Adiponectin and Bariatric Surgery: Associations With Diabetes and Cardiovascular Disease in the Swedish Obese Subjects Study

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OBJECTIVE

Adiponectin has been implicated in the pathogenesis of type 2 diabetes, but its role for incident diabetes, myocardial infarction, or stroke in obesity is unclear. The aim of this study was to analyze the associations between systemic levels of adiponectin and the aforementioned outcomes in a population with severe obesity at high risk of diabetes and cardiovascular events.

RESEARCH DESIGN AND METHODS

We measured serum concentrations of total adiponectin in 3,299 participants of the prospective controlled Swedish Obese Subjects (SOS) Study (bariatric surgery group, *n* = 1,570; control group given usual care, *n* = 1,729). Median follow-up periods ranged between 10 and 13 years for different outcomes.

RESULTS

In models containing both baseline adiponectin and 2-year changes in adiponectin, high baseline adiponectin and 2-year increases in adiponectin were associated with decreased risk of diabetes and myocardial infarction among controls. In the surgery group, the 2-year weight loss was paralleled by substantial increase in circulating adiponectin (1,807–1,958 ng/mL per 10-kg weight loss). However, neither baseline adiponectin nor 2-year increases in adiponectin were associated with risk of diabetes or myocardial infarction in the fully adjusted models in the surgery group. No associations were found for stroke in either group.

CONCLUSIONS

Taken together, baseline adiponectin and 2-year changes were associated with incident diabetes and myocardial infarction in the control group but not in the surgery group. Baseline adiponectin did not predict treatment benefit of bariatric surgery.

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Adiponectin has anti-inflammatory, insulin-sensitizing, and atheroprotective effects in rodents (1). Although circulating concentrations of adiponectin are uniformly reduced in obesity, their clinical relevance in humans seems more complex (2). Whereas there is a consistent inverse association between circulating concentrations of adiponectin and risk for type 2 diabetes (3), associations with incident cardiovascular events are still controversial (4–6).

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We and others found positive correlations of adiponectin levels with age (7), whereas few studies have investigated intraindividual changes of adiponectin over time (8,9) and their predictive value for disease outcomes (10–13). Adiponectin levels increase concomitantly with weight loss due to lifestyle intervention or bariatric surgery (10,14), but it has not been investigated in detail whether changes in adiponectin are associated with the incidence of diabetes or cardiovascular events.

The ongoing prospective controlled Swedish Obese Subjects (SOS) Study investigates the impact of bariatric surgery on morbidity and mortality in a large, nonrandomized cohort. In this study, bariatric surgery decreased the incidence of diabetes and cardiovascular events and also reduced the mortality rate compared with usual care (15–20). It is not known whether baseline concentrations and/or changes in adiponectin over time are associated with these outcomes in a population with severe obesity. Moreover, it is unclear whether changes in adiponectin simply reflect weight changes over time or whether associations between changes in adiponectin and disease risk may be independent of weight loss. The latter scenario appears conceivable because adiponectin levels are only partially explained by obesity, and other factors such as glucose tolerance, dyslipidemia, and inflammation are additional independent determinants (4,7,8). Our study therefore aimed to assess associations between baseline adiponectin levels and incident diabetes, myocardial infarction, and stroke in this severely obese population and to investigate whether changes in serum adiponectin during the first 2 years of the study are associated with the aforementioned outcomes.

RESEARCH DESIGN AND METHODS

Study Participants and Intervention

The SOS Study is an ongoing, nonrandomized, matched, prospective, controlled intervention study as described in detail previously (15–21). The study design is shown in detail in Supplementary Fig. 1. Briefly, between 1 September 1987 and 31 January 2001, a total of 4,047 obese men and women were enrolled at 25 surgical departments and 480 primary health care centers in Sweden. Subjects were included between the ages of 37 and 60 years if they had a BMI $\geq$34 kg/m^2 for men and $\geq$38 kg/m^2 for women. Exclusion criteria were identical for all study participants as reported before (17).

Of the individuals who were enrolled in the study, 2,010 chose bariatric surgery. These subjects underwent fixed or variable gastric banding, vertical banded gastroplasty (VBG) or gastric bypass (21). To this surgery group, 2,037 control individuals were matched contemporaneously using 18 matching variables predicted to possibly affect prognosis as described (20). The 18 variables used for matching were sex, postmenopausal status, age at exam, daily smoking, diabetes, weight, height, hip circumference, waist circumference, systolic blood pressure, triglycerides, total cholesterol, current health, monotony avoidance, psychasthenia, quality of social support, quality of social support, and stressful life events. An automated matching procedure was performed by a computer algorithm designed to minimize differences between the two treatment groups with respect to any of 18 matching variables. Hence the final matching result could not be influenced by the investigators. The control group received the nonsurgical treatment for obesity that was established at the primary health care center at which they were registered. This nonsurgical treatment was not standardized and ranged from sophisticated lifestyle intervention and behavior modification to, in some practices, no treatment whatsoever. The study was approved by seven regional ethics review boards in Sweden. All patients gave informed consent to participate in the study. The study is registered at ClinicalTrials.gov (NCT0147952).

The current study is explorative, and all analyses were carried out per protocol; i.e., initial controls who underwent bariatric surgery during the follow-up (n = 121) and patients in the surgery group who underwent a second bariatric surgery resulting in a change of the original surgery group (n = 307) were excluded, which reduced the sample size to n = 1,916 and 1,703 in the control and surgery group, respectively (total n = 3,619).

Outcome Measures

The primary outcome of the SOS Study was overall mortality, and secondary outcome variables included diabetes and cardiovascular events. All participants were examined at matching and baseline examinations and after 0.5, 1, 2, 3, 4, 6, 8, 10, 15, and 20 years. Blood samples were taken at matching and baseline examinations as well as after 2, 10, 15, and 20 years. The baseline questionnaire included items on previous diagnosis of diabetes, myocardial infarction, and stroke. The schedule, questionnaires, physical examinations, and laboratory measurements were identical for both groups.

We considered a participant to have type 2 diabetes if he or she reported the use of diabetes medication or if there was documentation of a fasting venous whole-blood glucose level of 110 mg/dL (6.1 mmol/L) or higher (measured until 2009). If fasting venous plasma glucose was measured instead (after 2009), the cutoff value for a diagnosis of diabetes was 126 mg/dL (7.0 mmol/L) or higher (18).

Cardiovascular events were defined as incident fatal and nonfatal myocardial infarction or incident stroke, whichever occurred first. As described previously (17), the following ICD-9/International Statistical Classification of Diseases, Tenth Revision, codes were used: codes 410/I21, I22 for myocardial infarction and codes 431/I61 (intracerebral bleeding); 433; 434/I63, I65, I66 (intracerebral artery occlusion); and 436/I64 (acute but nondefined stroke in terms of bleeding or occlusion) for stroke. Angina pectoris, claudication, transitory ischemic attacks and subarachnoidal bleeding were not included in our outcome variables. Incident cases were identified by cross checking the SOS database against the Swedish National Patient Register, the Cause of Death Registry, and the Registry of the Total Population.

Median duration of follow-up for incident diabetes, cardiovascular

events, myocardial infarction, and stroke was 10, 13, 13, and 13 years, respectively.

Laboratory Measurements

Serum concentrations of total adiponectin were determined using the Quantikine ELISA kit from R&D Systems (Wiesbaden, Germany). Serum samples were from examinations at study baseline and at follow-up after 2 and 10 years using identical standard operating procedures for blood collection, processing, and storage. All blood samples were obtained in the morning after a 10–12-h fast. Sufficient baseline serum samples were not available for 187 controls and 133 individuals in the surgery group, so serum adiponectin was measured for 3,299 participants at baseline. In addition, serum samples were available from 2,886 participants after 2 years and from 2,312 participants after 10 years. Adiponectin measurements were performed consecutively in the same laboratory (German Diabetes Center). Mean intra-assay and interassay coefficients of variation were 3 and 13%, respectively. The limit of detection was 3.9 ng/mL. All samples gave values above the limit of detection. C-reactive protein (CRP) was measured with an ultrasensitive immunoturbidimetric method (Sentinel, Milan, Italy) using the Architect c8200 analyzer (Abbott Laboratories, Abbott Park, IL). Urinary albumin excretion was calculated based on 24-h urine collection, according to the formula, [urine albumin concentration (mg/L) * urine volume (L)] / urine collection time (min), and expressed as milligrams per 24 h.

Statistical Analyses

Mean values and SDs (or proportions) were used to describe the baseline characteristics of the study population stratified into treatment groups or according to the incidence of outcomes. Student *t* test, ANCOVA, and Fisher exact test were used to test for differences between groups. Individuals with prevalent diabetes were excluded for the analysis of diabetes incidence. Associations between changes in adiponectin and changes in body weight were assessed by linear regression analysis, and an interaction test was used to test for differences in the strength of the association between the different treatment groups. Hazard ratios (HRs) and corresponding 95% CIs for the association between baseline adiponectin or 2-year changes in adiponectin were calculated with Cox proportional hazards regression models and standardized to 1,000 ng/mL of the respective value. Individuals with incident events before the 2-year follow-up examination were excluded when 2-year changes in adiponectin were analyzed with regard to the respective outcome. The interaction between adiponectin and sex was analyzed for each outcome, but no significant interaction was observed, so analyses were performed for men and women combined. All *P* values are two-sided. Statistical analyses were performed using the Stata statistical package version 10.1 (StataCorp LP, College Station, TX).

RESULTS

Cohort Description

Baseline characteristics of the 3,299 SOS Study participants for whom samples were available for adiponectin measurements are given in Table 1. Briefly, individuals in the surgery group were slightly younger and heavier and had slightly less favorable metabolic risk factors than individuals in the control group. Supplementary Tables 1 and 2 show that the group of individuals for whom baseline or 2-year data for adiponectin were lacking was comparable to the rest of the cohort, although individuals without data for adiponectin were more likely to be female in both control and surgery groups.

During follow-up, there were 487 incident cases of diabetes (380 and 107 in the control and surgery group, respectively), 278 (155/123) incident cardiovascular events (myocardial infarction or stroke, whichever came first), 169 (91/78) incident cases of myocardial infarction, and 128 (72/56) incident cases of stroke (Table 2). Median follow-up periods ranged between 10 and 13 years. Supplementary Tables 1–6 show the baseline characteristics of the study population stratified by all four outcomes for each treatment group.

Adiponectin Levels at Baseline

At baseline, mean serum adiponectin was 8,268 (SD 4,886) ng/mL in the control group and 7,470 (SD 4,178) ng/mL in the surgery group ($P < 0.001$) (Table 1). In the conventionally treated control group, individuals who suffered from incident diabetes, cardiovascular events, or myocardial infarction during the follow-up period had lower serum adiponectin levels at baseline compared with individuals that remained free from these diseases (Table 2). No differences in baseline serum adiponectin levels were found for individuals with or without incident stroke (Table 2). In the surgery group, individuals with incident diabetes had lower baseline adiponectin levels than those who remained free from diabetes during follow-up, while no there were no differences in baseline adiponectin in individuals with and without cardiovascular events (Table 2).

Associations Between Baseline Adiponectin and Incident Diabetes

High baseline adiponectin levels were associated with decreased incidence of diabetes in both the control group (HR [95% CI] for 1,000 ng/mL of adiponectin 0.911 [0.879–0.943]) and in the surgery group (HR 0.907 [0.852–0.966]) after adjustment for sex, age, and BMI (Table 3, model 1). After adjustment for additional baseline confounders, including lipids, lipid-lowering medication, blood pressure, antihypertensive medication, glucose, insulin, CRP (as proinflammatory immune marker), impaired kidney function (assessed by urinary albumin excretion), and sleep apnea (both comorbidities of obesity) (Table 3, model 3), high baseline serum adiponectin remained associated with lower diabetes risk in the control group (HR [95% CI] for 1,000 ng/mL of adiponectin 0.949 [0.915–0.985]). In the surgery group, which had a much smaller number of cases than the control group, the effect estimate was rather similar but only borderline significant due to a wider 95% CI (0.935 [0.874–1.000]).

Associations Between Baseline Adiponectin and Cardiovascular Disease

In the control group, high baseline adiponectin levels were associated with

Table 1—Baseline characteristics of the study population by treatment group

	Control		Surgery		
	Mean or median*	SD or IQR*	Mean or median*	SD or IQR*	*P*
n	1,729		1,570		
Sex (% male)	30.3		30.9		0.716
Age (years)	48.9	6.2	47.2	6.0	<0.001
Body weight (kg)	114.4	16.2	121.0	16.8	<0.001
BMI (kg/m^2)	40.0	4.7	42.4	4.5	<0.001
Systolic blood pressure (mmHg)	137.9	17.9	145.4	18.8	<0.001
Diastolic blood pressure (mmHg)	85.1	10.6	90.1	11.3	<0.001
Total cholesterol (mmol/L)	5.61	1.05	5.86	1.13	<0.001
HDL cholesterol (mmol/L)	1.35	0.33	1.35	0.32	0.883
Triglycerides (mmol/L)*	1.73	1.12	1.91	1.17	<0.001
Fasting blood glucose (mmol/L)†	5.0	1.9	5.2	2.1	<0.001
Insulin (μU/mL)*	15.2	11.9	18.3	12.4	<0.001
Diabetes (%)	13.3		18.2		<0.001
Urinary albumin excretion (μg/min)*	7.6	10.2	8.9	13.9	<0.001
Sleep apnea (%)	22.2		25.0		0.059
Alcohol consumption (g/day)*	2.1	7.0	2.3	6.8	0.530
Smoking (%)	20.4		24.5		0.005
Lipid-lowering medication (%)	2.0		1.7		0.600
Blood-pressure-lowering medication (%)	27.8		30.1		0.134
Surgical treatment (banding, VBG, GBG) (%)	NA		16.1/68.1/15.9		NA
Adiponectin (ng/mL)	8,268	4,886	7,470	4,178	<0.001
CRP (mg/L)*	4.55	6.11	5.65	6.62	<0.001

Data sets were complete or almost complete for control and surgery groups (*n* = 1,718–1,729 and 1,564–1,570, respectively) apart from HDL cholesterol (*n* = 1,678 and 1,504, respectively). IQR, interquartile range; GBG, gastric bypass; NA, not applicable. *Data are given as median values and interquartile range. †Venous whole-blood glucose was measured in the SOS Study until 2009 (Central Laboratory, Sahlgrenska University Hospital, accredited according to ISO/IEC 189). After 2009, plasma venous glucose was measured instead, and venous plasma glucose levels were converted to blood glucose according to the instructions from Central Laboratory (blood glucose = plasma glucose / 1.12). The data here are presented as fasting whole-blood glucose levels.

decreased risk for cardiovascular events and myocardial infarction after adjustment for sex, age, and BMI (Table 3, model 1), but after adjustment for additional confounders, the associations were attenuated to nonsignificance (Table 3, model 2). In the surgery group, there were no significant associations between baseline adiponectin and cardiovascular events. Additional adjustment for high-sensitivity CRP, kidney function, and sleep apnea had virtually no impact on HRs (Table 3, model 3).

Table 2—Serum adiponectin levels at baseline (mean/SD) stratified by incidence of outcomes

	Adiponectin (ng/mL)		Adiponectin (ng/mL)		
Outcome/treatment group	No incident outcome	*n*	Incident outcome	*n*	*P**
Diabetes					
Control	**9,064 (5,047)**	1,117	**7,280 (4,331)**	380	**<0.001**
Surgery	**7,792 (4,189)**	1,173	**6,774 (3,381)**	107	**0.015**
Cardiovascular events					
Control	**8,410 (4,894)**	1,531	**7,170 (4,780)**	155	**0.003**
Surgery	7,539 (4,176)	1,416	7,157 (4,484)	123	0.334
Myocardial infarction					
Control	**8,399 (4,898)**	1,595	**6,482 (4,496)**	91	**<0.001**
Surgery	7,534 (4,207)	1,491	7,024 (4,086)	78	0.313
Stroke					
Control	8,316 (4,897)	1,614	7,842 (4,851)	72	0.422
Surgery	7,507 (4,157)	1,483	7,543 (5,279)	56	0.950

**P* values refer to the comparison of adiponectin levels in individuals with incident outcome to those without incident outcome. Significant associations are highlighted in boldface.

Baseline Adiponectin and Treatment Benefit

We found no interaction between baseline adiponectin levels and treatment group with respect to incidence of diabetes (*P* for interaction 0.787) or cardiovascular events (*P* for interaction 0.268). In other words, the strengths of the associations between adiponectin and risk of diabetes (or cardiovascular events) did not differ significantly between surgery and control groups.

Changes in Adiponectin and Body Weight During Follow-Up

Mean adiponectin levels increased by 4,877 ng/mL ($P < 0.001$) in the surgery group during the first 2 years of follow-up parallel to a loss of 23.7% of body

Table 3—Association between baseline serum adiponectin and incidence of diabetes, cardiovascular events, myocardial infarction, and stroke

Outcome/treatment group	Events/number at risk*	Model 1		Model 2		Model 3		Model 4	
		HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Diabetes									
Control	380/1,497	**0.911**	**0.879–0.943**	**0.947**	**0.914–0.982**	**0.949**	**0.915–0.985**	**0.904**	**0.868–0.942**
Surgery	107/1,280	**0.907**	**0.852–0.966**	0.943	0.885–1.004	0.935	0.874–1.000	0.949	0.889–1.013
Cardiovascular event									
Control	155/1,686	**0.949**	**0.901–0.999**	0.979	0.933–1.028	0.979	0.932–1.029	0.955	0.907–1.005
Surgery	123/1,539	0.975	0.923–1.029	1.006	0.958–1.056	1.011	0.962–1.062	1.002	0.954–1.053
Myocardial infarction									
Control	91/1,686	**0.905**	**0.827–0.990**	0.933	0.854–1.020	0.934	0.855–1.021	**0.891**	**0.812–0.977**
Surgery	78/1,539	0.973	0.911–1.040	0.995	0.933–1.061	0.998	0.935–1.066	0.998	0.932–1.070
Stroke									
Control	72/1,686	0.982	0.929–1.037	1.016	0.960–1.076	1.017	0.957–1.081	1.000	0.951–1.051
Surgery	56/1,539	0.998	0.921–1.083	1.042	0.980–1.107	1.050	0.984–1.121	1.036	0.973–1.103

HRs are from Cox proportional hazards models. HRs are given per 1,000 ng/mL of baseline serum adiponectin. SDs of baseline adiponectin for the control and surgery groups were 4,886 and 4,178 ng/mL, respectively. Model 1 is adjusted for sex, age, and BMI at baseline. Model 2 is model 1 + total cholesterol, HDL cholesterol, triglycerides, systolic blood pressure, alcohol consumption, smoking, use of lipid-lowering medication, use of blood-pressure-lowering medication at baseline, and *a*) blood glucose and serum insulin at baseline for incidence of diabetes or *b*) diabetes status at baseline for the other end points. Model 3 is model 2 + CRP, urinary albumin excretion, and sleep apnea (self-reported). Model 4 is model 3 + 2-year change in adiponectin. Significant associations are highlighted in boldface. *Model 4 is not directly comparable to models 1–3, because the numbers of individuals without and with incident end points were restricted to those who also had data for 2-year adiponectin available.

weight ($P < 0.001$). In the control group, adiponectin levels decreased slightly but significantly by 262 ng/mL ($P < 0.001$), while body weight was virtually unchanged (0.1%; $P = 0.638$). Overall, associations between 2-year changes in serum adiponectin and body weight changes were similar in men and women in the SOS cohort (Supplementary Fig. 2), and all further data are therefore presented for men and women combined. Supplementary Fig. 3 shows 2-year changes in adiponectin and body weight changes stratified by treatment group.

The correlation between changes in serum adiponectin and changes weight was more pronounced in the surgery groups (serum adiponectin increased 1,807, 1,950, and 1,958 ng/mL per 10-kg weight change for gastric banding, VBG, or gastric bypass, respectively) compared with the control group (1,031 ng/mL per 10-kg weight change; $P < 0.001$ for interaction) (Supplementary Fig. 4). However, there were no statistically significant differences in the slopes between the three surgical groups. These results were not affected by adjustment for baseline age, sex, BMI, and adiponectin levels (data not shown).

Weight loss and reductions in adiponectin levels were less pronounced after 10 years than after 2 years, but associations between 10-year changes in adiponectin and body weight changes were similar to associations for 2-year changes (Supplementary Figs. 5 and 6).

Association Between 2-Year Changes in Adiponectin and Study Outcomes

Two-year increases in adiponectin were associated with lower risk of diabetes in both the control and the surgery group after adjustment for multiple confounders, including baseline adiponectin levels (HR [95% CI] 0.844 [0.798–0.894] and 0.913 [0.842–0.990], respectively) (Table 4, model 3). Again, adjustment for CRP, kidney function, and sleep apnea as comorbidities of obesity had only a minor influence on the observed effect sizes (model 4). Where additional adjustment for changes in BMI (model 5) abolished the association in the surgery group, the HR was almost unchanged in the control group.

Two-year increases in adiponectin were also associated with lower risk of myocardial infarction among controls after adjustment for multiple confounders, including baseline adiponectin. This risk reduction was independent of BMI changes. There were no associations between 2-year changes in adiponectin and the incidence of cardiovascular events or stroke in either treatment group (Table 4).

When 2-year changes in adiponectin were included in the analysis of baseline adiponectin levels in relation to incident outcomes (Table 3, model 4), the associations between high serum adiponectin levels at baseline and reduced risk of diabetes remained significant in the control group (HR [95% CI] 0.904 [0.868–0.942]), and the association between high adiponectin and reduced risk of myocardial infarction was strengthened in controls (HR [95% CI] 0.891 [0.812–0.977]) compared with model 3. In contrast, inclusion of 2-year adiponectin changes did not affect the nonsignificant associations between adiponectin and outcomes in the surgery group (Table 3, model 4).

In a sensitivity analysis, we recalculated all models presented in Tables 3 and 4, substituting BMI with waist circumference as measure of abdominal obesity, and found that HRs were virtually unchanged (data not shown).

CONCLUSIONS

In this study we show that in models containing baseline adiponectin and 2-year changes in adiponectin, high serum adiponectin and its 2-year increases were associated with reduced

Table 4—Association between 2-year changes in adiponectin and incidence of diabetes, cardiovascular events, myocardial infarction, and stroke

Outcome/treatment group	Events/number at risk	Model 1		Model 2		Model 3		Model 4		Model 5	
		HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Diabetes											
Control	363/1,262	**0.851**	**0.807–0.897**	**0.844**	**0.801–0.890**	**0.844**	**0.798–0.894**	**0.840**	**0.793–0.890**	**0.861**	**0.808–0.916**
Surgery	105/1,186	**0.913**	**0.846–0.985**	**0.914**	**0.844–0.989**	**0.913**	**0.842–0.990**	**0.919**	**0.846–0.997**	1.014	0.908–1.133
Cardiovascular event											
Control	118/1,406	0.926	0.842–1.019	0.939	0.853–1.035	0.954	0.887–1.026	0.957	0.891–1.028	0.961	0.891–1.038
Surgery	110/1,410	0.978	0.937–1.020	0.991	0.951–1.034	0.988	0.950–1.029	0.987	0.948–1.027	1.000	0.952–1.051
Myocardial infarction											
Control	69/1,408	**0.839**	**0.715–0.986**	0.860	0.731–1.013	**0.852**	**0.745–0.973**	**0.860**	**0.757–0.977**	**0.858**	**0.750–0.981**
Surgery	69/1,410	0.982	0.933–1.033	0.997	0.949–1.048	1.002	0.954–1.052	1.003	0.955–1.054	1.013	0.950–1.080
Stroke											
Control	56/1,413	1.018	0.922–1.123	1.028	0.923–1.144	1.036	0.938–1.144	1.032	0.935–1.139	1.038	0.933–1.154
Surgery	51/1,412	0.986	0.927–1.050	0.997	0.936–1.062	0.977	0.924–1.034	0.973	0.918–1.032	1.003	0.938–1.071

HRs are from Cox proportional hazards models. Individuals with incident events before the 2-year follow-up examination were excluded. HRs are given per 1,000 ng/mL of 2-year change of adiponectin. SDs for 2-year changes in adiponectin for the control and surgery groups were 2,635 and 5,418 ng/mL, respectively. Model 1 is adjusted for baseline adiponectin. Model 2 is model 1 + sex, age, and BMI at baseline. Model 3 is model 2 + total cholesterol, HDL cholesterol, triglycerides, systolic blood pressure, alcohol consumption, smoking, use of blood-pressure-lowering medication at baseline, baseline adiponectin, and *a*) blood glucose and serum insulin at baseline for incidence of diabetes or *b*) diabetes status at baseline for the other end points. Model 4 is model 3 + CRP, urinary albumin excretion, and sleep apnea (self-reported). Model 5 is model 4 + 2-year changes in BMI. Significant associations are highlighted in boldface.

risk for diabetes and myocardial infarction in the control group (i.e., obese patients given usual care). For stroke, there were no significant associations with baseline adiponectin or its changes after adjustment for multiple confounders. Furthermore, baseline adiponectin was not a predictor of the treatment benefit of bariatric surgery in terms of effects on incidence of diabetes and cardiovascular events during follow-up.

In the surgery group, body weight decreased and serum adiponectin increased markedly. Two-year increases in adiponectin were associated with decreased risk of diabetes, but this association was fully explained by weight changes in the surgery group. No associations were found between baseline adiponectin, its 2-year changes, and incident cardiovascular events in the fully adjusted models.

Associations between adiponectin levels and cardiometabolic outcomes have not been investigated in a large severely obese population before. This is important, as these associations appear to differ between populations (e.g., general population, individuals with preexisting cardiovascular disease, inflammatory conditions). In addition, our study also investigates the relationship between weight changes, changes in adiponectin levels, and disease incidence and compares the associations in a conventionally treated obese patient group and a group of obese patients with surgically induced weight loss.

Association Between Weight Loss and Increased Levels of Circulating Adiponectin

The upregulation of adiponectin after bariatric surgery has been reported before in smaller cohorts without suitable control group or without comparison between different types of surgery. We observed a similar (22,23) or greater (24) increase of serum adiponectin per kilogram weight loss than previous studies. Our data extend the current literature by the observation that the type of surgery does not influence the strength of this association, and our findings also suggest that the increase in adiponectin per kilogram lost is greater after surgery

than in the control group given usual care. Although the direct comparison of effect sizes between surgery and control groups in the SOS Study is complicated by the different ranges of weight changes, the data suggest that the increase in circulating adiponectin after surgery may partly be mediated by mechanisms independent of the prevailing weight loss. In our control group, the association between changes in serum adiponectin and weight changes was similar to that observed in the lifestyle group of the Diabetes Prevention Program (DPP; +500 ng/mL per 5-kg weight loss over 1 year) but higher than in the DPP control group (+300 ng/mL) (10). This difference can result from higher baseline BMI—and thus lower adiponectin levels—in the SOS Study compared with the DPP.

Adiponectin and Incident Diabetes

Whereas previous studies investigated associations between baseline adiponectin and outcomes such as diabetes (24), we also examined whether associations between baseline adiponectin and changes in adiponectin with various outcomes can be explained by baseline BMI and BMI changes. We found that high baseline adiponectin was associated with reduced risk of diabetes. Thus we show that the inverse association between baseline adiponectin and incident diabetes is also present in a cohort with severe obesity, whereas previous cohort studies focused on considerably less obese individuals (24). Moreover, increases in adiponectin were also associated with lower risk of diabetes among controls. Importantly, both associations were independent of each other and remained significant even after extensive adjustment, which included baseline BMI and 2-year changes in BMI. One-year changes in adiponectin and weight have been examined in the aforementioned DPP (10). In the DPP, incident diabetes was more strongly associated with baseline adiponectin levels than with 1-year changes in adiponectin after adjustment for baseline weight and 1-year weight changes. The SOS cohort differed from the DPP cohort by higher degree of obesity, larger weight loss in the surgery group, less ethnic heterogeneity, and longer follow-up. We can therefore not exclude that our finding that upregulation of adiponectin is independently associated with lower risk of diabetes is specific for an obese cohort and may not be generalizable to less obese individuals.

In the surgery group, the association between baseline levels of circulating adiponectin and diabetes risk was not significant after adjustment for multiple confounders (model 3, HR [95% CI] 0.935 [0.874–1.000]), but the HR was comparable to the control group, and the difference in statistical power caused by the lower number of cases in the surgery group most likely contributed to this result. We are not aware of any other study that investigated associations of adiponectin changes after bariatric surgery on clinical outcomes. Moreover, baseline adiponectin levels did not modify the benefit of bariatric surgery with respect to the incidence of diabetes and can therefore not be used to improve the selection of candidates for bariatric surgery if the aim is to prevent diabetes.

Adiponectin, Myocardial Infarction, and Stroke

Inverse associations between adiponectin and cardiovascular risk would be biologically plausible because adiponectin has been shown to decrease the expression of adhesion molecules on endothelial cells, thereby reducing monocyte attachment; to activate endothelial nitric oxide synthase; to stimulate endothelial cell migration, differentiation, and survival; and, finally, to diminish the formation of atherosclerotic lesions (1). The divergent data in the literature regarding whether or not adiponectin is a cardioprotective adipokine may, in part, be due to differences in outcome definitions, which may or may not include cardiovascular mortality, myocardial infarction, stroke, angina, and revascularization with percutaneous coronary intervention or coronary artery bypass grafting. It has been suggested that associations between adiponectin and cardiovascular disease depend on the outcomes that are included in the analysis (25), and this is supported by our data from the SOS Study, which indicate that myocardial infarction and stroke should be analyzed separately. If only studies that have a similar outcome based on fatal and nonfatal myocardial infarction are considered, the direction of association correlates with the stage of cardiovascular disease at study baseline: on the one hand, usually no (26–28) and, less frequently, inverse (29) associations with risk of myocardial infarction predominate in cohorts that were population based and/or mostly without preexisting cardiovascular disease at baseline (30). On the other hand, positive associations were found mainly (31–33), albeit not exclusively (34), in individuals with a history of cardiovascular disease. The latter finding may be explained as "reverse epidemiology" in which upregulated adiponectin concentrations represent a compensatory mechanism to counteract metabolic, vascular, and proinflammatory stress (4,5). This explanation is more likely than the alternative that adiponectin directly damages the vasculature. Although animal models and preclinical studies are conflicting regarding whether or not adiponectin contributes to lower cardiovascular risk (1,35), there are no data that adiponectin can actually increase this risk.

Against this background, our data are novel because they provide first estimates for associations between adiponectin and cardiovascular outcomes in a large obese cohort (i.e., in a cohort with relatively low baseline adiponectin levels) and also include adiponectin changes. We show that high baseline adiponectin and increases in adiponectin are both independently associated with low risk of myocardial infarction among the control individuals without surgical intervention when both variables are included in the same model. These associations are not explained by baseline BMI or BMI changes, and we do not find evidence of "reverse epidemiology" in this group of individuals.

In contrast, there was no association with the risk of stroke. This supports the notion that there is only a partial overlap in inflammation-related risk factors for both conditions and that adiponectin has no protective effects

against cerebrovascular events. The findings of the SOS cohort on stroke are in line with the majority of previous prospective studies in leaner cohorts that also revealed no association between adiponectin and incidence of stroke after adjustment for confounders (12,30,36–38). However, it should be noted that stroke can be ischemic or hemorrhagic, and the type of stroke was not defined in our study. One recent study reported that higher baseline adiponectin was associated with higher risk of ischemic stroke in men (39), and we cannot exclude that associations between adiponectin and stroke may depend on the type of stroke.

In contrast with the control group, there was no evidence for associations between circulating adiponectin, myocardial infarction, and stroke in the surgery group. We have shown before that higher plasma insulin at baseline was related to the effectiveness of surgery in the prevention of cardiovascular events (17), but this was not the case for adiponectin levels at baseline in the current study. However, additional studies are needed to identify biomarkers at baseline that are associated with health outcomes of bariatric surgery and thus help identify individuals who benefit most from this intervention and others for whom nonsurgical treatment may be preferable.

Strengths and Limitations

The main strengths of the current study are the large size of the cohort, the long follow-up, and the opportunity to investigate associations between adiponectin and various outcomes in severely obese individuals without and with bariatric surgery as intervention.

The main limitation of the SOS Study is that it was not randomized. However, this should not affect the estimates of associations between adiponectin and outcomes within each group. In addition, the SOS Study included white middle-aged obese men and women from Sweden, so our data may be generalizable to comparable populations in Europe or North America but not necessarily to populations with different ethnic backgrounds or different age ranges. Another limitation of our study is that the diabetes follow-up did not include oral glucose tolerance tests or HbA_{1c} measurements, and some individuals may therefore have been misclassified. No autoantibodies were determined to exclude cases of type 1 diabetes or latent autoimmune diabetes in the adult, but based on the age of onset and risk factor profile, it can be assumed that the vast majority of patients with incident diabetes have type 2 diabetes. We only measured total adiponectin and not its different isoforms. However, recent studies indicate that total adiponectin and high-molecular-weight adiponectin are closely correlated and that their associations with incident diabetes or cardiovascular events are rather similar (28,40). Finally, it should also be noted that the statistical power to reveal associations differed by outcome, as we had more cases for incident diabetes in both groups compared with incident myocardial infarctions and strokes.

Conclusion

Bariatric surgery led to a substantial increase in circulating adiponectin in the SOS Study irrespective of the type of surgery. We show for the first time in a large obese population that baseline adiponectin concentrations and their changes over 2 years were inversely associated with risk of diabetes and myocardial infarction in the control group independently of each other and independently of weight changes. In contrast, these associations were not significant in the surgery group. Neither baseline adiponectin nor its 2-year changes were associated with risk of stroke in either group. Baseline levels of adiponectin were not associated with the impact of bariatric surgery on any of the outcomes investigated here and can therefore not be used as predictor of treatment benefit.

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References

1. Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. Nat Rev Immunol 2011;11:85–97
2. Cook JR, Semple RK. Hypoadiponectinemia—cause or consequence of human "insulin resistance"? J Clin Endocrinol Metab 2010; 95:1544–1554
3. Li S, Shin HJ, Ding EL, van Dam RM. Adiponectin levels and risk of type 2

diabetes: a systematic review and meta-analysis. JAMA 2009;302:179–188

4. Rathmann W, Herder C. Adiponectin and cardiovascular mortality: evidence for "reverse epidemiology". Horm Metab Res 2007;39:1–2
5. Sattar N, Nelson SM. Adiponectin, diabetes, and coronary heart disease in older persons: unraveling the paradox. J Clin Endocrinol Metab 2008;93:3299–3301
6. Savopoulos C, Michalakis K, Apostolopoulou M, Miras A, Hatzitolios A. Adipokines and stroke: a review of the literature. Maturitas 2011;70:322–327
7. Herder C, Hauner H, Haastert B, et al. Hypoadiponectinemia and proinflammatory state: two sides of the same coin?: results from the Cooperative Health Research in the Region of Augsburg Survey 4 (KORA S4). Diabetes Care 2006;29:1626–1631
8. Arawaka N, Daimon M, Oizumi T, et al. Correlation between change in body weight rather than current body weight and change in serum adiponectin levels in a Japanese population — the Funagata study. Metabolism 2006;55:324–330
9. Okauchi Y, Kishida K, Funahashi T, et al. Changes in serum adiponectin concentrations correlate with changes in BMI, waist circumference, and estimated visceral fat area in middle-aged general population. Diabetes Care 2009;32:e122
10. Mather KJ, Funahashi T, Matsuzawa Y, et al.; Diabetes Prevention Program. Adiponectin, change in adiponectin, and progression to diabetes in the Diabetes Prevention Program. Diabetes 2008;57: 980–986
11. Drechsler C, Krane V, Winkler K, Dekker FW, Wanner C. Changes in adiponectin and the risk of sudden death, stroke, myocardial infarction, and mortality in hemodialysis patients. Kidney Int 2009;76:567–575
12. Kizer JR, Arnold AM, Jenny NS, et al. Longitudinal changes in adiponectin and inflammatory markers and relation to survival in the oldest old: the Cardiovascular Health Study All Stars study. J Gerontol A Biol Sci Med Sci 2011; 66:1100–1107
13. Tabák AG, Carstensen M, Witte DR, et al. Adiponectin trajectories before type 2 diabetes diagnosis: Whitehall II study. Diabetes Care 2012;35:2540–2547
14. Butner KL, Nickols-Richardson SM, Clark SF, Ramp WK, Herbert WG. A review of weight loss following Roux-en-Y gastric bypass vs restrictive bariatric surgery: impact on adiponectin and insulin. Obes Surg 2010; 20:559–568
15. Sjöström L, Lindroos AK, Peltonen M, et al.; Swedish Obese Subjects Study Scientific Group. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. N Engl J Med 2004;351: 2683–2693
16. Sjöström L, Narbro K, Sjöström CD, et al.; Swedish Obese Subjects Study. Effects of bariatric surgery on mortality in Swedish obese subjects. N Engl J Med 2007;357: 741–752
17. Sjöström L, Peltonen M, Jacobson P, et al. Bariatric surgery and long-term cardiovascular events. JAMA 2012;307: 56–65
18. Carlsson LM, Peltonen M, Ahlin S, et al. Bariatric surgery and prevention of type 2 diabetes in Swedish obese subjects. N Engl J Med 2012;367:695–704
19. Romeo S, Maglio C, Burza MA, et al. Cardiovascular events after bariatric surgery in obese subjects with type 2 diabetes. Diabetes Care 2012;35:2613–2617
20. Sjöström L, Larsson B, Backman L, et al. Swedish obese subjects (SOS). Recruitment for an intervention study and a selected description of the obese state. Int J Obes Relat Metab Disord 1992;16:465–479
21. Sjöström L. Surgical intervention as a strategy for treatment of obesity. Endocrine 2000;13:213–230
22. Holdstock C, Engström BE, Öhrvall M, Lind L, Sundbom M, Karlsson FA. Ghrelin and adipose tissue regulatory peptides: effect of gastric bypass surgery in obese humans. J Clin Endocrinol Metab 2003;88:3177–3183
23. Kopp HP, Krzyzanowska K, Möhlig M, Spranger J, Pfeiffer AF, Schernthaner G. Effects of marked weight loss on plasma levels of adiponectin, markers of chronic subclinical inflammation and insulin resistance in morbidly obese women. Int J Obes (Lond) 2005;29:766–771
24. Lin E, Phillips LS, Ziegler TR, et al. Increases in adiponectin predict improved liver, but not peripheral, insulin sensitivity in severely obese women during weight loss. Diabetes 2007;56:735–742
25. Kizer JR, Barzilay JI, Kuller LH, Gottdiener JS. Adiponectin and risk of coronary heart disease in older men and women. J Clin Endocrinol Metab 2008;93:3357–3364
26. Sattar N, Wannamethee G, Sarwar N, et al. Adiponectin and coronary heart disease: a prospective study and meta-analysis. Circulation 2006;114:623–629
27. Karakas M, Zierer A, Herder C, et al. Leptin, adiponectin, their ratio and risk of coronary heart disease: results from the MONICA/ KORA Augsburg Study 1984-2002. Atherosclerosis 2010;209:220–225
28. Pischon T, Hu FB, Girman CJ, et al. Plasma total and high molecular weight adiponectin levels and risk of coronary heart disease in women. Atherosclerosis 2011;219: 322–329
29. Pischon T, Girman CJ, Hotamisligil GS, Rifai N, Hu FB, Rimm EB. Plasma adiponectin levels and risk of myocardial infarction in men. JAMA 2004;291:1730–1737
30. Kanhai DA, Kranendonk ME, Uiterwaal CS, van der Graaf Y, Kappelle LJ, Visseren FL. Adiponectin and incident coronary heart disease and stroke. A systematic review and meta-analysis of prospective studies. Obes Rev 2013;14:555–567
31. Cavusoglu E, Ruwende C, Chopra V, et al. Adiponectin is an independent predictor of all-cause mortality, cardiac mortality, and myocardial infarction in patients presenting with chest pain. Eur Heart J 2006;27:2300–2309
32. Schnabel R, Messow CM, Lubos E, et al. Association of adiponectin with adverse outcome in coronary artery disease patients: results from the AtheroGene study. Eur Heart J 2008;29:649–657
33. Wilson SR, Sabatine MS, Wiviott SD, et al.; TIMI Study Group. Assessment of adiponectin and the risk of recurrent cardiovascular events in patients presenting with an acute coronary syndrome: observations from the Pravastatin Or atorVastatin Evaluation and Infection Trial-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22). Am Heart J 2011;161:1147–1155, e1
34. Wannamethee SG, Welsh P, Whincup PH, et al. High adiponectin and increased risk of cardiovascular disease and mortality in asymptomatic older men: does NT-proBNP help to explain this association? Eur J Cardiovasc Prev Rehabil 2011;18:65–71
35. Nawrocki AR, Hofmann SM, Teupser D, et al. Lack of association between adiponectin levels and atherosclerosis in mice. Arterioscler Thromb Vasc Biol 2010; 30:1159–1165
36. Söderberg S, Stegmayr B, Stenlund H, et al. Leptin, but not adiponectin, predicts stroke in males. J Intern Med 2004;256:128–136
37. Matsumoto M, Ishikawa S, Kajii E. Association of adiponectin with cerebrovascular disease: a nested case-control study. Stroke 2008;39:323–328
38. Rajpathak SN, Kaplan RC, Wassertheil-Smoller S, et al. Resistin, but not adiponectin and leptin, is associated with the risk of ischemic stroke among postmenopausal women: results from the Women's Health Initiative. Stroke 2011;42: 1813–1820
39. Prugger C, Luc G, Haas B, et al.; PRIME Study Group. Multiple biomarkers for the prediction of ischemic stroke: the PRIME study. Arterioscler Thromb Vasc Biol 2013; 33:659–666
40. Kizer JR, Arnold AM, Benkeser D, et al. Total and high-molecular-weight adiponectin and risk of incident diabetes in older people. Diabetes Care 2012;35: 415–423