Chapter 12
Insulin Resistance and Cardiovascular Disease

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Keywords  atherosclerosis, insulin resistance, type 2 diabetes mellitus, cardiovascular disease, metabolic syndrome X, visceral adiposity, compensatory hyperinsulinemia, inflammation, oxidative stress, endothelium, vascular smooth muscle, intracellular signaling proteins, early growth response 1 protein, primary prevention, lifestyle risk reduction

Introduction

Atherosclerosis is a major cause of debilitation and mortality in the United States and worldwide. Its sequelae of heart disease and strokes account for approximately one-third of all deaths in the United States (1). Individuals with metabolic syndrome and/or type 2 diabetes (T2DM) are at markedly increased risk for developing atherosclerosis. Furthermore, cardiovascular disease (CVD) is the leading cause of death in diabetes (2). Unfortunately, a recent analysis of data from the Framingham Heart Study shows that the proportion of CVD that can be attributed to diabetes has increased over the 50 years of the study (3). Insulin resistance is a key underlying feature of both metabolic syndrome and T2DM. Specific mechanisms for the association between insulin resistance and atherosclerosis are incompletely understood, but many investigators have shed light on this complex and important clinical problem.

Background

The link between coronary heart disease and diabetes was noted in 1883 by Vergely (4). The increased incidence of CVD in diabetes has been corroborated in many subsequent studies (5–7). Furthermore, investigators have demonstrated that plasma insulin levels in the highest quintile of the populations studied predict the development of CVD in subjects without diabetes (8–11). On the other hand, “android obesity”, or what is now termed “visceral adiposity”, was noted to be strongly associated with diabetes and atherosclerosis over half a century ago (12) and
confirmed by many investigators since then (13, 14). The term “Syndrome X” was coined by Reaven in a Banting lecture (15) to encompass several metabolic abnormalities noted to occur in the same individual and postulated to be important for the pathogenesis of coronary artery disease. As described by Reaven initially, this syndrome included resistance to insulin-stimulated glucose uptake, glucose intolerance, hyperinsulinemia, increased very low density lipoprotein (LDL) triglyceride, decreased high density lipoprotein (HDL) cholesterol, and hypertension. This syndrome has been termed the “insulin resistance syndrome” (16), and most recently, “metabolic syndrome” (17). Additional factors have been added to this cluster including visceral adiposity, endothelial dysfunction, inflammation, small dense LDL cholesterol, pro-coagulant factors, and hyperuricemia.

Insulin resistance plays a central role in the pathophysiology of T2DM and metabolic syndrome (15, 18). Insulin resistance is defined clinically as a situation in which higher than usual concentrations of insulin are needed to maintain normoglycemia (19). There are several hallmarks of insulin resistance, including selective impairment of the phosphatidylinositol (PI) 3-kinase intracellular signaling pathway in response to insulin, compensatory hyperinsulinemia, intact signaling along the extracellular signal-regulated kinase (ERK) 1/2 mitogen-activated protein (MAP) kinase signaling pathway, elevated free fatty acids, and inflammation (20–25).

Compensatory hyperinsulinemia arises to promote glucose uptake in adipose tissue and skeletal muscle, and glucose utilization in all insulin target tissues (20, 21). Results have been mixed in proving whether compensatory hyperinsulinemia in the setting of insulin resistance has any independent detrimental effects or whether it is merely a marker of insulin resistance, with insulin resistance exerting its pro-atherogenic action via other mechanisms. Several retrospective clinical studies support the hypothesis that hyperinsulinemia per se is detrimental, increasing the risk for CVD and other diseases (11, 26), while others do not support the idea that hyperinsulinemia is an independent cardiovascular risk factor (27, 28).

On the other hand, numerous studies demonstrate associations among insulin resistance, CVD, and mortality (29–32). Furthermore, insulin resistance itself, as determined by decreased insulin-mediated glucose disposal, predicts that increased CVD risk (33), insulin sensitivity (determined by the frequently sampled intravenous glucose tolerance test and the Bergman minimal model), and atherosclerosis, measured by carotid artery intimal-medial thickness (IMT), are directly related (34).

Resistance to insulin action at the level of skeletal muscle results in impairment of glucose disposal, whereas insulin resistance at the level of adipose tissue results in loss of inhibition of lipolysis, resulting in high circulating free fatty acids that provide ample substrate for excessive hepatic triglyceride production. At the same time, insulin resistance at the level of the liver results in excessive hepatic glucose output that contributes to compensatory hyperinsulinemia. Lastly, visceral adiposity results in secretion of inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), and relatively low adiponectin levels. Determining the precise mechanisms for insulin-resistance-associated atherosclerosis and CVD has been difficult because of the abnormalities often associated with insulin resistance: abnormal lipid metabolism with elevated triglycerides, low HDL cholesterol and...