

Intrahepatic Lipids Are Predicted by Visceral Adipose Tissue Mass in Healthy Subjects

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Intracellular fat accumulation in the liver (1) and abdominal obesity (2–4) have both been related to reduced insulin action. An association between visceral and hepatic lipids has been demonstrated in healthy subjects and patients with type 2 diabetes (5). However, this association was not found in a cohort of nondiabetic subjects (1,6,7).

The aim of the present study was to analyze the relationships between body fat distribution and hepatic lipids (measured using ¹H-magnetic resonance spectroscopy) in a large heterogeneous cohort of healthy subjects at increased risk of type 2 diabetes. For this purpose, we used a whole-body magnetic resonance imaging scan to measure various fat depots.

RESEARCH DESIGN AND METHODS

Subjects ($n = 78$) were selected from TULIP (Tübingen Lifestyle Intervention Program). Persons recruited for TULIP are healthy subjects at increased risk for type 2 diabetes, namely family members of type 2 diabetic patients, obese or overweight subjects (BMI >27 kg/m²), subjects with impaired glucose tolerance, and women with a history of gestational diabetes. Subjects with clinically suspected alcohol abuse were

excluded from the study. All subjects included in the present study were studied before starting a standardized exercise and dietary intervention program. The local ethics committee approved all protocols, and all subjects gave informed written consent.

Magnetic resonance examinations

A whole-body imaging protocol was applied for recording a set of 90–120 parallel transverse slices. Slice thickness was 10 mm for the entire body, with interslice gaps of 10 mm. T1-weighted contrast was applied, allowing semiautomatic quantitative assessment of fatty tissue and other tissue types in each cross section (Fig. 1A, *a* and *b*). Hepatic fat content was determined by localized STEAM ¹H-magnetic resonance spectroscopy (TR = 4 s, TE = 10 ms; 32 scans) in the seventh segment of the liver. The lipid content was quantitatively assessed by analyzing the signal integral (methylene and methyl signals between 0.7 and 1.5 ppm), using the liver water signal integral as an internal reference (Fig. 1A, *e* and *f*).

Statistical analyses

All data are given as means \pm SE unless otherwise stated. Distribution was tested

for normality using the Shapiro-Wilk *W* test. Nonnormally distributed parameters were log transformed to achieve normal distribution before statistical analyses. To adjust the effects of covariates and identify independent relationships, we performed multivariate linear regression analyses. A *P* value <0.05 was considered statistically significant. The statistical software package JMP (SAS Institute, Cary, NC) was used.

RESULTS

Characteristics of the study group and influence of sex on fat depots

Subjects ($n = 78$ [35 men and 43 women]) ranged from lean to obese (BMI 30.5 ± 0.54 kg/m² [range 20–47]). Whole-body fat (37.5 ± 0.95 vs. $28.8 \pm 1.01\%$, $P < 0.0001$) and non-visceral adipose tissue (VAT) (34.3 ± 0.9 vs. $23.7 \pm 1.0\%$, $P < 0.0001$) were higher in women than in men. In contrast, VAT (3.22 ± 0.18 vs. $5.14 \pm 0.31\%$, $P < 0.0001$) and hepatic lipids (5.98 ± 1.00 vs. $10.42 \pm 1.55\%$, $P = 0.003$) were lower in women than in men).

Relationship between anthropometric measurements, VAT/non-VAT, hepatic lipids, and insulin sensitivity

VAT was correlated with hepatic lipids in women ($R = 0.52$, $P < 0.001$) and men ($R = 0.48$, $P < 0.01$) (Fig. 1B), while whole-body fat was positively correlated with hepatic lipids in women ($R = 0.51$, $P = 0.004$) but not in the smaller group of men ($P = 0.32$). In the whole group, the relationship between hepatic lipids and whole-body fat ($P < 0.01$) was significant after adjusting for the independent effects of sex and age. This model explained 26% of the variation in hepatic lipids. Visceral adipose fat mass was correlated with hepatic lipid content in univariate regression analyses ($R = 0.58$, $P < 0.0001$).

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Received for publication 14 May 2004 and accepted in revised form 17 August 2004.

Abbreviations: VAT, visceral adipose tissue.

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A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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After adjusting for sex, age, waist-to-hip ratio, and non-VAT, only VAT was significantly correlated with hepatic lipids ($P < 0.0001$), explaining 38% of the variation in hepatic lipids.

In men and women, hepatic lipids were positively correlated with fasting insulin ($R = 0.35$, $P = 0.05$ for men and $R = 0.59$, $P < 0.0001$ for women) and negatively correlated with insulin sensitivity (estimated from oral glucose tolerance test using a validated index (8) ($R = -0.56$, $P < 0.001$ for men and $R = -0.61$, $P < 0.0001$ for women) (Fig. 1B). Fasting blood glucose was not correlated with hepatic lipids ($R = 0.16$, $P = 0.37$ in men and $R = 0.28$, $P = 0.08$ in women), whereas fasting free fatty acids were correlated with hepatic lipids in men ($R = 0.45$, $P = 0.01$) but not in women ($R = 0.07$, $P = 0.65$).

CONCLUSIONS— There have been several studies investigating determinants of liver fat (1,5,7). Kelley et al. (5) demonstrated that VAT was the most important factor among other parameters, such as subcutaneous adipose tissue or BMI, in healthy volunteers and patients with type 2 diabetes. Tiikkainen et al. (7) showed that liver fat was strongly associated with fat in the diet. They found that liver fat correlates strongly with intake of saturated fat. They also provide data suggesting that mobilization of hepatic triglycerides may also play an important role. However, no association between liver fat and VAT was observed (1,7). To address this issue, we quantified visceral and subcutaneous adipose tissue using a new methodology applying a whole-body magnetic resonance imaging scan. With this method, we were able to quantify the different fat depots and express VAT mass in relation to overall body weight. We found that VAT was an important predictor of hepatic lipid content independent of obesity/subcutaneous adipose tissue in a large and heterogeneous nondiabetic population.

The two previous studies not demonstrating an association between liver fat and VAT in nondiabetic subjects (1,7) applied a different multislice technique (standardized 16 slices in the abdominal region recorded starting from a reference point) to quantify intra-abdominal fat. Our whole-body protocol analyzes the amount of body fat and its distribution

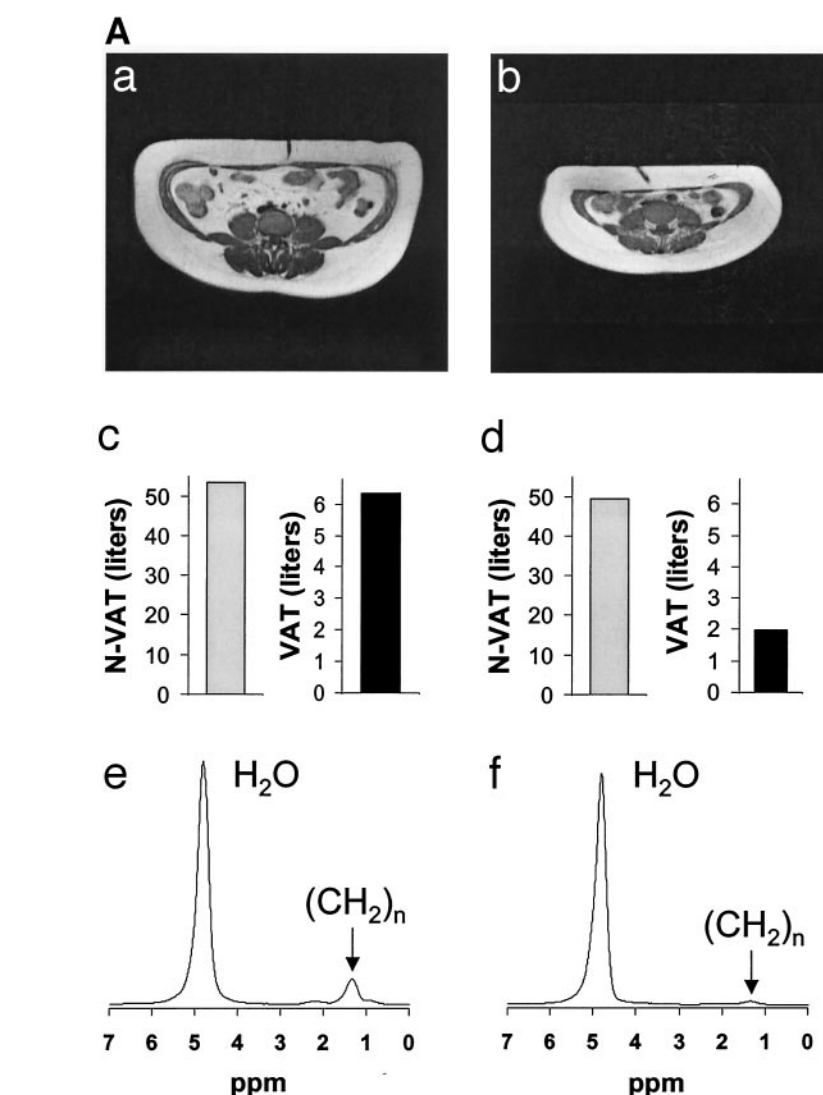


Figure 1—A: Magnetic resonance examinations in a 43-year-old woman (total body fat 43%, VAT 5%, non-VAT 38%, hepatic lipids 9.5% of the signal (a, c, and e, left column) and in a 40-year-old woman (total body fat 44%, VAT 2%, non-VAT 42%, hepatic lipids 2.5% of the signal (b, d, and f, right column). Total body and visceral fat were measured by T1-weighted magnetic resonance imaging. Hepatic lipids were measured by volume localized ¹H-spectroscopy. a and b: Cross-sectional image of the abdomen (umbilicus level). Despite a similar amount of subcutaneous fat, visceral fat depots are clearly higher in the case shown in a. c and d: Absolute contents of non-VAT and VAT in both subjects. e and f: ¹H-spectra from the liver indicate clearly higher hepatic lipid content in e compared with f. The higher hepatic lipid content is found in the subject with more visceral fat (a). B: Relationship between hepatic lipids and visceral lipids, fasting insulin, and insulin sensitivity estimated from the oral glucose tolerance test using a validated index (8) plotted separately for women (upper row) and men (lower row).

from head to toe. The recorded number of slices with 10 mm thickness and a corresponding 10-mm gap, therefore, depends on the individual height of the subject. Applying this technique, one may be able to quantify the individual fat depots more precisely. This may help to determine the variability in liver fat in heterogeneous nondiabetic populations.

In conclusion, we demonstrate that increased VAT is a strong predictor of increased hepatic triglyceride content independent of overall obesity or waist-to-hip ratio. Whether other factors, such as adipokines or polymorphisms in genes regulating lipid metabolism, affect hepatic lipids independent of VAT needs to be determined.

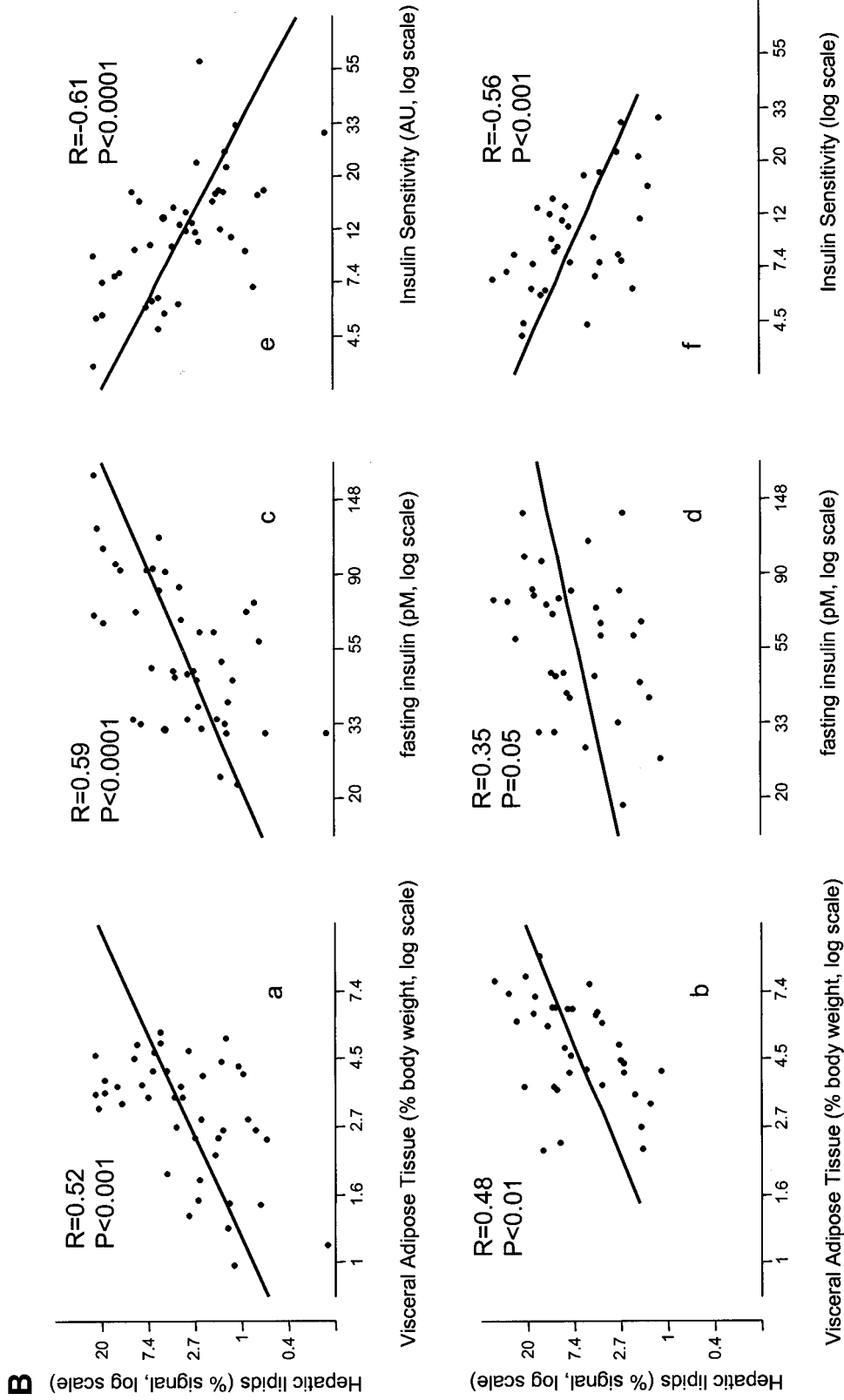


Figure 1—Continued.

Acknowledgments— This study was supported by a research grant from the Deutsche Forschungsgemeinschaft (KFO 114/1).

We thank all the research volunteers for their participation. We gratefully acknowledge the excellent technical assistance of Holger Putzhammer, Renate Umbach, Elke Maerker, Anna Teigeler, and Heike Luz.

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