CONSIDERING THE LONG LATENT PHASE of atherosclerotic progression before symptoms are manifested, the ability to evaluate arterial function before the development of angiographically measurable atherosclerotic plaque is an important aspect of early detection and risk classification (17, 20, 70). Several noninvasive and, thus, easy to obtain measures of arterial structure and function have been shown to be clinically useful, including measurement of carotid intima-media thickness (IMT), endothelial function, and arterial compliance (13, 14, 37, 86, 91, 102).

Carotid IMT, a subclinical marker of atherosclerosis, is a strong marker of cardiovascular disease burden and is related to coronary artery disease, stroke, and cardiovascular mortality in adults (54, 69). Decreases in endothelial function have been associated with and shown to be prognostic of increased cardiovascular events (86, 91). Decreased endothelial function may also adversely affect peripheral blood delivery and metabolism during exercise (49). Similarly, arterial stiffness has been associated with adverse cardiovascular outcomes (11, 51, 59, 102). In addition, arterial stiffness may negatively affect myocardial performance due to increased afterload and poten-

ially lead to decreased coronary flow (49, 50, 70). Furthermore, arterial stiffness has been hypothesized to lead to microvascular disease, which may cause additional end-organ damage such as stroke or renal failure (70). Consequently, the markers of arterial structure and function discussed above are associated with adverse outcomes in adults.

Atherosclerosis starts in childhood, and postmortem studies have identified fatty streaks in the intima of large arteries in children and adolescents (66). Early manifestation of atherosclerosis is related to traditional risk factors (9). In fact, traditional cardiovascular risk factors that are present in childhood predict cardiovascular disease risk in adulthood (4, 8, 9). Furthermore, recent studies suggest that risk factors such as hypertension, elevated low-density lipoprotein (LDL)-cholesterol, low high-density lipoprotein (HDL)-cholesterol, and obesity can predict the development of increased arterial stiffness and decreased arterial compliance in adulthood (45, 56). These findings are consistent with data showing that children with traditional risk factors also exhibit reduced arterial function (2, 89). This review will briefly describe arterial structure and function findings in healthy children. We will then review the effect of cardiovascular risk factors and the impact of interventions, such as exercise and nutrition, on arterial function in children.
MEASURING ARTERIAL STRUCTURE AND FUNCTION

IMT. IMT can be reliably measured using high-resolution ultrasound. It is often measured at the common carotid artery, since IMT at this site is related to adverse cardiovascular events (54, 69). Several measures of the far wall are made over a distance of 1 cm and about 1–2 cm proximal to the bifurcation, and a mean value for the selected area is provided, using automated wall-tracking software (13, 69). Measures are made from the leading edge of the lumen-intima interface to the media-adventitia interface (44). Some researchers prefer to measure IMT at the femoral artery, because IMT at this site appears to be more readily impacted by interventions such as exercise (27, 62). However, femoral IMT has not been empirically evaluated as thoroughly as carotid IMT. Although IMT measurements are highly reliable, the resolution of the ultrasound images can be a significant limitation, as differences between groups and changes in IMT are often less than 5/100 mm.

Endothelial function. The endothelium produces nitric oxide (NO), mediated by the enzyme endothelial NO synthase (eNOS). NO induces potent vasodilation through relaxation of the vascular smooth muscle (15–17, 20, 83). Endothelial function can be evaluated by measuring the arterial response to infused vasoactive substances, such as acetylcholine, which increases NO production (16, 83). However, the invasive nature of this approach is generally not considered ethical or appropriate for use in healthy children. Endothelial function can be assessed noninvasively using flow-mediated dilation (FMD). By inducing a hyperemic stimulus, the artery dilates as a result of NO release produced by shear stress. The amount of dilation can be accurately measured using high-resolution ultrasound, thus providing an index of endothelial function (16, 17, 20, 99).

Conduit-artery endothelial function is usually evaluated in the brachial artery. The artery is visualized by ultrasound in the longitudinal plane above the antecubital fossa. Following a resting image, a blood pressure (BP) cuff is typically placed on the forearm and inflated to 250 mmHg, or to at least 50 mmHg above systolic pressure, for 4–5 min. Alternately, the cuff could be placed on the upper arm, although upper-arm placement may induce a vasodilatory response that probably reflects vasodilatory mechanisms other than NO (10). Following release of cuff pressure, the artery is continually imaged for 2 min and evaluated for percent maximal dilation from baseline, using automatic edge-detection software. However, recent data indicate that, for some populations, an imaging time longer than 2 min, and as much as 5 min, may be needed (12). The hyperemic response is also typically evaluated during the first 15–30 s following cuff release, using pulsed Doppler, and is then often used as an index of the vasodilatory stimulus. Recent evidence, however, suggests that the vasodilatory response needs to be adjusted for shear rate to accurately evaluate endothelial function (12). Following measures of FMD (and a 10-min rest period), the endothelium-independent vasodilatory response is often evaluated following administration on nitroglycerine. The artery is visualized continuously for 4–5 min after administration. The nitroglycerin-induced vasodilation is considered an index of smooth muscle function (20). Although smooth muscle function is sometimes reduced in clinical populations (37), it is not as sensitive an indicator of cardiovascular risk as endothelial function and is often not prognostic of future events (77). Since many factors affect endothelial function, it is important to control for as many factors as possible, including time of day, medication, caffeine, antioxidants, high-fat foods, smoking, alcohol, exercise, and menstrual status. [For a more complete description of the specific methodology, see Corretti et al. (20), Celermajer et al. (17), and Black et al. (12).] It should be noted that, even with careful control and appropriate measurements, the day-to-day variability of endothelial function often exceeds measured differences between groups.

Arterial compliance. Arterial compliance is evaluated using noninvasive methods such as high-resolution ultrasound or pulse wave velocity (PWV). Ultrasound measurements of the carotid artery or the aorta are usually obtained, but peripheral measurements can also be made, such as of the brachial artery. These measures provide information on the amount of change in lumen size from diastole to systole, by evaluating the increase in lumen diameter during systole. Since compliance is dependent on local distending pressure, it is important to measure local BP. For this purpose, an estimate of the contralateral carotid artery BP is commonly obtained, using handheld applanation tonometry (2, 72). Other variables commonly used include the beta (β) stiffness index, a measure of arterial stiffness shown to be relatively independent of BP (81), and the incremental elastic modulus (Ep). Ep is a measure of the intrinsic elastic properties of the arterial wall material and is influenced less by vessel geometry (44). Ultrasound measurements of arterial compliance are reasonably reliable, but day-to-day variability can exceed commonly reported group differences, and, frequently, measurements are limited by a lack of direct BP measurements of the imaged artery.

PWV is a measure of the speed of the arterial pressure wave propagation and is an index of arterial wall stiffness (2, 21). The arterial pulse wave is noninvasively recorded using pressure-sensitive transducers or Doppler ultrasound, and a simultaneously recorded electrocardiogram is often used as a timing marker. Measurements are typically made from the carotid to the femoral artery (central stiffness) or from the femoral to the dorsalis pedis artery (peripheral stiffness). However, carotid-to-radial artery measurements are also common (whole body compliance). The time delay from the proximal to the peripheral artery is measured and then divided by the distance between the measurement sites to calculate the velocity (21). A higher velocity indicates a stiffer artery. Muscular peripheral arteries are stiffer than less muscular central arteries; thus PWV is higher in peripheral arteries. Since BP significantly influences PWV, it is important to measure PWV and BP simultaneously. Only central PWV has been a consistent predictor of clinical outcomes, even though peripheral and whole body PWV are commonly reported.

DEVELOPMENTAL ASPECTS OF ARTERIAL STRUCTURE AND FUNCTION IN HEALTHY CHILDREN

IMT. The developmental changes of IMT during the developmental years have not been clearly elucidated. Some studies have shown carotid IMT to increase linearly with age in children (35, 44), but this finding has not been consistent, as others have found little change in IMT during childhood (55, 84). These different findings are probably related to the very
small changes observed in IMT between 7 and 18 yr of age. Jourdan et al. (44) showed that median carotid IMT increased linearly from 0.384 to 0.400 mm between 10 and 20 yr of age, but when splitting their sample into three age groups, this trend was less clear. Thus, if carotid IMT changes throughout childhood, these changes are very small (16/1,000 mm) and their clinical or functional relevance questionable. Changes in femoral IMT have been more consistent, showing a small linear increase with age in children (44, 84), but again the clinical or functional relevance of these changes is unknown.

These changes in both carotid and femoral IMT are accompanied by increases in arterial size, including luminal diameter (44, 84), suggesting that the increase in IMT may be a function of increased overall arterial size. Postmortem studies of the aortas of children have shown that both intimal and medial thickness and density increase from birth throughout childhood (30, 96). The density changes were primarily a function of increased “packing” of the elastic fibers, suggesting that changes in IMT in children might also impact functional arterial properties.

Endothelial function. Unlike IMT and arterial compliance (see below), endothelial function, as measured by FMD, does not appear to change throughout childhood in normal, healthy, nonobese children (46, 60, 94, 104). Regardless of age, the mean FMD in healthy nonobese children is typically between 8% and 11% (Fig. 1). However, the range of a normal FMD response is very large, with the 95% confidence interval reported by between 4 and 18% among healthy children (94, 104). This response is similar to that of healthy young and middle-aged adults (17, 20). However, it is unclear if this large range of normal values is due to normal biological variability or due to measurement error, making comparisons of data between studies very difficult. Thus, even though FMD is reduced in both children and adults with cardiovascular risk factors (2, 17, 20, 89), it is difficult to make individual determinations of what constitutes an “abnormal” FMD response in children. Furthermore, the clinical implications of low FMD in children are unknown.

Arterial compliance. Both aortic and carotid compliance decrease throughout childhood and adolescence (3, 44, 55, 88), with the fastest decline observed during the first few years of life. Interestingly, aortic capacitance (flow at a given pressure) increases throughout childhood, primarily as a function of increased arterial size (3, 88), whereas the distensibility of the arterial wall actually decreases (3, 88). Carotid compliance decreases by 10–28% between 5 and 20 yr of age, coupled with increases in Ep and β-stiffness of 9–30%. Thus, although the trend for an increase in arterial wall stiffness is clear, the amount of change appears to be variable between studies.

The increase in arterial capacitance suggests that arterial buffering capacity (the ability of the aorta to facilitate increased blood flow with minimal changes in BP) increases independently from changes in arterial wall elasticity in children, since both EP and β-stiffness continually increase throughout childhood (88). Thus the increase in arterial size appears to offset the increase in wall stiffness, preventing an increase in afterload that could adversely affect ventricular performance (49, 50, 70). This is different from the effect of aging in adults, where arterial capacitance decreases concomitant with an increase in arterial wall stiffness (6, 7). The age-associated increase in arterial wall stiffness in children is also supported by several studies showing increases in both aortic and peripheral PWV from childhood through puberty (6, 7, 18, 19, 67). The increases in arterial stiffness are usually observed in both boys and girls without any sex differences (44, 55, 67). However, Ahimastos et al. (3) demonstrated that, in males, both central and peripheral PWV increased with age, whereas the reverse was true in females whose central PWV was lower postpuberty compared with prepuberty, suggesting that large vessels are more distensible postpuberty.

Although the mechanism of the age-associated increase in arterial wall stiffness in children is not clear, it is often assumed to be associated with changes in elastin and collagen in the media. However, this association is primarily based on studies in adults (85), although some evidence exists in children (30, 96). It has been suggested that the degeneration of the arterial wall begins in childhood, causing decreases in elastin, increases in collagen, and ultimately the beginning of the atherosclerotic process (8, 66, 67). This proposition appears to be plausible when considering that risk factors such as BP, body mass index (BMI), physical inactivity, and high dietary fat intake are related to arterial stiffness in healthy children (44, 87).

### INFLUENCE OF CARDIOVASCULAR RISK FACTORS ON ARTERIAL FUNCTION IN CHILDREN

Childhood obesity is associated with arterial dysfunction from adolescence through adulthood (107). Although the carotid distensibility was reduced and stiffness increased with increasing BMI at any age, these changes were especially pronounced at a young age (107). Obesity in children has also been associated with increased carotid IMT (60, 105). Carotid IMT has been found to be 9–25% higher and directly correlated to BMI in obese children, with the increased IMT being independent of vessel size. However, not all studies (94) have found increased IMT in obese children. Interestingly, the higher IMT was found in overweight and mildly obese children, whereas Tounian et al. (94) found no difference in carotid IMT between severely obese children and normal-weight controls. Nevertheless, all of these studies showed a decrease in endothelial function in the obese or overweight children, with mean FMD of 5–6% in the obese cohorts compared with ~10% in normal-weight controls. Endothelium-independent vasodilation was also significantly lower in the severely obese

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**Fig. 1.** Reported mean and SD of flow-mediated dilation in healthy youth and youth with obesity, hyperlipidemia, and Type 1 diabetes. Reference numbers appear above each bar. A repeating reference number implies multiple subsamples within the study.
Arterial function in children, but not in the mildly obese/overweight children, suggesting severe obesity may directly impact smooth muscle function. In addition, arterial stiffness is commonly much higher in obese compared with normal-weight children (40, 41, 94). For example, the aortic stiffness index was 38% higher, the elastic modulus 58% higher (40), and the carotid Ep 75% higher (94) in obese compared with control children.

Metabolic syndrome in children, defined according to the Third National Health and Nutrition Examination Survey (NHANES III) criteria (22), appears to further deteriorate arterial structure and function. Obese children with metabolic syndrome had not only greater IMT, but also greater systolic and diastolic arterial diameter, coupled with a greater cross-sectional area of the intima-media complex compared with healthy control children (38). This suggests that children with metabolic syndrome exhibit evidence for early arterial remodeling. However, since this study did not compare the children with metabolic syndrome to obese children without metabolic syndrome, the unique effects of metabolic syndrome could not be determined. Iannuzzi et al. (39), however, did show that carotid stiffness was higher in children with metabolic syndrome compared with obese children (with a similar BMI) without metabolic syndrome, suggesting that arterial function is indeed further deteriorated in the presence of metabolic syndrome compared with obesity alone.

The mechanisms through which obesity impacts arterial structure and function are unclear at this time. Endothelial dysfunction and arterial stiffness may be related to increased low-level inflammation, as obese children consistently exhibit higher levels of C-reactive protein (CRP) compared with nonobese children (38, 39, 60). However, BMI alone has been shown to contribute to endothelial dysfunction, even when controlling for CRP, suggesting an inflammation-independent but obesity-dependent factor. Higher leptin levels in obese individuals may be involved, since a dose-response relationship exists between leptin and atherosclerosis (68, 89). Furthermore, leptin has been associated with arterial stiffness independent of inflammation and insulin resistance (90). Other factors that may have a role are insulin resistance, increased blood lipids, and BP (38, 39, 60, 94). However, most of these metabolic factors have not been related to arterial stiffness, suggesting a different mechanism for this variable. It is likely that arterial wall remodeling is involved, but the specific changes that may occur are unknown. It is also possible that autonomic dysfunction may contribute, as vagal tone is related to FMD and arterial stiffness following exercise (36, 46).

Increased carotid IMT is a common finding among children with familial hypercholesterolemia (52, 73, 98). These changes in IMT are often accompanied by endothelial dysfunction (2, 17, 23). Arterial stiffness may also be increased in hypercholesterolemic children (2, 53), although this is not a universal finding (42). The exact mechanisms for these changes in arterial structure and function are not clear but are probably related to detrimental effects of hypercholesterolemia on the arterial wall that lead to increased expression of adhesion molecules, LDL infiltration and oxidation, and increased inflammation (82). However, LDL-cholesterol has not always been associated with decreased arterial structure and function (52, 73, 87), suggesting a more complex interactive process.

Hypertension is related to arterial dysfunction in adults, but little information exists in children with essential hypertension. Ep was increased in children with both elevated BP and elevated cholesterol (80). Others have shown that offspring of hypertensive parents have increased aortic and carotid stiffness (26, 58), suggesting a genetic link. Furthermore, BP is strongly related to PWV in children (87), and it is a strong determinant of the increased carotid IMT in obese children (38). Consequently, even though evidence for the direct impact of hypertension on arterial function is lacking, increased BP appears to be related to increased arterial stiffness and IMT in children.

Several studies have shown an increase in carotid IMT among Type 1 diabetic children and adults (43, 63, 64, 92). This increase in IMT has been related to higher insulin dose, suggesting that high levels of insulin may have a detrimental influence on the arterial wall. However, recent data in adults showed that progression of IMT thickness was reduced in subjects receiving intensive diabetes treatment (65). Therefore, it is likely that a more complex relationship exists between insulin and IMT.

Children with Type 1 diabetes also exhibit lower FMD compared with controls (43, 74, 92). The reduced FMD has been attributed to increased inflammatory status (71) or a combination of inflammation and expression of human leukocyte antigen, suggesting a genetic influence as well. Others have shown a relationship between FMD and LDL-cholesterol (43), suggesting an influence of lipid status, but this is not a universal finding (92). Folate status has also been related to FMD, which implies a potential influence of homocysteine levels on FMD in children with Type 1 diabetes (74). Recent evidence (32) also suggest increased arterial stiffness in children with Type 1 diabetes. These findings show that Type 1 diabetes in childhood is clearly associated with decrements in arterial structure and function.

**EFFECTS OF INTERVENTIONS**

Lifestyle interventions, using aerobic exercise training, weight loss, or dietary modifications, have been successful in improving arterial health and in treating arterial dysfunction associated with morbidity in adults (93). This positive response has led to a speculation that lifestyle modifications in childhood may lead to improved arterial health in adulthood. Recent work (see Fig. 2) has shown that various intervention strategies, such as physical activity, diet, and supplementation with antioxidants, can improve arterial function in youth with and without cardiovascular morbidities (23–25, 60, 61, 76, 94, 103, 106).

Limited work on the relationship between physical activity and arterial health in healthy children has provided contradictory findings. Abbott et al. (1) found that habitual physical activity levels as measured with doubly labeled water independently predicted brachial FMD among 5- to 11-yr-old children. Follow-up tertile analysis showed that the most active children had significantly greater FMD compared with their least active peers. Similarly, Schack-Nielsen et al. (87) showed that the amount of time 10-yr-old children spend in play or sport participation is inversely related and independently contributes to the arterial stiffness of both the aorto-radial and the aorto-femoral segments. In contrast, Reed and coworkers (79) found no significant relationship between the total amount of physical activity, estimated with a 7-day questionnaire, and arterial compliance in 9- to 11-yr-old children. These disparate results...
may reflect a weak relationship between physical activity and arterial function in healthy children or known difficulties in accurately estimating physical activity levels. To reach definitive conclusions, however, considerably more work is needed.

Limited cross-sectional research suggests that aerobic fitness may contribute to improved endothelial function in healthy children (79, 95). In one study, aerobic fitness explained 23% of the variance in femoral FMD among children aged 11–14 yr (95). Similarly, performance on a 20-m shuttle-run appears to contribute to large- and small-artery compliance (15% and 7%, respectively), with children who show the highest performance score also showing higher arterial compliance than those with the lowest performance scores (79). In contrast, 12-yr-old boys who had undertaken swim training (8–10 h/wk) for at least 4 yr have demonstrated higher upper-limb PWV and lower pressure-corrected index of distension compared with age- and sex-matched nonswimmers (97). Furthermore, the child swimmers showed PWV values similar to those of adults, suggesting an early detrimental effect of high-volume swim training on upper-limb arterial stiffness in children. These findings underscore the importance of considering the type of exercise stimulus in evaluating the effect of exercise training on arterial function in youth. It is also evident that the mode, volume, and duration of exercise training that may improve arterial stiffness and endothelial function in healthy children remain largely unknown.

The seemingly favorable response of the arterial system of healthy children to physical activity and exercise is probably related to increased NO bioavailability. This is thought to result from the upregulation of eNOS gene expression in response to vascular wall shear stress caused by exercise-related increases in systemic blood flow (31, 33, 34). Since basal NO levels also contribute to arterial compliance, this may also partially explain the positive effect of physical activity on PWV.

Similar to physical activity, an 11-yr-long dietary intervention (low saturated fat) was shown to have long-term beneficial effects on endothelial function in boys, but not in girls (78). The intervention, which was initiated in infancy, improved brachial FMD in boys at age 11 yr compared with controls. This effect was nonsignificant after adjustment for cholesterol levels at age 3 yr, suggesting that the relationship between endothelial function and diet was mediated by changes in cholesterol levels.

There is more information available on the effect of various interventions on the arterial function in youth with morbidities that may contribute to early atherosclerosis, such as obesity, Type 1 diabetes, and hyperlipidemia, probably because children with these conditions show disrupted endothelial function (Fig. 1) (23–25, 60, 61, 76, 94, 103, 106). Recent evidence suggests that this unfavorable profile may be reversed to a certain extent by various intervention strategies. Notably, endothelial function is nearly normalized following several types of interventions in various populations of children with risk factors (Fig. 2).

Among overweight and obese children and adolescents, arterial health may improve following short-term lifestyle interventions, using either exercise training or dietary modifications, or a combination of exercise and diet (47, 48, 100, 101, 104). Exercise training alone improves and nearly normalizes brachial FMD in obese children and adolescents (48, 100, 101). This positive outcome appears to result after only 6–8 wk of exercise training conducted three to four times per week and incorporating either 60 min of sport and play activities (101) or 30–50 min of progressively increased aerobic exercise at 50–80% of the age-predicted maximum heart rate (48), or a combination of aerobic and resistance exercise training (100). Interestingly, the exercise-induced improvement in endothelial function was reversed after only 6 wk of inactivity (100), thus justifying a recommendation for continuous exercise training (100, 104).

Six weeks of a dietary intervention, consisting of a well-balanced hypocaloric diet, improved endothelial function in overweight and obese children aged 9–12 yr (104). Analogous short-term benefits have been obtained from combinations of dietary modification and exercise training (47, 104), potentially surpassing those of diet alone (104). In contrast, carotid IMT (104) has not been shown to be responsive to short-term lifestyle interventions in this population of children.

The rapid improvement in endothelial function to short-term interventions suggests that exercise and/or dietary intervention improves NO-mediated vasodilator function, probably through both direct and indirect effects (31). It is likely that shear stress-mediated improvement in NO availability occurs as well as possible changes in the effect of free radical degradation of NO availability (31). However, short-term interventions appear to have little effect on vascular remodeling, suggesting functional changes precede structural changes.

Longer-term interventions have demonstrated improvements both in carotid IMT and in endothelial function of overweight or obese youth (60, 104, 106). Six months of exercise training improved FMD and carotid IMT in obese youth aged 11–16 yr compared with age-matched controls (60). Similar results have been documented in 9- to 12-yr-old children following 12-mo-long regimens of either dieting alone or diet and exercise, with the latter showing greater benefits than the former (104). However, a 12-mo-long intervention in obese prepubescents that included exercise training, nutrition education, and behavioral therapy showed improvements in brachial FMD and reduced carotid IMT only in those children who experienced substantial weight loss (106). Although only one of the three
aforementioned studies included a control group, thus making definitive inferences difficult, it does appear that long-term lifestyle modifications hold promise in reversing the impaired arterial health and atherosclerotic profile of youth with obesity.

Although the physiological mechanisms responsible for the above favorable outcomes in children with obesity remain speculative, they are likely multiple given the multidimensional nature of interventions. Exercise-induced upregulation of eNOS is one possible mechanism for the improvements in the atherogenic risk profiles in youth with obesity. However, changes in proinflammatory markers may also contribute to this favorable effect (89). Accordingly, increases in FMD and reductions in IMT following lifestyle interventions have been accompanied by reductions in proinflammatory markers (47, 60, 106). These reductions in inflammation may be mediated by accompanying weight loss and/or decreases in abdominal fat (92). Furthermore, acute inflammation increases arterial stiffness (70), also suggesting an inflammatory link to improvements in arterial compliance.

The potential for improving arterial health through exercise and diet in children with Type 1 diabetes has not been explored. However, 8 wk of supplementation with either folic acid or vitamin B6, or a combination of the two, improved endothelium-dependent dilation of the brachial artery compared with placebo in this population (57, 74). This effect occurs rapidly within 2 h of treatment, and it is maintained over an 8-wk supplementation period (57). One possible mechanism responsible for the improved endothelial function following folic acid therapy relates to an improvement in eNOS regulation or production induced by DHA (28). Similar results were reported when the same diet was used in adolescents with familial hyperlipidemia (24, 25, 28, 29, 61). Short-term supplementation with docosahexaenoic acid (DHA), an omega-3 fatty acid found in fish oil, combined with a diet in accordance with the National Cholesterol Education Program Step II, increased brachial artery FMD compared with both diet alone and diet plus placebo (28). This favorable adaptation was hypothesized to result from possible improvements in eNOS regulation or production induced by DHA (28). Similar results were reported when the same diet was used in conjunction with antioxidant vitamin C and E supplementation (29). Interestingly, short-term dieting alone did not induce any appreciable changes in FMD (28, 29). Conversely, 6 wk of antioxidant therapy alone, using tocopherol and vitamin C, induced marked improvements in the brachial FMD of children with hyperlipidemia compared with controls (61). Antioxidants are thought to reduce inflammation and inactivation of eNOS caused by free oxygen radicals, thus increasing NO availability and improving endothelial function.

CONCLUSIONS AND FUTURE DIRECTIONS

The normal development of IMT, endothelial function, and arterial stiffness among healthy children and adolescents is reasonably well described in the literature. There are very small increases in IMT during childhood, endothelial function does not appear to be different between children and adults, and arterial stiffness increases linearly from 5 to 20 yr of age. Cardiovascular risk factors such as obesity, metabolic syndrome, hyperlipemia, hypertension, and Type 1 diabetes can negatively impact IMT and endothelial function at an early age, although it is currently unknown if the changes in arterial function in children have the same pathophysiological implications as in adults. Nevertheless, exercise training, dietary intervention, or vitamin and folic acid supplementation can partially or almost completely offset the alterations in IMT and endothelial function that accompany cardiovascular morbidities. However, any improvements appear to be rapidly reversed with cessation of the interventions.

Little is known regarding the mechanisms that cause the alterations in arterial structure and function in youth with cardiovascular risk factors. There is also little empirical information regarding the mechanisms that produce the improvements seen in arterial structure and function following exercise, diet, vitamin C, or folic acid supplementation. Furthermore, the most effective way to intervene and improve arterial function and structure in function in youth with cardiovascular risk factors remains speculative. In particular, the most appropriate exercise prescription, type of diet, supplementation regimen, or combination thereof have not been fully described. Also, there is no information to date on the effect of Type 2 diabetes on arterial structure and function in children, which may be of considerable concern considering the rapid increase in the prevalence of this condition during the past several years. Most important, the effect reduced arterial function in childhood has on arterial function and risk of cardiovascular disease in adulthood has not been elucidated to date. We also do not know if reducing the risk factors in childhood, leading to improvement in arterial structure and function, will affect the risk for cardiovascular events in adulthood. To provide these answers, well-designed empirical work must be conducted in the years ahead.

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