Effect of bariatric surgery on both functional and structural measures of premature atherosclerosis

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Aims
To bridge the beneficial metabolic effects of pronounced weight loss on one side and the data on morbidity and mortality on the other side, we investigated the impact of profound weight loss on structural and functional markers of early atherosclerosis.

Methods and results
Thirty-seven obese adults were examined before and 18 months after bariatric surgery. Carotid intima–media thickness (CIMT), brachial flow-mediated dilation (FMD), nitroglycerine-mediated dilation, and abdominal fat distribution were assessed by high-resolution ultrasound. Surgery resulted in a body mass index decrease of 9.1 ± 4.9 kg/m² with concomitant improvements in glucose and lipid metabolism. Carotid intima–media thickness diminished from 0.56 ± 0.09 to 0.53 ± 0.08 mm (n = 37; P = 0.004). Flow-mediated dilation improved from 5.81 ± 3.25 to 9.01 ± 2.93% (n = 25; P < 0.001). Both CIMT and FMD were associated with intra-abdominal fat diameter.

Conclusion
The present results demonstrate that bariatric surgery-induced diminution of visceral fat improves both functional and structural markers of early atherosclerosis, providing a link between the weight loss-associated improvements of traditional and non-traditional risk factors and the reduced long-term morbidity and mortality after bariatric surgery.

Keywords
Atherosclerosis • Obesity • Bariatric surgery • Weight loss • Intima media thickness • Flow mediated vasodilation

Introduction
Obesity, defined as a body mass index (BMI) above 30 kg/m², is a leading cause for increased morbidity and mortality. In particular, it is associated with the development of type 2 diabetes mellitus, cardiovascular disease (CVD), an increased incidence of certain forms of cancer and respiratory complications, among others.1

Carotid artery intima–media thickness (CIMT) as well as endothelial function—measured by flow-mediated dilation (FMD)—are established markers of subclinical atherosclerosis and can be assessed non-invasively with high resolution ultrasound. Carotid artery intima–media thickness is associated with traditional and non-traditional risk factors,2 and was found to be disproportionally increased in patients with metabolic syndrome.3,4 Flow-mediated dilation was also shown to correlate with CVD risk factors,5 and is related to the extent and severity of coronary artery disease.6 Moreover, CIMT and FMD are independent predictors for future vascular events.7,8

Surgical intervention has been demonstrated to result in an efficient and long-term weight loss and the amelioration of most obesity associated risk factors,9,10 thereby reducing overall mortality and morbidity.11,12

However, so far no data exist on substantial weight loss-induced changes in CIMT, and reports implying that intentional weight loss improves impaired endothelial function as assessed by FMD are contradictory.13,14 We therefore examined the effect of bariatric surgery-induced pronounced weight loss on CIMT and endothelial dysfunction in a prospective study design.
Methods

Subjects

Patients desiring surgical intervention for the treatment of obesity were initially referred to the surgical department to determine the patients’ eligibility for surgery. If a subject was eligible, an operation was scheduled after work up at the department for psychosomatic medicine and the outpatient clinic for metabolism, where patients were consecutively screened for eligibility and enrolled when informed consent was given. The total number of patients undergoing bariatric surgery during the recruitment period was 449, of whom 184 were eligible for the study. Written informed consent for was given by 181 patients, who underwent CIMT and FMD measurements before surgery. Prospective CIMT and FMD data were obtained in 37 patients. Inclusion criteria were a BMI \(>35\) kg/m\(^2\) and at least one comorbidity (hypertension and dyslipidaemia) or a BMI \(>40\) kg/m\(^2\). Exclusion criteria were overt diabetes, uncontrolled hypertension (\(>160/90\) mmHg), history of CVD, secondary causes of obesity, pregnancy, lipid lowering or antipsychotic medication, and alcohol consumption of more than 20 g alcohol per day. Three patients received thyroid hormone preparations and three patients antihypertensive therapy. Drug doses were not modified in the course of the study. Five patients were current smokers and self-reported smoking 5–10 cigarettes a day. Acute infectious and inflammatory diseases were excluded by taking a medical history and performing physical and laboratory examinations. The study subjects were examined within a 2 month period prior to the bariatric procedure and 18 months after either laparoscopic adjustable gastric banding (n = 29) or gastric bypass (n = 8). The surgical procedures were performed at the Department of Surgery, Medical University Innsbruck as previously described.\(^{15}\)

Informed consent was obtained from all subjects. All procedures were performed in accordance with institutional guidelines of the Department of Internal Medicine I at the Medical University Innsbruck and the study was approved by the local ethical committee.

Brachial artery study

Endothelial-dependent dilation (FMD) and endothelial-independent dilation (nitroglycerine-mediated dilation (NMD)) were determined as previously described.\(^{16}\) Variation coefficient in our laboratory was less than 3%, based on measurements taken from the same subjects on separate days. Smokers refrained from smoking on the morning prior to the ultrasound examination. Due to nitroglycerine-induced headache in 10 patients at the examination before surgery, these patients refused to repeat the NMD measurement at follow-up. Thus, we obtained complete prospective NMD data sets of 15 patients for further analysis.

Carotid artery study

Longitudinal B-mode scans of the common carotid artery were obtained immediately after the brachial artery studies as previously reported.\(^{16}\) The far wall was assessed just proximal to the carotid bulb (last 2 cm) to identify the maximal CIMT, defined as the distance between the junction of the lumen and the intima and that of the media and adventitia. Three measurements of the right and left carotid artery were averaged to determine the CIMT. In case of atherosclerotic plaques in the carotid arteries indicating an advanced stage of atherosclerosis, these patients (n = 12) were excluded from further FMD and NMD analyses.

Abdominal ultrasound study and body composition

Subcutaneous (SFD) and visceral fat diameter (VFD) were determined as described by Pontiroli et al.\(^{17}\) Measurements were performed in triplicates. Body composition (lean mass and fat mass) was determined by impedance analysis using InBody 3.0 Body Composition Analyzer from Biospace Europe (Dietzenbach, Germany) with an integrated scale. All measurements were taken in the morning in the fasted state.

Laboratory analyses and risk calculations

Blood was drawn after an overnight fast from the antecubital vein into EDTA tubes (1.6 mg/mL) and was centrifuged at 3000 rpm for 10 min at 4°C immediately after collection. Plasma samples were stored at –80°C until assayed.

Plasma triglycerides (TG), total cholesterol, and high density lipoprotein cholesterol (HDL-C) were quantified using a commercially available enzymatic kit (Roche Diagnostic Systems, Basel, Switzerland). Low density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula. Plasma glucose was measured by the hexokinase method on a Cobas MIRA analyzer. Plasma insulin was determined by a micro particle enzyme immunoassay from Abbott (Wiesbaden, Germany). The homeostasis model of assessment of insulin resistance (HOMA-IR) was calculated by the following formula: fasting serum insulin concentration (\(\mu U/mL\)) \(\times\) blood glucose concentration (mmol/L)/22.5.

Framingham risk scores (FRS) were calculated using the ATP III charts.\(^{18}\) The risk factors considered were gender, preoperative age, smoking status, total cholesterol levels, HDL-C levels, blood pressure, and history of treated hypertension. From the Framingham charts, an estimated 10 year coronary heart disease (CHD) risk was assigned to each subject. According to the risk stratification proposed by Greenland et al.,\(^{19}\) all subjects were in the low-risk category (estimated 10 year CHD risk < 10%).

Statistical analysis

To avoid inflation of type I error in our study population, statistical analyses were limited to the primary outcome measures CIMT and FMD and anthropometric measures as well as the most important parameters of glucose and lipid metabolism, for which associations with both CIMT and FMD have been described in the past. The Shapiro–Wilk test was used to determine normal distribution of the data. Not normally distributed data (VFD, VFD/SFD ratio, insulin concentration, HOMA-IR, and TG levels) were log-transformed to approximate a more normal distribution; transformed values were used for further analyses. The paired-sample t-test was used to determine significant changes before and after bariatric surgery. Framingham risk scores were tested for significant differences by the Wilcoxon signed-ranks test due to the ordinal character of the variable. Differences in means between two groups were analysed using the independent samples t-test. Pearson correlation coefficients of both baseline and follow-up as well as delta values were calculated to test for associations of CIMT and FMD with age, sex, weight, BMI, fat mass, lean mass, waist, waist-to-hip ratio (WHR), systolic and diastolic blood pressure, SFD, VFD, hs-C-reactive protein, glucose, insulin, HOMA-IR, total cholesterol, HDL-C, LDL-C, and TG. Data are expressed as mean ± SD, while not normally distributed data are presented as median and interquartile range. A two-sided P-value smaller or equal to 0.05 was considered as statistically significant. All analyses were performed using SPSS 13 for Windows (SPSS, Chicago, IL, USA).
## Results

Median age of the study population was 35 years, ranging from 21 to 52 years. Anthropometric measures before and after bariatric surgery are given in Table 1. Biochemical parameters of glucose and lipid metabolism are presented in Table 2. While age and BMI were not significantly different between sexes at study entry, men had higher diastolic blood pressure, plasma glucose, total cholesterol, and TG levels as well as greater waist circumference and VFD (all $P < 0.05$). Measures of CIMT, FMD, blood pressure, and FRS are shown in Table 3. Individual changes in CIMT and FMD during the study are depicted in Figure 1. Regression of CIMT was observed in two-thirds of the study population. Flow-mediated dilation improved in 84% of patients, with FMD values increasing above 9% in 40% of the measured subjects.

At baseline, CIMT was correlated with age ($r = 0.417, P = 0.011$), sex ($r = 0.374, P = 0.025$), WHR ($r = 0.491, P = 0.003$), VFD ($r = 0.508, P = 0.001$), glucose ($r = 0.490, P = 0.002$), HOMA-IR ($r = 0.387, P = 0.028$), HDL-C ($r = -0.332, P = 0.048$), and TG ($r = 0.367, P = 0.028$). Flow-mediated dilation was associated with WHR ($r = -0.431, P = 0.028$), VFD ($r = -0.448, P = 0.017$), and TG ($r = -0.652, P < 0.001$). After surgery, CIMT was correlated with age ($r = 0.490, P = 0.002$), weight ($r = 0.332, P = 0.045$), waist ($r = 0.368, P = 0.027$), and VFD ($r = 0.607, P < 0.001$), whereas correlation of FMD with other variables were not significant. The associations between VFD and CIMT at both timepoints were still significant after adjustment for BMI or total fat mass. Whereas differences in CIMT were not related to changes in any of the other variables, improvement in FMD showed a negative association with the reduction of VFD ($r = -0.499, P = 0.011$), which remained significant when controlled for BMI ($r = -0.522, P = 0.009$) or total fat mass ($r = -0.494, P = 0.019$).

### Table 1 Anthropometric measures before and after bariatric surgery

<table>
<thead>
<tr>
<th>Parameter (n = 37)</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>125.5 ± 17.7</td>
<td>98.4 ± 18.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>42.42 ± 3.98</td>
<td>33.23 ± 4.78</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>55.2 ± 9.9</td>
<td>34.1 ± 10.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lean mass (kg)</td>
<td>71.1 ± 13.93</td>
<td>64.0 ± 12.37</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>113.7 ± 12.7</td>
<td>95.3 ± 12.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hip (cm)</td>
<td>136.8 ± 9.8</td>
<td>118.4 ± 10.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WHR</td>
<td>0.83 ± 0.10</td>
<td>0.81 ± 0.10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SFD (cm)</td>
<td>4.50 ± 1.25</td>
<td>3.16 ± 1.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VFD (cm)</td>
<td>6.30 (4.52)</td>
<td>1.80 (1.85)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VFD/SFD*</td>
<td>1.33 (1.19)</td>
<td>0.70 (0.49)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are given as mean ± SD. BMI, body mass index; WHR, waist-to-hip ratio; SFD, subcutaneous fat diameter; VFD, visceral fat diameter. *Median and interquartile range.

### Table 2 Parameters of glucose and lipid metabolism before and after bariatric surgery

<table>
<thead>
<tr>
<th>Parameter (n = 37)</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose metabolism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>98.2 ± 11.5</td>
<td>94.3 ± 7.5</td>
<td>0.015</td>
</tr>
<tr>
<td>Insulin (IU/L)*</td>
<td>15.6 (6.9)</td>
<td>7.1 (3.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HOMA-IR*</td>
<td>3.58 (1.92)</td>
<td>1.56 (0.78)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lipid metabolism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>194.5 ± 40.8</td>
<td>176.5 ± 30.8</td>
<td>0.003</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>49.4 ± 102</td>
<td>56.0 ± 12.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>120.1 ± 34.9</td>
<td>103.1 ± 28.3</td>
<td>0.003</td>
</tr>
<tr>
<td>TG (mg/dL)*</td>
<td>120 (58)</td>
<td>74 (48)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are given as mean ± SD. HDL-C, high density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low density lipoprotein cholesterol; TG, triglycerides. *Median and interquartile range.

### Table 3 Cardiovascular risk markers before and after bariatric surgery

<table>
<thead>
<tr>
<th>Parameter (n = 37)</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIMT (mm)</td>
<td>0.555 ± 0.086</td>
<td>0.524 ± 0.080</td>
<td>0.004</td>
</tr>
<tr>
<td>FMD (%) [n = 25]</td>
<td>5.81 ± 3.25</td>
<td>9.01 ± 2.93</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NMD (%) [n = 15]</td>
<td>16.55 ± 5.56</td>
<td>16.96 ± 4.62</td>
<td>0.483</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>131.9 ± 10.3</td>
<td>126.7 ± 9.9</td>
<td>0.011</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>84.5 ± 6.4</td>
<td>81.5 ± 8.8</td>
<td>0.072</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>100.3 ± 6.9</td>
<td>96.4 ± 8.6</td>
<td>0.016</td>
</tr>
<tr>
<td>Framingham risk score*</td>
<td>4 (10)</td>
<td>2 (7)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Values are given as mean ± SD. BP, blood pressure; CIMT, carotid artery intima–media thickness; FMD, flow-mediated vasodilation; MAP, mean arterial pressure; NMD, nitroglycerine-mediated vasodilation. *Median and interquartile range.

### Discussion

Bariatric surgery is a model system for metabolic effects of pronounced weight loss and several trials have demonstrated the beneficial effects of bariatric surgery-induced weight loss on traditional and non-traditional risk factors. Weight loss by either gastric banding or gastric bypass results in the majority of patients in improvement or resolution of hypertension, in a shift towards a more favourable lipid profile with decreased total cholesterol, reduced LDL-C, improved HDL-C, and lower triglyceride levels, as well as lowered fasting glucose levels and improved insulin sensitivity. These beneficial effects are partly mediated by reductions in both cholesterol ester transfer protein-activity and phospholipid transfer protein-activity. Several other biomarkers of obesity and atherosclerosis are modified by pronounced weight loss, such as hs-C-reactive protein, adiponectin, leptin, and...
matrix metalloproteinase-9. However, these are just surrogates of the metabolic improvements that should finally lead to decreased morbidity and mortality in these subjects.

The pivotal studies of Adams et al. and Sjostrom et al. reported for the first time data from large prospective trials on morbidity and mortality. In the study of Sjostrom et al., there was a significant reduction in the adjusted hazard ratio for death (29%) after an average follow-up of 10.9 years in the surgery group. Adams et al. reported that deaths from all causes were reduced by 40%, from diabetes by 92%, and from coronary artery disease by 56%.

To bridge the multiple beneficial metabolic effects of pronounced weight loss on one side and the data on morbidity and mortality on the other side, we investigated the impact of pronounced weight loss on structural and functional markers of early atherosclerosis in a cohort of obese subjects undergoing bariatric surgery. The main results of our study are that CIMT and FMD improve significantly after bariatric surgery induced reduction of body weight and subsequent improvements of cardiovascular risk factors, such as hypertension, insulin resistance, and dyslipidemia. This indicates that early atherosclerotic changes can be reversed by weight loss presumably resulting in reduced long-term cardiovascular risk.

In our study cohort, a mean BMI reduction of 9.9 kg/m² resulted in highly significant improvements of glucose and lipid metabolism, which were accompanied by an annual average CIMT decrease of 0.021 mm, suggesting that in clinically asymptomatic patients structural alterations of the carotid arteries can be reversed by pronounced weight loss. Similar findings were reported by Mavri et al. who investigated CIMT in obese women undergoing a weight reduction program, concluding that CIMT regression may be achieved by weight normalization. Furthermore, patients who had been treated with weight-reducing gastroplasty showed a CIMT progression rate comparable to lean subjects 4 years after the intervention, whereas the progression rate was almost three times higher in obese controls.

Regressions of CIMT were also reported for several atherosclerosis regression trials of lipid-modifying pharmacotherapy. In the Monitored Atherosclerosis Regression Study (MARS), Regression Growth Evaluation Statin Study (REGRESS), or the Atorvastatin vs. Simvastatin on Atherosclerosis Progression (ASAP) study, aggressive lipid lowering was associated with CIMT decreases in the range from −0.031 mm/2 years to −0.056 mm/2 years. Despite the difficulties in comparing CIMT data across interventional trials, in the present study bariatric surgery was similarly effective in reducing mean CIMT as aggressive statin therapy, indicating that pronounced weight loss may be associated with a similar beneficial impact in terms of atherosclerotic regression as aggressive statin therapy.

It has previously been demonstrated that CIMT and FMD provide distinct independent information about atherosclerosis. Whereas FMD identifies abnormalities of the endothelial function preceding the development of a structural lesion, CIMT indicates the presence of vascular damage, suggestive of a more advanced stage of atherosclerosis. Consequently, we analysed FMD in patients without atherosclerotic plaques in the carotid arteries to specifically investigate the early functional changes of the endothelium in asymptomatic subjects. The present study demonstrates that endothelial dysfunction is reversible by bariatric surgery-induced weight loss in obese adults. As impaired endothelial function is known to be associated with increased future cardiovascular risk, this intervention may be associated with long-term clinical benefit. Several other groups have demonstrated that lifestyle, dietary, and pharmacologic interventions improve endothelial function. In particular, Woo et al. described the reversibility of obesity-related endothelial dysfunction and CIMT-thickening in overweight children, who were randomly assigned to dietary modification or diet plus a supervised exercise program for 6 weeks and subsequently for 1 year. Similarly, improvement in FMD was observed in obese children undergoing a 6 week lifestyle
intervention, despite still being overweight at study end.\textsuperscript{34} Hamdy et al.\textsuperscript{35} reported that 6 months of weight reduction and exercise improve FMD in obese subjects with the insulin resistance syndrome.

Visceral fat accumulation plays a key role in the pathogenesis of CVD,\textsuperscript{36} also reflected by the association of VFD and CIMT, a precursor of atherosclerotic plaque development, in the present study. Our findings are in accordance with previous studies evaluating the relationship between abdominal obesity and atherosclerosis using CIMT as outcome measure. Abdominal obesity, determined by WHR, was independently associated with carotid artery wall thickening in a population of middle-aged women.\textsuperscript{37} In a larger scale study using computer-tomography for visceral adipose tissue measurement, visceral adipose tissue was associated with CIMT and plaque area.\textsuperscript{38} These observations were, however, limited by their cross-sectional design. In a prospective trial over 4 years in Finnish men, WHR and waist circumference were not significant, undermines the distinct atherogenic property of the visceral fat depot irrespective of total adiposity. The mechanism whereby excessive lipid storage in the visceral fat depot leads to deterioration of vascular health is complex and probably multifactorial. Several studies have pointed out that visceral obesity-associated alterations of the vasculature are likely a consequence of perturbation of the normal physiological balance of adipokines, glucose homeostasis, and lipid metabolism.\textsuperscript{36}

Based on the established association of visceral fat accumulation and cardiovascular risk as well as based on our findings we hypothesize that rather than weight loss itself, the reduction of visceral fat mass with consecutive beneficial effects on insulin resistance, dyslipidaemia, hypertension, (visceral) adipose tissue-derived adipokines and yet unidentified factors may be responsible for the regression of early atherosclerosis. As in trials on lipid or blood pressure lowering measures, CIMT regression was comparable to the one observed in our study despite greater reductions of LDL-cholesterol or blood pressure, our findings suggest that the combined effect on lipids, blood pressure, and glucose homeostasis may account for the observed improvements of CIMT and FMD.

Framingham risk scoring provides a valuable tool for CVD risk assessment and is widely used for the estimation of relative risk and absolute risk of a cardiac event in the near term (e.g. 10 years).\textsuperscript{42} However, despite the significant decrease in FRS, it may not accurately assess the amelioration of cardiovascular risk in our asymptomatic subjects. Framingham risk scores underestimated the risk derived from CIMT measures in nearly every second patient with an intermediate or low risk for future coronary diseases.\textsuperscript{43} Additionally, Lau et al.\textsuperscript{44} recently reported that a measure of FMD or carotid plaque burden significantly increases the accuracy of FRS in predicting coronary events in subjects of low-intermediate risk.

In summary, our results provide evidence that bariatric surgery-induced diminution of visceral fat improves both functional and structural markers of early atherosclerosis, thus providing a link between the weight loss-associated improvements of several cardiovascular risk factors and the reported reduced long-term morbidity and mortality after bariatric surgery.

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Conflict of interest: none declared.

References


