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ORIGINAL

S. Fischer • M. Hanefeld • S.M. Haffner • C. Fusch • U. Schwanebeck • C. Köhler • K. Fücker • U. Julius

Insulin-resistant patients with type 2 diabetes mellitus have higher serum leptin levels independently of body fat mass

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Abstract In obese people, an increase of plasma leptin levels is well-known and is seen as a consequence of the increased body fat mass. Moreover, a relationship between fasting concentrations of leptin and insulin has been described. Hyperinsulinemia is considered to be indicative of insulin resistance. We aimed at elucidating the interrelations between leptin, insulin and insulin resistance in type 2 diabetic patients. Under metabolic ward conditions, we investigated 21 moderately overweight men with type 2 diabetes. The patients had a mean age of 59.1 years, a mean body mass index (BMI) of 26.8 kg/m^2, and a mean diabetes duration of 82.5 months. All patients were treated with diet alone. We measured fasting leptin and insulin levels, body composition by determination of total body water, and insulin resistance by euglycemic hyperinsulinemic clamp technique. At univariate analysis, fasting leptin level significantly and positively correlated with BMI (r=0.49, p=0.02) and with fasting insulin (r=0.69, p=0.001), while it negatively correlated with the glucose disposal rate (r=-0.62, p=0.002). Furthermore, leptin was inversely correlated with HDL-cholesterol (r=-0.45, p=0.04). When excluding the influence of body fat mass or of BMI in partial correlation analysis, the correlations between leptin and insulin or insulin sensitivity remained significant. The relationship between insulin resistance (as measured directly in the clamp experiments) and leptin concentrations was also shown by subdividing the diabetic patients according to tertiles of insulin sensitivity. The highest fasting leptin levels were observed in those patients with the most expressed insulin resistance. Our data point to a functional relationship between insulin resistance and leptin concentrations in insulin-resistant type 2 diabetic men, independently of body composition. This relationship is believed to be mediated by insulin.

Key words Type 2 diabetes • Insulin • Leptin • Insulin sensitivity

S. Fischer (✉) • M. Hanefeld • C. Köhler • K. Fücker • U. Julius
Institute of Clinical Metabolic Research
Medical Faculty Carl Gustav Carus
University of Technology Dresden
Fetscherstrasse 74, 01307 Dresden, Germany

S.M. Haffner
Department of Medicine
University of Texas Health Science Center
San Antonio, Texas, USA

C. Fusch
Division of Neonatology
University Women's Hospital
Bern, Switzerland

U. Schwanebeck
Institute of Medical Informatics and Biometrics
Medical Faculty Carl Gustav Carus
University of Technology Dresden
Dresden, Germany

Introduction

In nondiabetic as well as in diabetic subjects significant correlations between body mass index (BMI) and fasting leptin concentrations have been shown [1–4]. Furthermore, a relationship between leptin and fasting insulin concentrations has been described [5–9]. In vitro investigations have shown that leptin modulates insulin activities in isolated hepatocytes of obese individuals [10]. An important question is the relation of leptin and insulin resistance in type 2 diabetic patients.

Leptin could play a role in the pathogenesis of insulin resistance because of the relationship between insulin resistance and obesity [11]. On the other hand, leptin could be associated with insulin resistance independently of obesity and hyperinsulinemia. Recently, in the Miami Community Health Study a significant inverse relation between leptin and insulin resistance was seen in nondiabetic men and women, independently of obesity and hyperinsulinemia. [12]. So far, little is known about this relation in type 2 diabetic patients. In some studies insulin sensitivity was not measured by clamp; only fasting insulin levels were estimated. In another study diabetic patients were treated with different antidiabetic drugs and had disturbed renal function [13]. However, it is known that glibenclamide significantly increases circadian levels of both insulin and leptin parallel with weight gain [14].

The aim of our study was to investigate the relationship between leptin and insulin sensitivity, measured directly by euglycemic hyperinsulinemic clamp, in type 2 diabetic patients who are treated with diet alone.

Patients and methods

Patients

We studied 21 male patients with type 2 diabetes (mean age 59.1 years; mean BMI 26.8 kg/m^2). All patients were treated with diet alone. The antidiabetic treatment (acarbose using a maximum of 300 mg/day or glibenclamide maximally 5 mg/day) was stopped at least 4 weeks before the start of the investigation. Inclusion criteria were: age between 35 and 70 years, BMI ≤32 kg/m^2 (stable body weight), HbA_{1C} level between 7% and 10.5% and diabetes duration ≥3 months. Exclusion criteria were: severe liver and renal diseases [serum glutamic-pyruvic transaminase (SGPT) ≥0.83 μmol·(l·s)$^{-1}$, serum glutamic-oxalacetic transaminase (SGOT) ≥0.83 μmol·(l·s)$^{-1}$ or creatinine ≥177 μmol·l^{-1}], hematologic diseases, cancer, hyperthyroidism, acute infections, use of beta blockers or of steroid hormones, and abuse of alcohol.

The investigations were performed under metabolic ward conditions between 8 and 12 AM, following a 12-hour overnight fasting period. On the day before the investigation, patients were given a standardized diet (2500 kcal, 50% carbohydrates, 35% fat, 15% protein).

The study protocol was approved by the Ethical Committee of the Medical Faculty of the University of Technology Dresden. All patients gave their written informed consent.

Methods

The euglycemic hyperinsulinemic clamp technique was performed according to De Fronzo et al. [15]. After measuring basal glucose (five times) and insulin (three times) concentrations during an interval of 20 minutes, we started the insulin infusion (short-acting human insulin; Actrapid, Novo Nordisk Copenhagen, Denmark). Insulin was administered in the first 10 minutes at a rate that depended on the square meters of body and that decreased from the first to the tenth minute: first minute, 127.6 mU·m^{-2}·min^{-1}; subsequent minutes, 113.6, 101.2, 90.2, 80.2, 71.4, 63.6, 56.8, 50.4 and 45.0 mU·m^{-2}·min^{-1}. Subsequently, insulin was infused at a constant rate of 40 mU·m^{-2}·min^{-1}. The plasma glucose concentration was examined at 5-minute intervals. The target plasma glucose level was 5.5 mmol·l^{-1}. Insulin was measured at 10-minute intervals after the start of the infusion.

A variable infusion of 20% glucose was adjusted to maintain the plasma glucose concentration for at least 60 minutes at the level of 5.5 mmol·l^{-1} (range, 5.3–5.7 mmol·l^{-1}). The steady-state phase was reached when the plasma glucose and insulin levels showed only insignificant variations. We calculated the insulin-stimulated glucose uptake (Mc) from glucose infusion rates at the constant rate of insulin infusion as a measure of insulin sensitivity (for total body mass as well as lean body mass).

Body composition was determined by measuring total body water using deuterium oxide diluted in serum [16]. The patients received an oral load of 0.8 ml 99.8% D_2O/kg body weight (maximum volume, 100 ml) on the evening before the day of the clamp investigation. Blood samples were drawn to estimate D_2O concentration 3 hours later [16]. No food or fluid intake was allowed during this period. The concentration of D_2O was measured by infrared spectrometry [16, 17]. The measurement error was below 0.8%. Lean body mass (LBM) was calculated from body water assuming a hydratation factor of 0.73 [18–21].

Analytical methods

Glucose and lipids were measured by enzymatic methods (hexokinase, CHOD-PAP (cholesterol-measurement), GPO-PAP (triglyceride-measurement) on the CIBA Express auto-analyzer). Insulin was measured by ^{125}I-radioimmunoassay (Diagnostic Products, Los Angeles, USA). Leptin concentration was measured by a commercial radioimmunoassay (Linco Research, St. Louis, MO, USA [2, 22]). Details of the methods have previously been published [14].

Statistical analysis

A normal distribution of the variables was ascertained by the Kolmogorov-Smirnov test. Differences between group means were tested by analysis of variance (ANOVA). Correlations were estimated by Pearson's correlation coefficients. Partial correlation coefficients were calculated after adjustment for BMI and body fat mass. We used the statistical program SPSS for Windows, version 6.

Results

We studied the relationship between leptin levels and insulin sensitivity in 21 diabetic men (Table 1) who were moderately overweight, had an average HbA_{1c} of 8.4%, and were rather insulin resistant (mean Mc, 2.6 mg/kg·min·insulin; range, 0.5–5.3; based on total body weight).

Table 1 Characteristics and metabolic parameters of 21 men with type 2 diabetes

Parameter	Mean (SEM)	
Age, years	59.1	(1.0)
BMI, $kg \cdot m^{-2}$	26.8	(0.6)
Body fat, kg	22.6	(1.2)
Body fat, %	28.3	(1.2)
Lean body mass, kg	56.6	(1.4)
Lean body mass, %	71.7	(1.2)
Waist-hip ratio	0.99	(0.01)
Fasting plasma glucose, $mmol \cdot l^{-1}$	12.0	(0.5)
Hba_{1c}, %	8.4	(0.2)
Duration of diabetes, months	82.5	(12.4)
Blood pressure, mmHg		
Systolic	141.2	(3.7)
Diastolic	83.6	(1.7)
Fasting insulin, $nmol \cdot l^{-1}$	0.21	(0.02)
Fasting leptin, $ng \cdot ml^{-1}$	7.8	(0.9)
Insulin-stimulated glucose uptake (Mc), mg/kg·min·insulin		
For total body mass	2.6	(0.3)
For lean body mass	3.6	(0.4)
Triglycerides, $mmol \cdot l^{-1}$	2.4	(0.3)
Cholesterol, $mmol \cdot l^{-1}$	5.9	(0.2)
HDL-cholesterol, $mmol \cdot l^{-1}$	0.98	(0.07)

BMI, body mass index; HbA_{1C}, glycosylated hemoglobin

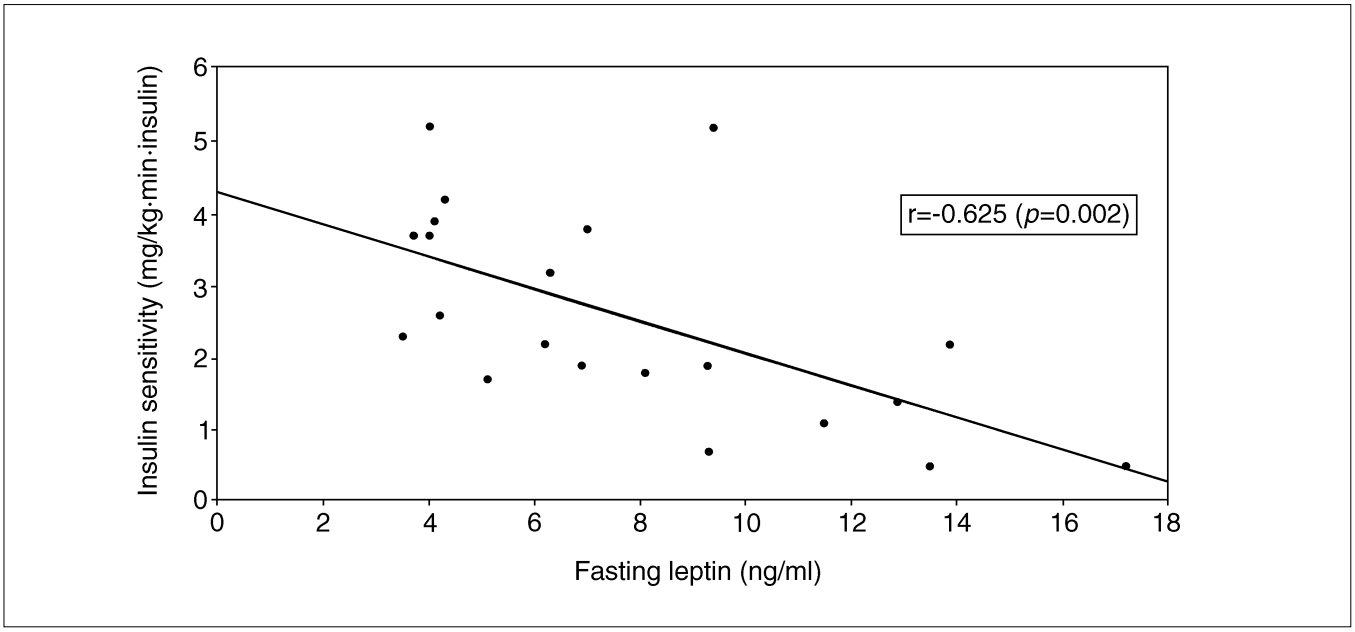

Fig. 1 Correlation between insulin sensitivity (Mc) and fasting leptin concentrations in male type 2 diabetic patients

Table 2 Correlation coefficients (Pearson's r) and partial correlation coefficients between fasting leptin values and parameters of body composition, insulin-stimulated glucose uptake and metabolism in 21 male patients with type 2 diabetes

	Not adjusted		Adjusted for body fat mass		Adjusted for BMI	
	r	*p*	r	*p*	r	*p*
BMI, $kg \cdot m^{-2}$	0.49	0.02	–	–	–	–
Body fat, kg	0.34	NS	–	–	–	–
Body fat, %	0.17	NS	–	–	–	–
Lean body mass, kg	0.35	NS	–	–	–	–
Lean body mass, %	-0.17	NS	–	–	–	–
Waist-hip ratio	-0.15	NS	-0.28	NS	-0.25	NS
Fasting plasma glucose	-0.40	NS	-0.50	0.025	-0.50	0.02
HbA_{1C}	-0.33	NS	-0.36	NS	-0.46	0.04
Triglycerides	0.30	NS	0.17	NS	0.08	NS
Cholesterol	-0.11	NS	-0.22	NS	-0.33	NS
HDL-cholesterol	-0.45	0.04	-0.38	NS	-0.32	NS
Fasting insulin	0.69	0.001	0.73	0.001	0.62	0.004
Blood pressure, systolic	0.24	NS	0.18	NS	0.10	NS
Blood pressure, diastolic	0.31	NS	0.28	NS	0.17	NS
Insulin-stimulated glucose uptake (Mc)						
For total body mass	-0.62	0.002	-0.59	0.006	-0.52	0.02
For lean body mass	-0.63	0.002	-0.62	0.003	-0.53	0.02

BMI, body mass index; *NS*, not significant

Table 3 Metabolic parameters of 21 men with type 2 diabetes, by tertiles of insulin sensitivity as determined by insulin-stimulated glucose uptake (Mc)[a]. Values are mean (SEM)

	Tertile 1 (≤1.8 mg/kg·min·insulin)	Tertile 2 (1.9–3.2 mg/kg·min·insulin)	Tertile 3 (>3.2 mg/kg·min·insulin)	ANOVA *p*
Mc, mean[a]	1.1	2.3	4.2	
Patients, n	7	7	7	
Age, years	61.3 (1.1)	55.6 (1.5)*	60.6 (1.8)‡	0.03
BMI, $kg \cdot m^{-2}$	27.6 (0.9)	27.2 (1.1)	25.5 (1.0)	NS
Body fat, kg	22.6 (1.5)	26.1 (1.2)	19.2 (2.5)‡	0.053
Body fat, %	27.7 (0.6)	32.3 (1.9)	24.8 (2.5)‡	0.032
Lean body mass, kg	58.6 (2.8)	55.0 (2.9)	56.4 (2.0)	NS
Lean body mass, %	72.3 (0.6)	67.6 (1.9)	75.1 (2.5)‡	0.032
Waist-hip ratio	0.99 (0.02)	1.00 (0.01)	0.98 (0.01)	NS
Fasting plasma glucose, $mmol \cdot l^{-1}$	10.6 (0.7)	13.2 (1.0)	12.2 (0.7)	NS
HbA_{1C}, %	8.1 (0.2)	8.4 (0.5)	8.8 (0.5)	NS
Triglycerides, $mmol \cdot l^{-1}$	2.4 (0.4)	3.2 (0.4)	1.4 (0.4)‡	0.031
Cholesterol, $mmol \cdot l^{-1}$	5.8 (0.3)	6.3 (0.5)	5.5 (0.2)	NS
HDL-cholesterol, $mmol \cdot l^{-1}$	0.9 (0.1)	0.8 (0.1)	1.2 (0.1)	NS
Fasting insulin, $nmol/l^{-1}$	0.27 (0.02)	0.19 (0.02)*	0.16 (0.02)*	0.004
Fasting leptin, $ng \cdot ml^{-1}$	11.1 (1.5)	7.2 (1.3)*	5.2 (0.8)*	0.012
Blood pressure, mmHg				
Systolic	150.7 (8.1)	137.1 (4.3)	135.7 (5.2)	NS
Diastolic	87.8 (3.0)	80.0 (2.2)	82.8 (3.2)	NS

Student-Newman-Keuls test *$p<0.05$ vs. tertile 1; ‡ $p<0.05$ vs. tertile 2

[a] Per total body weight

BMI, body mass index; *NS*, not significant

At univariate analysis, fasting leptin level significantly and positively correlated with BMI and fasting insulin levels, while it negatively correlated with HDL-cholesterol and Mc (Table 2 and Fig. 1). When excluding the influence of body fat mass or of BMI in partial correlation analysis, the correlations between leptin and insulin or Mc values remained significant (Table 2).

We grouped the patients into tertiles depending on their insulin-stimulated glucose uptake (Table 3). Fasting leptin concentrations were highest in the group with the most expressed insulin resistance.

Discussion

The aim of our investigation was to evaluate the relationship between leptin concentrations and insulin sensitivity in type 2 diabetes. Because of the well-known gender difference in leptin levels, we have only included male diabetic patients. All patients were insulin-resistant. We observed a negative relationship between insulin sensitivity and serum leptin concentrations. Patients with the severest insulin resistance, as measured by clamp technique, had the highest serum leptin concentrations. This relationship was not influenced by body fat mass (directly measured by an isotopic dilution technique) or by BMI, and was similar to that of insulin sensitivity with insulin levels.

Previous papers reporting on lean and obese nondiabetic subjects have already shown elevated leptin levels to be associated with insulin resistance [12, 23, 24], independently of body fat mass [23, 25] or BMI [26]. Our data for the first time demonstrate that this relationship is present in insulin-resistant type 2 diabetic men as well. Comparing with normal Mc values as described by Schalin-Jäntti et al. [27], our patients have an highly expressed insulin resistance. In the literature there are only few data dealing with serum leptin concentrations in type 2 diabetic patients. Usually, these patients were treated with sulfonylureas or insulin and had partly disturbed renal function. The antidiabetic therapy influences serum insulin levels, while glibenclamide increases serum leptin concentrations [14]. In the UKPD Study, leptin was associated with insulin after adjusting for BMI [28]. Patients on sulfonylurea or insulin therapy had both increased insulin and leptin levels [13, 28].

In general it is accepted that serum leptin concentrations are positively associated with obesity and hyperinsulinemia [12, 23, 24, 29]. Other studies have emphasized the significance of body fat content as regulator of serum leptin levels [30]. Another study did not find an independent correlation between leptin and insulin resistance [31].

On the other hand, insulin resistance may indirectly contribute to hyperleptinemia by increased insulin levels [13]. The exact sequence of these regulations is not yet understood. In the Miami Community Health Study, the relationship between leptin level and insulin resistance per se was reduced but not eliminated after accounting for concomitant hyperinsulinemia in young to middle-aged, nondiabetic subjects [12]. It is interesting that, on the other hand, leptin exerts a direct stimulatory effect on glucose uptake in skeletal muscle and an inhibitory effect on both basal and glucose-stimulated pancreatic insulin secretion [32].

Thus, the relationship between leptin and insulin respectively insulin sensitivity independently of BMI suggests the important role of insulin and insulin sensitivity in regulation of serum leptin concentrations in type 2 diabetic patients. This central role of insulin is also demonstrated by the finding that insulin induces leptin synthesis in cultured adipocytes [7, 33] in a dose-dependent manner [33]. Irrespective of the degree of obesity, the presence of chronic hyperinsulinemia increases adipose tissue leptin synthesis and secretion in insulin-resistant subjects [24]. Obesity can intensify the situation by increasing adipose tissue mass and insulin resistance [24].

In euglycemic hyperinsulinemic clamp studies, insulin regulated chronic plasma leptin concentrations in healthy subjects [23, 31, 34, 35] as well as in type 2 diabetic patients [5, 7].

Our data obtained in diabetic men are partly contradictory to results published for nondiabetic lean and obese subjects [8]. In the latter study leptin was strongly associated with obesity and to a lesser extent with insulin resistance. The cause of these differences could be that in nondiabetic subjects the degree of overweight is important for both insulin and leptin levels, whereas in type 2 diabetic patients the severity of insulin resistance determines these hormonal concentrations. The findings of Segal et al. [25] are in agreement with these data. Insulin-resistant lean men had higher plasma leptin levels than insulin-sensitive lean men independently of body fat.

In conclusion, our study indicates that insulin resistance as well as increased insulin levels are more important determinants for regulation of leptin levels than BMI, body fat content or body fat distribution as measured by waist-hip ratio (WHR) in moderately obese type 2 diabetic patients with severe insulin resistance and long-lasting diabetes.

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