Age- and sex-dependent normative values of liver fat in a healthy population with normal BMI on mDIXON MR sequences

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Aims and objectives

Liver steatosis is associated with the long-term development of type II diabetes and cardiovascular disease (1, 2). Accumulation of lipids in the liver is accompanied by infiltration and activation of immune cells, thus resulting in insulin resistance. Impaired insulin signalling in the liver increases endogenous glucose production, thus causing hyperglycaemia which may lead to type II diabetes and cardiovascular disease (CVD) (3). Moreover liver steatosis is a risk factor for the development of liver cirrhosis and hepatocellular carcinoma (HCC) (4) as well as for the development of postoperative complications following liver surgery (5).

For a long time histopathology was the gold standard for liver fat quantification. In the meanwhile there are several MR imaging techniques available for noninvasive liver fat detection: chemical shift imaging (6-8), frequency-selective imaging (9-11) and MR spectroscopy (12-15). Regardless of the MR imaging technique used (chemical shift imaging (16), frequency-selective imaging (10, 11) or MR spectroscopy (13, 15, 17-21)), the key step for liver fat quantification is to break the net MR signal into fat signal and water signal.

The two-point DIXON technique is a proton chemical shift imaging technique that produces separated water-only and fat-only images from a dual-echo acquisition (22).

The knowledge of the normative hepatic fat content might help the clinician to better estimate the risk of type II diabetes, cardiovascular disease and liver cirrhosis. Therefore, in this study we prospectively quantified the liver-fat-fraction in healthy volunteers estimated by two-point DIXON-fat-water-separation MR imaging at 3 Tesla.

The aim of this work was to define age- and sex-dependent reference standards of liver-fat-fractions.
Methods and materials

Study subjects

This was a prospective study with institutional review board approval and written informed consent from all study subjects. The study was Health Insurance Portability and Accountability Act (HIPAA) compliant and none of the authors had a financial interest. The present study included study subjects of a larger clinical trial of whole body MRs of healthy volunteers selected from 2011 to 2014 (unpublished data).

A total of 80 patients consecutively referred to MR imaging of the whole body for a larger clinical trial (40 women; mean age, 39.6±12.16 years; age range, 21-62 years; 40 men; mean age, 39.70 ± 11.23 years; age range, 20-61 years, 10 men/10 women per decade) were included for evaluation of liver fat. One patient was slightly older than 60 years in both gender.

Inclusion criteria were (a) normal BMI (18.5 to 26 kg/m2); (b) age between 20 and 60 years; (c) healthy. Exclusion criteria were: (a) contraindication for MR imaging (claustrophobia, metal, pacemaker, pregnancy); (b) surgery, especially osteosynthesis because of the susceptibility artefacts (they lead to fat/water signal swaps); (c) systemic diseases (chronic obstructive pulmonary diseases, diabetes, metabolic diseases, rheumatologic disorders, tumors, chronic pain syndrome); (d) vascular problems (coronary heart disease, peripheral artery disease); (e) alcohol addiction, drug abuse. All subjects had to fill in a questionnaire concerning the above mentioned inclusion and exclusion criteria.

Clinical examination

For each subject the following parameters were determined: age, height, weight, BMI, waist and hip measurement and abdominal girth. The body fat was measured by two different fat analyzers (special bioelectrical impedance instruments measuring via the electrical body resistance with foot sensor pads on a bathroom scale similar device (TANITA UM-018) (FA1) or with hand sensor pads on a handheld device (OMRON BF300) (FA2) respectively).

Data acquisition
The whole body MR scans were performed in a 3 Tesla MR imager (Ingenia, Philips Healthcare, Best, The Netherlands). The examination took 1 hour. The subjects were embedded with both arms near the body in supine position.

The study MR imaging protocol included axial T1-sequences and axial DIXON-sequences (fat-water separation 2-point DIXON) in the whole body. Depending on the body length of the subject 9 to 10 axial sequences were combined to cover the region of interest (from head to knee joint). The DIXON sequence had the following parameters: number of dimensions, 3; sequence type, 3D FFE T1; number of echoes, 2; orientation, transverse; acquired voxel dimensions (mm), 2.0, 2.0, 4.0; reconstructed voxel dimensions (mm), 1.0, 1.0, 2.0; inter-slice gap (mm), 0.0; field of view, 560 x 352; number of sections, 80; TR, 4.2 msec; TE, 1.2 and 3.1 msec; flip angle, 5°; number of signal averages, 2; SENSE acceleration factor (AP/SI), 2.0 and 2.0; fold-over direction, AP; water-fat shift (pixel), 0.292; receiver bandwidth (Hz pixel\(^{-1}\)), 1485.1; single series acquisition time (sec), 16.4; scanning duration (min), in total 28:20. For this study only the two relevant axial DIXON sequences containing the parts of the liver were used for the read-out. A 15-element dS head coil, in the table integrated, automatically centering at the imaged anatomy, a 16 channel posterior coil and two 16 channel anterior coils were used for signal reception, while the scanner’s dual transmit body coil was used for RF transmission.

Data analysis

Image analysis was performed with DICOM Viewer Osirix v 5.9 (PIXMEO®, Geneva, Switzerland) by a board certified radiologist specialized in liver MR imaging with 9 years of experience (CR). Mean dual-echo fat-signal fractions (FSF) of the liver were determined in 5 different liver segments (Segment II, III, VI, VII, VIII) from signal intensities of the ROIs (regions of interest) on fat- and water-only images. First the ROIs were positioned in the 5 different liver segments of the water signal-only images (Figure 1) avoiding vessels and biliary ducts or areas affected by imaging artefacts and were then copied to the fat signal-only images (Figure 2).

The mean signal intensity values within these ROIs of the water signal-only images and the fat signal-only images were noted. The fat signal fraction was then calculated using the following equation (23).

\[
\text{FSF}_{\text{fatwat}} \text{ \%} = \left( \frac{\text{signal}_{\text{fat}}}{\text{signal}_{\text{water}} + \text{signal}_{\text{fat}}} \right) \times 100
\]

Statistical Analysis
Descriptive statistics were obtained (reported as mean ± standard deviation) and statistically tested for normality with the Kolmogorov-Smirnov test.

ANOVA analysis were performed to test FSF differences among age subgroups and were corrected for BMI in a general linear model with multivariate analysis (p<0.05, corrected for multiple comparisons).

Correlation between MRI FSF measurements and age, weight, height, BMI, waist-, hip-, abdominal girth-measurements and the body fat measured by two different fat analyzers (FA1 and FA2 respectively) were assessed using Pearson’s correlation analysis (results were corrected for multiple comparisons).

Correlation between FSF and gender as well as age group were assessed with the Spearman’s rank correlation coefficient.

All statistical analyses were performed using commercially available software (SPSS, release 22.0, Chicago, IL USA).
**Fig. 1:** Axial water signal-only MR image in a 29 year old woman. Regions of interest (ROIs) were placed in liver segment II (FSF4), III (FSF5), VI (FSF3), VII (FSF1) and VIII (FSF2) in the water signal-only images and then copied to the fat signal-only images.

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Fig. 2: Corresponding fat signal only MR-images.

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Results

BMI of the women ranged from 17.47 to 26.03 kg/m² with a mean BMI of 21.67 ± 2.07 kg/m² (weight range 43.6 to 86 kg; height range 158 to 183 cm). BMI of the men ranged from 19.40 to 26.23 kg/m² with a mean BMI of 22.99 ± 1.82 kg/m² (weight range 56.3 to 92 kg; height range 169 to 200 cm).

Body measurements of the women: Waist measurements ranged from 61 to 85 cm (mean 71.43 cm ± 5.62), abdominal girth measurements ranged from 66 to 97 cm (mean 77.78 cm ± 7.81), hip measurement ranged from 78 to 109 cm (mean 93.8 cm ± 6.89). Waist-to-hip-ratio ranged from 0.73 to 0.96 (mean 0.83 ± 0.07).

Body measurements of the men: Waist measurements ranged from 75 to 99 cm (mean 84.05 cm ± 6.06), abdominal girth measurements ranged from 78 to 102 cm (mean 89.02 cm ± 6.13), hip measurement ranged from 83 to 160 cm (mean 99.35 cm ± 11.42). Waist-to-hip-ratio ranged from 0.53 to 0.99 (mean 0.90 ± 0.08).

Body fat measured via bioelectrical impedance of the women: FA1 measurements ranged from 13.0 to 39.0 % (mean 28.01 % ± 5.61), FA2 measurements ranged from 13.0 to 33.3 % (mean 22.10 % ± 5.33).

Body fat measured via bioelectrical impedance of the men: FA1 measurements ranged from 5.4 to 31 % (mean 17.8 % ± 4.73), FA2 measurements ranged from 5.0 to 22.3 % (mean 14.06 % ± 4.95).

The calculated FSFs (%) of women and men are shown in Figure 3 for each age group and overall age groups (Figure 4 and 5). Both gender show an increase of the FSF with increasing age group with a peak in the age group 40-49 years and a decrease thereafter again. The highest amount of FSF beyond the 5 measured segments was measured in FSF 3 in both genders.

Correlation of FSF with gender, age and age subgroups:

The Spearman correlations between FSFs and gender were significant for FSF1, FSF3 and FSF5 and with a strong tendency for FSF2 and FSF4 (p_{FSF1}=0.020, p_{FSF2}=0.059, p_{FSF3}=0.013, p_{FSF4}=0.056, p_{FSF5}=0.013).
Pearson correlations between FSFs and age were significant for women in all segments except FSF4 ($p_{FSF1}=0.001$, $p_{FSF2}=0.010$, $p_{FSF3}=0.002$, $p_{FSF4}=0.258$, $p_{FSF5}=0.059$), however after correction for multiple comparisons only FSF1, FSF2 and FSF3 were still significant. Similar correlations (Spearman) were shown between FSFs and age groups with significance for FSF1, FSF2 and FSF3 ($p_{FSF1}=0.000$, $p_{FSF2}=0.035$, $p_{FSF3}=0.003$, $p_{FSF4}=0.425$, $p_{FSF5}=0.16$), however after correction for multiple comparisons only FSF1 and FSF3 were still significant.

None of the Pearson correlations between FSFs and age were significant for men in all segments ($p_{FSF1}=0.097$, $p_{FSF2}=0.133$, $p_{FSF3}=0.471$, $p_{FSF4}=0.450$, $p_{FSF5}=0.991$). Similar correlations (Spearman) were shown between FSFs and age groups, significant only for FSF2 ($p_{FSF1}=0.096$, $p_{FSF2}=0.026$, $p_{FSF3}=0.505$, $p_{FSF4}=0.316$, $p_{FSF5}=0.681$), not significant anymore after correction for multiple comparisons.

The ANOVA FSF differences among age subgroups for women were significant in three of 5 different liver segments (FSF1, FSF2, FSF3): $p_{FSF1} = 0.002$, $p_{FSF2} = 0.033$, $p_{FSF3} = 0.004$, $p_{FSF4} = 0.092$, $p_{FSF5} = 0.062$, however after correction for multiple comparisons only FSF1 and FSF3 were still significant. Also after correction for BMI in a general linear model with multivariate analysis the FSF differences among age subgroups for women were significant in three of 5 different liver segments (FSF1, FSF3, FSF5): $p_{FSF1} = 0.006$, $p_{FSF2} = 0.057$, $p_{FSF3} = 0.011$, $p_{FSF4} = 0.053$, $p_{FSF5} = 0.049$ and after correction for multiple comparisons only FSF1 was still significant.

The ANOVA FSF differences among age subgroups for men were not significant for all segments ($p_{FSF1}= 0.301$, $p_{FSF3}= 0.315$, $p_{FSF4}= 0.128$, $p_{FSF5}= 0.405$) except for FSF2 ($p_{FSF2}=0.04$), however after correction for multiple comparisons none of the FSFs were significant anymore. Also after correction for BMI in a general linear model with multivariate analysis the FSF differences among age subgroups for men were not significant for all segments ($p_{FSF1}= 0.414$, $p_{FSF3}= 0.771$, $p_{FSF4}= 0.310$, $p_{FSF5}= 0.550$) except for FSF2 ($p_{FSF2}=0.040$) and after correction for multiple comparisons none of the FSFs were significant anymore.

**Correlation of FSF with Body parameters:**

There were no significant Pearson correlations of all FSFs with height, weight, BMI, waist-, hip- and abdominal girth-measurements in women. There were a few significant Pearson correlations in men concerning FSF2 with weight ($p=0.034$), BMI ($p=0.006$), waist measurement ($p=0.002$) and abdominal girth ($p=0.004$); FSF4 with waist
measurement (p=0.029), however after correction for multiple comparisons only FSF2 with BMI, waist and abdominal girth were still significant.

There were no significant Pearson correlations of all FSFs with body fat measurements by two different fat analyzers (special bioelectrical impedance instruments) in women except FSF5 with body fat measured via FA2 (p=0.027), however after correction for multiple comparisons not significant anymore. In men Pearson correlations of FSFs with body fat measurements were significant for FSF2 with body fat measured via FA1 (p=0.000) and FA2 (p=0.005), FSF4 with body fat measured via FA1 (p=0.027), FSF5 with body fat measured via FA1 (p=0.004), however after correction for multiple comparisons only FSF2 with FA1 and FA2 as well as FSF5 with FA1 were still significant.
**Fig. 3:** Calculated mean FSFs for the different age subgroups for women and men. Correlation between FSF and age group was assessed with the Spearman`s rank correlation coefficient, correlations between FSF and age was assessed with Pearson`s analysis. P-value < 0.05 was significant. *Spearman rank, ** Pearson

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Fig. 4: Age group dependence of the FSFs in women. FSF1 = segment VII, FSF2 = segment VIII, FSF3 = segment VI, FSF4 = segment II, FSF5 = segment III.

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**Fig. 5:** Age group dependence of the FSFs in Men. FSF1 = segment VII, FSF2 = segment VIII, FSF3 = segment VI, FSF4 = segment II, FSF5 = segment III.

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Conclusion

In our study we reported the normative values for liver fat content evaluated in a large cohort of healthy volunteers of different age (20-60 years) and gender measured on MR.

In the past, liver fat quantification was determined by liver biopsy. In consideration of this invasive method, no population-based histologic studies of liver biopsies have been performed in normal living subjects, because liver biopsies are seldom performed without a clinical indication. Traditionally, liver fat content >50 mg/g (5% by wet weight) is diagnostic of hepatic steatosis (24, 25).

Nowadays noninvasive methods like localized proton magnetic resonance spectroscopy (MRS) can accurately measure hepatic triglyceride content (13, 26, 27). In a larger trial of 2,287 participants hepatic triglyceride was positively correlated with BMI; 95% of the 345 participants with normal BMI and no risk factors for fatty liver disease had less than 5.56% hepatic triglyceride by weight, with a minimum of 1.9% of tissue by weight (20, 28), measured by proton magnetic resonance spectroscopy. In our study we didn’t find a correlation of liver fat signal fraction with BMI for women, and for men only for FSF2 (liver segment VIII), but our healthy population ranged within the normal BMI only. Moreover, in our study, body fat measurements didn’t correlate with liver FSFs in women, and in men correlations were only found for FSF2 (liver segment VII) and FSF5 (liver segment III).

According to NIH/WHO BMI guidelines as reported by Gallagher et al (29) international healthy body fat percentages (measured via dual-energy X-ray absorptiometry) for subjects with normal BMI (18.5 to 25 kg/m2) range in the age group from 20-39 years from 8-20% for men and 21-33% for women respectively and in the age group 40-59 years from 11-22% for men and 23-34% for women respectively, which means increasing body fat with age. Indeed, in our study there was no significant correlation between FSFs and BMI and body fat, but liver FSFs showed a significant correlation with age for women and a tendency for men.

In the last years, multiple DIXON MR studies were performed for liver fat quantification. Recently, it has been demonstrated that this simple MR imaging sequence is able to accurately quantify and display liver fat fraction (7, 8, 14, 16, 21, 30-33), as well as muscle fat fraction (34, 35). These studies found a strong correlation between fat fraction estimated with dual-echo dual-flip-angle SPGR MR imaging and that measured with MR spectroscopy and/or histopathologic examination (36, 37). Acquisition of least 2 echoes are required; more echoes allow e.g., quantification of interfering effects, such as caused by increased tissue-iron contents and concomitant rapid decay of transverse magnetisation (38).
In a recent study of our department (39) with patients without diffuse liver disease FSFs in liver segment II and VIII ranged from 0.1 to 32.4% (mean 6.2 % ± 5.1) and from 0.1 to 32.3 % (mean 6.0% ± 5.3) respectively. In our study, all individuals (with normal BMI) showed a liver fat signal fraction (FSF) range of 0.6 to 8.9 % for women (mean 3.9 %) and a range of 2 to 13 % for men (mean 4.7 %). Specifically for segment II (= FSF4) the values represent with a range of 0.58 to 7.21 (mean 3.83% ± 1.49) for women and a range of 2.79 to 12.82% (mean 4.57% ± 1.91) for men and for segment VIII (= FSF2) with a range of 1.52 to 7.12% (mean 3.88% ± 1.34) for women and a range of 1.81 to 10.16 % (mean 4.76% ± 1.91) for men. As we selected strictly for healthy volunteers in this study, the FSF of our study cohort is lower than in the recent study with patients (39).

Study limitations: Fat-/water swaps especially at the liver dome (segment VII/VIII) - ROIs were not drawn in these regions. The two-point DIXON technique does not correct for potentially confounding T1 and T2* relaxation effects. In our study, we used a 2-point DIXON sequence which is more susceptible for iron-induced artefacts. But first, our patients were healthy and second we excluded liver iron deposition visually on the correlating T1-weighted image. In areas of extensive breathing no measurements were performed in this segment. No liver biopsy as gold standard, which is ethically not possible.

In conclusion, the liver fat fraction increased with age with a peak in the fifth decade for both genders and decreased again thereafter. Men had a higher fat fraction than women in all age groups. The knowledge of the normative hepatic fat content should help the clinician to better estimate the risk of long-term development of type II diabetes and cardiovascular disease.
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