Arterial Structure and Function After Recovery From the Metabolic Syndrome

The Cardiovascular Risk in Young Finns Study

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Background—The reversibility of ultrasonographic vascular changes associated with the metabolic syndrome (MetS) recovery is unknown. We examined whether spontaneous recovery from MetS (according to the International Diabetes Federation definition) has a favorable effect on vascular properties and evaluated the associations between lifestyle factors and MetS recovery.

Methods and Results—We measured carotid artery intima-media thickness, distensibility, and brachial flow-mediated dilatation by ultrasound in 1673 subjects of the Young Finns Study cohort (age, 31.5±5.0 years in 2001) who participated in follow-up studies in 2001 and 2007. At baseline, no differences in intima-media thickness, carotid artery distensibility, or flow-mediated dilatation were observed between the recovery group (baseline-only MetS) and those with incident (only at follow-up) or persistent (both at baseline and follow-up) MetS. After 6 years, the recovery group had smaller intima-media thickness (mean±SEM, 0.62±0.01 versus 0.68±0.01 mm; P=0.0009) and higher carotid artery distensibility (1.98±0.07%/mm Hg versus 1.56±0.04%/mm Hg; P=0.001) compared with the persistent group and higher flow-mediated dilatation compared with the control group (9.91±0.51% versus 8.57±0.12%; P=0.03). The recovery group had reduced intima-media thickness progression compared with the persistent group (0.036±0.005 versus 0.079±0.010 mm; P=0.001) and reduced carotid artery distensibility change compared with the incident group (−0.12±0.05%/mm Hg versus −0.38±0.10%/mm Hg; P=0.03) over the 6-year follow-up. Differences in carotid artery distensibility levels were attenuated (P=0.11) after the inclusion of weight change in the models. MetS recovery was paralleled with significant reductions in waist circumference that independently correlated with increased physical activity and increased attention paid to health habits during the follow-up.

Conclusion—Recovery from the MetS was associated with positive effects on vascular properties during a 6-year follow-up period of young adults. (Circulation. 2010;121:392-400.)

Key Words: cardiovascular diseases ■ carotid arteries ■ exercise ■ obesity

T he cause of cardiovascular disease is multifaceted.1 The metabolic syndrome (MetS) is a constellation of several interrelated cardiometabolic risk factors, including obesity, hypertension, dyslipidemia, hyperglycemia, and insulin resistance, often accompanied by hyperinsulinemia.2,3 Subjects with MetS are at increased risk of developing type 2 diabetes mellitus and clinical cardiovascular disease.4,5

Clinical Perspective on p 400

Carotid intima-media thickness (IMT), carotid artery distensibility (Cdist), and brachial flow-mediated dilatation (FMD) assessed noninvasively by ultrasound are preclinical markers of vascular health. Increased IMT and impaired Cdist and FMD reflect early atherosclerosis and have been found to predict cardiovascular events.6–8 In cross-sectional settings, we and others10 have previously shown that young adults with MetS have increased IMT and decreased Cdist. In addition, MetS is associated with accelerated IMT progression.11–13 Favorable changes in markers of subclinical atherosclerosis have been shown to occur in response to modifications in cardiovascular risk factors.14–19 However, the reversibility of arterial structure and function associated with MetS is unknown.

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The objective of this study was to address this gap in the literature. First, we determined whether recovery from MetS diagnosis over 6 years has a favorable effect on vascular properties. Second, we examined the associations between lifestyle factors and MetS recovery. We addressed these objectives in a population-based sample of young adults (n=11005; mean age at baseline, 31.5 years) participating in the Cardiovascular Risk in Young Finns Study.

Methods

Subjects
The Cardiovascular Risk in Young Finns Study is an ongoing epidemiological study to assess risk factors underlying cardiovascular disease. The first cross-sectional survey was conducted in 1980 when 3596 randomly selected children and adolescents (age range, 3 to 18 years) participated. Thereafter, several follow-up studies have been performed. IMT, Cdist, and FMD were measured in the follow-up studies conducted in 2001 (n=2265) and 2007 (n=2197).

The study flow diagram is shown in Figure 1. The sample for the present analysis (mean age at baseline, 31.5 years in 2001; age range, 24 to 39 years) included those subjects who had undergone ultrasound examinations during both the 2001 and 2007 follow-ups (n=11005). The subjects having incomplete metabolic risk factor data from these study years (n=94), subjects with type 1 diabetes mellitus (n=12), and those female participants who were pregnant at either time point (n=30) were excluded. A total of 1673 men and women were included in the present analysis. Subjects gave written informed consent, and the study was approved by local ethics committees.

Clinical Characteristics
Height, weight, and waist circumferences were measured. Body mass index was calculated as weight in kilograms divided by height in meters squared. Blood pressure was measured with a random-zero sphygmomanometer. The average of 3 measurements was used in the analysis.

Venous blood samples were collected after a 12-hour fast. Lipid determinations for triglycerides, total cholesterol, and high-density lipoprotein (HDL) cholesterol were done with standard methods. Low-density lipoprotein (LDL) cholesterol was calculated with the Friedewald formula for subjects with triglycerides <4 mmol/L. Glucose concentrations were analyzed enzymatically, and serum insulin was measured by microparticle enzyme immunoassay kit. High-sensitivity serum C-reactive protein (CRP) was analyzed by an automated analyzer with a latex turbidimetric immunoassay kit. Details of methods have been described previously.

Smoking habits, physical activity, and attention paid to health habits were ascertained with questionnaires. Physical activity is represented as a metabolic equivalent index by assessing the duration, intensity, and frequency of physical activity, including leisure-time physical activity and commuting. As part of the questionnaire, participants were asked to indicate the degree to which they paid attention to healthy lifestyle habits: (1) not at all, (2) quite a lot, (3) quite little, or (4) considerable. Information on food consumption was assessed with food frequency questionnaires. In 2001, a short nonquantitative food frequency questionnaire with 20 items (representing the main food groups) was used to estimate the number of weekly portions of selected food groups. In the latest follow-up in 2007, the participants completed a more comprehensive, semi-quantitative 128-item food frequency questionnaire that provided an estimate of food consumption in grams per day. Detailed information on the food frequency questionnaires and their validity has been published elsewhere.

Ultrasound Imaging
An ultrasound imaging device with a high-resolution system (Sequoia 512, Acuson, Calif) was used. Ultrasound studies were performed by trained sonographers following a standardized protocol. Measurements were made offline from stored digital images. All ultrasound scans were analyzed by 1 reader (same reader in 2001 and
A series of multiple regression models. The models included age- and sex-specific treatment for this lipid abnormality, reduced HDL cholesterol (<1.036 mmol/L [40 mg/dL] in men, <1.295 mmol/L [50 mg/dL] in women) or specific treatment for this lipid abnormality, reduced blood pressure (blood pressure ≥130/85 mm Hg) or treatment of previously diagnosed hypertension, or raised fasting plasma glucose (5.6 mmol/L [101 mg/dL]) or previously diagnosed type 2 diabetes mellitus. 

Significant linear trends from the control group to the persistent group were observed for waist circumference, body mass index (BMI), weight, blood pressure, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, glucose, insulin, CRP, and metabolic equality index at follow-up.

### Six-Year Risk Factor Changes

Table 2 shows the age- and sex-adjusted changes in risk factors and lifestyle habits between 2001 and 2007. A linear increasing trend from the control group to the persistent group was observed for change in waist circumference, BMI, weight, triglycerides, glucose, and insulin, and a decreasing trend for change in HDL cholesterol was seen. The most favorable changes were observed in the recovery group during the 6-year follow-up period. Despite nonsignificant trends, we observed a difference in systolic blood pressure and CRP between the recovery and incident groups ($P<0.0001$ and $P<0.0001$, respectively) and between the
Table 1. Characteristics of Study Subjects

<table>
<thead>
<tr>
<th>Subjects, n</th>
<th>Year</th>
<th>Control Group</th>
<th>Recovery Group</th>
<th>Incident Group</th>
<th>Persistent Group</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>2001</td>
<td>32.7±4.9</td>
<td>32.8±4.7</td>
<td>33.4±4.6</td>
<td>31.5±5.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>2001</td>
<td>47</td>
<td>55</td>
<td>63</td>
<td>41</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>2001</td>
<td>80±10</td>
<td>95±10</td>
<td>89±10</td>
<td>102±10</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>2001</td>
<td>23.6±3.4</td>
<td>29.2±4.3</td>
<td>26.5±3.6</td>
<td>31.2±4.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>2001</td>
<td>70.1±12.9</td>
<td>86.1±16.1</td>
<td>79.8±12.9</td>
<td>94.8±16.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Triglycerides,* mmol/L</td>
<td>2001</td>
<td>1.1 (0.3–1.3)</td>
<td>1.0 (0.3–1.3)</td>
<td>1.0 (0.3–1.3)</td>
<td>1.0 (0.3–1.3)</td>
<td>0.11</td>
</tr>
<tr>
<td>CRP,* mmol/L</td>
<td>2001</td>
<td>0.65 (0.27–1.34)</td>
<td>1.91 (0.86–3.76)</td>
<td>0.89 (0.36–1.88)</td>
<td>1.75 (0.91–3.05)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>2001</td>
<td>4.93±0.40</td>
<td>5.14±0.44</td>
<td>5.14±0.37</td>
<td>5.42±0.91</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Insulin,* IU/L</td>
<td>2001</td>
<td>5.6 (4.0–8.0)</td>
<td>9.5 (7.0–13.0)</td>
<td>7.3 (5.0–10.0)</td>
<td>12.6 (9.0–18.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Vegetable consumption,* frequency/wk</td>
<td>2001</td>
<td>5.8 (3.0–9.5)</td>
<td>5.3 (3.9–9.5)</td>
<td>5.4 (3.0–6.3)</td>
<td>5.0 (3.0–6.3)</td>
<td>0.2</td>
</tr>
<tr>
<td>Fruit consumption,* frequency/wk</td>
<td>2001</td>
<td>5.9 (3.0–9.5)</td>
<td>5.6 (3.0–9.5)</td>
<td>5.3 (3.0–9.5)</td>
<td>5.0 (3.0–6.3)</td>
<td>0.03</td>
</tr>
<tr>
<td>Meat consumption,* frequency/wk</td>
<td>2001</td>
<td>3.3 (1.3–6.3)</td>
<td>3.5 (3.0–6.3)</td>
<td>3.6 (3.0–6.3)</td>
<td>3.5 (3.0–6.3)</td>
<td>0.2</td>
</tr>
<tr>
<td>Fish consumption,* frequency/wk</td>
<td>2001</td>
<td>1.1 (0.3–1.3)</td>
<td>1.0 (0.3–1.3)</td>
<td>1.0 (0.3–1.3)</td>
<td>1.0 (0.3–1.3)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Values are mean±SD or geometric mean (25th–75th percentiles) as appropriate. P values are from linear regression models adjusted for age and sex.

*Geometric mean values.

recovery and persistent groups (P < 0.02 and P < 0.002, respectively).

Next, age- and sex-specific standardized changes in multiple lifestyle variables (physical activity, attention paid to health habits, and alcohol, vegetable, fruit, meat, and fish consumption) were regressed against change in metabolic components. In these models, all lifestyle variables were included simultaneously in the models as covariates. Decrease in physical activity and decrease in attention paid to health habits were independently associated with increase in waist circumference (β = −0.05±0.02, P < 0.005; and β = −0.08±0.02, P < 0.0001, respectively). A decrease in attention paid to health habits was independently associated with an increase in systolic blood pressure (β = −0.06±0.02; P < 0.03), and an increase in physical activity was associated with an increase in HDL cholesterol (β = 0.06±0.03; P = 0.03).
Association Between MetS Status and Vascular Measures

Figure 2 shows the age- and sex-adjusted mean values of IMT, Cdist, and FMD between study groups in 2001 and 2007. At baseline, in 2001, subjects in the recovery group had lower Cdist compared with the control group. At the follow-up in 2007, subjects in the recovery group had smaller IMT (Figure 2A) and higher Cdist (Figure 2B) compared with subjects with persistent MetS. The difference in Cdist at baseline between the recovery and control groups was diminished at the follow-up in 007. In addition, those in the recovery group had a higher FMD compared with subjects in the control group at the follow-up in 2007. In addition, those in the recovery group had higher FMD compared with subjects in the control group at the follow-up in 2007 (Figure 2C).

Next, we assessed whether weight change or MetS component changes have accounted for the findings. These analyses were performed as follows. First, we included changes in weight, waist circumference, systolic blood pressure, triglycerides, HDL cholesterol, and glucose one at a time in the models to assess the effect of individual risk components. Second, we included all variables simultaneously as covariates. Results for IMT and FMD in 2007 were attenuated when weight change was included as a covariate (\( P < 0.0001 \)). Of the individual MetS component changes, inclusion of the 6-year change in waist circumference and triglycerides also diluted the difference between the recovery group and the persistent group (\( P = 0.54 \) and 0.20, respectively). The results remained similar after inclusion of baseline Cdist in the model.

Discussion

In the present study, we observed that recovery from the MetS over a 6-year period had a positive effect on vascular properties. Subjects in the MetS recovery group had smaller IMT and higher Cdist after the follow-up compared with subjects with persistent MetS, although at baseline there were no differences. In addition, those in the recovery group had a decreased rate of IMT progression compared with subjects who had persistent MetS and a decreased rate of Cdist progression compared with subjects with incident MetS over the 6-year period. Differences in Cdist levels and regression between study groups were attenuated when weight change was taken into account.

To the best of our knowledge, this is the first study to demonstrate the reversibility of subclinical atherosclerotic markers associated with recovery from MetS diagnosis. Our findings are in line with earlier reports demonstrating the effects of MetS exposure on the vasculature. We and others have shown that MetS is associated with accelerated IMT progression. In addition, all current MetS definitions identify individuals with evidence of increased IMT and decreased Cdist. It has been established that preclinical atherosclerosis is not an irreversible but rather a dynamic process. Different interventions on cardiovascular risk factors...
(dyslipidemia, hypertension, diabetes mellitus, and obesity) have been shown to slow or even regress the progression of atherosclerosis. Pathological data from deceased subjects have shown that in young adults (age, 30 to 39 years) preclinical atherosclerotic lesions in the common carotid artery were dominated by foam cell formations. The internalization of LDL particles (which may be enzymatically and oxidatively modified) by macrophages results in the forma-
tion of foam cells, which are known to predispose to fatty-streak formation in atherosclerosis. Foam cell formation is an early manifestation of atherosclerosis, and modified LDL particles may still be subsequently cleared from the artery wall to the liver by HDL cholesterol. Furthermore, we have previously shown that 6-year change in HDL cholesterol was inversely associated with IMT progression. The reversibility of foam cell lesions may explain the dynamic ultrasonographic changes in common carotid artery in subjects with MetS observed in this study. On the basis of these data, favorable changes in vasculature can be achieved by improving metabolic risk factors.

The difference in Cdist change between the recovery group and the incident group was diluted after adjustment for weight or waist circumference changes, suggesting that favorable changes in Cdist may have been mediated by weight loss. In addition, subjects who were recovered from MetS diagnosis had reduced their adiposity levels compared with the other study groups. We also observed that a decrease in physical activity and attention paid to health habits were independently associated with an increase in waist circumference. Furthermore, paying less attention to health habits was independently associated with an increase in systolic blood pressure and an increase in physical activity associated with an increase in HDL cholesterol. Previous studies conducted in samples of overweight adults suggest that weight loss induced by nutritional and exercise intervention is associated with correction of arterial structure and function. As reported in other studies, the weight change observed in the recovery group was associated with favorable changes in blood pressure, lipids, glucose, and insulin. All these metabolic changes have been validated as determinants of vascular structure and function across all age groups. In addition, insulin has been hypothesized as the main mechanism responsible for changes in sympathetic stimulation, which is accompanied by a reduction in Cdist.

In the present study, we unexpectedly observed that in the control and persistent groups, FMD values increased over the 6-year period. We have previously shown in this cohort a curvilinear association between BMI and FMD, so that these variables are directly associated in subjects with BMI values less than $33 \text{ kg/m}^2$. This prior finding provides a possible explanation for the present observation because subjects in the control and persistent groups had increased BMI levels during the 6-year follow-up.

Our study has limitations. In our laboratory, the reproducibility of IMT measurements is fairly good (coefficient of variation, 6.4%), whereas the coefficient of variation values for Cdist and FMD are higher (14.3% and 26.0%, respectively). Therefore, because of the large within-subject variability of especially FMD, the nonsignificant differences in FMD and FMD change between the recovery group and the persistent and incident groups should be interpreted cautiously. Another potential limitation of our study was selection bias resulting from loss to follow-up. However, we observed no difference in MetS prevalence at baseline among subjects who were lost to follow-up between 2001 and 2007 compared with participants at both time points. When comparing baseline risk factors in the recovery and persistent MetS groups, we observed that subjects in the recovery group

**Figure 3.** Comparison of age- and sex-adjusted values (mean and 95% confidence intervals) of (A) IMT progression, (B) Cdist regression, and (C) FMD progression between study subjects (recovery vs control, recovery vs incident, and recovery vs persistent). Comparisons were performed with ANCOVA followed by the Tukey multiple-comparison posthoc test.
had more favorable levels of metabolic variables. It is therefore possible that those with less severe MetS may be more likely to recover. However, at baseline, no differences in vascular parameters were observed between the MetS study groups. Because our study cohort was racially homogeneous, the generalizability of our results is limited to white European subjects. In addition, we are not currently able to study these associations with clinical outcome of cardiovascular events. Instead, we have used vascular ultrasound measures as indicators of the atherogenic process. Strengths of this study include the large, randomly selected cohort of young men and women free of clinical cardiovascular disease.

A better understanding of the underlying mechanisms and the development of lifestyles involved in the dynamics of atherosclerosis are needed for developing early interventions to reduce the incidence of later cardiovascular disease in young adults. Adverse developments of lifestyles in childhood and young adulthood are known to have a strong influence on all the components of MetS and thus on the progression of atherosclerosis. The present study suggests that arterial structure and function may be restored in young adults with MetS by improving metabolic risk factors and weight reduction.

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Disclosures

None.

References


**CLINICAL PERSPECTIVE**

Increased carotid intima-media thickness and impaired carotid artery distensibility and brachial flow-mediated dilatation reflect early atherosclerosis and have been found to predict cardiovascular events. Preclinical atherosclerosis is a reversible, dynamic process. Different interventions on cardiovascular risk factors (dyslipidemia, hypertension, diabetes mellitus, and obesity) have been shown to slow or even regress atherosclerosis. However, the reversibility of ultrasonographic preclinical vascular changes associated with metabolic syndrome recovery is unknown. Our results from a population-based study of young adults (n=1673; age, 24 to 39 years at baseline) suggest that arterial structure and function are restored after spontaneous recovery from the metabolic syndrome. Furthermore, recovery from the metabolic syndrome was associated with weight loss, increased physical activity, and favorable changes in blood pressure, lipids, glucose, and insulin. Therefore, major efforts are needed for the reduction of overweight and an increase in physical activity, particularly in young adults with the metabolic syndrome to reduce the risk of cardiovascular disease later in their life.
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