Overweight and obesity have become major public health issues. According to the most recent National Health and Nutrition Survey (NHANES III, 1988 to 1991), 40% of all men and 26% of all women in the United States are overweight, and 20% and 26%, respectively, are obese. Projected adult obesity rates are 30% in 2015 and >40% in 2025. Although the public awareness of adult obesity is growing, the magnitude of this problem among children still remains widely unknown. According to the NHANES III database, the percentage of overweight children (>95th percentile) has tripled between the 1960s and the 1990s and today reaches approximately 14% among both boys and girls. The steepness of this increase is twice as high as in the adult population, where the increase of obesity in the same time period was 1.6-fold.

See p 1981

It is, however, difficult to compare the prevalence of obesity between children and adults because of the lack of generally accepted definitions for children. Although body mass index (BMI) >25 indicates overweight and >30 defines obesity in adults, the diagnosis of overweight in children relies on age-adjusted percentiles. In the context of NHANES III, children are classified as being at risk of overweight when between the 85th and 94th percentiles and are called overweight when ≥95th percentile. In the United States, the term obesity is reserved for clinically diagnosed cases. For the purpose of their study published in the present issue of Circulation, Woo and colleagues used the age-adjusted BMI cutoff points suggested by Cole et al and defined overweight as a BMI between 21 and 23 and obesity as a BMI ≥23.

Several environmental factors contribute to the obesity epidemic that is now being observed among children: the sustained excess of energy-dense foods with refined carbohydrates and high saturated fat (the age groups between 0 and 19 years are those with the highest intake of saturated fats per total calories consumed), as well as insufficient consumption of fruit and vegetables. The impact of these nutritional factors is further aggravated by an increasingly sedentary lifestyle—attributed in part to urbanization, which limits the opportunities for physical activity, and the predominance of electronic entertainment over physical activity.

In addition to these external influences, a genetic predisposition for obesity has often been discussed as a contributing factor for the increasing prevalence of overweight. However, it is unlikely that genetic background would explain the growing obesity epidemic of the past several years; a population gene pool does not change significantly within a decade. Twin studies suggest that only a minor proportion of the tendency toward obesity is inherited, and the primary genetic disorders presenting with childhood obesity (Prader-Willi syndrome, Bardet-Biedl syndrome, etc) are extremely rare.

What do the epidemiological figures of increasing obesity among children imply? According to a recent survey of a population-based sample of 195 005 randomly selected American adults, obesity is associated with a relative adjusted risk of 3.4 for diabetes mellitus, 3.5 for hypertension, 1.9 for hypercholesterolemia, and 1.8 for poor health. Although the data in childhood are less exhaustive, about 60% of overweight 5- to 10-year-old children are reported to have at least one associated cardiovascular risk factor, and 25% have 2 or more. Diabetes mellitus, hypercholesterolemia, and arterial hypertension have all been shown to promote atherosclerosis by their cumulative effects on the vascular endothelium.

**Prognostic Impact of Endothelial Dysfunction**

Data from long-term follow-up studies in adults show that the impaired endothelium-dependent arterial vasorelaxation in response to increases in blood flow or muscarinic stimulation with acetylcholine is not just an innocent bystander of atherosclerosis. Rather, it is a necessary stage in the transition from normal vascular function to overt atherosclerosis. Inasmuch as it precedes atheroma formation by years, it is increasingly used as a surrogate cardiovascular end point. The prognostic impact of endothelial dysfunction is well documented in adults: The cumulative cardiovascular event rate among patients with severe coronary endothelial dysfunction was 14% over a mean of 2.3 years' follow-up and close to 20% over 8-year follow-up, as compared with <5% among patients with normal endothelial function. Presuming that this clinical time course may also be valid for younger age groups, we may expect the first publications on increased rates of myocardial infarction among obese young adults before the present decade is over.

What can be done to improve this sober outlook? The basic therapeutic principles are well established: diet and exercise.

In the present issue of Circulation, Woo and colleagues report the results of dietary modification alone or in combi-
nation with exercise training in a cohort of 82 overweight children aged 9 to 12 years. They used a noninvasive ultrasound measurement of endothelial function in the brachial artery and an assessment of intima-media thickness of the carotid artery as established cardiovascular surrogate end points. Although both interventions were effective in improving endothelial function at 6 weeks, the extent of the improvement was significantly greater in the diet-plus-exercise group as compared with diet alone. At 1 year, intima-media thickness as a second surrogate end point for progression of atherosclerosis was lower in the group continuing exercise training as compared with the groups of children on diet only and those who discontinued the training program.

There are a number of important limitations with regard to this study. First of all, the trial lacks a proper control group without any intervention, one reason being that data on a control group were previously published by the authors elsewhere. Second, the study does not include a physical exercise–only group, which would have provided additional information on the relative efficacy of diet versus physical exercise in improving endothelial function. Third, both dietary interventions and diet plus exercise did not affect BMI. Even body fat proportion was unchanged in the diet-only group, although it was significantly reduced by 13% with diet plus exercise.

Despite these limitations, the value of the article by Woo et al7 lies in the topic addressed: It provides conclusive evidence that aggressive lifestyle modification by diet and physical exercise training are needed in overweight children to correct endothelial function as a marker of cardiovascular risk.

Their results are consistent with numerous in vitro and in vivo studies addressing the effects of hypercholesterolemia and sedentary lifestyle on endothelial function and the value of diet and exercise for improving vascular relaxation.

**Effects of Diet on Endothelial Function**

It is not obesity itself that causes endothelial dysfunction but rather the hypercaloric high-fat diet that precedes the weight gain. A single high-fat meal—representative of the fast food that is so popular among children—impairs vasoreactivity in normocholesterolemic healthy men for up to 4 hours. The decrease in endothelium-dependent flow-mediated vasodilation was inversely correlated with the 2-hour postprandial change in triglycerides and was not observed after pretreatment with antioxidants like vitamin C and E or after a Mediterranean-style meal (rich in vegetables, fruits, omega-3–rich fish, and canola oils). How could hypertriglyceridemia be related to elevated oxidative stress? It has been proposed that central obesity is accompanied by increased cytosolic triglyceride storage in the majority of tissues (including the endothelium and vascular smooth muscle cells) and hence high intracellular concentrations of long-chain acyl-coenzyme A esters. These esters inhibit mitochondrial adenine nucleotide translocators, leading to intramitochondrial ADP deficiency, a major factor for increased mitochondrial production of reactive oxygen species. Oxidative stress, in turn, causes premature NO degradation to peroxynitrite and endothelial dysfunction.

In obese adults (BMI 35±5), a low-calorie diet can significantly enhance flow-mediated brachial artery vasodilation by 60% and reduce body weight by 11%. The observation that both changes were not correlated is consistent with the notion that the diet-related factors like high triglycerides may be involved.

However, pathological vasoreactivity in obesity is a complex multifactorial phenomenon. Increased serum levels of vasoconstrictive prostaglandins, proinflammatory cytokines, and adiponectin and changes in lipoproteins (elevated serum LDL and chylomicron remnants, lowered HDL) have all been implicated in its pathogenesis.

LDL reduction by either diet or statin therapy has been related to improved endothelial function in previous intervention studies. Although statin therapy has been effectively used to normalize endothelial dysfunction in children with familial hypercholesterolemia, the consensus is that pharmacological interventions should not be the first choice to treat alimentary-induced hypertriglyceridemia and endothelial dysfunction in obesity.

Although the mechanisms by which diet alone improves endothelial function remain far from being fully understood, evidence is accumulating that a combined reduction of LDL and other atherogenic lipoproteins, reduced rate of hyperglycemia, and lower oxidative stress are involved.

**Effects of Exercise on Endothelial Function**

Exercise training reduces cardiovascular events (1) by modifying classical cardiovascular risk factors and (2) by direct shear stress–mediated effects on the vascular endothelium.

The interaction between cardiorespiratory fitness and the development of cardiovascular risk factors has recently been assessed in a longitudinal 15-year follow-up study of 2478 young adults aged 18 to 30 years at the start of the study. It was evident that a low cardiorespiratory fitness as determined by baseline treadmill examination was associated with a relative risk of 3.7 for developing diabetes (as compared with the high fitness tertile), 4.1 for acquiring a metabolic syndrome, 2.6 for becoming hypertensive, and 1.3 for having hypercholesterolemia. Interestingly, all of these statistical hazard ratios were no longer significant after adjustment for baseline BMI and weight change during follow-up. This finding indicates that BMI and weight change are inversely correlated with the individual level of cardiorespiratory fitness in young adults. According to data in older men, low cardiovascular fitness seems to become an independent predictor of cardiovascular events among all BMI groups later in life.

The efficacy of regular physical exercise for improving glycemic control and preventing the development of overt-type diabetes in patients with pathological glucose tolerance is well documented. On a molecular basis, regular exercise appears to increase the membrane density of the GLUT4 transporter protein, thereby increasing the velocity of glucose uptake into the skeletal muscle. Thus, glucose levels are lowered, and insulin action is improved. Because hyperglycemia may promote endothelial cell nitric oxide synthase (ecNOS) uncoupling and endothelial dysfunction by glyco-
syalation of tetrahydrobipterin, improved glycemic control is
directly associated with improved vasoreactivity.

Other important risk-modifying interactions have been
documented between regular physical exercise and reduction
of endothelial dysfunction in hypertension and hyperchole-
sterolemia (for review, refer to Ballady21).

However, even in the absence of known cardiovascular risk
factors, physical exercise has potent effects on pathological
endothelial function; a 4-week, high-intensity, supervised
training intervention in patients with stable coronary artery
disease was successful in attenuating the pathological vaso-
constriction in response to acetylcholine and significantly
improved agonist-mediated increases in coronary blood
flow.22 A number of direct shear stress–mediated effects on
endothelial function have been described in recent years:
augmented ecNOS expression, increased ecNOS phosphory-
lation by Akt,23 reduced NAD(P)H oxidase activity by
downregulation of the angiotensin AT1 receptor (unpublished
data), enhanced antioxidative protection by endothelial cell
superoxide dismutase induction,24 and others.

In sharp contrast to the situation in adult cardiology,
conclusive data on the interaction between exercise and
endothelial function in children have long been lacking—a
gap now filled by the trial conducted by Woo et al.2 Perhaps
the major reason for the paucity of studies in this area was the
classical image of youth as a period of vigorous sports, wild
ball games, and uninterrupted health. To many, it may
therefore come as a surprise that a rapidly growing proportion
of children have adopted the sedentary lifestyle and unhealthy
eating habits of their parents. Although the reasons are as
diverse as the socioeconomic changes that have occurred over the
past 2 decades, the implications for healthcare profession-
als are clear.

There is growing need for interdisciplinary action among
pediatricians, nutrition experts, physiotherapists, and cardiolo-
gists to develop comprehensive, aggressive, lifestyle-
modifying programs involving both diet and exercise for
children with overt overweight/obesity. Such therapeutic
interventions need to be complemented by a primary preven-
tion strategy against childhood obesity, including more
emphasis on healthy food and physical fitness at school.

References
635–643.
obesity-related vascular dysfunction in children. Circulation. 2004;109:
for child overweight and obesity worldwide: international study. BMJ.
2000;320:1–6.
childhood and adolescence: diagnosis, treatment, and prevention. Int J
diabetes, and obesity-related health risk factors, 2001. JAMA. 2003;289:
76–79.
patients with mild coronary artery disease and endothelial dysfunction.
8. Schächinger V, Britten MB, Zeller A. Prognostic impact of coronary
vasodilator dysfunction on adverse long-term outcome of coronary heart
with arterial endothelial dysfunction and intima-media thickening. Int J
Obesity. In press.
10. Vogel RA, Corretti MC, Plotnick GD. Effect of a single high-fat meal on
11. Vogel RA, Corretti MC, Plotnick GD. The postprandial effect of com-
ponents of the Mediterranean diet on endothelial function. J Am Coll
12. Bakker SJL, Ijzerman RG, Teerlink T, et al. Cytosolic triglycerides and
oxidative stress in central obesity: the missing link between excessive
atherosclerosis, endothelial dysfunction, and beta-cell failure? Athero-
13. Raitakari M, Iivonen T, Ahotupa M, et al. Weight reduction with very-
low-caloric diet and endothelial function in overweight adults: role of
C on endothelial function of hypercholesterolemic patients. Atheroscle-
men and postmenopausal women with low levels of HDL cholesterol
endothelial function in children with familial hypercholesterolemia. J Am
Coll Cardiol. 2002;40:2117–2121.
young adulthood and the development of cardiovascular risk factors.
18. Wei M, Kampert JB, Barlow CE, et al. Relationship between low car-
diorespiratory fitness and mortality in normal-weight, overweight, and
diabetes mellitus by changes in lifestyle among subjects with impaired
20. Goodyear LJ, Hirshman MF, Horton ES. Exercise-induced translocation
of skeletal muscle glucose transporter. Am J Physiol. 1991;261:
E795–E799.
improves endothelial function in patients with coronary artery disease by
increasing phosphorylation of endothelial nitric oxide synthase. Circulation.
endothelial function in patients with coronary artery disease. N Engl
24. Fukai T, Siefried MR, Fukai M, et al. Regulation of the vascular extra-
cellular superoxide dismutase by nitric oxide and exercise training. J Clin

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