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Research article

# Assessment of the degree of abdominal myosteatosis by magnetic resonance imaging in subjects with diabetes, prediabetes and healthy controls from the general population

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ABSTRACT

*Objectives:* Intra- and intermyocellular lipid deposition and adipose tissue are part of glucose homeostasis and insulin resistance; however, their role in type 2 diabetes mellitus (T2DM) remains unclear. We assessed differences in the degree of abdominal myosteatosis among subjects with T2DM and prediabetes.

*Materials and Methods:* Asymptomatic subjects from the general population were classified as subjects with T2DM, prediabetes or healthy controls and underwent multi-echo Dixon magnetic resonance imaging (MRI) (TR 8.90 ms, six echo times, flip-angle 4°). Abdominal myosteatosis was quantified as proton-density fat-fraction ($PDFF_{muscle}$) by a standardized segmentation-algorithm. Cardiometabolic risk factors were prospectively obtained in a comprehensive health assessment and visceral and subcutaneous adipose tissue (VAT and SAT) were quantified semi-automatically. Uni- and multivariate quantile regression were used to examine associations.

*Results:* Among 349 included subjects (mean age: 56.0 ± 8.0years, 56.7% males), 45 were classified as subjects with T2DM and 84 with prediabetes (12.9% and 24.1%; respectively). Median $PDFF_{muscle}$ was significantly higher in subjects with T2DM and prediabetes compared to healthy controls (13.1% (IQR10.5–16.6%); 11.1% (IQR8.9–15.0%) and 10.1% (IQR7.5–13.3%); respectively, $p < 0.001$). The observed differences were independent of age and gender (all $p < 0.002$) but attenuated after adjustment for BMI (β: −0.02, 95%CI: −1.49 to 1.44, $p = 0.974$; β: 0.47, 95%CI: −0.91 to 1.86, $p = 0.506$; prediabetes and T2DM, respectively). This effect was attributable to VAT, which remained independently associated with $PDFF_{muscle}$ after full adjustment (β: 0.01, 95%CI: 0.01–0.02, $p = 0.002$).

*Conclusions:* There are significant differences in the degree of abdominal myosteatosis between subjects with T2DM, prediabetes and healthy controls, that may be confounded by VAT. However, abdominal myosteatosis by MRI might serve as a cardiometabolic imaging-biomarker, specifically in the setting of impaired glucose metabolism.

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## 1. Introduction

Diabetes mellitus (DM) as one of the most common metabolic disorders, affects more than 415 million people worldwide [1]. Furthermore, over 318 million people in the world are estimated to suffer from the precursor stage of DM, prediabetes [1], a condition with impaired glucose metabolism, which is highly likely to progress to an established type 2 DM (T2DM). Due to ongoing demographic transition and progressive aging of the population, the prevalence of both entities will further increase and DM-related comorbidities, long-term complications and DM-associated mortality will become a major healthcare burden [1,2]. Thus, further research on pathophysiological changes as potential risk factors specifically in the context of prevention as well as early diagnosis and treatment of asymptomatic subjects with impaired glucose metabolism in incident prediabetes and DM is needed.

A major risk factor for the development and progression of T2DM is the metabolic syndrome with its symptoms high fasting serum triglycerides, low high-density lipoprotein (HDL), elevated fasting plasma glucose and blood pressure as well as abdominal obesity [3]. Despite abdominal adipose tissue compartments, such as visceral and subcutaneous adipose tissue (VAT and SAT) [4], ectopic lipid deposits for example in liver or skeletal muscle play an important role in the pathophysiology of insulin resistance [5–7]. Since skeletal muscle is a major target organ of insulin, recent data suggest that changes in fat content, such as intermyocellular-intrafascial adipose tissue infiltration or intramyocellular lipid deposition, may be strong correlates of an impaired glucose homeostasis [6–8]. Furthermore, myosteatosis may be a potential mediator of development and progression of insulin resistance, cardiovascular risk factors and other DM-related comorbidities and complications [2,8,9]. Yet, it remains unclear whether myosteatosis is a causal mechanism or just a coincidental bystander in insulin resistance and T2DM. Thus, further research is needed to asses both, DM-related change of myosteatosis and its pathophysiological relevance and clinical implications as a potential diagnostic and prognostic imaging-biomarker in impaired glucose metabolism.

Therefore, we systematically determined the degree of abdominal myosteatosis by a magnetic resonance imaging (MRI)-based, manual abdominal skeletal muscle segmentation in subjects with T2DM, prediabetes and healthy controls from a population-based cohort. Furthermore, we assessed associations with cardiometabolic risk factors as well as other adipose tissue compartments. We hypothesized that there are differences in the degree of abdominal myosteatosis, which are independently associated with impaired glucose metabolism and may therefore serve as imaging-biomarkers in cardiometabolic risk stratification.

## 2. Materials and methods

### 2.1. Ethics statement

The study was approved by the local institutional review board of the Ludwig-Maximilian-University Munich. Written informed consent was obtained from all participants. All methods and analyses were carried out in accordance with the approved protocol and guidelines and all records were anonymized.

### 2.2. Study design and population

Subjects were derived from the KORA-FF4 study (2013–2014, n = 2279), a 14-year follow-up study of the population-based Cooperative Health Research in the Region of Augsburg (KORA) survey S4 (1999–2001, n = 4261) in Southern Germany. The design of the KORA studies has been described in detail previously [10]. 400 eligible subjects underwent whole-body MRI according to previously described inclusion and exclusion criteria [10]. A comprehensive health assessment was prospectively performed for all subjects to obtain potential covariates, such as diabetes status and other cardiometabolic risk factors.

### 2.3. Covariates

To determine the glycemic status, a 75 g oral glucose tolerance test was performed for all subjects not yet being diagnosed with T2DM. According to the WHO-definition, subjects were classified as subjects with established T2DM (two-hour plasma glucose following a 75 g oral glucose tolerance test (OGTT) ≥11.1 mmol/l and/or fasting plasma glucose (FPG) ≥7.0 mmol/l), as subjects with prediabetes with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) (OGTT 7.8–11.0 mmol/l and/or FPG 5.6–6.9 mmol/l) or healthy controls (OGTT < 7.8 mmol/l and/or FPG < 5.6 mmol/l) [11]. The body mass index (BMI) was calculated as weight in kg divided by body height squared in $m^2$. Hypertension was determined according to the WHO-definition as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90mmHg or current intake of antihypertensive medication [12]. Alcohol consumption and smoking status was classified by self-report as no alcohol at all (0 g/day), moderate alcohol consumption (males: 0.1–39.9 g/day, females: 0.1–19.9 g/day) or heavy alcohol consumption (males: > 40 g/day, females: > 20 g/day) and never-smoker, ex-smoker and current (regular or sporadic) smoker. Regarding physical activity, subjects were categorized as physically active (regular physical activity ≥1 h/week) or physically inactive (irregular physical activity < 1 h/week, almost no physical activity and no physical activity at all). Routinely intake of medication was generally categorized according to most recent guidelines. Statins, fibrates or other lipid-lowering medication were categorized as lipid-lowering medication, medication containing glucocorticoids or mineralocorticoids was categorized as systemic corticosteroids which were separated from non-steroidal anti-inflammatory drugs (NSAIDs, for example ASS100 or ASS300).

### 2.4. MR imaging protocol and data acquisition

MR examinations were performed in supine position on a 3-Tesla Magnetom Skyra (Siemens Healthineers, Erlangen, Germany) using an 18-channel body surface coil in combination with a table-mounted spine matrix coil. The complete imaging protocol as well as technical specificities have been described in detail elsewhere [10].

For the determination of the degree of abdominal myosteatosis, skeletal muscle fat content was quantified using a T2*-corrected, multi-echo 3D-gradient-echo Dixon-based sequence (multi-echo Dixon) with the following parameters: time to repetition (TR) 8.90 ms, time to echo (TEs) opposed-phase 1.23 ms, 3.69 ms and 6.15 ms, TEs in-phase 2.46 ms, 4.92 ms and 7.38 ms, flip angle 4°, readout echo bandwidth 1080 Hz/pixel, matrix 256 × 256, slice thickness 4 mm. Data were acquired during a single breath-hold of 15 s. The post-processing algorithm using the Software MR LiverLab (Version VD13, Siemens Healthineers, Cary, USA) automatically calculated water- and fat-only images as DICOM-files from the original data of the six echos. The obtained fat signal-fraction maps are based on the signal ratio of fat to the summed signal of water and fat (proton-density fat-fraction) and corrected for confounding effects of T1- and T2*-decay, quantitatively coding the mean proton-density fat-fraction (PDFF) in degrees of grey values of each voxel (1 intensity value = 0.1% fat content) [13]. Furthermore, coronal two-point Dixon gradient-echo (GRE) sequences (TR 4.06 ms, TE 1.26 ms and 2.49 ms, flip angle 9°, slice thickness 1.7 mm, isotropic in-plane resolution 1.7 mm) were used for the identification of L3 vertebra on axial slices by cross-reference.

### 2.5. MR image analysis and skeletal muscle segmentation

The DICOM-files of the fat signal-fraction maps were implemented into the commercially available Software OsiriX (V8.5.1, Pixmeo SARL,