Plasma Amine Oxidase: A Postulated Cardiovascular Risk Factor in Nondiabetic Obese Patients

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Increased activity of semicarbazide-sensitive plasma amine oxidase (SSAO), an enzyme converting various amines, has been implicated in the generation of endothelial damage through formation of cytotoxic reaction products. We investigated if SSAO activity is elevated in morbidly obese patients, which might contribute to the increased cardiovascular risk associated with obesity. SSAO activity was determined in 74 nondiabetic, obese patients (median body mass index [BMI]: 42.9 kg/m^2) and in 32 healthy, non-obese controls (median BMI: 23.3 kg/m^2) using a radiometric assay based on the conversion of [^{14}C]benzylamine. SSAO and parameters of glucose and lipid metabolism were compared for subgroups of obese patients with normal (n = 49) and impaired (n = 25) glucose tolerance using nonparametric statistical tests. Median SSAO activity was 434 μU/mL in obese patients, which was significantly higher than in healthy, non-obese controls (median SSAO activity: 361 μU/mL). Median SSAO activity in patients with normal and impaired glucose tolerance was 423 and 464 μU/mL, respectively. SSAO activity was not correlated with any other clinical or laboratory parameters characteristic of the metabolic alterations associated with obesity. Elevated SSAO activity is found in nondiabetic, morbidly obese patients and might be an interesting independent risk factor for obesity-related cardiovascular morbidity. Long-term follow-up of SSAO and its possible role in pathogenic events is warranted since intervention with specific SSAO inhibitors is available.

OBESITY IS A condition of deregulated energy balance commonly observed in humans and represents a growing health care problem due to the increased morbidity and mortality associated with it.[1,2] Obesity is linked to numerous metabolic disorders, including glucose intolerance, insulin resistance, hyperinsulinemia, impaired fibrinolysis, and dyslipidemia, which mediate the high risk for developing atherosclerosis, hypertension, diabetes mellitus, and osteoarthritis.[3-5] As a consequence of these metabolic perturbations, obesity is associated with an increased risk for developing cardiovascular diseases.[5,6] To date, the pathophysiologic mechanisms responsible for the correlation of obesity with an increased cardiovascular risk have not been elucidated. It has been proposed that oxidative stress resulting from activated neutrophils[7] and elevated levels of leptin, which is produced by adipocytes and was shown to cause endothelial dysfunction,[8] might be important for obesity-related cardiovascular morbidity.

Another interesting factor that might play a role in the cardiovascular risk profile, but has previously not been investigated in regard to obesity is semicarbazide-sensitive plasma amine oxidase (SSAO). This enzyme is a member of the class of copper-containing amine oxidases (EC 1.4.3.6) and is also commonly referred to as plasma amine oxidase, serum amine oxidase, or benzylamine oxidase.[9] Human SSAO converts numerous primary amines, including aliphatic monoamines, tyramine, tryptamine, and dopamine, and its activity is usually measured with the nonphysiologic substrate benzylamine.[10] SSAO has been proposed to be involved in the development of vascular endothelial damage through formation of cytotoxic reaction products, specifically hydrogen peroxide, formaldehyde, and methylglyoxal produced from methylamine and aminoacetone, respectively.[11] SSAO-catalyzed conversion of methylamine to formaldehyde was shown to have severe cytotoxic effects on cultured endothelial cells, and this could efficiently be blocked by specific inhibition of SSAO activity.[12] Formation of formaldehyde from methylamine or adrenaline in vivo under conditions of stress were subsequently proposed to constitute a risk factor for initiation of endothelial injury and angiopathy.[13,14]

SSAO activity was found to be elevated in patients with insulin-dependent and with non–insulin-dependent diabetes mellitus and was therefore implicated in the development of microvascular complications in these patients.[15,16] In a study of insulin-dependent diabetics, higher SSAO activity was found in subgroups with retinopathy and nephropathy,[15] whereas in another study of insulin-dependent and non–insulin-dependent diabetic patients, SSAO activity was found to be positively correlated with body weight and body mass index (BMI).[16] Because no studies have been published investigating alterations of SSAO activity in morbidly obese patients who commonly develop cardiovascular complications, we asked whether obesity is associated with an elevated activity of this potentially harmful enzyme. We were especially interested to study SSAO in subgroups of obese patients without diabetes and to find possible correlations of SSAO with other parameters indicative of obesity-related metabolic changes.

MATERIALS AND METHODS

Study Subjects

A total of 74 nondiabetic, morbidly obese patients who were referred to our departments between June 1998 and February 2000 for weight reduction and who did not suffer from accompanying cardiovascular, liver, or kidney diseases were included in this study. In our cohort,

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morbid obesity was defined by a BMI $>$ 40 kg/m^2 or a BMI $>$ 35 kg/m^2 in association with the comorbidities, arthropathy and/or pathologic alterations of glucose and lipid metabolism. The patient population of this study is typical for bariatric surgery and consisted of 61 women (82%) and 13 men (18%) with a median age of 35 years (range, 18 to 58 years), a median BMI of 42.9 kg/m^2 (range, 35.4 to 71.0 kg/m^2), and a median body weight of 121 kg (range, 97 to 230 kg). Among these patients, 12 (16%) were cigarette smokers, and 4 patients were taking oral contraceptives. The study was performed according to institutional regulations, and written consent was obtained from all patients, although all relevant analyses were performed with samples withdrawn for regular laboratory checks.

Patients were grouped according to glucose tolerance parameters, including blood glucose concentration determined after overnight fasting (fasting glucose) and glucose tolerance determined by an oral glucose tolerance test in which plasma glucose concentration was determined 2 hours after ingestion of 75 g glucose (tolerance glucose). Forty-nine patients (66%) with normal glucose tolerance having fasting glucose levels below 1.1 g/L and tolerance glucose below 1.4 g/L were defined as group 1. Twenty-five patients (34%) with impaired glucose tolerance indicative of incipient diabetes who either showed a fasting glucose concentration of 1.1 to 1.26 g/L or tolerance glucose of 1.4 to 2.0 g/L were defined as group 2. Obese patients with overt diabetes mellitus with fasting glucose levels $>$ 1.26 g/L or tolerance glucose $>$ 2.0 g/L and serum insulin levels $>$ 20 mU/L were not included in this study. A group of 32 healthy, non-obese volunteers (9 women, 23 men) with a median age of 32.5 years (range, 23 to 39) and a median BMI of 23.3 kg/m^2 (range, 21.2 to 27.5) served as controls. As the gender ratio was significantly different between patients (82% female) and controls (28% female), a statistical test was performed to exclude that SSAO activity was different for men and women within each group (P = .476 and P = .782 for controls and patients, respectively; Mann-Whitney test).

Laboratory Methods

For determination of SSAO activity, blood samples were collected in tubes containing K_2-EDTA (final concentration, 1.6 mg/mL) after 12-hour fasting from an antecubital vein. Samples were centrifuged for 10 minutes at 1,500 $\times$ g at 4°C, and the plasma was stored at -75°C until analyzed. SSAO activity was determined using a radiometric assay based on the conversion of [^{14}C]benzylamine[17] with slight modifications. Briefly, 20 μL plasma was incubated for 60 minutes at 37°C with 10 nCi [7-^{14}C]benzylamine (0.2 Ci/mol, 0.1 mmol/L, Amersham Pharmacia Biotech, Amersham, UK) in 100 mmol/L sodium phosphate buffer pH 7.2 in a total volume of 100 μL. The reaction was terminated by addition of 10 μL 10% perchloric acid. The reaction product [7-^{14}C]benzylaldehyde was extracted into toluene containing 0.35% 2,5-diphenyloxazole and measured by liquid scintillation analysis. Substrate conversion was linear for at least 90 minutes using these assay conditions. For each sample, the mean enzyme activity from 2 independent determinations was calculated in μU/mL in which 1 μU converts 1 pmol of benzylamine per minute at 37°C. The detection limit of the SSAO assay is 2 μU (2 pmol/min) and intra- and interassay coefficients of variation were found to be 2.4% and 3.1%, respectively. The median SSAO activity determined in healthy, non-obese, nondiabetic volunteers was found to be 361 μU/mL (range, 184 to 435 μU/mL) and never exceeded 450 μU/mL. The following control experiments were performed to confirm that only copper-containing plasma monoamine oxidase activity was measured: preincubation of samples with 100 μmol/L semicarbazide (Sigma, Vienna, Austria), a specific inhibitor of copper-containing amine oxidases, reduced benzylamine conversion to background levels. Preincubation of samples with 10 μmol/L clorgyline and 10 μmol/L deprenyl (Sigma), specific inhibitors of mitochondrial flavin adenine dinucleotide (FAD)-containing monoamine oxidases A and B, did not alter benzylamine conversion. Background activity was obtained with the diamine oxidase substrate [1,4-^{14}C]putrescine (0.22 Ci/mol, 0.45 mmol/L, Amersham Pharmacia Biotech).

Plasma liver and kidney function parameters were determined using standard procedures. Plasma glucose concentrations and serum cholesterol and triglyceride levels were determined enzymatically using comercially available kits (Cholesterol PAP, MA Kit; Roche, Vienna, Austria; triglycerides PAP, UNI-Kit II; Roche). High-density lipoprotein (HDL)-cholesterol was determined using a method based on precipitation with dextrane sulfate and magnesium chloride[18] and low-density lipoprotein (LDL)-cholesterol was calculated according to the Friedewald formula.[19] Serum insulin was determined by the IMx insulin assay (Abbott, Vienna, Austria) and C-peptide by a radioimmunoassay (C-PEP-RIA-CT, Biosource, Nivelles, Belgium). Glycated hemoglobin (HbA_{1c}), a parameter that might be indicative of SSAO-mediated vascular damage and had been shown to be positively correlated with SSAO activity in diabetic patients,[15] was measured by a microcolumn method (Quick-Sep; Isolab, Norton, OH) after elimination of the aldimin-transformed parts.

Statistical Analyses

Statistical analyses were performed using the SPSS for Windows Version 10.0 software package (SPSS, Chicago, IL). Differences between patient groups and controls were analyzed with the Mann-Whitney test and the χ^2 test, where applicable. Correlation of SSAO activity with patient characteristics and with other laboratory parameters was investigated by Spearman's correlation statistics. A 2-tailed P value below 5% was considered statistically significant.

RESULTS

Plasma amine oxidase (SSAO) activity was determined in a total of 74 nondiabetic, morbidly obese patients who were differentiated according to glucose tolerance characteristics and grouped into patients with normal glucose tolerance (group 1, n = 49) and patients with impaired glucose tolerance (group 2, n = 25) as described above. Patient characteristics and laboratory parameters of glucose and lipid metabolism, as well as SSAO activity, are presented in Table 1, and a box plot of the SSAO activity in patients and controls is shown in Fig 1. Patients with impaired glucose tolerance (group 2) had significantly higher fasting glucose concentration, HbA_{1c}, insulin, and C-peptide and significantly lower levels of total and HDL-cholesterol than the patients with normal glucose tolerance (group 1).

The median SSAO activitiy for the obese patients (median BMI of 42.9 kg/m^2) was 434 μU/mL, which was significantly higher ($P < .01$) than the median SSAO activity of 361 μU/mL determined for the control group (median BMI of 23.3 kg/m^2). Median SSAO activity was higher in the group of patients with impaired glucose tolerance (464 μU/mL, group 2) compared with the group with normal glucose tolerance (423 μU/mL, group 1), but this difference was not statistically significant. Although a significant correlation of SSAO activity and BMI was found for all individuals analyzed (n = 106, r = .250, P = .01), no significant correlation was found within the group of obese patients (n = 74, $r = -0.074$, P = .531).

Evaluation of clinical and laboratory parameters did not show any significant correlation with SSAO activity for non-

Table 1. Patient Characteristics, Laboratory Parameters, and SSAO Activity

Parameter	Controls	Patients	Group 1	Group 2
No.	32	74	49	25
Age (yr)	32.5 (23-39)	35.0 (18-58)	36.0 (19-58)	34.0 (18-50)
Sex (female/male)	9/23	61/13*	44/5	17/8*
Weight (kg)	75 (60-89)	121 (97-230)*	120 (97-230)	128 (100-210)
Height (m)	1.7 (1.6-1.9)	1.7 (1.5-1.9)	1.7 (1.5-1.9)	1.7 (1.6-1.9)
BMI (kg/m^2)	23.3 (21.2-27.5)	42.9 (35.4-71.0)*	42.5 (35.4-71.0)	43.3 (38.3-61.4)
Fasting glucose (g/L)	–	1.00 (0.73-2.30)	0.97 (0.73-1.09)	1.13 (0.88-2.30)*
HbA_{1c} (%)	–	5.4 (4.0-7.9)	5.1 (4.0-6.0)	5.5 (4.6-7.9)*
Insulin (mU/L)	–	15.8 (4.2-50.5)	12.8 (4.2-19.4)	25.7 (11.6-50.5)*
C-peptide (μg/L)	–	1.4 (0.6-2.6)	1.2 (0.6-1.5)	1.8 (1.0-2.6)*
Cholesterol (mg/L)	–	1,940 (1,040-2,790)	1,990 (1,300-2,790)	1,860 (1,040-2,430)*
HDL-cholesterol (mg/L)	–	440 (180-1,020)	500 (180-1,020)	420 (280-810)*
LDL-cholesterol (mg/L)	–	1,130 (350-1,950)	1,140 (620-1,950)	1,090 (350-1,610)
Triglyceride (mg/L)	–	1,360 (620-6,840)	1,210 (620-6,840)	1,450 (800-5,400)
SSAO (μU/mL)	361 (184-435)	434 (198-817)*	423 (198-801)	464 (247-817)

NOTE. Patients: all patients with morbid obesity, group 1: obese patients with normal glucose tolerance, group 2: obese patients with impaired glucose tolerance. Parameters are presented as median (ranges). Differences between patients and controls as well as between groups 1 and 2 were analyzed with the χ^2 test (sex) and the Mann-Whitney test (all other parameters), respectively, and significant differences are indicated by $*P < .05$.

diabetic obese patients (Table 2). To detect possible differences of parameters in obese patients with normal and elevated SSAO activity, groups of patients with SSAO activity below and above 450 μU/mL were compared. This value was chosen arbitrarily as a safe upper limit of normal SSAO activity, because it was never exceeded in healthy controls. As shown in Table 3, the 45 nondiabetic, obese patients with normal SSAO activity (SSAO $\leq$ 450 μU/mL) did not differ significantly from the 29 patients with elevated SSAO activity (SSAO $>$ 450 μU/mL) in age, sex, BMI, fasting glucose concentration, HBA_{1c}, insulin, C-peptide, total cholesterol, HDL-cholesterol, and triglyceride concentration, but had a higher LDL-cholesterol concentration (1,250 *v* 945 mg/L, $P < .05$). Further analyses showed that SSAO activity was not significantly different in smokers and nonsmokers or in patients taking oral contraceptives.

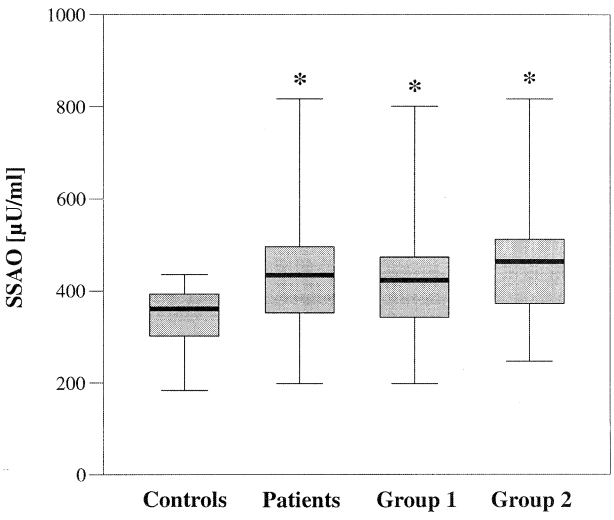

Fig 1. Box plot of SSAO activity in controls (n = 32) and morbidly obese patients (n = 74). Group 1 (n = 49) and group 2 (n = 25) represent subgroups of morbidly obese patients with normal and impaired glucose tolerance, respectively. The boxes represent the first and third quartile, the vertical lines the ranges, and the respective median value is shown by a thick horizontal line within each box. Statistically significant differences between patient groups and controls were analyzed with the Mann-Whitney test (*$P < .01$).

DISCUSSION

This is the first study investigating alterations of plasma amine oxidase activity in nondiabetic, morbidly obese patients. Previous studies have shown that SSAO activity was significantly increased in patients with diabetes mellitus and positively correlated with body weight and BMI in a diabetic cohort.[15,16] Our study excluded patients with diabetes mellitus to assess the effect of morbid obesity on SSAO activity independent of diabetes. Interestingly, we found a significantly

Table 2. Correlation of SSAO Activity With Other Parameters in Nondiabetic, Obese Patients

Parameter	No.	Coefficient	*P* Value
Age	74	0.072	.544
BMI	74	−0.074	.531
Glucose	65	0.162	.197
HbA_{1c}	51	−0.052	.717
Insulin	35	0.068	.699
C-peptide	35	0.184	.291
Cholesterol	68	−0.067	.586
HDL-cholesterol	68	−0.056	.648
LDL-cholesterol	66	−0.140	.263
Triglyceride	68	0.110	.371

NOTE. Parameters were correlated with SSAO activity using Spearman correlation statistics.

Table 3. Comparison of Parameters in Nondiabetic, Obese Patients With Normal and Elevated SSAO Activity

Parameter	SSAO ≤ 450 μU/mL	SSAO > 450 μU/mL
No.	45	29
Age (yr)	36 (19-55)	37 (18-52)
Sex (female/male)	38/7	23/6
BMI (kg/m^2)	42.3 (35.4-61.4)	42.5 (39.1-54.6)
Fasting glucose (g/L)	0.99 (0.86-1.13)	1.01 (0.90-1.25)
HbA_{1c} (%)	5.4 (4.5-5.9)	5.5 (4.7-5.9)
Insulin (mU/L)	13.3 (5.7-40.4)	20.2 (4.2-50.5)
C-peptide (μg/L)	1.32 (0.75-2.05)	1.42 (0.60-2.61)
Cholesterol (mg/L)	2,010 (1,100-2,700)	1,765 (1,550-2,600)
HDL-cholesterol (mg/L)	450 (330-660)	535 (320-1,020)
LDL-cholesterol (mg/L)	1,250 (510-1,950)	945 (590-1,720)*
Triglyceride (mg/L)	1,470 (860-2,680)	1,245 (720-1,700)
SSAO (μU/mL)	375 (198-440)	488 (464-817)*

NOTE. Nondiabetic, obese patients (n = 74) were grouped with SSAO activity in the normal range (≤ 450μU/mL) and in patients with elevated SSAO activity (> 450 μU/mL). Parameters are presented as median (ranges). Differences between these groups were analyzed with the χ^2 test (sex) and the Mann-Whitney test (all other parameters), respectively, and significant differences are indicated by $*P < .05$.

higher median SSAO activity in obese patients than in nonobese controls. Subgroups of obese patients both with a normal glucose tolerance and with an impaired glucose tolerance, indicative of incipient diabetes, exhibited elevated SSAO activity. Our results indicate that obesity is associated with an elevated activity of this enzyme independent of diabetes.

In the study group of morbidly obese patients without diabetes, SSAO activity was not significantly correlated with any of the laboratory parameters of glucose and lipid metabolism. In contrast to other studies investigating SSAO alterations in diabetic populations,[15,16] we did not find a significant correlation of SSAO activity with BMI, HbA_{1c}, or serum triglyceride in nondiabetic, obese patients. However, there was a significant positive correlation of BMI and SSAO activity when all subjects, ie, patients and controls, were included in the analysis. Differentiation of obese patients with SSAO activity in the normal range and with elevated SSAO activity showed that those patients with elevated SSAO activity had a significantly decreased LDL cholesterol concentration, but did not differ in any of the other laboratory parameters. Because no significant correlation of LDL-cholesterol and SSAO activity was found for obese patients (Table 2), there is no obvious explanation for the decreased LDL-cholesterol concentration in patients with elevated SSAO activity.

SSAO is a normal component of human plasma where it appears to act as a scavenger for various monoamines released into the circulation.[9] The source of SSAO is currently a matter of speculation. Besides the plasma enzyme, homologous membrane-bound forms of copper-containing amine oxidases have been described.[9,17,20] Currently, it is not known if the membrane-bound and soluble forms of these enzymes are alternative products encoded by the same gene or if they are transcribed from different genes. The membrane-bound form has also been characterized as vascular adhesion protein-1 (VAP-1), which in addition to mediation of lymphocyte adhesion, was later shown to possess amine oxidase activity.[21-23] A soluble form of VAP-1, termed soluble VAP-1 (sVAP-1) was found to be present in plasma and was shown to be identical to SSAO.[24,25] Because increased levels of sVAP-1 were observed in patients with inflammatory liver diseases, it was concluded that the liver might be the source of the soluble protein.[25] However, as copper amine oxidases are also strongly expressed in adipocytes,[20,26] these cells could also be a source of SSAO, and the abundant fat cell mass would explain the increased SSAO activity in obese patients. It is also not clear if the origin and cause of elevated SSAO activity are different in patients with different diseases.

We were originally prompted to investigate alterations of SSAO activity in obese patients by previous studies of patients with diabetes mellitus demonstrating elevated SSAO activity and a positive correlation of SSAO activity and body weight.[15,16] In these studies, elevated SSAO activity had been implicated in the development of vascular complications in diabetic patients. It has been shown in in vitro studies that certain metabolites of the SSAO reaction, including methylglyoxal and formaldehyde, lead to damage of endothelial cells, and that these toxic effects can efficiently be blocked by inhibition of SSAO activity.[12,27] It was concluded that in diabetic patients with elevated SSAO activity increased production of the respective cytotoxic compounds directly or by formation of advanced glycation end products causes long-term endothelial damage and vascular complications.[11,12,15,27] Further studies will have to show if the same pathologic phenomena occur in morbidly obese patients with elevated SSAO activity and if SSAO is useful for assessment of cardiovascular risk in these patients. Apart from its enzymatic activity, it is presently not clear how alterations of the plasma concentration of SSAO/sVAP-1 might influence lymphocyte adhesion mediated by the membrane-bound form of the protein abundantly present on certain endothelial cells, smooth muscle cells, and adipocytes.[28]

Because morbidly obese patients commonly encounter cardiovascular diseases,[5,6] our finding of increased SSAO activity in these patients might provide at least one explanation for their increased cardiovascular risk. Long-term follow-up studies will be important to demonstrate the role of elevated SSAO activity in the development of vascular damage in obese patients. If increased SSAO activity does, indeed, turn out to be an important factor in the pathogenesis of cardiovascular comorbidities associated with morbid obesity, inhibition of SSAO activity constitutes a potential treatment option. In this respect, application of SSAO-inhibiting drugs, such as hydralazine and aminoguanidine, has previously been proposed for vascular cytoprotection in patients with diabetes mellitus.[11,27] However, as SSAO-inhibiting compounds also inhibit other copper-containing amine oxidases, including the histamine-oxidizing enzyme, diamine oxidase,[29] their effects on other metabolic pathways must be carefully monitored. Additionally, it will be interesting to find out if successful weight reduction in obese patients is accompanied by a decrease of SSAO activity thus indicating that alteration of SSAO activity is a reversible metabolic change.

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