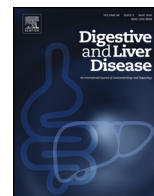




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Liver, Pancreas and Biliary Tract

Fat accumulates preferentially in the right rather than the left liver lobe in non-diabetic subjects

Hua Bian^{a,b,*}, Antti Hakkarainen^c, You Zhou^{a,e}, Nina Lundbom^c, Hannele Yki-Järvinen^{a,d}

^a Minerva Foundation Institute for Medical Research, Helsinki, Finland

^b Department of Endocrinology, Zhongshan Hospital, Fudan University, Shanghai, China

^c Department of Radiology, Helsinki Medical Imaging Center, Helsinki University Central Hospital, University of Helsinki, Helsinki, Finland

^d Department of Medicine, University of Helsinki, Helsinki, Finland

^e Systems Immunity University Research Institute and Division of Infection and Immunity, School of Medicine, Cardiff University, Cardiff, United Kingdom

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ABSTRACT

Aims: To examine the distribution of liver fat (LFAT) in non-diabetic subjects and test whether the fat in the right as compared to the left lobe correlates better with components of the metabolic syndrome or not.

Methods: In this cross sectional study, we determined LFAT by ¹H-MRS in the right lobe (LFAT^{MRS}), and by MRI (LFAT^{MRI}) in four regions of interest (ROIs 1–4, two in the right and two in the left lobe) in 97 non-diabetic subjects (age range 22–74 years, BMI 18–41 kg/m²) and compared the accuracy of LFAT^{MRI} in the different ROIs in diagnosing non-alcoholic fatty liver disease (NAFLD) using areas under the receiver operator characteristic (AUROC) curves.

Results: 38% of the subjects had NAFLD (LFAT^{MRS}). LFAT^{MRI} was significantly higher in the right (5.7 ± 0.5%) than the left (5.1 ± 0.4%) lobe (p < 0.02). The AUROC for LFAT^{MRI} in the right lobe for diagnosing NAFLD was significantly better than that in the left lobe. The relationships between several metabolic parameters and LFAT^{MRI} in the left lobe were significantly worse than those for LFAT^{MRS} while there was no difference between LFAT^{MRS} and right lobe ROIs.

Conclusions: Liver right lobe contains more fat and correlates better with components of the metabolic syndrome than the left in non-diabetic subjects.

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1. Introduction

Studies performed in dogs over 100 years ago showed that blood flow from the splenic vein streamlined to the left lobe of the liver, while blood from the superior mesenteric vein was directed to the right lobe [1,2]. Similarly, studies in humans have shown that blood from the superior mesenteric vein, which drains the right colon, ileum and jejunum, is directed to the right lobe while blood from the spleen and left colon drain to the left lobe [3]. In obese subjects, the rate of visceral lipolysis is increased compared to non-obese subjects and can account for up to 50% of free fatty acids (FFA) delivery to the liver [4]. Many obese subjects accumulate fat in the liver due to non-alcoholic causes (NAFLD) and therefore possibly an increased flux of FFA from visceral fat to the superior

mesenteric vein. Studies using Doppler ultrasonography in healthy volunteers have shown that in response to a meal, intrahepatic portal vein blood flow increases more in the right than the left lobe [5]. FFA delivery from both the meal and from visceral lipolysis might preferentially increase liver fat content more in the right than the left lobe. Metabolic consequences of hepatic insulin resistance in NAFLD such as hyperinsulinemia and hypertriglyceridemia could therefore also be better correlated with fat in the right than the left lobe.

Few data are available examining fat distribution in the human liver. In an autopsy study, Merat et al. [6] analyzed three different parts of the liver (2 × 2 × 2 cm each) and found steatosis to be unevenly distributed (kappa = 0.64). Larson et al. [7] and Merriman et al. [8] took liver biopsies from the right and left lobes of morbidly obese patients and found low variability for steatosis between right and left lobes. However, multiple liver biopsies can not be used to assess heterogeneity of liver fat because of risks of bleeding.

Magnetic resonance imaging (MRI) methods enable accurate assessment of liver steatosis [9,10]. Until now, only one study has been published where heterogeneity of liver fat was analyzed in

* Corresponding author at: Minerva Foundation Institute for Medical Research, University of Helsinki, Biomedicum 2U, Tukholmankatu 8, 00290 Helsinki, Finland. Fax: +358 9 191 25701.

E-mail address: bianhuaer@126.com (B. Hua).

hospitalized patients with type 2 diabetes, who were using oral hypoglycaemic agents or insulin, and the right lobe was found to contain more fat than the left lobe [11]. However, the pathways leading to NAFLD may differ between type 2 diabetic patients and non-diabetic subjects [12], and the drugs, especially insulin and glitazones could affect the routes which regulate intrahepatic fat content [13,14]. Regional variation in liver fat content in non-diabetic subjects has not been examined.

The liver is the source of glucose and (VLDL) triglycerides after an overnight fast, two of the key components of the metabolic syndrome. The liver, once fatty, becomes resistant to the normal actions of insulin to inhibit the production of glucose and VLDL [15]. This leads to hyperglycemia and stimulation of insulin secretion as well as hypertriglyceridemia [16]. All components of the metabolic syndrome are significantly correlated with liver fat content [15]. However, if there is, as discussed above, more fat in the right than the left lobe, the former might be better correlated with features of insulin resistance than the latter. Indeed, identification of the region, which best correlates with features of insulin resistance, could be considered as the region which physiologically defines the most relevant area of fat accumulation in the liver, and provides the area which enables the most accurate diagnosis of NAFLD.

In the present study, we hypothesized that the right lobe of the human liver would contain more fat than the left lobe in non-diabetic subjects, and that fat in the right as compared to the left lobe might correlate better with components of the metabolic syndrome. To this end, we quantified liver fat by MRI in 4 different regions of interest (ROIs) in 97 non-diabetic subjects, and also measured liver fat by proton magnetic resonance spectroscopy ($^1\text{H-MRS}$), the golden standard for measurement of liver fat content.

2. Methods

2.1. Subjects

We analyzed data from all non-diabetic subjects studied since August 2007 when we added an in-phase (IP) and out-of-phase (OP) imaging sequence to our MRI protocol to enable monitoring of spatial distribution of fat in the liver. This sequence covers the whole liver and allows to quantitate the intensity of the liver. The group comprised of 97 subjects (56 women, 41 men), who met the following inclusion criteria: i) age 20–75 years, ii) no known acute or chronic disease other than obesity, hypertension or NAFLD. iii) No evidence of advanced fibrosis as determined using the NAFLD fibrosis score [17]. Exclusion criteria included i) diabetes, ii) autoimmune liver disease (past medical history); iii) viral liver disease (positive for HBsAg or HCVAb), iv) drug-induced liver disease (past medical and drug use history), v) excessive use of alcohol (more than 20 g/day for men, more than 10 g/day in women [18]), vi) pregnancy or lactation. All protocols were in accordance with the Helsinki Declaration of 1975 and approved by the ethics committee of the Helsinki University Central Hospital, and each subject provided written informed consent.

Eligible subjects were studied after an overnight fast. At this visit, body weight and height, waist and hip circumferences were measured, % body fat and blood pressure were recorded, and blood samples were taken for measurement of biochemical parameters as detailed below. On a second occasion, $^1\text{H-MRS}$ and MRI studies were performed to quantitate liver fat (vide infra).

2.2. % liver fat ($^1\text{H-MRS}$)

Localised single voxel ($2 \times 2 \times 2 \text{ cm}^3$) proton spectra were acquired using a 1.5-T whole-body system (Siemens Magnetom Avanto, Erlangen, Germany), which consisted of a combina-

tion of whole-body and loop surface coils for radiofrequency transmitting and signal receiving. T1- and T2-weighted high-resolution MR images were used for localisation of the voxel of interest within the right lobe of the liver. $^1\text{H-MRS}$ measurements of the liver fat were performed in the middle of the right lobe at a location that was individually determined for each subject by a single operator; vascular structures and subcutaneous fat tissue were avoided when selecting the voxel. Single voxel spectra were recorded using the point resolved spectroscopy (PRESS), with an echo time of 30 ms, a repetition time of 3000 ms, 1024 data points over 1000 kHz spectral width with 16 averages. A short echo time and long repetition time were chosen to ensure a fully relaxed water signal, which was used as an internal standard. Chemical shifts were measured relative to water at 4.70 ppm. The methylene signal, which represents intracellular triglyceride, was measured at 1.3 ppm. Signal intensities were quantified by using a jMRUI v3.0 analysis program [19] with an advanced method for accurate, robust and efficient spectral fitting (AMARES) [20]. Signal intensities were corrected for T2 relaxation as previously described [21]. Spectroscopic intracellular triglyceride content (LFAT) was expressed as a ratio of the area under the methylene peak to that under the methylene and water peaks. LFAT% was converted from signal ratios to volume fractions by applying the method validated by Longo et al. [22] and using experimentally determined values by Szczepaniak et al. [23] ($\times 100 = \% \text{ liver fat}$). This measurement has been validated against histologically determined lipid content [24] and against estimates of fatty degeneration or infiltration by X-ray computer-assisted tomography by us [25] and others [26]. All spectra were analysed by a physicist who was unaware of any of the clinical data. The reproducibility of repeated measurements of LFAT in non-diabetic subjects studied on two occasions in our laboratory is 11%. NAFLD was defined as in the population-based Dallas Heart Study, as a LFAT% > 5.55% [27].

2.3. Liver fat fraction (MRI)

A body coil was used to obtain coronal scout images of the upper abdomen. A stack of transaxial IP and OP T1-weighted dual-echo fast spoiled-gradient recalled images were obtained in two breath holds using following imaging parameters: 103 ms repetition time, 2.12 ms (OP)/4.8 ms (IP) echo time, 80° flip angle, 24 slices ($\times 2$), 1 cm slice thickness, 512×448 matrix and $5 \text{ dm} \times 4.37 \text{ dm}$ field of view, the same matrix and field was used for all patients. Transaxial abdominal scans encompassing the entire liver were acquired in two breath-holds using the magnet mentioned above. Each 2D slice was displayed on the video screen. Using the Image J 1.46r software to analyze the intensity of the liver, four ROIs (1–2 cm in diameter) were obtained in the liver above the portal vein (two in the right lobe and two in the left lobe, Fig. 1). ROIs 1–4 were located in liver segments II, IV, VIII, VII, respectively. The standard deviation of the signal intensity measurements within each ROI was kept to less than 10%. The ROIs included areas of parenchyma that did not contain vessels or artifacts, and the ROIs were in corresponding locations in the paired IP and OP MR images. The signal intensity of the spleen was measured as the mean intensity from the three 1 to 2 cm ROIs (Fig. 1). LFAT $^{\text{MRI}}$ was quantified on T1-weighted dual-echo gradient-echo MR images as the percentage of relative signal intensity loss of the liver on OP images, with the following formula: $(S_{\text{in}} - S_{\text{out}})/S_{\text{in}} \times 100$, where SI is the mean liver signal intensity divided by the mean spleen signal intensity, S_{in} is IP signal intensity, and S_{out} is OP signal intensity [10]. LFAT $^{\text{MRI}}$ was converted to $^1\text{H-MRS}$ % units (% liver fat by MRI, LFAT $^{\text{MRI}}$) using the equation relating MRI and $^1\text{H-MRS}$ measurements (see Section 3).

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