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Translational

Deep subcutaneous adipose tissue lipid unsaturation associates with intramyocellular lipid content

Jesper Lundbom[a,b,c,*], Alessandra Bierwagen[a,b], Kálmán Bodis[a,b], Julia Szendrödi[a,b,d], Jaakko Kaprio[e,f,g], Aila Rissanen[h,i], Nina Lundbom[c], Michael Roden[a,b,d,1], Kirsi H. Pietiläinen[e,h,j,1]

[a] Institute for Clinical Diabetology, German Diabetes Center (DDZ), Leibniz Center for Diabetes Research, Heinrich Heine University, Düsseldorf, Germany
[b] German Center for Diabetes Research (DZD), München-Neuherberg, Düsseldorf, Germany
[c] HUS Medical Imaging Center, Radiology, Helsinki University Central Hospital, University of Helsinki, Helsinki, Finland
[d] Department of Endocrinology and Diabetology, Medical Faculty, Heinrich-Heine University, Düsseldorf, Germany
[e] FIMM, Institute for Molecular Medicine, University of Helsinki, Helsinki 00014, Finland
[f] Finnish Twin Cohort Study, Department of Public Health University of Helsinki, Helsinki 00014, Finland
[g] National Institute for Health and Welfare, Department of Health, Helsinki 00271, Finland
[h] Obesity Research Unit, Research Programs Unit, Diabetes and Obesity, University of Helsinki, Helsinki 00014, Finland
[i] Department of Psychiatry, Helsinki University Central Hospital, Helsinki, Finland
[j] Endocrinology, Abdominal Center, Helsinki University Central Hospital and University of Helsinki, Helsinki 00290, Finland

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ABSTRACT

Background. Obese twins have lower saturated and higher long-chain polyunsaturated fatty acids (FA) in subcutaneous adipose tissue (SAT) compared to their lean monozygotic (MZ) co-twin. Whether this holds for metabolically distinct deep (DSAT) and superficial (SSAT) depots is unknown. Here we use non-invasive magnetic resonance spectroscopy (MRS) to measure the FA unsaturation in body mass index (BMI) discordant MZ twins in DSAT and SSAT and their relationship to ectopic fat content and body fat distribution. The main finding is further confirmed in an independent cohort using standardized measurement times.

Methods. MRS and magnetic resonance imaging were used to measure DSAT and SSAT unsaturation and their relationship to intramyocellular lipids (IMCL), hepatocellular lipids (HCL) and the amount of subcutaneous (SAT) and visceral adipose tissue (VAT) in 16 pairs of healthy monozygotic twins (MZ) discordant for BMI. A second independent cohort of 12 healthy volunteers was used to measure DSAT unsaturation and IMCL with standardized measurement time. One volunteer also underwent repeated random measurements of DSAT unsaturation and IMCL.

Abbreviations: MRS, magnetic resonance spectroscopy; MRI, magnetic resonance imaging; MZ, monozygotic; DSAT, deep subcutaneous adipose tissue; SSAT, superficial subcutaneous adipose tissue; IMCL, intramyocellular lipids; FA, fatty acid; PUFA, polyunsaturated fatty acid; SAT, subcutaneous adipose tissue (volume around waist); VAT, visceral adipose tissue (volume around waist); HCL, hepatocellular lipids; PRESS, point resolved spectroscopy sequence; NEFA, non-esterified fatty acid; BMI, body mass index; TA, tibialis anterior; T_1, longitudinal relaxation time; T_2, transverse relaxation time; T1/2, half-life time constant; TE, echo time; UI, unsaturation index (olefinic/methylene); VOI, volume-of-interest; IPR, intra-pair resemblance.

* *Corresponding author at:* Institute for Clinical Diabetology, Deutsches Diabetes-Zentrum (DDZ), Leibniz-Zentrum für Diabetes-Forschung, an der Heinrich-Heine-Universität Düsseldorf, Auf'm Hennekamp 65, 40225 Düsseldorf. Tel.: +49 211 33 82 228; fax: +49 211 3382 603.
E-mail addresses: jesper.lundbom@ddz.uni-duesseldorf.de, jesse.lundbom@gmail.com (J. Lundbom).
[1] Equal contribution.

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Results. In accordance with biopsy studies SSAT unsaturation was higher in the heavier twins (15.2 ± 1.0% vs. 14.4 ± 1.5%, $P = 0.024$) and associated with SAT volume ($R = 0.672$, $P = 0.001$). DSAT unsaturation did not differ between twins (11.4 ± 0.8 vs. 11.0 ± 1.0, $P = 0.267$) and associated inversely with IMCL content ($R = -0.462$, $P = 0.001$). The inverse association between DSAT unsaturation and IMCL was also present in the participants of the second cohort ($R = -0.641$, $P = 0.025$) and for the repeated sampling at random of one person ($R = -0.765$, $P = 0.027$).

Conclusions. DSAT and SSAT FA unsaturation shows distinct associations with obesity and IMCL in MZ twins, reflecting compartment-specific metabolic activities. The FA unsaturation in the DSAT depot associates inversely with IMCL content, which raises the possibility of cross talk between the DSAT depot and the rapid turnover IMCL depot.

1. Introduction

Interest in adipose tissue fatty acid (FA) composition has mainly focused on its use as a marker of dietary fat intake, while other factors contributing to the FA profile of adipose tissue have received less attention. The overall degree of unsaturation of fat seems to vary between different fat depots [1], which indicates tissue-specific non-dietary modification of FA composition and likely arises from differences in the metabolic activity. How the metabolic activity of the tissue impacts the FA pattern is still unclear, but may include tissue-specific FA synthesis, desaturation and selective mobilization [2–4].

Adipose tissue is now considered an active endocrine organ that modulates interorgan crosstalk through adipokines [5]. Recently, also FA has been defined as adipokines or "lipokines" that can modulate liver and muscle function [6]. Thus, altered FA adipose tissue composition may lead to changes in the non-esterified FA (NEFA) secretion patterns and in turn exert effects throughout the body. Although adipose tissue triglycerides are considered the long-term energy reserves of the body, adipose tissue fat storage, lipolytic activity and blood flow are regulated on an intraday basis [7,8]. During the postprandial period, lipolysis is suppressed and fat storage upregulated, while even a single bout of exercise increases lipolytic release of NEFA from adipose tissue [9]. Adipose tissue fat turnover is decreased in obesity, along with an increase in fat storage and decrease in lipolytic activity, rendering adipocyte turnover a potential target for treating metabolic diseases [10].

NEFA released from adipose tissue during exercise is mainly taken up by skeletal muscle, where they are oxidized or stored as intramyocellular lipids (IMCL). Interestingly, IMCL are rapidly depleted by a single bout of exercise [11], associate with insulin resistance [12], but are also paradoxically increased in insulin-sensitive athletes [13]. Insulin resistance is an early sign of obesity related metabolic disorders and is associated with increased visceral and ectopic fat accumulation, in IMCL as well as in the liver. Impaired suppression of adipose tissue NEFA release by insulin is thought to lead to ectopic fat accumulation [9].

Studies on human adipose tissue FA composition have almost exclusively been conducted on adipose tissue samples obtained by needle aspiration biopsy. This introduces limitations due to variable tissue sampling. Recently, magnetic resonance spectroscopy (MRS) has emerged as a non-invasive alternative for measuring adipose tissue unsaturation [14]. In addition to allowing repeated sampling of the same location, MRS can also distinguish between deep (DSAT) and superficial subcutaneous adipose tissue (SSAT), which are separated by a MRI visible fascia and exhibit marked differences in FA composition [15] and metabolic activity [16]. Of note, traditional adipose tissue sampling techniques generally have not differentiated between these two subcutaneous adipose depots [17].

Body fat distribution has an important genetic component [18,19], which may also hold true for FA composition in adipose tissue [20]. Monozygotic twin pairs (MZ) discordant for body mass index (BMI) provide a means to study environmental factors affecting human metabolism, while controlling for genetic influences. As the MZ twin pairs have the same genomic sequence, any observed phenotype differences can be mostly attributed to external, acquired factors, ranging from somatic mutations, to diet, microbiome and physical activity. Our previous twin study found lower saturated stearic acid (18:0) and higher long-chain polyunsaturated arachidonic acid (20:4n-6) in the adipose tissue of obese compared to their lean monozygotic (MZ) co-twin [21]. This study, however, did not differentiate between the DSAT and SSAT compartments.

The present study now examined whether twins from MZ pairs discordant for BMI also display depot specific differences in adipose tissue unsaturation (DSAT and SSAT), and how the unsaturation relates to body fat distribution and ectopic fat. Additional measurements were performed to corroborate the findings in a second cohort with measurements standardized to the fasting state.

2. Materials and Methods

2.1. Participants

Two separate cohorts were recruited, an initial twin cohort and a second cohort for further testing and confirming the findings obtained in the twin cohort in a more general population and in the fasted state. The twin cohort consisted of 32 MZ twins (16 males, 16 females, 16 pairs) aged 33–36 years specifically recruited for discordance in BMI, drawn from a large cohort of twins born 1975–1979 in Finland (the FinnTwin16 study) [22]. None of the twins had any comorbidities or medications. The twins underwent a full measurement protocol for MRI and MRS (see details below), with the exception of SSAT unsaturation, which could not be