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Obesity, Metabolic Syndrome, and Cardiovascular Disease

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ABSTRACT: Early childhood overweight and obesity have alarmingly increased over the years. Adulthood obesity is a well demonstrated significant independent predictor of cardiovascular risk (CVR) and/or mortality, which predisposes to the major components of metabolic syndrome (MS). Evidence of MS in obese children has been also reported associated with biochemical and inflammatory factors that affect vascular physiologic function. Assessment of vascular function can be measured noninvasively in children allowing early detection of endothelial dysfunction and severe increase of arterial stiffness before clinical manifestations of atherosclerosis. Impairment of endothelial function related to the severity of obesity and to the degree of insulin resistance is considered as a condition that confers a premature atherogenicity status and is linked to adult conventional cardiovascular risk factors. Adipose tissue factors that interfere with insulin action and endothelial cell function have also been identified as major precursors of CVR factors. The metabolic and cardiovascular consequences of childhood obesity are well demonstrated and have a major impact on the development of atherosclerosis and lifetime CVR. The development of programs involving both diet and exercise for children with overt overweight/obesity appears to be essential to improve vascular function and metabolic disorders. Such interventions should be complemented by a primary prevention against childhood obesity. (***Pediatr Res* 61: 653–659, 2007**)

An alarming increase in overweight has been noticed amongst children and adolescents. For example, in the United States of America as part of the National Health and Nutritional Examination Survey (NHANES) between 1999 to 2002, 31% of children and adolescents aged 6 to 19 y were at risk for overweight or obesity and 16.0% were overweight (1). In 2002, the prevalence of overweight in 6 to 12-y-old Swiss boys and girls was of respectively 16.6 and 19.9% (2). In the past the role of adult obesity as an independent cardiovascular risk (CVR) factor has remained controversial, because of its frequent coexistence with other CVR and metabolic disorders, such as hypertension, dyslipidemia and insulin resistance (3,4). It is now well demonstrated that obesity is a significant independent predictor of CVR (5,6) and/or mortality (7). CVR factors act early in life and have a major impact on the development of atherosclerosis and lifetime risk of cardiovascular disease. Atherosclerosis has been shown to have a long preclinical phase, with development of pathologic changes in arteries of children and young adults, well before clinical manifestations of the disease appear in adults. Foetal (8) and early postnatal factors (9) may influence or program the development of atherosclerosis and its complications. The relationship between the extent of early atherosclerotic lesions in children and their blood lipid levels has also been established (10).

This programming might occur directly *via* an effect on vascular physiology (11) or else *via* the programming of CVR factors such as obesity (12). Obesity in childhood has adverse effects on adult cardiovascular health that are independent of adult weight (13). The Bogalusa Heart Study has suggested that parents contribute to their children's risk of developing the MS (14). Obesity is a well-established independent risk factor for coronary artery disease but the mechanisms that relate fat mass to vascular health are poorly understood. Excess fat, and particularly visceral fat, predispose to the major components of MS and several definitions of this syndrome have been developed for adults: the World Health Organization (WHO) based on disease processes (15), the Adult Treatment Panel III (ATPIII) (16), the European group for the Study of Insulin Resistance (EGIR), the American college of Endocrinology Task Force on the Insulin Resistance Syndrome (17) and more recently the International Diabetes Federation (18,19). Following the WHO criteria, MS includes increased blood pressure, abdominal obesity, elevated triglyceride levels, low HDL (HDL), insulin resistance and microalbuminuria and it influences cardiac risk. MS exists in adults, and many of the variables appear to be present in childhood and adolescents. The prevalence of MS in children and adolescents (3% to 4%) (20) is lower than that reported by several studies in adults (21–24). Ornstein and Jacobson proposed a definition of the MS in children and adolescents based on ATP III criteria and cut-off values for the various features of the MS in children and adults (20). Evidence is also provided that the MS is accompanied by a thrombotic and proinflammatory state, as well as hyperuricemia (25).

OBESITY BIOMARKERS OF METABOLIC SYNDROME

Obese individuals who more commonly show features of the MS exhibit a clustering of phenotypes associated with increased cardiovascular risk. Insulin resistance is suggested to be central of this syndrome's pathogenesis and explains the

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Abbreviations: BP, blood pressure; **CVD,** cardiovascular disease; **CVR,** cardiovascular risk; **EPC,** endothelial progenitor cells; **FMD,** flow mediated dilation; **IMT,** intima media thickness; **MS,** metabolic syndrome; **PWV,** pulse wave velocity; **VCAM,** vascular cell adhesion molecule

association between obesity and vascular dysfunction. However, recent additions to this clustering, such as an elevation of levels of plasminogen-activator inhibitor, microalbuminaria and endothelial dysfunction cannot be clearly explained by insulin-mediated mechanisms. Moreover, obesity is associated with features of acute-phase activation and low-grade inflammation is recognized as a component of atherosclerosis (26). C-reactive protein (CRP), IL-6, fibrinogen and TNF-α are associated with adiposity in children (27,28). Markers of systemic low-grade inflammation worsen with increasing adiposity (29). The molecular mechanism of CRP related to insulin resistance has been examined with the purpose that CRP induces the phosphorylation of jun N-terminal kinase (JNK) and Insulin receptor substrate-1 (IRS-1) Ser307 site through a spleen tyrosine kinase (Syk) and RhoA-activation signalling pathway (30). An increased level of isoprostanes, as a measure of oxidative stress, was seen in association with greater adiposity in adolescents (27). All these factors could affect vascular function by their local and distant actions. Inter-related metabolic, biochemical and inflammatory factors associated with obesity have an effect on vascular structure and endothelial function (31) and are summarized in the Table 1. It has been hypothesized that both insulin resistance and endothelial dysfunction have a common background, possibly *via* inflammatory mediators released from adipose tissue (32) or even a common risk factor in the perinatal period. Foetal and early postnatal nutrition have been postulated to be the "common soil" that programmes the development of the MS thus affecting the propensity to both clinical CVD and noninsulin-dependent diabetes. Low birth weight as a result of preterm birth does not seem to be associated with endothelial dysfunction (33). However, an association between intrauterine growth retardation (IUGR) and endothelial dysfunction has been demonstrated (11). Evidence of reduced muscle uptake of glucose but normal endothelial function in men with low birth weight also suggests that programming of insulin resistance can occur independently of an effect on endothelial function (34). Many interactions between metabolism and vascular tissues contribute to major relationships between insulin resistance and endothelial function (35). Adipose tissue has become increasingly important in understanding the role of obesity in vascular disease. It produces several biologically-active cytokine-like molecules that could mediate the increased risk of CVD associated with obesity. The two most promising of such molecules for an effect on vascular function are leptin and adiponectin. The action of leptin could be mediated *via* receptors widely distributed on endothelial cells, to stimulate smooth muscle cell proliferation and migration, and hence impair arterial elasticity. This suggests that a high leptin concentration is a key link between obesity and vascular disease (36). Adiponectin, which acts as a regulator of MS (37), might be cardio-protective by inhibiting TNF- α-mediated monocyte adhesion, formation of foam cells and smooth muscle cell proliferation and also by promoting blood vessel growth and endothelial NO production (38). Endothelial function is impaired in adiponectin knock-out mice, whereas forced adiponectin expression reduces atherosclerotic lesions in a mouse model of atherosclerosis (39). Hypoadiponectin has been associated with impaired endothelial function in patients with mild hypertension and type 2 diabetes and in healthy adult controls (40). There are relatively few data for human beings, especially for young individuals, that support an independent anti-atherogenic action of adiponectin. Adiponectin contributes to the maintenance of insulin sensitivity in young, nonobese individuals but does not affect the development of early endothelial dysfunction (41). Leptin, adiponectin, free fatty acids (FFA), and ghrelin are emerging biomarkers of insulin resistance (42–45); the three latest have also been implicated as biomarkers of coronary artery disease (46–48). Many prospective studies have shown that individuals with MS have a greater risk of developing type 2 diabetes and cardiovascular disease. Assessment of CVD risk and MS in children and adolescents has involved the analysis of serum or plasma biomarkers including total cholesterol (TC), triglycerides (TG), HDL cholesterol (HDL-C), insulin and C-peptide. Lipids and lipoproteins play an important role in the development as well as in consequences of MS. The dislipidemia results in increased production of TG and secretion of very low density lipoprotein along with associated abnormalities like reduction of in HDL-C and increased density of LDL. Hypertriglyceridemia is associated with predominance of small dense LDL particles which is due to relative depletion of unesterified cholesterol, esterified cholesterol and phospholipids with either no change or an increase in LDL triglyceride. Small dense LDL is more toxic to endothelium, can transit through endothelial basement membrane easily, ad-

Table 1. *Metabolic biomarkers and their roles*

Class	Members	Role
Lipids and lipoproteins	Low density/lipoprotein particle number	Vascular injury
Adipokines	Leptin	
	Adiponectin	Modulation of insulin sensitivity Anti-inflammatory action
	Resistin	Impairment of glucose tolerance
Inflammatory markers	C-Reactive protein	Endothelial cell activation
	C3/ASP (Acylation Stimulating Protein)	Induction of tissue damage
Cytokines	Tumor Necrosis Factor α receptor 2	Insulin resistance
	IL-6	Atherothrombosis
	IL-8	Neutrophils attraction to endothelium
Chemokines	Monocyte Chemotactic Protein-1 (MCP-1)	
	Eotaxin	Induction of cell adhesion molecule expression
Hemostatic markers	Plasminogen Activator Inhibitor-1	Insulin resistance

heres well to glycosaminoglycans, is more susceptible to oxidation and is more selectively bound to scavenger receptors on monocytes derived macrophages (49). Recently, emerging biomarkers such as apolipoprotein (apo)-AI and apo-B have been proposed as precise predictors of atherogenicity and CVD risk (50).

ASSESSMENT OF THE IMPACT OF OBESITY ON CARDIOVASCULAR FUNCTION

Obesity might also promote preclinical atherosclerotic changes *via* a direct effect on vascular physiology. Greater adiposity in childhood or adolescence has been associated with greater cardiovascular and all-cause mortality in adult life (51–54). Several reports now suggest that obesity impairs vascular function (55). Obese individuals show an impaired endothelial-mediated vasodilator response to increase blood flow (56) and to insulin (57). Similarly, obesity is associated with greater arterial stiffness (58–62) and visceral adiposity is particularly detrimental (63). The precise mechanism by which obesity in childhood increases CVR above that of fatness in adult life remains unexplained. One possibility is that of a prolonged exposure of arteries to the metabolic milieu associated with obesity (such as a high insulin concentration) (13). Endothelial dysfunction and arterial stiffness in young individuals who are obese is now a strong evidence from an early age. The underlying mechanism for this effect is contentious. Childhood obesity exerts its effects on coronary heart disease by way of its persistence into adulthood (64). The tools to obtain functional and morphologic characteristics of arteries in adults have been successfully used to analyze arterial function in the pediatric population. Ultrasound evaluation of morphology and mechanical properties of great elastic arteries and endothelial function of brachial artery have been used in the clinical setting to assess coronary risk in childhood obesity as well as in other high cardiovascular risk populations like heterozygous familial hypercholesterolemia (65–67), type 1 diabetes (68,69) or homozygous homocystinuria (70). These advanced methods in cardiovascular imaging research detect early anatomic evidence of atherogenesis. Thickening of the intima and media of the great vessels can be visualized, mechanical properties of such vessels can be measured and endothelial function can be assessed by reactive hyperemia, after release of a tourniquet inflated above the systolic pressure to induce ischemia in the forearm, described as FMD and contribute to reveal early atherogenesis in children and adolescents. Mechanical properties measure the early sign of atherosclerosis using the state of elasticity or stiffness of the arterial wall. Arterial compliance and distensibility is determined by arterial transmural pressure and its structural components of mainly collagen and elastin. Arterial stiffness correlates closely with early atherosclerosis disease and has been well demonstrated in obese children (58,59,61). Arterial stiffness can be estimated from the incremental elastic modulus independently of the pressure or indirectly from the PWV using tonometry of applanation. PWV represents the time that the pulse wave takes to travel a given distance along the vasculature and is derived from the complex interactions between the ventricular performance, the physical properties of the arterial system, and rheological characteristics of the blood (71). The faster is PWV and the greater is the arterial stiffness. Additionally, analysis of the pulse wave form by tonometry of applanation provides a noninvasive means to record local arterial blood pressure and wave reflection (72). PWV of the upper limbs was used for the first time by Toto-Moukouo *et al.* to evaluate mechanical properties of large arteries in adult obese hypertensive individuals. In this population, a significant positive correlation was observed between the degree of obesity and PWV independently of age, gender and level of BP (73). Increased aortic stiffness has been shown in obese adults to be more related to body fat repartition, assessed by waist circumference and visceral adiposity, than to increased BMI (74–76). Noninvasive assessment of vascular function has become a surrogate for more invasive identification of cardiovascular disease. The procedure has little risks, allows studies of large populations and serial individual follow-up over time. These approaches give an estimation of the local or regional function of the examined arterial bed. These various studies in pediatric populations indicate that endothelial dysfunction and carotid thickening found in conditions predisposing to atherosclerosis may be present at a young age (68,69,77–80). However, the thickness of the arterial wall can be a matter of debate.

Indeed, a majority of studies (81–86) report an increased in carotid IMT in obese children when compared with lean controls. It was also described an association between IMT and BP (81,83), and some of these studies included obese children with hypertension (82,83) or with BP values significantly increased when compared with their referents (83). Furthermore, some of these obese children have a dyslipidemia. A recent publication (87) has reported the absence of significant increase of IMT in severely obese children with a mean age of 12 y old. This result is in accordance with our previously reported findings in severe obese children with a mean age of 12.6-y-old (58). In these two studies the patients had a normal BP. This arterial phenotypic change occurs in situation of hypertension but also in situation of dyslipidemia (88). These alterations of vascular function in at-risk children could be useful markers of preclinical vascular disease and may help evaluate the risk modification by therapeutic interventions. Additionally, these methods could be a useful tool for risk stratification in children at risk, thereby permitting identification of children who would benefit most from intensified therapy. Longitudinal studies from childhood to adulthood have suggested that being obese or overweight in early life may be associated with increased atherosclerosis, including increased carotid artery IMT, as well as increased morbidity and mortality from cardiovascular causes. Juonala *et al.* (89) demonstrated that subjects who had been overweight or obese in youth had significantly higher carotid IMT values in adulthood compared with subjects who had been lean in youth, but subjects who had been obese in the youth but were nonobese as adults had IMT values comparable with subjects who had remained consistently nonobese. This relationship is mostly explained by significant tracking of body mass from youth to adulthood. Endothelial dysfunction is one of the

earliest signs of increased risk for cardiovascular disease and has been shown to be predictive of cardiovascular events (90). In obese children, endothelial dysfunction is related to the severity of obesity, as well as to the degree of insulin resistance (58) and contributes to early atherogenesis during childhood because endothelial cells are important in the regulation of vasomotion, thrombosis and inflammation. Consequently, the brachial artery endothelium function measured by flow-mediated endothelial-dependent vasodilatation is impaired. Other measures of the function and integrity of the endothelium include various biochemical markers such as circulating adhesion molecules (ICAM-1, VCAM-1 E-selectin), molecules that increase during endothelial damage (von Willebrand factor, soluble thrombomodulin) and circulating endothelial progenitor cells (EPC). Low circulating EPC level may thus represent a useful marker of future cardiovascular events (91). The significance of endothelial dysfunction and intima-medial thickening and their long-term consequences remain unknown. Endothelial dysfunction and alteration of the mechanical properties of the arterial wall are observed early in life in children harboring classic cardiovascular risk factors or conditions known to confer a risk of premature atherosclerosis in adults.

RELATIONSHIP BETWEEN MS AND VASCULAR FUNCTION

Obesity in children has been associated with decreased arterial elasticity (58, 60, 62, 84). Childhood obesity has been demonstrated to have predictive value for decreased arterial elasticity in adulthood (61). The association of obesity with metabolic disorders like hyperinsulinemia has been shown to decrease arterial elasticity (92) and was associated independently with carotid artery elasticity. Overweight has been related with low-grade inflammation (93). Yasmin *et al.* showed that CRP correlates directly with arterial stiffness (94). Subclinical inflammation characterized by elevation of CRP has been described as an early complication of childhood obesity which contributes to an later increased burden of type 2 diabetes mellitus in this population (95). Serum concentration of inflammatory biomarkers, such as CRP and also serum amyloid A (SAA), interleukine-6 (IL-6), have emerged as independent predictors of vascular incident and MS (96). Furthermore, elevation in leptin levels, a hormone that plays a key role in the regulation of appetite and body weight, has been related to impaired arterial distensibility in children (97). Increasing CRP concentration was considered as an early complication of childhood obesity in a specific population that exhibit an enhanced cardiovascular risk profile mediated by central adiposity (95). Elevated BP measured in childhood obesity is considered as an independent predictor of arterial elasticity in young adults and contributes to accelerate atherosclerosis, collagen synthesis, arterial smooth muscle hyperplasia and hypertrophy, which lead to increased arterial stiffness (13). A recent study reported an increased risk of elevated BP, high concentrations of total cholesterol, LDL cholesterol, and triglycerides; and a low concentration of HDL cholesterol in overweight Korean children and adolescents (98). An association between micro-albuminuria and insulin resistance (99,100) or increased blood glucose levels (101,102) has also been previously demonstrated in adults. The effect of childhood obesity and obesity-related CVR factors on glomerular and tubular protein excretion was demonstrated by the link between enhanced albuminuria and presence of the features of the MS in children (103). In the near future, a better knowledge of children obesity associated with the appropriate intervention upon obesity-related factors could lead to prevent adult obesity, the MS and CVR.

PREVENTION APPROACHES

The incidence of overweight children aged between 6 and 11 y has more than doubled while the incidence for adolescents from age 12 to 19 has tripled between 1980 and 2000 (104). The metabolic and cardiovascular consequences of childhood obesity and their link are well demonstrated and have to be carefully considered to prevent rather than treat this disease. The relationship between obesity, metabolic syndrome and CVR and the sites of possible intervention are illustrated by the Fig. 1.

SECONDARY PREVENTION

Changes of traditional cardiovascular risk factors and vascular function may promote long-term cardiovascular benefits of treating childhood overweight and obesity. The link between improvement of vascular function and dietary weight loss has been established in adults (105–108) but has not been repeatedly associated with improved endothelial function (109,110). In obese children, combined dietary and exercise treatment improve the factors of metabolic syndrome (111–113). However, this improvement is attenuated or absent when dietary treatment is used in the absence of concurrent exercise therapy (114).

Woo *et al.* found that in overweight and obese 9–12 y olds, 6 weeks of dietary modification alone or diet plus a supervised structured exercise programme were both associated with increased FMD. However, the changes were significantly

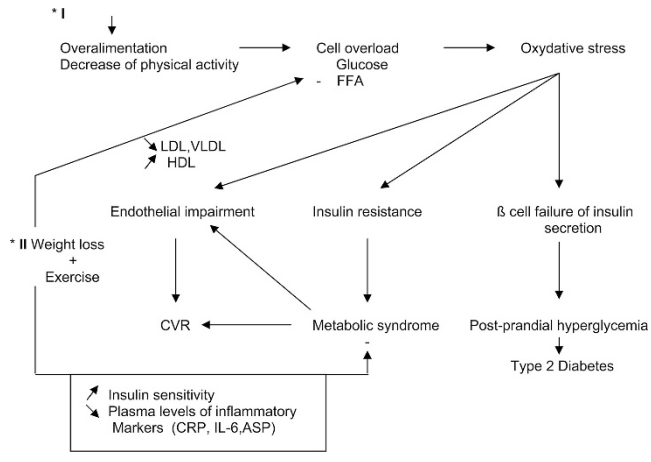

Figure 1. Illustration of the relationship between obesity, metabolic syndrome, bioactive cytokines and CVR. The sites of interventions are illustrated by the symbol (*) and characterize the primary (I) and the secondary (II) prevention of obesity.

greater after diet plus exercise compared with diet alone. Exercise and diet continued for one year resulted in further improvement in FMD and a regression of IMT. In contrast, although some benefit continued to exist at one year, the FMD returned toward baseline in those subjects who ceased exercise. At one year, diet alone also induced a small but significant reduction in IMT. It appears that dietary therapy has a limited long-term benefit, but effectiveness of exercise alone for improving endothelial function, in the absence of dietary therapy is modest and the FMD is still relatively low when compared with the control subjects (115–117). According to the results obtained in these studies, a combination of optimal diet and exercise training may successfully restore vascular function to near normal values. It was demonstrated that exercise training (118) or medical or surgical treatment (119) reverses endothelial dysfunction associated with obesity in adults. In adults it has been demonstrated that weight loss is associated with reduction of the progression rate of carotid IMT after 4 y but no reduction of IMT (120). In a recent study performed in obese children, it has been demonstrated that a 6-mo program of enhanced physical exercise improves the endothelial function of the radial artery, reduces IMT of the carotid artery, systolic BP and left ventricular mass (117). The length of time required to produce sustained and stable changes after intervention to improve vascular status remains unknown; however it has been showed that improvement of endothelial function was reversible within 8 wk after cessation of training in adults and adolescents (121,122).

PRIMARY PREVENTION

The serious and lifelong health complications of excess body weight suggest that providing resources for primary prevention in children is advantageous. The preschool years have been identified as a crucial time to intervene, as early childhood interventions may promote lifelong healthy behaviors before the development of unhealthy behaviors (123,124). Furthermore, early childhood interventions that coincide with early adiposity rebound are considered critical to help prevent obesity later in life (125). Indeed, it has been showed that increases in BMI and the propensity of overweight and obesity follow a quadratic growth curve with the steepest increase before and during puberty (126). Children with higher baseline BMI have a steeper increase in BMI-levels over time supported by studies on tracking (127–133).

Therefore, to curb the nation's obesity epidemic, innovative approaches toward the primary prevention of obesity in young children are urgently needed. Features of this ambitious prevention program should include adapted feeding from the birth to elderly, healthy dietary habits and regular physical activity that could be expected to have effects on body composition. The information of the side effects of obesity on cardiovascular function by mass media campaigns, the participation of industries to promote or prevent various types of consumption, will facilitate a wide participation of such program. Committing resources to high-risk groups might also possibly be an effective approach. Thus, the prevention of obesity among children and adolescents might be possible.

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