INTRODUCTION

During the past two decades, there has been an increasing recognition of the significance of a clustering of cardiovascular disease (CVD) risk factors, leading expert panels to formally link them as the metabolic syndrome (1,2). Although there has been controversy regarding the criteria to be used in defining the metabolic syndrome, and the utility of the term itself (3-5), it is clear that the featured components of central obesity, hypertension, dyslipidemia, and abnormal glucose metabolism commonly coexist in individuals at high risk for CVD and type 2 diabetes mellitus (T2DM). It has been widely recognized that insulin resistance (IR) plays a central, unifying role in the pathophysiology of this syndrome. In this chapter, we will focus on the associations between IR and the dyslipidemia characterized by high plasma triglyceride (TG) levels, reduced plasma high-density lipoprotein (HDL) cholesterol concentrations, and abnormalities in low-density lipoprotein (LDL) composition and size in the face of relatively normal plasma LDL cholesterol (LDL-C) levels.

EPIDEMIOLOGY OF DYSLIPIDEMIA AND INSULIN RESISTANCE

It has been clear for many years that individuals with T2DM have increased plasma TG and decreased plasma HDL cholesterol (HDL-C) levels compared with their counterparts without diabetes (6-8). However, it is also well recognized that IR is associated

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with increased plasma TG levels and increased rates of very-low-density lipoprotein (VLDL) production, even in the absence of diabetes (9,10). More recently, the role of IR in determining levels of HDL-C and both the size and composition of LDL has also been demonstrated (11). Thus, IR has been associated with the pattern B profile of LDL in which LDL-C cholesterol levels that are normal or slightly elevated are associated with increased numbers of small, dense LDL particles that are depleted of cholesteryl esters (CE) (12). This lipoprotein pattern was first called hyperapobetalipoproteinemia, a disorder noted to be present in many individuals with premature coronary heart disease (CHD) (13).

As noted above, much of the literature to date has examined dyslipidemia seen in the setting of T2DM (8,10). However, the Insulin Resistance Atherosclerosis Study demonstrated the progressive changes in lipoprotein composition among study subjects with normal glucose tolerance, impaired glucose tolerance, and T2DM. In that study, worsening glucose tolerance was correlated with a progressively more unfavorable lipoprotein profile, both in terms of concentrations and compositional abnormalities (14,15). Furthermore, the relationship between insulin-mediated glucose disposal and dyslipidemia was consistent and did not differ by gender or ethnicity (16). Interestingly, an analysis of those study subjects who did not have diabetes at baseline demonstrated more unfavorable baseline metabolic characteristics among those individuals who eventually developed T2DM ("converters") compared to those who remained diabetes-free at follow-up ("nonconverters") over a mean period of 5.2 years (17). Thus, converters to T2DM had higher baseline levels of fasting insulin and glucose and decreased insulin sensitivity compared to their counterparts who did not develop diabetes. Additionally, converters were noted to have worse lipoprotein concentrations and compositional changes at baseline compared to nonconverters. Chief among these differences were higher baseline TG and lower baseline HDL-C concentrations as well as larger VLDL particle size and higher concentrations of small HDL particles seen among converters. As expected, LDL-C concentrations at baseline were similar between both groups; in fact, they were similar to those of individuals with preexisting diabetes at baseline. These results support previous findings of an increased prevalence of risk factors for CVD in individuals with pre-diabetes (18).

In addition to derangements in fasting plasma lipoprotein levels and composition, postprandial lipoprotein abnormalities have been closely linked to IR. Postprandial dyslipidemia is primarily characterized by an increase in chylomicrons and their remnant particles, although VLDL can also accumulate. There is a strong correlation between fasting and postprandial TG levels, but increased postprandial lipemia has been shown to occur even in the setting of normal fasting TG levels and satisfactory glycemic control among individuals with T2DM (19,20). The importance of abnormalities in postprandial lipid metabolism is underscored by their association with the presence of atherosclerotic CVD (19,21,22).

NORMAL LIPID AND LIPOPROTEIN PHYSIOLOGY

The association of IR with dyslipidemia is multifactorial and complex, but a better understanding of the lipid abnormalities present in individuals with IR can be gained through an understanding of normal lipoprotein physiology. Lipoproteins are macro-molecular complexes composed of varying amounts of lipids and proteins. The hydro-