Differentiated Long-Term Effects of Intentional Weight Loss on Diabetes and Hypertension

C. David Sjöström, Markku Peltonen, Hans Wedel, Lars Sjöström

Abstract—The beneficial effects of weight loss in the obese have been widely accepted. Still, there is a lack of controlled studies displaying large maintained weight losses over long periods (>4 years). We wanted to examine the results of long-standing intentional weight loss on the development of diabetes and hypertension in severely obese individuals over an 8-year period. In the ongoing prospective Swedish Obese Subjects (SOS) study, 346 patients awaiting gastric surgery were matched with 346 obese control subjects on 18 variables by a computerized matching program. The controls were drawn from a registry consisting of 1508 obese potential controls examined at primary health care centers in Sweden. Of the 692 selected patients (body mass index $41.2 \pm 4.7$ kg/m$^2$ [mean±SD]), 483 (70%) were followed for 8 years. No significant weight changes occurred in the obese control group over 8 years. Gastric surgery resulted in a maximum weight loss of $-31.1 \pm 13.6$ kg after 1 year. After 8 years, the maintained weight loss was still $20.1 \pm 15.7$ kg (16.3±12.3%). Whereas this weight reduction had a dramatic effect on the 8-year incidence of diabetes (odds ratio 0.16, 95% CI 0.07 to 0.36), it had no effect on the 8-year incidence of hypertension (odds ratio 1.01, 95% CI 0.61 to 1.67). A differentiated risk factor response was identified: a maintained weight reduction of 16% strongly counteracted the development of diabetes over 8 years but showed no long-term effect on the incidence of hypertension. (Hypertension. 2000;36:20-25.)

Key Words: obesity ■ hypertension, essential ■ diabetes mellitus ■ weight control ■ clinical trials

Obesity is associated with an elevated prevalence of hypertension and non–insulin-dependent diabetes mellitus. Epidemiological studies as well as intervention studies indicate that weight loss is associated with reductions of blood pressure and glucose levels and with a decreased incidence of hypertension and non–insulin-dependent diabetes mellitus. For instance, we have previously demonstrated a linear relationship between weight loss lasting 2 years and reductions in blood pressure and glucose levels. Compared with weight-stable obese control subjects, a 23% maintained weight reduction for 2 years resulted in a 2.5-fold reduction in the incidence of hypertension and a 32-fold reduction in the incidence of non–insulin-dependent diabetes mellitus.

However, little is known about the effects of weight loss on hypertension and diabetes in the long run. This may be related to the circumstance that weight reductions are almost impossible to maintain over long periods of time with nonsurgical obesity treatments. Thus, small weight losses and lack of control groups for comparison with surgically treated patients make it difficult to evaluate the beneficial effects of weight loss from available interventions. Furthermore, studies evaluating the effects of weight loss on hypertension have mean follow-up periods not exceeding 4.5 years. Concerning diabetes, however, one retrospective study followed patients after gastric surgery for an average of 9 years. The Swedish Obese Subjects (SOS) study is so far the only prospective intervention study comparing the development of cardiovascular risk factors in obese patients treated with gastric surgery versus matched severely obese control subjects over a long (10-year) period of time. In the present study, the 8-year incidence of diabetes and hypertension in the 2 groups are compared.

Methods

General Design
SOS is an ongoing project consisting of a registry and an intervention study. The registry study is a health examination of obese individuals undertaken by 480 primary health care centers in Sweden. From the registry, eligible patients are recruited into the intervention study. This study consists of 2 groups: 1 surgically treated group and 1 matched conventionally treated control group. The 2 groups will contain 2000 subjects each, and the follow-up period will be 10 years. When selecting controls from potential controls in the registry, a computerized matching program takes the following 18 variables into account: gender (absolute match), age, weight, height, waist circumference, hip circumference, systolic blood pressure (SBP), serum cholesterol, serum triglycerides, smoking, diabetes, premenopausal/postmenopausal state among women, 4 psychosocial variables known to be associated with mortality (current health, availability of social interaction, availability of attachment, and stressful life events), and 2 personality traits related to treatment preferences (psychasthenia and monotony avoidance). The program selects the
potential control whose matching variables move the matching variable means of the control group toward the means of the surgery group as much as possible. Thus, a group and not an individual match is undertaken. A surgically treated patient and his/her control started the intervention on the operation day of the former. Inclusion criteria for the intervention study are an age of 37 to 60 years and started the intervention on the operation day of the former. Inclusion criteria for the intervention study are an age of 37 to 60 years and previously experienced (not within the last 6 months) myocardial infarction were not. All details of the study design have been published before.12

<table>
<thead>
<tr>
<th>Variable</th>
<th>Matching (All)</th>
<th>Inclusion (All)</th>
<th>Changes: 8-y Inclusion (Completers)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control (n = 346)</td>
<td>Surgery (n = 346)</td>
<td>Control (n = 346)</td>
</tr>
<tr>
<td>Age, y</td>
<td>47.7 ± 6</td>
<td>46.5 ± 6 *</td>
<td>48.5 ± 6</td>
</tr>
<tr>
<td>Women, %</td>
<td>65.9</td>
<td>65.9</td>
<td>65.9</td>
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<tr>
<td>Smokers, % (units)</td>
<td>27.8</td>
<td>31.5</td>
<td>28.9</td>
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<tr>
<td>Diabetes, % (units)</td>
<td>6.1</td>
<td>7.8</td>
<td>12.5</td>
</tr>
<tr>
<td>Hypertension, % (units)</td>
<td>37.1</td>
<td>42.5</td>
<td>40.8</td>
</tr>
<tr>
<td>BP medication, % (units)</td>
<td>19.4</td>
<td>23.1</td>
<td>21.4</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>117.4 ± 16.6</td>
<td>119.7 ± 15.6</td>
<td>115.2 ± 17.7</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>41.0 ± 4.7</td>
<td>41.6 ± 3.9</td>
<td>40.2 ± 5.1</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>142 ± 20</td>
<td>141 ± 19</td>
<td>139 ± 18</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>89 ± 11</td>
<td>89 ± 11</td>
<td>87 ± 10</td>
</tr>
<tr>
<td>Energy intake, MJ/d</td>
<td>12.1 ± 5.7</td>
<td>12.5 ± 4.9</td>
<td>10.8 ± 4.6</td>
</tr>
<tr>
<td>Alcohol intake, g/d</td>
<td>5.3 ± 7.4</td>
<td>5.5 ± 7.3</td>
<td>5.7 ± 9.0</td>
</tr>
<tr>
<td>Physical activity score (leisure)</td>
<td>1.6 ± 0.53</td>
<td>1.6 ± 0.57</td>
<td>1.6 ± 0.54</td>
</tr>
<tr>
<td>Physical activity score (work)</td>
<td>1.8 ± 0.75</td>
<td>2.0 ± 0.80 †</td>
<td>1.8 ± 0.71</td>
</tr>
</tbody>
</table>

Values are mean ± SD. BP indicates blood pressure.

*T < 0.001 and † P < 0.05 vs control. Both groups contained 68% women after 8 years.

Treatments and Study Groups
For the purpose of the present study, 8-year results from the first 346 patients included in the surgically treated group and their 346 matched controls were used. These controls were drawn from a registry that 8 years ago consisted of 1508 obese potential controls. Because of mortality, dropouts, and pending data (26 patients), 8-year data were not available in 95 surgically treated patients and in 114 controls when the data file was compiled. Thus, the 8-year follow-up rates were 73% and 67%, respectively. Table 1 shows characteristics of all 692 patients at matching and at inclusion into the intervention study.

Among the 346 surgically treated patients, 227 had originally received vertical banded gastroplasty, 86 had received gastric banding, and 33 had received gastric bypass.13 Corresponding figures among patients followed for 8 years (Completers) were 164, 63, and 24 patients, respectively. These operations were performed at 25 surgical departments located throughout Sweden. It was neither feasible nor scientifically desirable to introduce a standardized treatment for the controls at the 480 participating primary health care centers. Instead, SOS controls received the customary obesity treatment of the site to which they belonged. No antiobesity drugs were registered in Sweden during the study period. Given the poor long-term results after traditional obesity management,5 poor weight loss effects were anticipated after nonsurgical treatment. Thus, these patients were expected to constitute a control group, which would not, on average, experience intentional weight loss.

Measurements
The following anthropometric measurements have been used in the present report: body weight to the nearest 0.1 kg without shoes in indoor clothing and body height to the nearest 0.01 m. SBP and phase-5 diastolic blood pressure (DBP) were measured once after 15 minutes with patients in a supine position. The patients spent the last 5 of these 15 minutes in complete rest. Cuff width and upper arm circumference were recorded in each individual case. The blood pressures were adjusted for any incongruities in these measurements before analysis.14 Energy and alcohol intake were measured by a questionnaire,15 validated in obese and nonobese subjects. The level of physical activity during work and leisure time was recorded by 4 graded scales.16

Criteria for Health and Disease
The diagnosis of diabetes was based on self-reported data collected in questionnaires. The diagnosis of hypertension required an SBP of at least 160 mm Hg or a DBP of ≥95 mm Hg or medication prescribed specifically against hypertension. The incidence calculations are based on the diagnoses of maintained diabetes and hypertension among individuals who were not affected by diabetes or hypertension, respectively, at the start of the intervention. Independent analyses were undertaken at 2 and 8 years.

Statistical Methods
Incidence calculations were performed on completers as well as on all included patients. When all included patients were analyzed, missing data were handled by last-value imputation, according to intention-to-treat principles. The intention-to-treat and completer analyses resulted in almost identical results.

The statistical calculations were performed with Stata (StataCorp, 1999); t tests, paired t tests, and ANOVA according to the general linear model were used. For comparisons of changes in proportions between 2 groups, a 2-sample McNemar test17 was used. Unconditional logistic regression was used for comparing incidences in the 2 treatment groups, because these were matched on a group level and not on an individual level. The control group was always used as a reference.

Matching and Dropout Analysis
The automatic matching program produced 2 groups that, with the exception of age (controls were 1.1 years older), were not signific-
significantly (P<0.01) larger weight reduction than did the completers population. Each of the 3 surgical groups had a different pattern (Figure 2). During the first 6 months of rapid weight loss among surgical completers, SBP was reduced by 19.0 mm Hg and DBP was reduced by 7.0 mm Hg (unadjusted changes). In spite of a continuous, albeit slower, decrease in weight, SBP and DBP remained low. In relative terms, the difference in weight change between the 2 groups (20.7 kg) was highly significant (P<0.001). At 8 years of follow-up, the conventional patients had the same weight as at inclusion, whereas the surgical completers had gained 6.4 kg of weight (Figure 1). These weight changes were associated with significantly higher BMI and blood pressures among surgically treated patients, whereas the prevalence of diabetes did not differ significantly between the 2 groups at inclusion (Table 1).

Future dropout individuals tended to have a less favorable risk profile than the completers did. Within the control group, dropouts compared with control completers showed a higher prevalence of diabetes (22% versus 8%, P=0.002) and smoking (40% versus 24%, P=0.0001) at inclusion. Dropouts within both groups had lower scores for physical activity during leisure time than did the completers (P<0.05) at inclusion. Other variables reported in Table 1 did not differ. All dissimilarities between the groups at inclusion into the intervention were adjusted for in the calculations when appropriate. The adjustments had almost no effect on the incidence calculations.

**Results**

**Weight Changes**

Figure 1 shows weight changes among completers over 8 years. The conventionally treated control group was essentially weight stable over the entire period. The surgical groups reached minimum weights after 1 year and then started a slow relapse. Gastric bypass was more efficient than was vertical banded gastroplasty (P=0.057) and banding (P=0.034, ANOVA, Tukey). For the surgical completers as a whole, body weight was reduced from 120.4 kg to 114.7 kg, whereas the controls did not change significantly in weight (from 114.7 kg to 115.4 kg) (Table 1). The difference in weight change between the 2 groups (20.7 kg) was highly significant (P<0.001). In relative terms, the weight change at 8 years was -16.3 ± 12.3% in the surgical group and 0.9 ± 10.8% in the control group.

**Diabetes Prevalence and Observed Blood Pressures**

Whereas the unadjusted prevalence of diabetes among controls followed for 8 years increased from 7.8% to 24.9% during the study period, the surgically treated group had an almost stable prevalence of 10.8% at inclusion and 10.5% at 8 years (P<0.0001 for change in proportions over time between the 2 groups, not shown).

The course of blood pressure over the study period showed a different pattern (Figure 2). During the first 6 months of rapid weight loss among surgical completers, SBP was reduced by 11.4 ± 19.0 mm Hg and DBP was reduced by 7.0 ± 11.0 mm Hg (unadjusted changes). In spite of a continuous, albeit slower,
weight loss during the following 6 months, the reduction in DBP ceased, whereas SBP seemed to increase. From 1 year, SBP and DBP of the surgically treated group increased gradually over the remaining 7 years. For adjusted blood pressure values, see Figure 2. Among control completers, SBP increased gradually, by 5.5±19.0 mm Hg (P<0.001), over the 8 years, whereas DBP was reduced by 2.2±10.5 mm Hg (P<0.002) (Table 1, unadjusted changes). As a consequence of these changes, there was no difference in SBP between the 2 completer groups after 8 years. This was true also after adjustments (Figure 2). The adjusted DBP was, in fact, 2.5 mm Hg (95% CI 0.5 to 4.5, P=0.012) higher in the surgically treated group than in the control group after 8 years, despite a significantly lower body weight.

Incidence Calculations
The 2-year unadjusted diabetes incidence among control completers was 4.7% compared with 0.0% (P=0.0012) among surgically treated completers. The corresponding figures at 8 years were 18.5% and 3.6%, respectively (P=0.0001) (Figure 3). Although the unadjusted 2-year incidence of hypertension was lower among surgically treated completers (3.2%) than among control completers (9.9%, P=0.032), there was no difference after 8 years (26.4% versus 25.8%, respectively; P=0.91) (Figure 3).

Table 2 illustrates that the odds ratios became very similar independent of whether they were calculated on completer or intention-to-treat populations with or without adjustments.

The likelihood for the surgically treated group compared with the control group to develop diabetes after 8 years was on the order of 0.16. The odds ratio for hypertension was on the order of 0.27 at 2 years but close to 1 at 8 years (Table 2).

Post Hoc Calculations
In an attempt to better understand the unexpected relapse in blood pressure within the surgically treated group, several post hoc analyses were undertaken. A rebound in blood pressure among surgically treated patients was also evident when analyzing men and women or smokers and nonsmokers separately (not shown). Among initially hypertensive completers (for control group, n=97, body weight 115.5±18.7 kg, SBP 152±17 mm Hg, DBP 95±10 mm Hg, and use of antihypertensive medication 49%; for the surgical group, n=125, body weight 122.9±16.5 kg, SBP 156±19 mm Hg, DBP 98±9 mm Hg, and use of antihypertensive medication 50%), the prevalence of hypertension at 8 years was 75% among controls and 72% in the surgically treated group (P=0.59), despite a 2-year prevalence of 74% and 53%, respectively (P=0.0012). At 8 years, the 2 initially hypertensive groups weighed 115.8±20.8 and 101.4±17.6 kg, respectively (P<0.0001).

Over the last 7 years of observation, the surgically treated completers regained 11.1±13.1 kg. Changes in blood pressure between years 1 and 8 were examined for surgically treated patients with weight regains above the median (AM group) and below the median (BM group). The increase in SBP was 14.7±21 mm Hg in the AM group and 8.4±21 mm Hg in the BM group (P=0.018). The corresponding increases in DBP were 7.3±12 and 2.9±11 mm Hg, respectively (P=0.004). Thus, a larger relapse in body weight was related to a larger regain in blood pressure. However, even in those 44 surgically treated patients who did not show any weight relapse after year 1 (weight change 1 to 8 years, −9.0±9.8 kg), SBP increased (from 138.5±18.1 to 145.3±17.7 mm Hg, P=0.037), whereas DBP remained stable (from 84.9±8.5 to 83.4±10.2 mm Hg, P=0.230).

The 8-year body weight was significantly related to the 8-year SBP and DBP (P<0.01). Table 3 examines the 8-year SBP and DBP of surgically treated completers as a function of the components of present body weight, ie, the inclusion...
body weight, the weight decrease during the first year, and the weight increase during the remaining 7 years. Inclusion weight was not significantly related to the 8-year blood pressure levels in this study group consisting of obese individuals only. A large weight reduction during the first year tended to be related to lower SBP and DBP levels. Weight increases during the last 7 years were significantly related to higher 8-year blood pressures, in agreement with calculations for the AM and BM groups mentioned above.

Discussion
This 8-year report from the SOS study illustrates that conventional nonpharmacological obesity treatment in the hands of a primary health care system has no effect on body weight, whereas gastric surgery, depending on the chosen technique, results in 18- to 30-kg maintained weight loss. This intentional weight loss in severely obese individuals reduces the 8-year incidence of diabetes to one fifth. In contrast, the effect on blood pressure seems to be of a transitory nature, with no persistent improvement after 8 years.

Diabetes type 2 and insulin resistance are known to react favorably to weight reduction.1,3,11 Our present long-term results are in accordance with these earlier findings. However, our long-term results are not in agreement with earlier controlled studies with a shorter follow-up, indicating the effect of weight loss on blood pressure in hypertensive as well as normotensive subjects.16 Where other investigators have concluded that even small (2- to 3-kg) net weight losses are in accordance with these earlier findings. How-ever, our long-term results are not in agreement with earlier controlled studies with a shorter follow-up, indicating the effect of weight loss on blood pressure in hypertensive as well as normotensive subjects.16 Where other investigators have concluded that even small (2- to 3-kg) net weight losses might be beneficial for the control of hypertension,6 the present study shows that over a long period, not even a maintained 16% weight loss is sufficient to achieve a reduction of the 8-year incidence of hypertension in the severely obese. Our new findings are also in conflict with previous uncontrolled studies involving the surgical treatment of obesity that had shorter follow-up periods, indicating a favorable effect on hypertension.8,9

A regain of blood pressure after weight loss has been shown also in other studies. However, the follow-up periods have usually been too short to allow a complete relapse.5,19–21 In a recently published drug trial, we observed that 6% weight reduction of the placebo group was associated with a complete relapse of the initial blood pressure reduction within 1 year, whereas 8% to 10% weight reduction of the treatment group resulted in no relapse during the first year but in a partial relapse after 2 years.21 Thus, both the degree of weight loss and the length of the observation period may have an impact on the degree of maintained blood pressure reduction being observed. In accordance with one previous study,22 the present data set suggests that the direction of ongoing weight change is more closely related to blood pressure than the initial body weight is. However, neither our data nor previous data22 permit a separation of the effects on blood pressure that are exerted by ongoing weight change from the effects caused by time (aging). It may well be that remaining obesity in the surgically treated patients could have induced a reappearance of hypertension during the course of the study independent of ongoing weight increase. In fact, the post hoc analyses of the weight-stable surgically treated individuals in the present study suggest that this may be the case.

Blood pressure reductions after weight loss have been associated with improvements of insulin resistance and suppression of sympathetic nervous activity.23 Many studies have proposed insulin as a sympathetic activator24 and also as a link between diabetes and hypertension.25 Given the divergent effects of weight reduction on diabetes and hypertension, insulin does not seem to be the only mediator of hypertension or sympathetic nervous system hyperactivity seen in the obese.

One obvious limitation of the present study is that the 2 treatments were not randomly assigned. Although the current postoperative mortality is only 0.22% (4 of 1815), much higher figures (1% to 5%) were prevailing in 1987, when the SOS study was planned. This was why the ethics committees in Sweden did not approve of a randomized design. However, the computerized matching program of the SOS study, which cannot be influenced by the investigators, created 2 study groups that (with the exception of age) were not significantly different with respect to 18 variables related to risk and treatment preferences (see Methods). Age was adjusted for in our calculations but did not contribute significantly to the adjusted incidence of diabetes or hypertension. In fact, adjustments for several potential confounders had only a marginal effect on the unadjusted odds ratio. Thus, the likelihood seems high that the matching procedure created 2 comparable groups. Another possible bias in the present study is that the diagnosis of diabetes was based on self-reported data, which might have led to an underestimation of the number of affected individuals. However, both the baseline prevalence and the 2-year incidence closely match earlier measured values from the SOS study.4 (Biochemistry is available only at 0, 2, and 10 years in the SOS intervention study.) Therefore, we have no reason to believe that the self-reported 8-year data concerning diabetes would diverge substantially from measured values. A third bias of the present study might have been the comparatively high number of diabetic patients at inclusion among future control

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>Mean±SD</th>
<th>8-y SBP</th>
<th>8-y DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion weight</td>
<td>120±16 kg</td>
<td>0.15</td>
<td>0.014</td>
</tr>
<tr>
<td>ΔWeight 0–1 y</td>
<td>−31±14 kg</td>
<td>0.19</td>
<td>0.099</td>
</tr>
<tr>
<td>ΔWeight 1–8 y</td>
<td>11±13 kg</td>
<td>0.28</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Values are β coefficients and P values. Both equations are significant (P<0.05).
dropouts. However, if these patients had stayed in the study to the same extent as in the surgical group, the 8-year prevalence of diabetes in controls would probably have been even higher. This would have resulted in an even larger difference between controls and surgically treated patients. Such a shift seems particularly likely considering the low recovery rate from diabetes among severely obese patients who have not lost weight. Furthermore, this dropout did not affect the incidence calculations.

In conclusion, this controlled intervention against obesity has identified a differentiated risk factor response. Although diabetes is favorably influenced by an intentionally reduced body weight, there seems to be no persistent effect on hypertension despite a maintained 16% weight reduction after 8 years.

Acknowledgments

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References

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