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Obesity and Pathogenesis of Atherosclerosis

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In the 1970s, investigators first identified increased cardiovascular disease (CVD) risk in persons with greater abdominal adiposity. Abdominal imaging with computerized tomography subsequently showed that a greater CVD risk was linked to visceral abdominal fat rather than subcutaneous fat in the abdomen. Increased fat deposition in unusual areas may be associated with a greater risk for CVD. Investigators have reported that a greater amount of epicardial fat is associated with an increased risk for CVD. It is thought that the fat around the heart is metabolically active.

Greater insulin resistance is associated with heightened CVD risk. Clinical investigators have often used simple metabolic measures like the homeostasis model to assess insulin resistance (HOMA-IR), which is calculated by multiplying fasting glucose by fasting insulin and dividing by a constant. Insulin resistance assessed by this approach is correlated with the gold standard euglycemic–hyperinsulinemic clamp, and HOMA-IR is a practical approach to assess insulin resistance in the clinical setting.

Many investigators have considered clustering of metabolic syndrome traits as an indicator of insulin resistance, and reports have shown greater risk for CVD events in association with a greater burden of metabolic syndrome traits. HOMA-IR, as well as other surrogates of insulin resistance, helps to identify persons at high risk for the development of first CHD events. Steady state plasma glucose levels and the ratio of triglycerides to HDL-cholesterol have also been proposed as measures of insulin resistance that are associated with greater adiposity and CVD risk.

As fat accumulates, the local architecture of the tissue is altered and macrophages are attracted to the site. Macrophages and other cellular elements are accompanied by increased concentrations of interleukins, TNF-alpha, resistin, leptin, adiponectin, and plasminogen activator inhibitor-1 at the sites of fat deposition and in the plasma. These cytokines are highly related to the degree of insulin resistance, and a growing literature describes their effects on atherogenesis.

Interleukin-6 (IL-6) is directly produced in adipose tissue, it is associated with greater concentrations of C-reactive protein downstream, and the latter is a well-recognized determinant of greater CVD risk. Leptin also appears to be an important determinant of IL-6 and TNF-α levels. Leptin concentrations are increased in persons who are obese, and leptin resistance is common in these individuals. A greater risk for stroke and myocardial infarction has been identified in persons with increased leptin levels. Adiponectin is a cytokine that is produced in adipose tissue, and low concentrations have been associated with altered function of the arterial endothelium and increased risk for coronary artery disease.

The increased formation of reactive oxygen species is believed to be atherogenic. Other potential sources for greater oxidation include plasma triglycerides and free fatty acids. Increased concentrations of reactive oxygen species have been linked to abnormal regulation of nicotinamide adenine dinucleotide phosphate oxidase and altered concentrations of atherogenic cytokines that potentially foster greater atherogenesis.

The renin–angiotensin system is inextricably linked to the growth and maturation of adipocytes in adults. Upregulation of this system is associated with increased fat deposition and greater insulin resistance. In turn, there is greater angiotensin II production and dysregulation of

endothelial and myocardial functions. Some individuals develop hyperaldosteronism, and increased kallikrein concentrations and connective tissue growth factor have also been noted, especially in persons with type 2 diabetes mellitus.