterol transport (↑HDL cholesterol)

ABC—ATP-binding cassette; Apo—apolipoprotein; HDL—high-density lipoprotein; LDL—low-density lipoprotein; LDLR—LDL receptor; LPL—lipoprotein lipase; SR-BI—scavenger receptor BI.

Conclusions

Although much work has been done to elucidate the complex pathogenesis of the dyslipidemia of the metabolic syndrome, more human studies are still needed. The overproduction of VLDL particles and defective LPL-mediated lipolysis lead to increased fasting and postprandial TRL concentrations. The increased small, dense LDL and decreased HDL cholesterol concentrations appear to be secondary to the delayed metabolism of TRLs. The dyslipidemia associated with insulin resistance plays a major role in the development of atherosclerosis. PPARs (α, γ, and δ) are ligand-activated transcription factors belonging to the nuclear receptor family, and have an important role in the regulation of the expression of genes involved in lipoprotein metabolism. Specifically designed compounds with multiple PPAR-agonist activity could represent a possible solution to the radical treatment of the dyslipidemia of the metabolic syndrome.

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