Obesity, Arterial Stiffness, and Cardiovascular Risk

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Long-term follow-up studies have indicated that obesity is an independent predictor of cardiovascular risk in both genders. Increased arterial stiffness, as reflected by an increased pulse wave velocity, is significantly and independently associated with higher risk for cardiovascular morbidity and mortality. In recent years, it has been demonstrated that individuals with obesity are likely to have an increase in aortic stiffness, independent of BP level, ethnicity, and age. The pathophysiologic mechanisms that link abdominal adiposity to stiffening are not fully understood. This report focuses on the role of arterial stiffness in individuals with obesity and on the association between this hemodynamic feature and cardiovascular risk.

Toto-Moukouo et al. (9) were the first to evaluate the mechanical properties of large arteries in obese individuals. Pulse wave velocity (PWV) of the upper limbs was measured in 27 obese and 25 nonobese patients with sustained essential hypertension and was increased significantly in obese patients in comparison with nonobese patients. The result was independent of age, gender, and level of BP. In the overall population, a significant positive correlation ($r = 0.85, P < 0.001$) was observed between the degree of obesity and PWV. A study of partial correlation coefficients indicated that fasting blood level, cholesterolemia, and triglyceridemia did not influence the relationship. After body weight reduction, BP decreased and systemic arterial compliance increased, indicating that body weight reduction is associated with an enhanced arterial elasticity, as a result of BP reduction or not (9).

In recent years, its has been shown in adults (10–12) and children (13) but not constantly (14–16) that individuals with obesity have an increase in aortic stiffness, independent of BP level, ethnicity, and age. However, increased aortic stiffness has been shown to be more related to body fat repartition (assessed by WC [(11,14,17] and visceral adiposity [10,18]) than to increased BMI (10,11). More recently, total trunk fat (19) has been found to be associated adversely with PWV.

Physiopathology that links abdominal adiposity to stiffening is still largely unknown. Visceral adipocytes have an elevated lipolytic activity that results in increased free fatty acids release in the portal vein with an accumulation (liver, pancreas, and muscles) that contributes to insulin resistance. Furthermore, other mechanisms could be involved, such as increases in circulating proinflammatory cytokines or leptin (20,21). Indeed, high levels of leptin have been documented in individuals with obesity and found to be correlated with reduction in arterial distensibility (21). In addition to hypothalamic receptors, receptors for leptin have been observed on the vascular endothelium and on smooth muscle cells (22,23). Accordingly, leptin can exert receptor-mediated influence on vessel tone and growth and, in cell culture, stimulate vascular smooth muscle proliferation and migration (24). In addition, leptin induces oxidative stress in endothelial cells, and this action triggers the transcription of oxidant-sensitive genes that participate in atherogenesis. Finally, leptin increases sympathetic nervous activity, and chronic administration of leptin increases BP in several experimental models. It is possible that the high levels of leptin that are observed in obesity could contribute to its adverse effects on CV health. Last, it also has been proposed that an increase in circulating proinflammatory cytokines may contribute to the development of CV disease in obese individuals (20,25).

Because visceral obesity is linked more to arterial stiffness than to BMI, aortic stiffness and/or local measurements of arterial elasticity have been studied extensively in individuals with type 2 diabetes and individuals with metabolic syndrome (26–31). Reduced elasticity has been observed in both central and peripheral arteries, in contrast with hypertension, in which peripheral arteries but not central arteries have normal values of elasticity indices. In insulin-dependent patients with diabetes, arterial stiffness is predominantly and/or uniquely in-
increased in femoral arteries. Finally, in normotensive individuals, insulin infusion reduces wave reflections in the thoracic aorta (32). Insulin resistance in type 2 diabetes reduces the ability of insulin to decrease central aortic pressure. This action might predispose these patients to premature stiffening of large arteries and to the development of systolic hypertension and pulse pressure–related complications (33).

Several factors have been proposed to explain the increased stiffness that is observed in individuals with visceral obesity. Because in the forearm blood flow velocity is increased and arterial diameter is unchanged, a disrupted mechanism of endothelium-dependent flow dilation may be suggested and, therefore, a nitrite oxide disturbance. Furthermore, sympathetic neural activation may be a good explanation because, after weight loss, the increased stiffness is reversed in parallel with reduction of heart rate (34–36). However, microneurography has not yet been performed in parallel with changes in arterial stiffness. The reduced arterial elasticity may be the consequence of hyperglycemia’s and/or insulin’s acting either directly or through the development of advanced glycation end products. Nonenzymatic glycosylation of the matrix proteins of arterial vessels may enhance the production of cross-links between collagen fibers, which in turn are responsible for increased arterial stiffness and systolic hypertension (37). In rodent and human, the increased number of collagen cross-links may be reversed after administration of specific collagen cross-linking breakers (38,39).

At any level of systolic BP (SBP), aortic PWV is greater in patients with diabetes than in control subjects (30,40). Mortality risk doubles in patients with diabetes (2.34; 95% confidence interval [CI] 1.5 to 3.74) and in those with glucose intolerance (2.12; 95% CI 1.11 to 4.0) compared with control subjects. For all groups combined, age, gender, and SBP predict mortality. The addition of PWV independently predicts all-cause and CV mortality (1.08; 95% CI 1.03 to 1.14, for each 1-m/s increase) but displaced SBP (40). Glucose tolerance status and smoking are other independent contributors, with African-Caribbean patients experiencing reduced mortality risk (0.41; 95% CI 0.25 to 0.69). Therefore, aortic PWV is a powerful independent predictor of mortality in population samples of both diabetes and metabolic syndrome.

Finally, it is noteworthy that in individuals with obesity, increased aortic stiffness also may contribute to the development of cardiac hypertrophy, in addition to hypertension (1–5). Abdominal adiposity, measured with a simple clinical tool such as WC, alone (41) or combined with an hypertriglycerideremia (the “hypertriglyceridemic waist”) (42), remains a good CV predictor. Further studies should elucidate, among all unidentified factors, the specific role that is played by abdominal fat accumulation and metabolic adiposity signals in the recently observed associations among obesity, arterial stiffness, and CV risk.

References


