Effects of Diet and Exercise on Obesity-Related Vascular Dysfunction in Children

Kam S. Woo, MD; Ping Chook, MD; Chung W. Yu, PhD; Rita Y.T. Sung, MD; Mu Qiao, MS; Sophie S.F. Leung, MD; Christopher W.K. Lam, PhD; Con Metreweli, MD; David S. Celermajer, PhD

Background—The prevalence of obesity in both adults and children is increasing rapidly. Obesity in children is independently associated with arterial endothelial dysfunction and wall thickening, key early events in atherogenesis that precede plaque formation.

Methods and Results—To evaluate the reversibility of obesity-related arterial dysfunction and carotid intima-media thickening by dietary and/or exercise intervention programs, 82 overweight children (body mass index, 25±3), 9 to 12 years of age, were randomly assigned to dietary modification only or diet plus a supervised structured exercise program for 6 weeks and subsequently for 1 year. The prospectively defined primary end points were ultrasound-derived arterial endothelial function (endothelium-dependent dilation) of the brachial artery and intima-media thickness of common carotid artery. At 6 weeks, both interventions were associated with decreased waist-hip ratio (P<0.02) and cholesterol level (P<0.05) as well as improved arterial endothelial function. Diet and exercise together were associated with a significantly greater improvement in endothelial function than diet alone (P=0.01). At 1 year, there was significantly less thickening of the carotid wall (P<0.001) as well as persistent improvements in body fat content and lipid profiles in the group continuing an exercise program. Vascular function was significantly better in those children continuing exercise (n=22) compared with children who withdrew from the exercise program (n=19) (P<0.05).

Conclusions—Obesity-related vascular dysfunction in otherwise healthy young children is partially reversible with diet alone or particularly diet combined with exercise training at 6 weeks, with sustained improvements at 1 year in those persisting with diet plus regular exercise. (Circulation. 2004;109:1981-1986.)

Key Words: endothelium ■ exercise ■ atherosclerosis ■ lifestyle ■ obesity

The prevalence of obesity in adults is increasing rapidly in the developing world, having already become extremely common in industrialized nations. Of even greater concern, the prevalence of obesity is also increasing rapidly in children, now being >10% in developed countries.

Atherosclerosis is a complex multifactorial disease, the earliest stages of which are known to commence in childhood. We and others have demonstrated that obesity in children is independently associated with arterial endothelial dysfunction and wall thickening, key early events in atherogenesis and markers of arterial damage that precede plaque formation. To assess the reversibility of such early arterial damage in children, we studied obese children before and after random assignment to an intervention program of diet alone or diet with exercise training to define potentially effective strategies to improve obesity-related vascular abnormalities.

Methods

Subjects
We evaluated 82 overweight or obese children (body mass index \[\text{BMI}\] ≥21)* before and after an intervention program involving diet only or diet with regular exercise. To be eligible, children had to have a known medical illness and no alternative cause for their obesity, no family history of premature cardiovascular disease, be taking no regular medications or vitamin supplementation, and have resting brachial artery diameter >2.5 mm (previously shown by us to be the optimal size for vascular reactivity testing).

For the recruitment of obese children, invitations to participate were sent to apparently obese children 9 to 12 years of age by school teachers in 13 local primary schools; 170 children and their parents showed interest and were invited to the hospital for basic anthropometric measurements. All children who were obese (BMI ≥23)* or overweight (BMI, 21 to 23) were further assessed for any coexisting medical illnesses. Children with a history of diabetes, renal disease, or cardiovascular disease or those whose sexual maturity status was more advanced than Tanner stage 2 were excluded; 151 children were eligible by these criteria. Of these, 82 children agreed to participate and were enrolled into the intervention study.

Received March 25, 2003; de novo received October 23, 2003; revision received January 22, 2004; accepted February 3, 2004.

From the Department of Medicine and Therapeutics (K.S.W., P.C., M.Q.), the Department of Pediatrics (C.W.Y., R.Y.T.S., S.S.F.L.), the Department of Chemical Pathology (C.W.K.L.), and the Department of Diagnostic Radiology and Organ Imaging (C.M.), Prince of Wales Hospital, The Chinese University of Hong Kong; and the Department of Medicine (D.S.C.), The Royal Prince Alfred Hospital, University of Sydney, Sydney, Australia.

Correspondence to Prof K.S. Woo, Department of Medicine and Therapeutics, Prince of Wales Hospital, Shatin, Hong Kong. E-mail kamsangwoo@cuhk.edu.hk

© 2004 American Heart Association, Inc.

Circulation is available at http://www.circulationaha.org

DOI: 10.1161/01.CIR.0000126599.47470.BE

1981
Anthropometric Measurement and Clinical Examination
Each child visited the hospital initially for physical examination and venesection after a 12-hour overnight fast. Body weight was measured with an electronic body weight scale (Seca Delta Model 707) with subjects dressed in a light T-shirt and shorts. Height was measured with a Harpenden stadiometer. Body fat content was determined by dual-energy radiographic absorptiometry, with the fan beam model (Hologic QDR-4500). Fasting serum cholesterol and triglycerides were assayed enzymatically by using the Boehringer Mannheim Hitachi 911 analyzer. HDL cholesterol was measured after precipitation with phosphotungstate-magnesium. LDL cholesterol was calculated by the Friedewald formula.

Arterial Reactivity and Intima-Media Thickness Studies
The ultrasound method for measuring endothelium-dependent and endothelium-independent dilation was performed as described previously on days separate from exercise program. In brief, the diameter of the brachial artery was measured from high-resolution B-mode ultrasound images (ATL 5000 system, L10–5 transducer) at rest, in response to reactive hyperemia (with increased flow producing endothelium-dependent dilation EDD), again at rest, and after sublingual nitroglycerin (400 μg) (producing endothelium-independent vasodilation, NTG). The experiments were conducted in quiet environment, and no significant changes in their heart rate and blood pressure were observed.

For the evaluation of arterial intima-media thickness (IMT), carotid scans were performed by operators according to a standardized scanning protocol for the right and left carotid arteries, as described previously, using images of the far wall of the distal 10 mm of the common carotid arteries.

Scans were recorded on super-VHS videotape for subsequent off-line analysis at months after study acquisition. The scan analyzer was blinded to the identity of studied subjects and stage of the experiment. The accuracy, reproducibility, low interobserver error, and in control subjects over time for measurements of arterial physiology have been documented previously by us. Endothelium-dependent dilation of the brachial artery is mainly due to nitric oxide release by the endothelium, correlates well with coronary endothelial function in the same subjects, and appears to be predictive of cardiovascular events.

Intervenotional Programs
Of the 82 subjects, half were randomly assigned to dietary modification only and the other half to diet plus a regular supervised exercise program. After 6 weeks, 22 of the 41 children randomly assigned to diet plus exercise agreed to continue the weekly exercise program. After 6 weeks, 22 of the 41 children randomly assigned to diet plus exercise program, and the other 19 children stopped regular supervised exercise but continued 2-monthly diet monitoring program, as did all the original 41 diet only children, for 1 year (Figure 1). All children had to go through 9 stations in each session, twice per week for 6 weeks and then once weekly for 1 year. Aerobic exercise including dance was incorporated into the training. Each training session lasted 75 minutes, including 10 minutes of warm up, 30 minutes of resistance training, 10 minutes of aerobic exercise, 10 minutes of agility training, 5 minutes of cool-down, and short rest periods between stations. All children maintained an exercise intensity at 60% to 70% of predicted maximum heart rate during the aerobic exercise (using pulse oximetry). Participation in the exercise training program averaged 83% of scheduled visits during the first 6 weeks and 79% for subsequent visits.

Statistical Analysis
Descriptive data are expressed as mean±SD. Baseline characteristics and changes after intervention between groups were compared by use of independent-samples t tests. Within-group changes were assessed by paired Student’s t tests and repeated-measures ANOVA. The prospectively defined primary end points of the study were arterial endothelium-dependent dilation and intima-media thickness; all other comparisons were adjusted for multiple tests by use of Hochberg’s modification of the Bonferroni procedure. The determinants of endothelium-dependent dilation and carotid intima-media thickness (and their changes after intervention) were assessed by univariate and multivariate linear regression analyses with SPSS (version 10.0). Statistical significance was inferred at a 2-tailed probability value of <0.05.

Results
Short-Term (6-Week) Intervenotional Program in Overweight and Obese Children
The BMI of our subjects was 25.0±3.0. Fifty-four children were obese (BMI >23) and the 28 others were overweight, with BMI 21 to 23. Mean age was 9.9±1.0 years, and 54 were boys.
At baseline, the overweight children exhibited an impaired endothelium-dependent vasodilation (6.9 ± 2.0%) as compared with a previously described nonobese control group (9.7 ± 3.5%). The two intervention groups (diet only and diet plus exercise) were well matched for age, gender, BMI, body fat content, waist-to-hip ratio, lipid profiles, and glucose levels (Table 1). After intervention, waist-to-hip ratio decreased in both groups, but there was no significant change in body fat content, fat-free mass, and BMI. A significant decrease in total cholesterol was seen in both groups and in LDL cholesterol in the exercise group. Fasting glucose (P < 0.002) reduced slightly in the exercise group only. An improvement in EDD but not NTG of brachial artery after 6 weeks’ intervention was evident in both groups, but the changes were significantly greater after diet plus exercise than with diet alone (P = 0.01) (Table 1 and Figure 2). On

**Figure 2.** Endothelium-dependent dilation at baseline and after 6 weeks of intervention with either dietary modification only (left panel) or dietary modification plus supervised exercise program (right panel) (mean ± SD) presented. Improvement in EDD was significantly greater after diet with exercise, compared with diet only (P = 0.01).

### Table 1. Short-Term Results of the Interventional Programs in Overweight/Obese Children (Diet Only Versus Diet and Exercise)

<table>
<thead>
<tr>
<th></th>
<th>Diet Only</th>
<th>Diet Only</th>
<th>Diet Only</th>
<th>Diet Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>Baseline</td>
<td>6 Weeks</td>
<td>Baseline</td>
<td>6 Weeks</td>
</tr>
<tr>
<td>Male</td>
<td>41</td>
<td>41</td>
<td>41</td>
<td>41</td>
</tr>
<tr>
<td>Male</td>
<td>27</td>
<td>27</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>Mean age, y</td>
<td>9.9 ± 0.9</td>
<td>10.0 ± 0.9</td>
<td>10.0 ± 1.0</td>
<td>10.1 ± 1.0</td>
</tr>
<tr>
<td>Height, cm</td>
<td>143.3 ± 6.7</td>
<td>145.1 ± 6.9</td>
<td>146.1 ± 7.4</td>
<td>147.6 ± 6.9</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>50.3 ± 8.5</td>
<td>50.9 ± 8.2</td>
<td>54.6 ± 9.5</td>
<td>55.2 ± 9.5</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>37.3 ± 3.8</td>
<td>37.0 ± 3.5</td>
<td>37.9 ± 3.6</td>
<td>37.3 ± 4.0</td>
</tr>
<tr>
<td>Waist hip ratio</td>
<td>0.89 ± 0.07</td>
<td>0.86 ± 0.05</td>
<td>0.88 ± 0.05</td>
<td>0.85 ± 0.09</td>
</tr>
<tr>
<td>Fat free mass, kg</td>
<td>32.0 ± 5.7</td>
<td>32.3 ± 6.4</td>
<td>32.6 ± 8.3</td>
<td>32.8 ± 6.8</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.8 ± 0.9</td>
<td>4.5 ± 0.8</td>
<td>4.8 ± 0.9</td>
<td>4.5 ± 0.8</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.3 ± 0.3</td>
<td>1.2 ± 0.2</td>
<td>1.3 ± 0.3</td>
<td>1.2 ± 0.3</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>2.9 ± 0.9</td>
<td>2.7 ± 0.7</td>
<td>2.9 ± 0.9</td>
<td>2.6 ± 0.8</td>
</tr>
<tr>
<td>LDL/HDL cholesterol ratio</td>
<td>2.3 ± 0.8</td>
<td>2.4 ± 0.8</td>
<td>2.4 ± 0.9</td>
<td>2.2 ± 0.8</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.2 ± 0.5</td>
<td>1.2 ± 0.6</td>
<td>1.2 ± 0.5</td>
<td>1.5 ± 0.7</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>4.5 ± 0.5</td>
<td>4.3 ± 0.6</td>
<td>4.8 ± 0.3</td>
<td>4.4 ± 0.6</td>
</tr>
<tr>
<td>Brachial artery diameter, mm</td>
<td>2.8 ± 0.2</td>
<td>2.8 ± 0.2</td>
<td>2.8 ± 0.2</td>
<td>2.8 ± 0.2</td>
</tr>
<tr>
<td>Endothelium-dependent dilation, %</td>
<td>6.9 ± 2.0</td>
<td>7.5 ± 1.9*</td>
<td>6.8 ± 2.0</td>
<td>8.0 ± 1.8§</td>
</tr>
<tr>
<td>NTG-induced dilation, %</td>
<td>20.3 ± 2.3</td>
<td>20.5 ± 1.7</td>
<td>19.7 ± 2.0</td>
<td>20.1 ± 2.2</td>
</tr>
<tr>
<td>Hyperemia, %</td>
<td>626 ± 116</td>
<td>632 ± 107</td>
<td>614 ± 123</td>
<td>627 ± 110</td>
</tr>
<tr>
<td>Carotid IMT, mm</td>
<td>0.47 ± 0.05</td>
<td>0.47 ± 0.04</td>
<td>0.47 ± 0.04</td>
<td>0.46 ± 0.04</td>
</tr>
</tbody>
</table>

Comparing baseline and 6 weeks: *P < 0.002; †P < 0.02; ‡P < 0.05; §P < 0.0001.

Improvement in EDD was significantly greater in the diet with exercise group compared with diet only (P < 0.01).
multivariate analysis, both exercise training ($\beta=0.54$; $P=0.02$) and changes in LDL cholesterol ($\beta=0.54$; $P=0.03$) but not changes in waist-to-hip ratio or BMI were independently associated with the observed improvement in EDD (model $R=0.40$; $F=3.18$; $P=0.019$). Considering both interventions together, improvement in arterial endothelial function was seen both in children who were moderately overweight as well as those who were obese (Table 2).

**Discussion**

This study demonstrates that the vascular dysfunction associated with obesity in children is partially reversible by even a short program of dietary modification. The addition of an individualized exercise training program for children enhanced the beneficial arterial effects, which could be sustained when training continued for 1 year. These data underscore the potential importance of diet and exercise in improving outcomes from obesity-related arterial disease, even commencing from an early age.

Body mass index tends to increase in childhood and throughout life. In adults, obesity is regarded as BMI $\geq 30$. In children, by contrast, the 95th percentile for BMI is 21, and we therefore used this as our prospectively defined criterion for overweight (BMI, 21 to 23) and obesity (BMI $\geq 23$) in the current study. Because our study subjects were growing children, we also measured their height, weight, body fat content, fat-free mass, and waist-to-hip ratio as well as their BMI to provide more comprehensive measures of “fatness” before and after intervention. Only small changes in these parameters were observed during the short (6-week) intervention period; however, changes in body fat content were more obvious after 1 year.

After 6-week intervention, significant improvements in endothelium-dependent dilation were evident. The improvement in arterial endothelial function was greater in the diet and exercise group compared with the diet alone group, and independently correlated with long-term improvement in EDD (model $R=0.47$; $F=4.8$; $df=5$; $P=0.002$) after adjustment for age, blood pressure, and lipid levels.

**TABLE 2. Vascular Reactivity Changes in Overweight and Obese Children With Either Intervention (Diet Only or Diet With Exercise)**

<table>
<thead>
<tr>
<th></th>
<th>BMI 21–23 (n=28)</th>
<th>BMI $\geq$23 (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>6 Weeks</td>
</tr>
<tr>
<td>Brachial artery diameter, mm</td>
<td>2.7±0.1</td>
<td>2.7±0.2</td>
</tr>
<tr>
<td>EDD, %</td>
<td>7.4±2.1</td>
<td>8.4±2.0*</td>
</tr>
<tr>
<td>NTG-induced dilation, %</td>
<td>19.6±2.7</td>
<td>21.0±1.7</td>
</tr>
<tr>
<td>Hyperemia, %</td>
<td>612±121</td>
<td>622±103</td>
</tr>
</tbody>
</table>

*P<0.001 compared with baseline.
multivariate regression analysis confirmed the independent effect of exercise training on improved arterial function. Furthermore, the improvement in vascular reactivity was seen over a wide range of BMIs, from 21 to >25, highlighting the potential benefit of such intervention in overweight as well as obese children. Longer intervention and sustained for 1 year produced greater anthropometric and lipoprotein improvements and near normalization of vascular parameters, including endothelium-dependent dilation and carotid IMT. With detraining, some of the early improvements in arterial reactivity were lost, but their EDD at 1 year was still better than the diet only control group, whose vascular improvement was only transient. Although continued training in the exercise group (versus detraining) was voluntary rather than by randomization, our study results suggest the importance of perseverance with exercise and dietary programs in reversing obesity-related vascular dysfunction in children. As endothelial abnormalities are known to be associated with risk of future cardiovascular events, such changes may prove to be associated with clinical benefits in the longer term.

Several other groups have previously demonstrated that exercise improves arterial endothelial function in adults without vascular risk factors or with established coronary disease. Our current study extends these findings, documenting a benefit of exercise on obesity-related arterial disease, in an age group in which exercise capacity and enjoyment are usually at a high level. The mechanism of this benefit is thought to be related (at least in part) to shear stress–related upregulation of endothelial nitric oxide synthase and consequent improvements in vascular production of this vasodilator substance. Other contributing mechanisms might include improvements in insulin sensitivity, proinflammatory cytokines, and/or lipoprotein profiles.

Sedentary habits and a lifestyle lacking in exercise are becoming increasingly prevalent worldwide. Almost half of young people 12 to 21 years of age fail to engage in vigorous activity on a regular basis in the United States, and 1 in 4 children gets no physical education in school at all. Currently 1 in 10 American and British children are obese, and the prevalence of overweight is also rapidly increasing in Asia and the developing world. These factors are important contributors to the major public health problems of diabetes mellitus and coronary artery disease, affecting even developing countries such as China.

Limitations of the present study include the relative intensity of the exercise program, which might be difficult to apply and/or sustain in all obese children, and the possibility of a selection bias in the recruitment process. However, neither BMI nor school performance differed significantly in children who declined participation compared with those who were enrolled. Inclusion of an exercise only group, a nonintervention (ie, no change in lifestyle) group of obese children, and a nonobese sedentary and exercise control group may also have provided further information; however, we thought it difficult to recruit such subjects, particularly without dietary advice also. All ultrasound-derived vascular functions were measured by a blinded investigator, and the high reproducibility between serial observations and in control subjects over time have been documented by us previously. It is possible, however, that hormonal changes over time may have influenced vascular function in these children, but any such differences would be expected to be similar across all the groups of children studied. Furthermore, the improvement observed in carotid IMT after 1-year intervention, although statistically significant, was small and therefore of uncertain clinical significance; this small change may reflect the interaction between improved arterial structure with intervention, counterbalanced in part by the natural growth in vessel walls of children growing rapidly. In adults, 1 SD increase in carotid IMT has been associated with an 2-fold increased risk of ischemic stroke or myocardial infarction; thus even small changes of carotid IMT may correspond to important health gains at a population level.

The treatment of obesity remains difficult. Certain effective drug therapies have been withdrawn from the market because of dangerous cardiovascular effects, and therefore medical treatment of obesity is currently not available for overweight or obese children. Nonpharmacological measures such as diet and exercise therefore represent the mainstays of obesity prevention and treatment in developed and developing countries.
In summary, we have found that diet, especially combined with sustained exercise, improves early signs of arterial dysfunction and thickening in overweight and obese children. In this context, improving obesity-related arterial dysfunction in children by diet and exercise should be regarded as an important strategy for modifying vascular risk in this population.

Acknowledgments
This project was financially supported by the Hong Kong Institute of Heart Health Promotion, the Shaw Foundation, and the Research Grant Council of Hong Kong (CUHK4060/2000M). The authors wish to acknowledge the contributions of Sandy K.S. Chang of the Diestetics Department, Vesto Mo and Sandra Lee of the Physiotherapy Department, and Amy S.L. Lam of the Department of Medicine and Therapeutics of the Prince of Wales Hospital to this work.

References
Effects of Diet and Exercise on Obesity-Related Vascular Dysfunction in Children
Kam S. Woo, Ping Chook, Chung W. Yu, Rita Y.T. Sung, Mu Qiao, Sophie S.F. Leung, Christopher W.K. Lam, Con Metreweli and David S. Celermajer

Circulation. 2004;109:1981-1986; originally published online April 5, 2004;
doi: 10.1161/01.CIR.0000126599.47470.BE
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/109/16/1981

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/