

Session: Obesity & MRI

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Highlights:

- Amount and distribution of adipose tissue in the body as well as lipid content and composition in muscle and liver can be considered as biomarkers for pre-diabetes and obesity. New biomarkers indicating resting activity of brown adipose tissue and musculature are on the horizon.
- Selective MR imaging and/or spectroscopy techniques have to be applied together with suitable referencing strategies in order to achieve reliable quantitative data, which can be used as biomarkers.
- Correlations between MRI/MRS related biomarkers and “traditional” biomarkers derived from metabolic testing or blood samples are often limited. Many genetic, environmental and behavioural factors are influencing on the development of diabetes type 2 and obesity; and on the “traditional” and “MR-related” biomarkers as well.

Title: Emerging MRI Biomarkers of Obesity and Diabetes: Technical challenges, solutions and future directions

Target audience: Radiologists, MR technologists, Scientists interested in MR-related biomarkers of obesity and diabetes

Due to our modern lifestyle the number of people with metabolic diseases as diabetes type 2, with obesity and with so-called metabolic syndrome which later on often leads to cardiac infarction or stroke, is steadily increasing. For diagnosis of manifest diseases and for monitoring of their course several well-known “traditional” biomarkers already exist. Blood glucose levels, results of standardized glucose tolerance tests, body mass index, blood pressure, and so forth are examples of these established biomarkers. Clinical diagnosis and monitoring of manifest diseases are often mainly based on analysis of blood samples and sometimes on physical examinations and weighing.

In the past decades two developments took place simultaneously:

- MRI and MRS non-invasively provide insight into anatomy and tissue distribution in the human (and animal) body and allow quantitative analysis of tissue composition. New whole-body MR systems allow recording of highly resolved 3D data sets of the entire body in reasonably short measuring time.
- It is known that diabetes and obesity are diseases evolving over a long time of several years or even decades, before the disease manifests irreversibly. The course of this undesired progression towards manifest disease seems to be influenced by internal (genetic) and external (nutrition and physical activity) factors. It is evident that several organ systems are involved in the development of the diseases. More knowledge about the pathogenesis of the diseases is important for adequate prevention measures in general. Selection of optimal prevention strategies for each individual case is problematic.

Today it is not yet understood why some individuals tend to develop diabetes and others do not. It is also unclear why some individuals remain lean even with sedentary work in an office and other individuals are not able to keep their weight within a healthy range. On the other hand it is well known that metabolism in the body and individual behaviour are ruled by complex processes in different organ systems, and that those processes cannot be well followed using traditional biomarkers alone.

For this reason, testing the potentials of MRI and MRS for elucidation of relevant changes of volume, composition or even function of many organs (musculature, adipose tissue, liver, pancreas, and brain) is an exciting matter of current research. Interesting material about possible MR-related biomarkers has been presented during the ISMRM meeting in 2013 (1) and in the ISMRM workshop on fat-water separation in 2012 (2).

Musculature:

Skeletal musculature uses both fatty acids and glucose as source of energy. The amount of fatty acids inside myocytes (IMCL) can be assessed by ^1H spectroscopy (3,4). It was found by several groups that subjects with insulin resistance (and well trained subjects) show higher IMCL levels than insulin sensitive controls (5,6).

Several studies on regulation of IMCL during fasting or short or long term physical activity have been performed by different groups (7,8). Measuring glucose uptake in musculature can be done using ^{13}C spectroscopy (after administration of ^{13}C enriched glucose) (9) or by $^{18}\text{FDG-PET}$ (10). ^{31}P spectroscopy can be used for assessment of mitochondrial function by measuring the recovery of PCr after suitable exercises (11). Assessment of the individual level of muscular energy consumption at rest requires invasive tracer techniques (eg, $^{18}\text{FDG-PET}$). Repetitive incoherent motion sensitive MRI indicates strong inter-individual variability of mechanical muscle activity at rest, which could possibly indicate a new perspective for characterization of musculature by MRI.

Adipose tissue:

The volume and distribution of adipose tissue is highly variable in the human body. Volumes of different adipose tissue compartments can be assessed non-invasively by whole-body MRI (12,13). High correlation of visceral adipose tissue with insulin resistance and clearly lower metabolic influences of subcutaneous fat have been found and confirmed by several groups (14,15). The role of further adipose tissue compartments which seem to be regulated differently (eg, interscapular fat (16) and perivascular fat (17)) has been partly investigated in further studies. Localized ^1H spectroscopy of adipose tissue reveals variable fatty acid composition in different compartments (18) and also a clear dependence of the ratio between unsaturated and saturated fatty acids on the total volume of visceral fat (19).

Liver:

Hepatic lipid content can be quantitatively assessed by volume selective ^1H MRS and by chemical shift selective MRI approaches. ^1H MRS usually works using the water signal from liver as internal reference for quantification of lipids (20,21). Spectroscopy provides higher sensitivity than imaging even to low lipid fractions and also some information on fatty acid composition (22) (although quantitative assessment of fat composition in liver is clearly more demanding than of pure adipose tissue). Since liver fat is not distributed homogeneously in all subjects, fat selective imaging is often more accurate than spectroscopy in measuring the total fat fraction in liver and its

spatial distribution. Frequency selective excitation techniques (23), in-phase/opposed phase approaches (24), and derived DIXON (25) or IDEAL (26) techniques are applicable for such quantitative measurements. In those measurements, the water signal from liver can also be used as internal reference. On the other hand comparison of liver fat signals to signals recorded from adjacent pure subcutaneous fat (fat content approx. 95 %) allows more reliable quantification even in cases with clearly affected liver parenchyma (eg, in cirrhosis). Evaluation of T2* in liver has been shown to be a good marker for assessment of hepatic iron depositions (27).

Pancreas:

Several recent studies focused on quantitative assessment of lipids in pancreas. It is discussed that pancreatic lipids might affect insulin producing beta-cells negatively (due to lipotoxicity), and therefore some interest in MR measurements of pancreatic fat arose (28). In contrast to liver spatial distribution of lipids in pancreas is mostly inhomogeneous and concentrated along the duct structures or in peripheral areas (where fatty infiltration can be hardly distinguished from fatty material surrounding the pancreas). For this reason assessment of pancreatic fat as biomarker by spectroscopy or imaging remains critical.

Perfusion per volume in the endocrine part of the pancreas (Langerhans islets) is known to be clearly higher than in the exocrine part. Therefore a study examined pancreas perfusion by ASL techniques in healthy volunteers, and it was found that corpus and tail show slightly higher perfusion than the pancreas head (29). This is in accordance to the known higher density of Langerhans islets in the corpus and tail of the pancreas, but the role of perfusion measurements for assessment of the endocrine portion of the pancreas must be further investigated.

Brain:

MRI revealed macro- and micro-structural changes in the brain in diabetic and obese subjects (30,31). Furthermore, resting state activity assessed by functional MRI based on the BOLD effect was reduced in diabetic and obese subjects (32).

Summary:

Many studies in large cohorts with variable states of obesity or variable states of insulin resistance conducted in the past 15 years revealed clear correlations between quantitative MR data (MR-related biomarkers) and the status of the disease (which is characterized by “traditional” biomarkers). In addition, even promising correlations between MR-related biomarkers and success of therapeutic interventions (especially lifestyle interventions (33)) have been reported.

Altogether, MR-related biomarkers for diabetes and obesity are so far mainly reflecting volumes of specific tissue compartments or their composition (fat fraction in parenchyma and fatty acid composition in some cases). Already available and tested “MR biomarkers” seem not to be highly relevant for individual diagnosis, since diagnosis is performed using traditional biomarkers (eg, blood glucose levels or BMI). However, individual response to lifestyle interventions or other therapies can often be monitored better by MRI and MRS than by traditional biomarkers alone. Furthermore, assessment of MR biomarkers in cross-sectional or better longitudinal studies in large cohorts of pre-diabetic or slightly obese people allows us to learn more about the pathogenesis of the diseases. A final and important point is the potential role of “MR biomarkers” for the selection of the most promising lifestyle intervention and/or

drug therapy in individual patients in order to prevent the further development of the disease.

Recently, several new MR techniques for assessment of functional imaging of tissue perfusion, activity of brown adipose tissue and mechanical activity of skeletal musculature at rest have been proposed and tested (34). Their significance as biomarkers has to be evaluated in further studies.

List of established MR biomarkers for diabetes and obesity research

- assessment of whole body fat fraction
- visceral adipose volume
- subcutaneous adipose volume
- liver fat fraction
- concentration of intramyocellular lipids (IMCL) in calf muscles

List of MR biomarkers under investigation

- visceral and subcutaneous adipose tissue composition (saturated versus mono- and polyunsaturated fatty acids)
- special adipose tissue compartments: interscapular fat volume, perivascular fat volume, intermuscular fat volume (IMAT)
- signs of liver fibrosis (elastography, diffusion)
- pancreatic fat
- brown adipose tissue (BAT) volume

List of new (more functional) biomarkers

- brown adipose tissue (BAT) activity (eg, by BOLD)
- perfusion of liver and pancreas (eg, by IVIM)
- mechanical muscular activity at rest (eg, by IVIM)

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