Is Oxidant Stress a Connection Between Obesity and Atherosclerosis?

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The marked increase in the incidence of overweight and obese persons is recognized as one of the most serious public health issues in the United States. It is estimated that currently >60% of American adults are overweight and 20% are obese.1 Overweight and obesity are associated with a significantly increased mortality from atherosclerotic cardiovascular disease and other causes.2–4 Although obesity itself appears to augment the incidence of cardiovascular events, it is also associated with major risk factors for atherosclerosis including hyperlipidemia, diabetes mellitus, hypertension, and the metabolic syndrome.1,5 How obesity and each of these risk factors are involved mechanistically in atherosclerosis have been areas of intense research but are poorly understood. A panel of experts assembled by the National Institutes of Health recently concluded that the study of mechanisms by which obesity contributes to atherosclerosis should be a high priority.1 The report by Keaney et al8 in this issue of Arteriosclerosis, Thrombosis, and Vascular Biology provides evidence that increased systemic oxidant stress may be an important mechanism by which obesity increases the incidence of atherosclerotic cardiovascular disease.

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Enhanced oxidant stress, occurring either locally in the arterial wall or systemically, is one hypothesis to explain the development and progression of atherosclerosis in humans.7–9 In particular, oxidative modification of the lipid components of LDL has been hypothesized as causative. LDL is deposited in the vascular wall early in the course of atherosclerotic lesion development where it is oxidized.10 There is evidence both in vitro and in animal models of human atherosclerosis that oxidized lipids derived from LDL contribute to many of the stages of atherosclerotic development.7–13 Mechanisms that have been proposed to result in enhanced lipoprotein oxidation, either locally or systemically, and the progression and development of atherosclerosis include increased production of tumor necrosis factor and other cytokines, upregulation of NADPH oxidase(s) and other oxidative enzymes in vascular tissue, and increases in the renin angiotensin system.13–15

While animal and human epidemiologic studies carried out in the 1980s and 1990s suggested that antioxidants decrease atherosclerosis presumably by reducing oxidative stress, prospective clinical trials of antioxidant supplementation using vitamin E and other agents have been disappointing.16–20 Three large trials, ATBC, GISSI, and HOPE, involving tens of thousands of subjects failed to show a reduction of cardiovascular events when vitamin E was used at doses ranging from 50 to 400 IU/d.20–23 The large OX-HPS study combining vitamin E with other antioxidants also did not show a reduction in cardiovascular events.24 Further, a much smaller trial reported last year even suggested that vitamin E might be detrimental because it blunted a predicted rise in HDL cholesterol subfractions associated with statin and niacin therapy.25 On the other hand, two trials, CHAOS and SPACE, involving far fewer patients, reported a significant reduction, by almost 50%, in the incidence of cardiovascular events.26,27

So why do these discrepancies exist between human and animal studies and among various clinical trials? Several reasons have been proposed. The first relates to the fact that many reported animal studies used doses of antioxidants that were far greater than those administered to humans.20 Indeed, it can be inferred that vitamin E may be a low potency antioxidant.28 In support of this, both the CHAOS and SPACE studies, in which vitamin E appeared protective, used higher doses of the agent. Secondly, the endpoint of prospective human supplementation trials has been cardiovascular events as opposed to animal studies in which early evidence of atherosclerosis such as fatty streaks were quantified.29 The possible contribution of oxidant stress to early lesion development in humans has not been carefully studied. Third, it is the assumption of the prospective clinical trials reported that antioxidants decrease atherosclerosis by inhibiting oxidant stress. In no trial reported, however, was an assessment of oxidant stress undertaken in study participants nor was the ability of vitamin E to inhibit oxidative injury determined.20–27 Thus, it is impossible to determine whether vitamin E or other antioxidants inhibited oxidative injury in the populations studied. Despite these issues, the weight of evidence reported to date suggests that vitamin E is unlikely to prevent atherosclerotic cardiovascular events in humans. On the other hand, one cannot conclude from these clinical trials that oxidant stress is not involved in the development and/or progression of atherosclerosis.

Measurement of F2-isoprostanes (F2-IsopPs) is the most accurate method to quantify oxidant stress in humans.29,30 IsoPs are increased in persons with hypercholesterolemia, diabetes mellitus, and hyperhomocysteinemia, and in chronic heavy cigarette smokers,31–33 suggesting that certain popula-
tions at risk for atherosclerosis are under increased oxidative stress. These observations are important with respect to atherosclerotic cardiovascular disease because they suggest that oxidative injury may have a relatively more important role in the development and/or progression of the disease in certain human populations and that therapeutic strategies to decrease oxidative stress should, perhaps, be targeted to select individuals.

In the article by Keaney et al., it is reported that an association exists between increasing body mass index (BMI) and increasing systemic oxidant stress. Using the quantification of urinary F_2-IsosPs, the authors show in near 3000 patients involved in the Framingham Heart Study that enhanced IsoP formation in both men and women is strongly associated with increasing BMI. These findings add credence to two much smaller studies in which overweight/obesity was associated with enhanced oxidant stress. In addition to obesity, smoking and diabetes were independently associated with increased IsoP excretion. The importance of the work by Keaney et al. compared with previous reports, however, is that the study population was not a smaller, targeted one, but it involved a large community-based cohort of otherwise healthy individuals. A particularly relevant aspect of the present study with respect to determining the role that obesity-associated oxidant stress plays in atherosclerotic cardiovascular disease is the fact that participants in the trial will be followed over time so that clinical outcomes, such as cardiovascular events, can be correlated with excessive oxidant stress. In this respect, the present study allows for a more direct assessment of the extent to which oxidative injury contributes to atherosclerotic sequelae in humans than do previously reported antioxidant intervention trials.

An important question raised by this report relates to mechanisms by which overweight/obesity induces oxidant stress. It is likely that multiple pathways contribute because overweight/obesity is not only associated with increased oxidant stress but also with elevated systemic inflammation and activation of coagulation cascades. A number of pathways capable of generating injury-inducing free radicals derived largely from molecular oxygen are known to be perturbed in association with obesity. For example, the renin-angiotensin system is upregulated in obesity. Angiotensin II has been shown to induce NADPH oxidase in various tissues with a resulting increase in superoxide production. Angiotensin II has also been shown to increase LDL uptake by macrophages, resulting in enhanced lipoprotein oxidation. Further, obesity has been associated with reduced antioxidant defense mechanisms, including decreased erythrocyte glutathione and glutathione peroxidase. The extent to which these and other mechanisms contribute to obesity-associated oxidant stress needs to be explored and will likely provide key information about the importance of obesity in the development and progression of atherosclerosis.

The findings by Keaney et al. are not only important with respect to the study of basic mechanisms underlying oxidant stress associated with obesity, but they also have significant public health implications. Obesity is not going away any time soon and will likely increase in the US population over the next decade. Weight loss approaches are often ineffective, and thus it is clear that the medical community will be faced with an increasing number of persons with diseases associated with obesity including diabetes, hypertension, and atherosclerosis. Novel strategies to prevent and treat these disorders based on our understanding of the physiological perturbations associated with obesity need to be developed and tested. Keaney et al. provide insights into one mechanism, increased oxidant stress, that likely contributes to the pathological sequelae of obesity and that may be a target for interventions to decrease obesity-associated disease.

References


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