Elevated Serum Semicarbazide-Sensitive Amine Oxidase Activity in Non–Insulin-Dependent Diabetes Mellitus: Correlation With Body Mass Index and Serum Triglyceride

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Previous clinical studies reported elevated semicarbazide-sensitive amine oxidase (SSAO) activity in insulin-dependent diabetes mellitus (IDDM), but there are not sufficient data about SSAO in non–insulin-dependent diabetes mellitus (NIDDM). The present study was conducted to investigate serum SSAO activity in NIDDM patients compared with nondiabetic and IDDM patients. Serum SSAO activity in 61 patients with diabetes (n = 34 NIDDM and n = 27 IDDM) and 36 controls was determined using ^{14}C-benzylamine as a substrate. NIDDM and IDDM patients exhibited higher SSAO activity compared with controls ([mean ± SD] NIDDM, 164.60 ± 69.43 pmol/mg protein/h, $P < .0001$; IDDM, 143.91 ± 72.45 pmol/mg protein/h, $P < .002$; control, 91.46 ± 28.11 pmol/mg protien/h). There was a significant positive correlation between serum SSAO activity and the body mass index (BMI), body weight, hemoglobin A_{1c} (HbA_{1c}), fasting plasma glucose, and triglycerides. Within the control group, SSAO correlated with total cholesterol levels. The progression and severity of diabetic complications such as angiopathy may be exacerbated by cytotoxic metabolites (eg, formaldehyde and hydrogen peroxide) formed by SSAO. These results reveal the possibility that elevated serum SSAO activity in association with obesity and hyperlipidemia may be a cardiovascular risk factor in diabetes mellitus.

SEMICARBAZIDE-SENSITIVE amine oxidase (SSAO) differs from monoamine oxidase (MAO) in subcellular distribution, cofactor requirement, and inhibitor sensitivity.[1] SSAO is present in the plasma membrane of several tissues, eg, vascular smooth muscle cells, chondrocytes, and adipocytes, and is also found in human serum.[2-4] SSAO contains a cofactor with copper and a reactive carbonyl group (6-hydroxydopa, or pyridoxal, pyrroloquinoline quinone moiety) and is able to deaminate short-chain aliphatic biogenic amines such as methylamine or allylamine.[5] SSAO is inhibited by carbonyl reagents (eg, hydrazine) and insensitive to MAO inhibitors.[6] The reaction catalyzed by SSAO enzymes appears to be of the aminotransferase type, to produce aldehyde (eg, formaldehyde or acrolein), ammonia, and hydrogen peroxide.[7] These products are potentially cytotoxic; in particular, formaldehyde may be involved in the pathogenesis of angiopathy and retinopathy commonly observed in diabetes.[8]

The physiological and pathophysiological functions of SSAO are presently not well understood. According to some previous reports, serum MAO activity is elevated in diabetes.[9-10] A recent study has found a correlation between SSAO and glycosylated hemoglobin in insulin-dependent diabetes mellitus (IDDM). Plasma SSAO was elevated in IDDM compared with control subjects, especially in subgroups with either retinopathy or nephropathy.[11] It was reported that SSAO was increased in the blood and kidney of rats with streptozotocin-induced diabetes and also in the blood of sheep with alloxan-induced diabetes.[12-13]

Since there is currently no reliable animal model of non–insulin-dependent diabetes mellitus (NIDDM) and there are not sufficient human data regarding serum SSAO activity in NIDDM, the aim of the present study was to investigate serum SSAO activity in NIDDM patients compared with nondiabetic and IDDM patients.

SUBJECTS AND METHODS

Patient Selection

The study was approved by the institutional review committee, and the subjects provided informed consent. A total of 61 caucasian diabetics (29 men and 32 women) were selected at the Endocrinology Department of our clinic according to the following criteria: (1) age between 25 and 75 years, (2) diabetes mellitus as defined by World Health Organization criteria,[14] and (3) duration of diabetes longer than 5 years. Exclusion criteria were as follows: (1) a history or presence of malignancy, (2) intercurrent infection and/or fever, and (3) alcohol intake (>three drinks per day). IDDM patients were treated with human insulin (Humulin; Lilly, Indianapolis, IN). NIDDM patients were treated with the oral antidiabetics, glipizide (Minidiab; Pharmacia & Upjohn, Kalamazoo, MI), gliclazide (Diaprel; Servier, Gidy, France), or glybenclamide (Gilemal; Chinoin, Budapest, Hungary), and an appropriate diet.

A group of 36 caucasian nondiabetic control subjects were selected. Selection was made based on the following criteria: (1) age greater than 25 years, (2) physical examination normal, (3) no familial history of diabetes mellitus, (4) absence of any drug treatment in the previous 6 months, and (5) absence of impaired glucose tolerance or diabetes.

Anthropometric and Biochemical Variables

Body height (meters), body weight (kilograms), body mass index ([BMI] kilograms per meter squared), systolic and diastolic blood pressure, duration of diabetes (years), complications, and smoking habits (cigarettes per day) were registered in each case. Blood was drawn after an overnight fast for determination of glucose, total cholesterol, triglyceride, high-density lipoprotein (HDL) cholesterol (millimolars), hemoglobin A_{1c} (HbA_{1c}), and creatinine (micromolars) by standard laboratory methods.

Determination of Serum SSAO Activity

A radiometric procedure was adapted to determine human serum SSAO activity.[15] The radioenzymatic assay is based on extraction of

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Submitted March 5, 1998; accepted June 17, 1998.

Supported by a grant from the Medical Scientific Board of Hungary (T03 350/93 and ETT 460/96).

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0026-0495/99/4801-0019$03.00/0

^{14}C-Benzaldehyde formed by the enzyme from ^{14}C-Benzylamine. Benzylamine, chlorgyline, and semicarbazide were purchased from Sigma-Aldrich (St Louis, MO). ^{14}C-Benzylamine was obtained from Amersham International (Amersham, UK; specific activity, 2.04 GBq/mmol). All other chemicals were of analytical grade.

Ten milliliters of venous blood was withdrawn from each subject. The samples were collected in Vacutainer tubes (Becton Dickinson, France) without anticoagulant, maintained at +4°C during delivery, and centrifuged at 2,500 × *g* for 10 minutes. The serum was used for SSAO assay. SSAO enzyme preparations were preincubated with chlorgyline (10^{-4} mol/L) at room temperature for 20 minutes to ensure that any MAO activity, if present, was completely inactivated. The enzyme was then incubated in the presence of ^{14}C-Benzylamine (5×10^{-5} mol/L, 0.1 μCi) in a final volume of 200 μL at 37°C for 40 minutes. The enzyme reaction was stopped by adding 200 μL 2-mol/L citric acid. The oxidized products were extracted into 1 mL toluene:ethylacetate 1:1 vol/vol, of which 600 μL was then transferred to a counting vial containing 10 mL Aquasafe fluid (Zinsser Analytic, Haidenhead, UK). Radioactivity was assessed using a liquid scintillation counter (LS9000; Beckman, Irvine, CA). The protein content of the samples was determined according to the method of Bradford.[16] Serum SSAO activity was expressed as picomoles of oxidized substrate per milligram of protein per hour.

This method is sensitive and specific (in the presence of 1 mmol/L semicarbazide, there was no detectable enzyme activity) and is appropriate for the quick determination of several samples. The only disadvantage of the radiometric method is its high cost compared with fluorimetric and ion-exchange methods.[17-18]

Statistical Analysis

Clinical characteristics of IDDM and NIDDM patients and control subjects were compared using a Kruskal-Wallis ANOVA test. Values are expressed as the mean ± SD. Multiple regression analyses were performed separately in diabetic and control subjects to assess the combined influence of variables on SSAO activity. A P value less than .05 was considered statistically significant. Statistical analyses were performed using Statistica for Windows Version 5.0 software (StatSoft, Tulsa, OK).

RESULTS

Clinical characteristics of the diabetic and control subjects are summarized in Table 1. SSAO activity was significantly elevated in NIDDM and IDDM patients compared with control subjects. There was no significant difference in SSAO activity between patients with IDDM and NIDDM. IDDM patients were significantly younger and thinner than NIDDM patients. No difference was found in the duration of diabetes between IDDM and NIDDM subjects. IDDM patients exhibited a higher concentration of fasting plasma glucose than NIDDM subjects. With regard to the total cholesterol level, there was no significant difference between the study groups. In NIDDM patients, triglycerides were significantly higher compared with controls, and HDL cholesterol was significantly lower compared with IDDM patients. NIDDM patients had a significantly higher atherogenic index (total cholesterol to HDL cholesterol ratio) compared with IDDM patients.

Multiple regression analysis on all subjects demonstrated that there was a positive correlation between serum SSAO activity and the BMI (Fig 1). There was also a significant correlation between body weight, fasting plasma glucose, serum triglyceride, HbA_{1c}, and SSAO activity, respectively (Table 2). SSAO activity was independent of age, height, smoking habits, duration of diabetes, and HDL cholesterol. Within the control group, SSAO correlated with the total cholesterol level, atherogenic index, and body weight. Serum SSAO activity correlated negatively with serum creatinine in control subjects. In hypertensive nondiabetic patients, SSAO correlated with the BMI ($R^2 = .762$, $P < .006$); however, in normotensive controls, there was no correlation between the BMI and SSAO.

Regarding serum SSAO activity, there was no difference between men (129.84 ± 58.43 pmol/mg protein/h, n = 46) and women (133.37 ± 73.26 pmol/mg protein/h, n = 51), smokers (125.80 ± 88.31 pmol/mg protein/h, n = 22) and nonsmokers (150.47 ± 68.13 pmol/mg protein/h, n = 41), or hypertensive (96.02 ± 37.87 pmol/mg protein/h, n = 8) and normotensive controls (90.16 ± 25.39 pmol/mg protein/h, n = 28).

SSAO activity was significantly higher in obese patients (BMI > 25) with NIDDM (146.11 ± 64.92 pmol/mg protein/h, n = 19, $P < .003$), IDDM (164.49 ± 97.80 pmol/mg protein/h, n = 10, $P < .02$), or NIDDM and hypertension (200.25 ± 81.94

Table 1. Characteristics of the IDDM and NIDDM Patients and Controls

Characteristic	IDDM (n = 27)	NIDDM (n = 34)	Control (n = 36)	Comparison (*P*)		
				IDDM *v* Control	NIDDM *v* Control	IDDM *v* NIDDM
Serum SSAO activity (pmol/mg protein/h)	143.91 ± 72.45	164.60 ± 69.43	91.46 ± 28.11	<.0021	<.0001	NS
Sex (male/female)	12/15	17/17	16/20	—	—	—
Age (yr)	40.50 ± 11.97	56.27 ± 9.43	50.56 ± 14.90	<.0069	NS	<.001
Body weight (kg)	67.96 ± 13.73	81.48 ± 13.26	70.14 ± 14.04	NS	<.0035	<.001
BMI (kg/m^2)	23.90 ± 3.25	29.95 ± 4.35	25.23 ± 4.89	NS	<.0002	<.001
Duration of diabetes (yr)	16.94 ± 11.91	11.82 ± 10.30	—	—	—	NS
Fasting plasma glucose (mmol/L)	13.12 ± 4.45	9.83 ± 3.84	5.19 ± 0.45	<.0001	<.0001	<.003
HbA_{1c} (%)	8.88 ± 1.37	8.62 ± 1.39	7.09 ± 0.90	<.0001	<.0001	NS
Total cholesterol (mmol/L)	5.83 ± 1.54	6.17 ± 1.48	5.39 ± 1.37	NS	NS	NS
Triglyceride (mmol/L)	2.16 ± 1.51	2.98 ± 1.94	1.41 ± 0.52	NS	<.0003	NS
HDL cholesterol (mmol/L)	1.40 ± 0.52	1.03 ± 0.27	1.15 ± 0.34	NS	NS	<.01
Atherogenic index (total cholesterol/HDL cholesterol)	4.66 ± 1.73	6.30 ± 2.12	5.20 ± 1.73	NS	NS	<.03
Creatinine (μmol/L)	71.13 ± 17.70	75.32 ± 27.49	72.66 ± 12.30	NS	NS	NS

NOTE. Values are the mean ± SD.
Abbreviation: NS, nonsignificant.

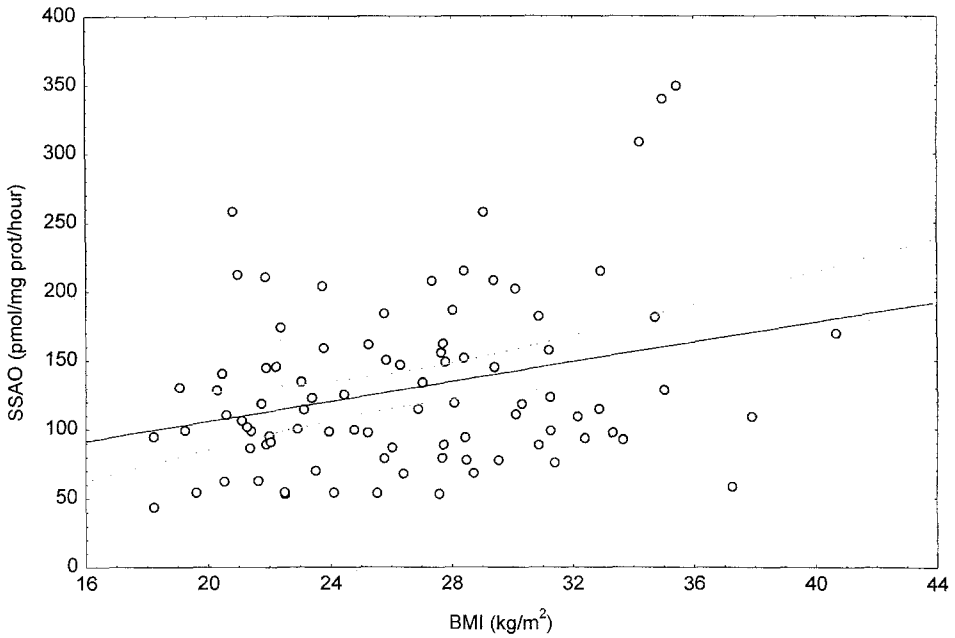

Fig 1. Correlation between serum SSAO activity and BMI. (—○—) Regression line. $r = .250$; SSAO = 41.710 + 3.426 · BMI.

pmol/mg protein/h, n = 10, $P = .0006$) than in obese control subjects (91.12 ± 25.20 pmol/mg protein/h, n = 14) (Fig 2). In obese patients with NIDDM and hypertension, SSAO activity was higher than in obese normotensive NIDDM patients; however, this difference was not significant ($P < .07$). The effect of hyperlipidemia on SSAO activity was investigated within the control, NIDDM, and IDDM groups. There was no difference in SSAO activity between hypertriglyceridemic, hypercholesterolemic subjects and patients with normal lipid levels.

DISCUSSION

The main finding of the present study is that elevated SSAO activity is related to the BMI and serum total cholesterol and triglyceride levels. In NIDDM patients, hypertriglyceridemia, hypertension, and obesity commonly occur together, and thus we investigated obese (BMI > 25) and non-obese subgroups. We observed a further increase in serum SSAO activity in obese diabetic patients compared with obese controls (Fig 2). Hypertension or hyperlipidemia alone did not produce a significant increase in SSAO activity; however, if NIDDM is associated with hypertension or hyperlipidemia, it results in a further elevation of SSAO activity.

The pathogenesis of vascular complications in diabetes is controversial. Endothelial dysfunction caused by various factors (ie, hyperglycemia, hyperinsulinemia, oxidative stress, etc.) signifies a high risk of microangiopathy and macroangiopathy.[19] Potentially cytotoxic metabolites (eg, formaldehyde or acrolein along with hydrogen peroxide and ammonia) are formed by SSAO during oxidative deamination of methylamine and allylamine.[20] It was observed on endothelial cells that the aforementioned cytotoxic metabolites, especially formaldehyde, may initiate endothelial injury and subsequent development of atherosclerosis.[21] Our observations suggest that increased SSAO activity in diabetes causes endothelial dysfunction and may be an additional risk factor for atherosclerosis. Formaldehyde not only induces protein cross-linking but also enhances the advanced glycation of proteins in vitro.[22] Glycated collagen is implicated in the pathogenesis of diabetic atherosclerosis and hypertension.

The correlation between SSAO and glycosylated hemoglobin is consistent with previous reports,[11] and raises the possibility

Table 2. Multiple Regression Analysis of Serum SSAO Activity

Independent Variable	IDDM		NIDDM		Control		All Subjects	
	Partial R^2	P	Partial R^2	P	Partial R^2	P	Partial R^2	P
Age (yr)	.445	NS	.590	NS	.463	NS	.278	NS
Body weight (kg)	.855	NS	.842	NS	.726	<.02	.707	<.01
BMI (kg/m²)	.858	NS	.831	NS	.730	NS	.750	<.02
Total cholesterol (mmol/L)	.668	NS	.208	NS	.254	<.02	.205	NS
HDL cholesterol (mmol/L)	.710	NS	.273	NS	.405	NS	.207	NS
Triglyceride (mmol/L)	.781	NS	.637	NS	.619	NS	.403	<.003
Atherogenic index	.069	NS	.032	NS	.137	<.05	.015	NS
Creatinine (μmol/L)	.474	NS	.522	NS	.438	<.04	.294	<.003
Fasting plasma glucose (mmol/L)	.565	NS	.527	NS	.343	NS	.447	<.004
HbA_{1c} (%)	.308	NS	.507	NS	.493	NS	.360	<.002

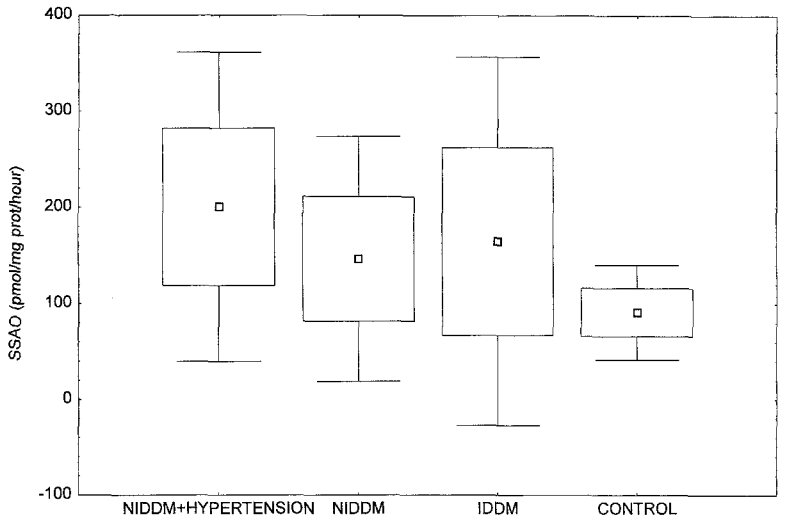

Fig 2. SSAO activity in obese patients (BMI > 25). ⊥, ±1.96 · SD; □, ± 1.00 · SD; □, mean. NIDDM + HYPERTENSION, 200.25 ± 81.94 pmol/mg protein/h, n = 10, *P* = .0006; NIDDM without hypertension, 146.11 ± 64.92 pmol/mg protein/h, n = 19, *P* < .003; IDDM without hypertension, 164.49 ± 97.80 pmol/mg protein/h, n = 10, *P* < .02; CONTROL, obese, 91.12 ± 25.20 pmol/mg protein/h, n = 14). Values are the mean ± SD. *P* value compares diabetic patients *v* controls.

that chronic nonenzymatic glycosylation processes may be influenced by SSAO activity. Aminoguanidine, a potent inhibitor of glycation and advanced-glycation end-product formation, has proved to be a SSAO inhibitor both in vivo and in vitro.[22]

The association of the total cholesterol level and atherogenic index with serum SSAO activity in control subjects was unexpected, but may indicate a relationship between hyperlipoproteinemia and elevated serum SSAO activity. Interestingly, if we add our results to the observations in chronic heart failure[23] and IDDM[11] patients, we find several risk factors for atherosclerosis that are correlated with SSAO: body weight, BMI, fasting plasma glucose, HbA_{1c}, serum triglyceride, total cholesterol, and plasma norepinephrine. A possible explanation for this finding is that endothelial injury caused by other risk factors may result in the liberation of membrane-bound SSAO from smooth muscle cells, smooth muscle–derived foam cells, or adipocytes.

This hypothesis is confirmed by recent genetic findings. Human placental copper-containing, topa quinone–containing amine oxidase and rat adipocyte membrane amine oxidase have been cloned.[24-25] The latter 97-kd amine oxidase has a single transmembrane segment and a large C-terminal extracellular domain containing the catalytic site. One partial sequence of this protein, which is likely secreted, is homologous to a region of human placental amine oxidase. Whether the soluble isoform of human SSAO is secreted, is a result of adipocyte or smooth muscle necrosis or damage, or has a different origin remains to be elucidated.

Hyperglycemia and hyperinsulinemia are known to be associated with a high risk for cardiovascular disease in NIDDM.[26] However, the risk of vascular complications is not equal among diabetic patients. The diabetic state itself is not sufficient to cause endothelial dysfunction.[19] Other genetic or environmental factors may influence the vulnerability of endothelial cells. One of these factors may be SSAO activity.

A possible explanation for the elevation of SSAO activity in diabetes may be that chronic hyperinsulinemia stimulates the sympathetic system, thereby resulting in elevated epinephrine levels.[27] In chronic heart failure, activation of the sympathetic system may have the same consequence.[28] Excessive release of epinephrine may lead to an increase in the production of methylamine by MAO-A.[29] Methylamine was confirmed to be a substrate of SSAO, and thus it is converted to toxic metabolites (formaldehyde, hydrogen peroxide, and ammonia) in the blood.

An elevation in both serum and kidney SSAO activity due to an increased v_{max} in streptozotocin-induced diabetic rats[12] and the high SSAO activity in rat retina[30] suggest that this enzyme may have an important role in the development of microangiopathy. Further prospective studies of SSAO activity are required to confirm the predictive role of this enzyme in early renovascular damage or the initial stage of retinopathy.

Previous clinical studies reported elevated serum amine oxidase activity in diabetes.[9-10] Some of these observations were made in the 1960s, and the formerly applied spectrophotometric method was less sensitive and specific than the radiometric procedure used in the present study. We failed to measure human serum SSAO levels after MAO inhibition with a fluorimetric method, due to the very low activity of SSAO. On the other hand, there is no clear distinction as to whether MAO or SSAO levels were measured in the aforementioned experiments. The applied 0.8-mmol/L Benzylamine concentration in these experiments suggests that these results less likely reflect SSAO because of the explicit substrate inhibition at this concentration.[31] In contrast to these findings, we failed to show any effect of age, sex, or smoking on SSAO activity. Thus, our results may be the first report of elevated SSAO activity in NIDDM.

The biological significance of increased serum SSAO activity in the pathogenesis of diabetic complications remains to be determined. Nevertheless, this enzyme may be a useful clinical marker in prognostic evaluation. Knowledge of the relationship between SSAO activity, hyperlipidemia, and obesity may lead to the development of new strategies for treatment and prevention of complications in diabetes mellitus.

ACKNOWLEDGMENT

The authors are grateful to Professor Franca Buffoni for suggestions and indispensable help and to Edit Oszvald for technical assistance.

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