Dyslipidemia of Obesity

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INTRODUCTION

The metabolic view of adiposity is that of another state of insulin resistance. Obesity , or an excess of body fat, favors the expression of the same main phenotypes as those described in other forms of insulin resistance, namely hypertension, fasting and postprandial hyperglycemia, and a dyslipidemia characterized by elevations in triglycerides, production of small, dense LDL particles and reduced HDL cholesterol. Excess fat is, on the average, harmful but it is most evident when it is carried intraabdominally (1). The dyslipidemia of obesity and presumably the actual cardiovascular risk conferred by obesity should be reversible by a hypocaloric diet and subsequent weight loss, but prospective data for such an effect is lacking. The evolving epidemic of obesity and its attendant impact on cardiovascular disease threatens to overturn the reduction in cardiovascular disease (CVD) prevalence the US has enjoyed over the past 4 decades (2).

THE DYSLIPIDEMIA OF OBESITY

The largest survey of the relationship of obesity on blood lipids is the National Health and Nutrition Examination Survey (NHANES; http://www.cdc.gov/nchs/nhanes.htm). Separate reports on the dyslipidemia of men (3), women (4) and children (5) and among other ethnic groups reflect a common dyslipidemic pattern as one of increased triglycerides, elevated non-HDL cholesterol, and lower HDL cholesterol. In young obese men and women, NHANES data demonstrated that total and LDL cholesterol levels were higher in the obese than the non-obese. It is important to point out that fatness per se, without separation by degree of obesity (overweight vs. obese) or distribution (central vs. peripheral) exerts a dose-response effect on blood lipids, specifically as increased VLDL triglycerides and cholesterol, reduced HDL cholesterol and a relative increase in small, dense LDL particles. On the average, the more fat, the more likely an individual will be dyslipidemic and to express elements of the metabolic syndrome. However, gram-for-gram, fat cells exert the most evident deleterious impact when they are located centrally (6). In comparison to peripheral fat, central fat is insulin resistant and more rapidly recycles fatty acids through lipolysis (7-10). Age and gender also are important modifiers of the impact of obesity on blood lipids. The younger obese has relatively larger changes in blood lipids at any given level of obesity. Overweight women may have somewhat

different patterns than obese men. For young women, excess body weight seems to be associated with higher total, non-HDL and LDL cholesterol levels, higher triglyceride levels, and lower HDL cholesterol levels. Total cholesterol:HDL cholesterol ratios seem to be highest in obese postmenopausal women, due to the much lower HDL cholesterol concentrations.

Overweight boys and girls also demonstrate this dyslipidemic atherogenic pattern reflected by positive correlations of BMI with triglycerides, LDL cholesterol, and triglycerides and a negative association with HDL cholesterol (11). The Bogalusa Study found adverse serum lipoprotein elevations primarily in obese girls but not in boys (12). These ominous changes in lipoproteins are probably reflected in arterial fatty streaks appearing in the early decades of life (13;14).

The dyslipidemic pattern described among American men, women and children has also been found in a variety of ethnic populations including Asians living in Singapore (15), Hispanic Americans (4) and American Indians (16).

WEIGHT LOSS

If obesity is associated with dyslipidemia, then an important practical issue is whether weight loss reverses those changes and results in a more beneficial lipid pattern. There is considerable confusion over the impact of weight loss on specific lipoprotein classes and this may be due to a failure to separate short-term or non-steady state weight loss from lipoprotein levels observed after a sustained weight loss and restoration of steady state. We will attempt to answer four questions relevant to the issue of weight loss and dyslipidemia: 1) What happens to lipoprotein levels during experimentally induced human obesity? 2) What happens to lipids during short-term (<12 weeks, non-steady state weight reduction) 3) What are the differences, if any, in lipoprotein levels after sustained weight loss during steady state? 4) What, if any, is the evidence that weight loss results in reduced cardiovascular risk?

Experimentally induced human obesity

The Vermont Study is the one contemporary study of controlled weight gain in confined volunteers under careful observation (17). Volunteers gained an average of 21% above their basal weight over a period of 6 months. Among 19 subjects, significant changes appeared paralleling those of the metabolic syndrome. These included increases in blood levels of triglycerides, glucose, insulin (both fasting and in response to glucose). Total cholesterol increased but the increment was of marginal significance. While this study demonstrated that many of the phenotypic changes of obesity are reproduced in the laboratory setting, relative to spontaneous obesity, volunteers in the Vermont Study may not have been genetically susceptible to spontaneous weight gain and the study neither was long term nor was steady state achieved. Evidence for this included a rapid, spontaneous return to their pre-experimental weight within a few months of terminating their participation. A surprisingly large number of calories were needed to maintain the experimental weight (2700/m^2) in comparison to that needed for the basal state (1800/m^2).

Short (12 weeks or less) and intermediate term (12-24 weeks) weight loss

The effect of a hypocaloric diet on lipoproteins can be relatively dramatic and rapid. Sharman (18) monitored lipoprotein levels among obese men during a 6 week low carbohydrate (ketogenic) diet and detected a 33% drop in serum triglycerides levels while LDL cholesterol, total cholesterol and oxidized LDL concentrations were unchanged. Of interest was a reported trend for LDL particle size to increase, a change that should reduce cardiovascular risk. Gower et al. (19) observed lipoprotein concentrations in premenopausal women dieting to a BMI <25. The duration of the diets were variable, but measurements at goal showed significant reductions in total and LDL cholesterol, and triglycerides while HDL concentrations increased in comparison to baseline.

Intermediate term diets (6 months in durations) are commonly reported since the FDA sets this duration for “clinical efficacy” of obesity drugs. Muls et al. (20) utilizing orlistat, a partial blocker of intestinal lipase, reported effects on lipid levels in a placebo controlled trial which included a diet of 30% fat (by calories) and a calculated deficit of 600 kcal/d. After 24 weeks, mean total cholesterol fell 11%, LDL fell 17.6% and there was no detectable change in triglycerides. In addition to producing an additional caloric deficit of ~300 kcal/d, orlistat specifically reduces fat absorption, so that its impact on lipoprotein levels may be due to both weight loss and pharmaceutical enhancement of a low fat diet. Dujovne et al., using a similar trial design utilizing sibutramine (MERIDIA) as an anorexogenic drug, reported that plasma triglycerides fell 33-72 mg/dl and HDL cholesterol levels rose 4.9 – 6.7 mg/dl (21).

Long Term Weight loss (1 year or longer)

In general, long term studies of weight loss in the obese show little consistent impact on lipoprotein levels. Ditschuneit et al. (22) followed 100 dieters and lipids were measured at 3, 6, 9, and 51 months. At 51 months, the mean body weight was 9% lower than at baseline. Total cholesterol dropped modestly, but the change was not significant. Regression analysis showed that those with the highest cholesterol levels demonstrated the greatest reduction in baseline cholesterol with weight loss. Krebs et al. (23) followed a group of 57 women who lost 5-10% of their body weight by 52 weeks. HDL, LDL and total cholesterol were unchanged and triglycerides were actually higher. Measurements made 12 weeks into the weight loss phase showed significant reductions in total cholesterol, LDL cholesterol, and triglycerides, while HDL cholesterol was similar to baseline.

Dattilo and Kris-Etherton (24) gathered some 70 studies of weight reduction and reported on the relationship between weight loss and plasma lipids in a meta-analysis. Weight reduction was associated with significant decreases in and positive correlations with total cholesterol, LDL cholesterol, VLDL cholesterol, and triglycerides. For every kilogram decrease in body weight, a 0.009 mmol/L increase in HDL cholesterol occurred for subjects at a stabilized, reduced weight and a 0.007 mmol/L decrease for subjects actively losing weight. HDL cholesterol generally decreases during acute, non-steady state phases of weight loss. In those trials that achieved a stable new weight, HDL cholesterol was increased by 0.14 mM for each kg lost.

Weight loss and cardiovascular risk

Although intuitively one would assume that weight loss has obvious cardiovascular benefits (25), we are unaware of any studies that prospectively demonstrate that weight reduction and the attendant changes in risk factors actually improve survival and reduce morbidity. Such a study is a major gap in the empiric clinical approach to obesity.

PATHOPHYSIOLOGY OF THE DYSLIPIDEMIA OF OBESITY

Central obesity is the main cause of the resistance to insulin-mediated glucose disposal and compensatory hyperinsulinemia, which are in turn responsible for most, if not all, of the associated lipoprotein abnormalities. There are three major components of the dyslipidemia that occur in obesity: increased fasting and postprandial triglyceride-rich lipoproteins (TRLs), decreased HDL, and increased small, dense LDL particles. Since the metabolism of all lipoproteins is highly interrelated (Figures 1 and 2), it is likely that a common fundamental metabolic defect explains all of the lipoprotein changes in the dyslipidemia of insulin resistant states. It is indeed rare that they are found separately in insulin resistant or obese individuals.

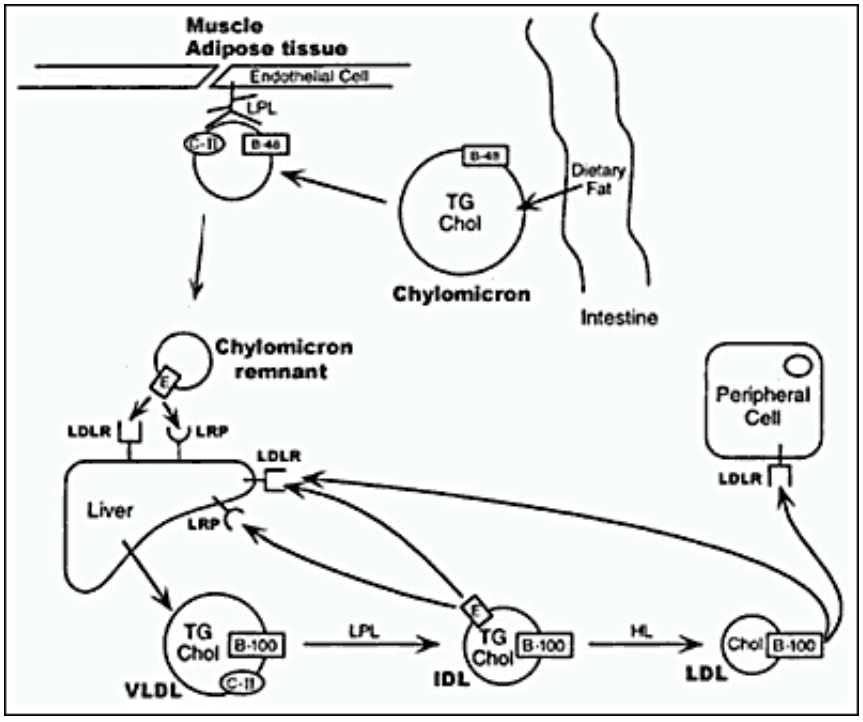

Figure 1.Metabolism of fasting and postprandial TRLs. TG indicates triglycerides; chol, cholesterol; B-48, B-100, C-II and E, specific apolipoproteins; LPL, lipoprotein lipase; HL, hepatic lipase; LDLR, LDL receptor; LRP, LDLR-related protein. Apo C-II's role is LPL activation, whereas apo E is fundamental for TRLs clearance.

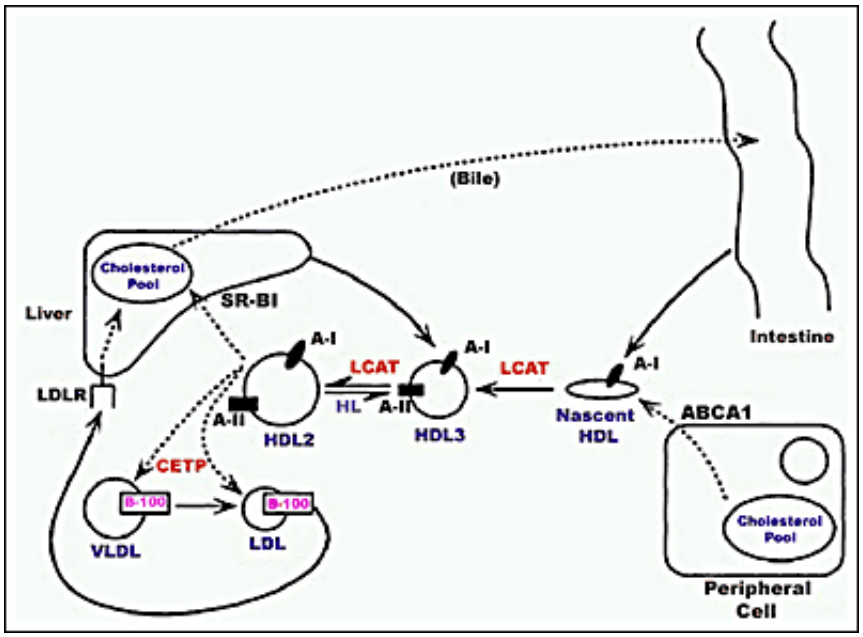

Figure 2.HDL metabolism. B-100, A-I and A-II indicate specific apolipoproteins; ABCA1, ATP-binding cassette A1; CETP, cholesteryl ester transfer protein; HL, hepatic lipase; LDLR, LDL receptor. LCAT (lecithin:cholesterol acyltransferase) is a key enzyme of reverse cholesterol transport, and esterifies all circulating unesterified cholesterol molecules. SR-BI (scavenger receptor class B, type I) is a HDL receptor that mediates selective cholesteryl esters uptake by cells.

Population-based studies have universally and consistently found positive associations of measures of insulin resistance with plasma total or VLDL triglyceride, and negative associations with HDL cholesterol concentration. The associations remained significant when adjusted for main covariates, like, age, smoking and physical activity for example, and appear to be consistent in both genders and among various populations, such as Whites (Framingham Heart Study (26), Paris Prospective Study (27), Quebec Cardiovascular Study (28)), Blacks (CARDIA (29)), Hispanics (San Antonio Heart Study (30)), Asians (31;32) and American Indians (Pima Indians (33), Strong Heart Study (34)). These studies clearly show a strong correlation of dyslipidemia with obesity, especially central deposition of fat.

PATHOGENESIS

Elevated fasting triglycerides

The hepatic overproduction of VLDL appears to be the primary and crucial defect of the insulin resistant state accompanying obesity and compensatory hyperinsulinemia (Figure 3). 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 (35).

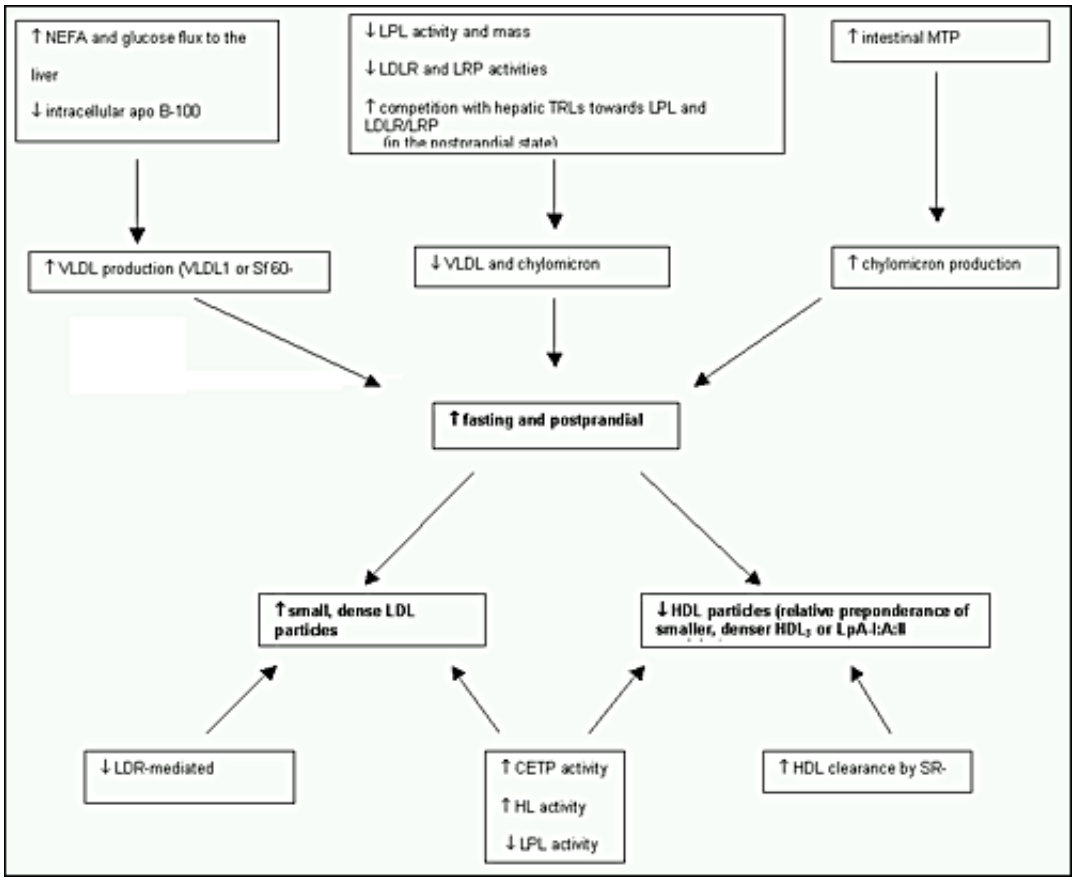

Figure 3.Pathogenesis of dyslipidemia in obesity. Central role of fasting and postprandial TRLs. See text and figures 1 and 2 for abbreviations.

Another key site in the regulation of VLDL secretion is the rate of apo B-100 degradation. Newly synthesized apo B-100 remains associated with the rough endoplasmic reticulum (RER) 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 reticulum (SER)/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 for 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 consequent imbalance between secretion and degradation in favor of the former (36).

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 (37). 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 (38;39). In addition, neither MTP nor newly synthesized triglycerides seems necessary for the later stages of apo B100-lipoprotein assembly and secretion in either HepG2 or McA-RH7777 cells (40).

Therefore, the end result in insulin resistant states is an increased assembly and secretion of VLDL.

In addition to increased synthesis, the insulin resistance of obesity is characterized by decreased clearance of TRLs. 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 (41;42).

VLDL particles are mainly cleared from circulation by the LDL receptor (LDLR), also referred to as 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 (SREBP-1) is selectively involved in the signal transduction pathway of insulin and insulin-like growth factor-I (IGF-I) leading to LDLR gene activation (43). The insulin resistance associated with obesity 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 decreasing mainly the production of large, VLDL1 (Sf 60-400), without affecting that of small TRLs, VLDL2 (Sf20-60) (44). This effect seems to be independent of the availability of NEFA (45). In type 2 diabetes insulin appears unable to inhibit acutely the release of VLDL1 from the liver, despite efficient suppression of serum NEFA (46). 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 (47), but also an increased clearance.

Elevated postprandial lipemia

Less is known about the mechanisms responsible of 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) (48).

Some investigators have examined the relation between postprandial lipemia and insulin resistance, plasma glucose and insulin response to a meal in healthy nondiabetic subjects (49). 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 plasma LPL activity was also demonstrated. Since 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 obesity and other insulin resistant states.

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 (50). Besides 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, independently 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 (51). 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 (52).

Insulin does not seem to influence LRP mRNA and protein expression acutely, while stimulates recycling of LRP from an endosomal pool to the plasma membrane thus increasing the cell surface presentation of LRP (53;54). 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 the controls (lean rats and nondiabetic rabbits) (55;56). These animal studies suggest that intestinal MTP could play some role in the postprandial dyslipidemia of diabetes in humans.

Increased small, dense LDL particles

Elevated LDL cholesterol is not a uniform characteristic of the dyslipidemia of obesity. In the insulin resistant state, the composition and distribution of LDL particles are altered, resulting in an increased concentration 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 since 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, since 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. In addition, the reduced diameter of these particles increases the probability of movement through endothelial fenestrations placing them in the subendothelial space where inflammation, leukocyte ingestion and transformation into plaque occur (57). All these modifications might result in a decreased LDLR-mediated clearance of small, dense LDL particles (58), which could contribute to their elevated plasma levels. 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 (59-61).

Decreased HDL cholesterol

HDL 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 the insulin resistance of obesity, 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 cleareance 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 such as obesity produces smaller HDL particles and facilitates HDL clearance (62). 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 to 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 (63). However, studies on knockout and transgenic human apo A-II mice have shown a clear role of this apolipoprotein in insulin sensitivity.

Leptin, tumor necrosis factor- a (TNF- a), resistin, and adiponectin represent the major hormone-like peptides, or adipocytokines, secreted by the adipocyte. Plasma leptin, tumor necrosis factor- a (TNF- a), and resistin levels are increased, whereas adiponectin levels are decreased in obesity. These adipocytokines have many metabolic effects on both glucose and lipoprotein metabolism, largely accounted for by the insulin resistant state accompanying obesity. However, a positive correlation between plasma adiponectin and HDL cholesterol levels seems to be independent of body fat mass and insulin sensitivity (64).

CONCLUSIONS

Although much work has been done to elucidate the complex pathogenesis of the dyslipidemia of obesity, 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.

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