Obesity and Oxidative Stress
A Direct Link to CVD?
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In this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Keaney and colleagues report that smoking, diabetes, and obesity are independently associated with increased oxidative stress in men and women in a large community-based cohort. While a number of investigators have examined the association between risk factors for cardiovascular diseases (CVDs) and markers of oxidative stress in small clinical samples, Keaney and colleagues used the Framingham Offspring Cohort to assess CVD risk and urinary concentrations of the F2-isoprostane 8-epiPGF2α, in more than 2800 men and women between 33 and 88 years of age. Although smoking and diabetes have been associated with increased oxidative stress in a number of studies, the finding that obesity, as measured by body mass index (BMI), is independently associated with oxidative stress is relatively new and confirms recent data from much smaller samples.

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F2-isoprostanes are prostaglandin-like products of the free radical-catalyzed peroxidation of arachidonic acid. They are formed in situ esterified to phospholipids and are released into plasma by phospholipases. Plasma and urinary F2-isoprostanes are established biomarkers of lipid peroxidation in vivo. In humans, F2-isoprostanes are elevated in the presence of diabetes, hypercholesterolemia, end stage renal disease and hemodialysis, hyperhomocysteinemia, and cigarette smoking. Elevated concentrations of F2-isoprostanes have also been found in human atherosclerotic lesions. In addition to serving as biomarkers of oxidative stress, F2-isoprostanes, including 8-epiPGF2α, exert (patho)physiological effects such as vasoconstriction. Obesity is epidemic in the United States. Among adults, the age-adjusted prevalence of obesity (BMI ≥ 30 kg/m²) has doubled in the past 20 years, from approximately 15% to 31%. In children and adolescents, the prevalence of overweight has tripled from 5% to 15%. Although it has been argued that the independent effect of obesity on CVD risk is small, obesity promotes clusters of risk factors that greatly increase CVD risk, and obese individuals experience substantially elevated morbidity and mortality from nearly all forms of CVD.

In addition to serving as a storage depot for lipid energy, adipose tissue is a metabolically active endocrine organ. The inflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) are expressed in human adipose tissue. In healthy men and women, systemic IL-6 concentrations increase with adiposity, and it has been estimated that as much as one third of the total circulating IL-6 originates from adipose tissue. The hepatic synthesis of the acute phase protein C-reactive protein (CRP) is largely regulated by IL-6. Elevated serum CRP concentrations are consistently associated with increased incident CVD, suggesting an important role of inflammation in cardiovascular pathology. Consistent with the notion that obesity is a chronic inflammatory state, BMI and waist-to-hip ratio are significantly and positively associated with serum CRP levels in large community-based cohorts.

Inflammation is a source of oxidative stress, which is also implicated in the development of atherosclerosis. Consistent with this notion, elevated levels of plasma and urinary F2-isoprostanes have been found in a number of inflammatory diseases. Increased production of reactive oxygen species may also enhance the inflammatory response by activating redox-sensitive nuclear transcription factors such as AP-1 and NF-κB. These transcription factors are essential for the inducible expression of genes associated with immune and inflammatory responses, including cytokines, cell adhesion molecules, and inducible NO synthase. Thus, the pro-inflammatory and pro-oxidant effects of increased adiposity represent a potential link between obesity and CVD.

The idea that obesity is a state of chronic oxidative stress and inflammation, even in the absence of other CVD risk factors, increases the importance of developing effective prevention and treatment strategies for obesity. Even moderate weight loss has been found to result in decreased circulating levels of TNF-α, IL-6, and CRP. Moreover, two recent studies found significant decreases in urinary 8-epiPGF2α in obese men and women after only 3 to 4 weeks on weight loss programs with dietary modifications and increased physical activity. Although these findings are encouraging, long-term controlled trials documenting the beneficial effects of weight loss on inflammation and oxidative stress, in addition to other CVD risk factors, are needed.

Because modification of eating and physical activity habits have been relatively unsuccessful in decreasing the prevalence of obesity from a public health standpoint, additional strategies must be considered for the prevention of obesity-associated CVD. If obesity is a condition of increased oxidative stress, obese individuals may benefit from antioxidant supplementation. Secondary prevention trials of vitamin E supplementation in individuals with CVD have been rather...
unsuccessful in lowering risk, but they have also been criticized for failing to include biomarkers of oxidative stress.28 Without such biomarkers, it is impossible to identify those individuals who may benefit the most from antioxidant therapy, and to determine whether antioxidant therapy had the intended effect of lowering oxidative damage and thus, potentially, CVD risk.

A number of intervention trials have examined the effect of antioxidant supplementation on plasma and urinary F2-isoprostanes. In apparently healthy adults without elevated F2-isoprostane levels, supplementation with vitamin E29,30 or vitamin C31 has not generally resulted in significant decreases in F2-isoprostane levels. In contrast, vitamin E supplementation of hypercholesterolemic and diabetic subjects, who have elevated plasma and urinary F2-isoprostane levels at baseline, significantly decreases these levels.6,7,32,33 Cholesterol-lowering therapy with the HMG-CoA reductase inhibitor simvastatin also decreased urinary 8-epi-PGF2α concentrations in hypercholesterolemic adults.34 However, the combination of simvastatin and 600 mg/d of vitamin E did not result in further decreases in urinary 8-epiPGF2α.

Data showing that cigarette smokers have lower plasma ascorbate levels35 and higher F2-isoprostane levels26 than nonsmokers indicate that smoking causes oxidative stress in vivo. Limited data suggest that supplementation with vitamin C36,37 but not vitamin E38,39 decreases F2-isoprostane levels in smokers. Interestingly, Dietrich and colleagues37 recently found that supplementation with 500 mg/d of vitamin C decreases plasma F2-isoprostane levels only in those smokers with a BMI greater than the sample median of 26.6 kg/m2. As in the study by Keaney and colleagues,1 those with higher BMI had higher F2-isoprostane levels at baseline,37 suggesting that an elevated level of oxidative stress is required to demonstrate an antioxidant treatment effect.

Although the current finding of an association between obesity and oxidative stress is strengthened by the use of a large community-based cohort and a validated biomarker of inflammation and oxidant stress,1 it is not possible to determine from this cross-sectional study whether obesity is a source of oxidative stress. The metabolic syndrome is characterized by the co-occurrence of multiple risk factors for CVD and type 2 diabetes, including overall and central obesity, insulin resistance, impaired glucose tolerance, hypertension, and the combination of low HDL cholesterol and high triacylglycerol levels.40 More recently, the metabolic syndrome has also been characterized as a prothrombotic and pro-inflammatory state. While Keaney and colleagues1 suggest that obesity is independently associated with oxidative stress, the close association of obesity with other conditions that potentially increase oxidative stress leaves open the possibility of residual confounding, ie, the association between oxidative stress and obesity may be related to other, unmeasured variables. Nevertheless, this study1 highlights the need for further investigations of the relationships between obesity, inflammation, oxidative stress, and CVD.17 If obesity is confirmed as a condition of increased oxidative stress, the potential for antioxidant therapy to decrease CVD risk in obese individuals needs to be explored.

References


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