Relationship Between Hepatic/Visceral Fat and Hepatic Insulin Resistance in Nondiabetic and Type 2 Diabetic Subjects

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Background & Aims: **Abdominal fat accumulation (visceral/hepatic) has been associated with hepatic insulin resistance (IR) in obesity and type 2 diabetes (T2DM). We examined the relationship between visceral/hepatic fat accumulation and hepatic IR/accelerated gluconeogenesis (GNG).** ***Methods:*** **In 14 normal glucose tolerant (NGT) (body mass index [BMI] = 25 ± 1 kg/m^2) and 43 T2DM (24 nonobese, BMI = 26 ± 1; 19 obese, BMI = 32 ± 1 kg/m^2) subjects, we measured endogenous (hepatic) glucose production (3-^{3}H-glucose) and GNG (^2H_2O) in the basal state and during 240 pmol/m^2/min euglycemic-hyperinsulinemic clamp, and liver (LF) subcutaneous (SAT)/visceral (VAT) fat content by magnetic resonance spectroscopy/magnetic resonance imaging.** ***Results:*** **LF was increased in lean T2DM compared with lean NGT (18% ± 3% vs 9% ± 2%, $P < .03$), but was similar in lean T2DM and obese T2DM (18% ± 3% vs 22% ± 3%; P = NS). Both VAT and SAT increased progressively from lean NGT to lean T2DM to obese T2DM. T2DM had increased basal endogenous glucose production (EGP) (NGT, 15.1 ± 0.5; lean T2DM, 16.3 ± 0.4; obese T2DM, 17.2 ± 0.6 μmol/min/kg$_{ffm}$; $P = .02$) and basal GNG flux (NGT, 8.6 ± 0.4; lean T2DM, 9.6 ± 0.4; obese T2DM, 11.1 ± 0.6 μmol/min/kg$_{ffm}$; $P = .02$). Basal hepatic IR index (EGP × fasting plasma insulin) was increased in T2DM (NGT, 816 ± 54; lean T2DM, 1252 ± 164; obese T2DM, 1810 ± 210; $P = .007$). In T2DM, after accounting for age, sex, and BMI, both LF and VAT, but not SAT, were correlated significantly ($P < .05$) with basal hepatic IR and residual EGP during insulin clamp. Basal percentage of GNG and GNG flux were correlated positively with VAT ($P < .05$), but not with LF. LF, but not VAT, was correlated with fasting insulin, insulin-stimulated glucose disposal, and impaired FFA suppression by insulin (all $P < .05$).** ***Conclusions:*** **Abdominal adiposity significantly affects both lipid (FFA) and glucose metabolism. Excess VAT primarily increases GNG flux. Both VAT and LF are associated with hepatic IR.**

Increased basal endogenous (primarily hepatic) glucose production, despite fasting hyperinsulinemia, is a characteristic feature of type 2 diabetes mellitus (T2DM)[1,2] and indicates the presence of hepatic resistance to the action of insulin.[1] This is substantiated further by the inability of insulin to normally suppress the increased basal rate of hepatic glucose output.[3] Excess abdominal fat accumulation, both visceral and hepatic, has been associated with abnormalities in glucose and lipid metabolism. In particular, both increased visceral adipose tissue (VAT) and intrahepatic fat content have been associated with hepatic insulin resistance (IR).[4–6] VAT is highly lipolytic and, according to the portal hypothesis, increased delivery of FFA into the portal circulation, and hence to the liver, leads to enhanced gluconeogenesis (GNG) and hepatic IR.[7] However, the portal hypothesis has remained untested in human beings because the portal circulation is inaccessible.

The past decade has witnessed an epidemic increase in the incidence of obesity[8] and nonalcoholic fatty liver disease (NAFLD), which includes both hepatic steatosis and steatohepatitis.[9–11] Both obesity and diabetes are important risk factors for the development of NAFLD.[9,10] Nondiabetic subjects with NAFLD manifest an impaired ability of insulin to suppress endogenous glucose production (EGP),[11,12] and a recent study showed that the amount of insulin required to achieve normoglycemia in T2DM was related closely to liver fat content.[13] A strong association between NAFLD and hepatic IR also has been shown,[11,14] and this relationship cannot be explained by obesity, age,

Abbreviations used in this paper: BMI, body mass index; C5, carbon 5; EGP, endogenous glucose production; FPI, fasting plasma insulin; GCRC, General Clinical Research Center; GNG, gluconeogenesis; IR, insulin resistance; NAFLD, nonalcoholic fatty liver disease; NGT, normal glucose tolerant; Ra, rate of appearance; Rd, rate of glucose disappearance; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; T2DM, type 2 diabetes mellitus.

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Table 1. Anthropometric and Clinical Characteristics

	NGT	T2DM lean	T2DM obese	*P* NGT vs all T2DM	*P* NGT vs lean T2DM	*P* lean vs obese T2DM
Number	14	24	19			
Sex, F/M	4/10	8/16	8/11	NS	NS	NS
Age, (*y*)	43 ± 3	54 ± 2	54 ± 3	.003	.006	NS
HbA1c, %	5.2 ± 0.1	8.4 ± 0.3	8.4 ± 0.3	< .0001	< .0001	NS
BMI, (kg/m^2)	24.8 ± 0.8	25.9 ± 0.4	31.6 ± 0.6	.001	NS	< .0001
Waist, (*cm*)	89 ± 4	94 ± 2	109 ± 3	.006	NS	< .0001
Total fat mass, %	24 ± 1	29 ± 1	39 ± 1	< .0001	.008	< .0001
SAT, (cm^2)	219 ± 17	233 ± 19	411 ± 27	.02	NS	< .0001
VAT, (cm^2)	95 ± 12	115 ± 6	185 ± 15	.005	NS	< .0001
Liver fat, %	9 ± 2	18 ± 3	22 ± 3	.005	.03	NS
Plasma total cholesterol, (*mmol/L*)	4.4 ± 0.2	4.3 ± 0.2	4.3 ± 0.1	NS	NS	NS
Plasma high-density lipoprotein cholesterol, (*mmol/L*)	1.03 ± 0.09	0.97 ± 0.05	0.88 ± 0.06	NS	NS	NS
Plasma low-density lipoprotein cholesterol, (*mmol/L*)	2.8 ± 0.1	2.6 ± 0.1	2.6 ± 0.1	NS	NS	NS
Plasma triglyceride level, (*mmol/L*)	1.2 ± 0.2	1.5 ± 0.1	1.8 ± 0.2	.02	NS	NS
AST level, (*U/L*)	24 ± 2	19 ± 2	25 ± 2	NS	NS	NS
ALT level, (*U/L*)	22 ± 2	23 ± 2	32 ± 4	NS	NS	.03
Systolic blood pressure, (*mm Hg*)	123 ± 4	125 ± 2	129 ± 3	NS	NS	NS
Diastolic blood pressure, (*mm Hg*)	72 ± 3	75 ± 1	76 ± 2	NS	NS	NS

or visceral fat content,[15] even though the prevalence of liver steatosis is higher in obese subjects and liver/visceral fat content are increased significantly in the elderly, even after accounting for total body fat content.[16]

The goals of the present study were as follows: (1) to quantitate hepatic IR and to define the contribution of increased GNG/glycogenolysis to the hepatic IR, and (2) to examine the relationship between increased visceral/hepatic fat content and hepatic IR/accelerated GNG in T2DM subjects during fasting and hyperinsulinemic conditions.

Materials and Methods

Subjects/Experimental Design

Forty-three subjects with T2DM spanning a wide range of obesity (body mass index [BMI], 23–39 kg/m^2; body fat, 21%–50%) and 14 lean normal glucose tolerant (NGT) subjects participated in the study. Obesity was defined as a BMI of greater than 30 kg/m^2 or a BMI of greater than 27 with a fat mass greater than 35%. Subjects were recruited from multiple advertisements in the newspapers and local community. All subjects who responded to the advertisement and who met entry criteria were recruited into the study. All studies were performed at the General Clinical Research Center (GCRC) of the University of Texas Health Science Center at San Antonio after an overnight fast. Subjects first received 75 grams of oral glucose tolerance test to establish the diagnosis of normal glucose tolerance or diabetes according to American Diabetes Association criteria. Within 5–10 days, subjects returned to the GCRC and euglycemic hyperinsulinemic clamp was performed with [3-^{3}H]-glucose to measure hepatic and total body (primarily represents muscle) insulin sensitivity.[17] The characteristics of the study population are shown in Table 1. None of the patients was treated with insulin, metformin, or thiazolidinediones. For subjects who were taking sulfonylureas, the medication was stopped 2 days before the study. Subjects were not taking any other drugs known to affect glucose tolerance. Patients were in good general health without evidence of cardiac, hepatic, renal, or other chronic diseases as determined by history, examination, routine blood chemistries, urinalysis, and electrocardiography. Subjects were not taking any medications known to affect glucose metabolism. No subject was involved in strenuous physical activity and body weight was stable (±3 lb) for at least 3 months before the study. The study protocol was approved by the Institutional Review Board of the University of Texas Health Science Center at San Antonio, and informed written consent was obtained from each patient before participation.

Lean Body and Fat Mass

Lean body mass was measured with an intravenous bolus (100 μCi) of ^3H_2O at time 0 of the OGTT. Plasma ^3H_2O radioactivity was determined at 90, 105, and 120 minutes, and fat and lean body mass were calculated as previously described.[18] The quantitation of abdominal subcutaneous and visceral fat areas at L4–L5 was performed using magnetic resonance imaging (1.9 T; Elscint Prestige Ltd., Elscint, Haifa, Israel)[19] and liver fat