Magnetic Resonance Imaging of Obesity and Metabolic Disorders: Summary from the 2019 ISMRM Workshop

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Magnetic Resonance Imaging of Obesity and Metabolic Disorders: Summary from the 2019 ISMRM Workshop

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ABSTRACT

More than 100 attendees from Australia, Austria, Belgium, Canada, China, Germany, Hong Kong, Indonesia, Japan, Malaysia, The Netherlands, The Philippines, Republic of Korea, Singapore, Sweden, Switzerland, United Kingdom, and the United States convened in Singapore for the 2019 ISMRM-sponsored workshop on MRI of Obesity and Metabolic Disorders. The scientific program brought together a multi-disciplinary group of researchers, trainees, and clinicians and included sessions in diabetes and insulin resistance; an update on recent advances in water-fat MRI acquisition and reconstruction methods; with applications in skeletal muscle, bone marrow, and adipose tissue quantification; a summary of recent findings in brown adipose tissue; new developments in imaging fat in the fetus, placenta, and neonates; the utility of liver elastography in obesity studies; and the emerging role of radiomics in population-based "big data" studies. The workshop featured keynote presentations on nutrition, epidemiology, genetics, and exercise physiology. Forty-four proffered scientific abstracts were also presented, covering the topics of brown adipose tissue, quantitative liver analysis from multi-parametric data, disease prevalence and population health, technical and methodological developments in data acquisition and reconstruction, newfound applications of machine learning and neural networks, standardization of proton density fat fraction measurements, and X-nuclei applications. The purpose of this article is to summarize scientific highlights from the workshop and identify future directions of work.

Keywords: obesity and metabolic disorders; adipose tissue and fat quantification; skeletal muscle; diabetes and insulin resistance; liver elastography; bone marrow; proton density fat fraction

Abbreviations

BAT	brown adipose tissue
CSE	chemical shift encoded
EMCL	extramyocellular lipids
FAC	fatty acid composition
IMCL	intramyocellular lipids
MRE	magnetic resonance elastography
MRI/S	magnetic resonance imaging/spectroscopy
PDFF	proton density fat fraction
SAT	subcutaneous adipose tissue
T2D	type 2 diabetes
VAT	visceral adipose tissue
WAT	white adipose tissue

Introduction

Research in obesity and metabolic disorders using magnetic resonance imaging and spectroscopy has increased significantly in recent years (1). MRI/S are widely used to achieve quantitative endpoints such as fat accumulation in SAT and VAT depots, organs, and muscles (2, 3). This ISMRM-sponsored workshop (https://www.ismrm.org/workshops/2019/ObMet/) was held in Singapore from July 21-24, 2019 and followed the first event in 2012 (4). More than 100 participants attended the workshop from (see Supporting Information Table S1). Over 40 proffered abstracts were presented, focusing on population findings, developments in the proton density fat fraction imaging biomarker, methodological and technical advances in pulse sequences and machine learning, liver physiology, and brown adipose tissue. This article summarizes scientific highlights and insights towards future directions of research from the workshop's invited lectures (see Supporting Information Table S2 for list of speakers). This overview groups each speaker's contributions into several themes, including (a) precision medicine, big data and "imaging-omics" in large population studies, (b) nutrition, metabolism, diabetes, and insulin resistance in Asian and Latino cohorts, (c) advances in chemical-shift-encoded water-fat imaging, (d) BAT imaging, (e) fetal and placenta imaging, (f) liver elastography, and (g) muscle and bone marrow imaging. The reader is referred to online Supporting Information for additional excerpts from speakers.

Prelude

Fritz Schick, Christiani Jeyakumar Henry, and Jürgen Machann provided outlines of the obesity and type 2 diabetes epidemic worldwide and the existing role of MRI/MRS in research and clinical medicine (5). Dr. Schick noted that according to statistics from the United States Center for Disease Control, the prevalence of obesity and diabetes continues to rise, and on average a person in the United States now consumes 400 more calories daily than five decades

ago (6). Additionally, the time spent on physical activity and energy expenditure has markedly decreased, with sedentary behavior becoming dominant. Recent World Health Organization 2014 data shows that more than 1.4 billion adults worldwide are overweight (BMI ≥ 25 kg/m^2) and obese, whilst 1.2 billion were undernourished, marking the first time in history of this imbalance

In the context of energy expenditure, the concept of under- and over-nutrition and basal metabolic rate was the topic of focus for Dr. Henry. Basal metabolic rate is the minimal energy requirement needed to sustain life at resting state and to maintain basic organ functions. It was shown that the liver, brain, heart and kidney expend the most energy. Humans consume on average 1 ton of food per year, yet most of us fluctuate less than +/- 2 kg in body weight per year and do not become obese. Basal metabolic rate is therefore the fundamental mechanism that enables us to maintain relative weight constancy.

Dr. Machann described in detail MRI/S-based body composition phenotyping and ectopic fat distribution in subjects with increased risk for T2D. Conventional T1-imaging remains a robust approach to assess lean and adipose tissue distributions (7, 8). While manual histogram-based threshold segmentation of such whole-body data remains time consuming, advanced fuzzy-clustering and deep learning algorithms can perform such tasks quickly (9, 10). Cross-sectional gender differences from German studies were shown, where men and women exhibit dissimilar patterns in SAT and VAT despite similar age and BMI, as well as differential findings of FAC in the superficial SAT, deep SAT, and VAT depots (11). Unsaturated fatty acid levels are highest in SAT of the lower legs, followed by abdominal superficial SAT, abdominal deep SAT, VAT, and bone marrow. Through such data, Dr. Machann identified a specific phenotype, dubbed metabolically healthy obesity. This group represents subjects with BMI > 30 kg/m^2, but exhibit adequate insulin sensitivity. In contrast to metabolic healthy obesity, there is also a

metabolically unhealthy obesity phenotype, where subjects have similar BMI but low insulin sensitivity and excess VAT.

Big Data and "Imaging-omics"

To better understand disease processes, data from genotypes, phenotypic variations, lifestyles, and quantitative imaging biomarkers need to be analyzed in an integrated fashion. Neerja Karnani reviewed recent "big data" machine-learning efforts in Singapore aimed to promote an integrative approach in providing precision medicine from multi-omics data. Molecular data (genetics, epigenetics, lipodomics), environment and microbiome data (12-14) and imaging data are being bridged to predict health risks and provide a deeper understanding of metabolic adversities. It is important to implement large population-based studies to assess genetic and lifestyle effects on disease processes, to stratify groups for risk, and to assess differential responses to therapeutic intervention). While it is important to have large quantities of data in any epidemiology study, having an integrative data analysis provides stronger insights into the developmental origins of metabolic health adversities, identifies human variations, and facilitates timing of optimal intervention therapies. Dr. Karnani highlighted two Singapore studies, where ethnic differences in the genotypes of the cohort exist (15, 16).

Magnus Borga discussed radiomics in the context of MRI-based quantitative body composition analysis. There are four key steps: image acquisition (i.e., pulse sequence, protocol), tissue segmentation (i.e., organ, structure, region-of-interest), feature extraction (i.e., size, shape, area, volume, quantitative imaging biomarkers), and data analytics (i.e., data mining, hypothesis testing, cluster and pattern analysis). Dr. Borga reiterated the importance of quantitative MRI and the need for strict reproducibility criteria throughout the processing chain, such that generalized thresholds and reference values can be had (17). While scanner-to-

scanner reproducibility in multi-center trials is critical, so is within-scanner repeatability. Likewise, standardized protocols and post-processing pipelines that allow flexibility in protocol parameters is paramount. Representative data from the UK Biobank study, which encompasses nearly 500,000 subjects, 100,000 of which will receive brain, cardiac, and whole-body MRI exams, were shown. To date, over 40,000 participants have been scanned (18), where six distinct propensity clusters, showing different risks for metabolic disease depending on their whole-body composition analysis profile have been introduced (19).

Diabetes and Insulin Resistance in Asian and Latino Cohorts

Tai E. Shyong and Gabriel Shaibi examined T2D and insulin resistance in Asian and Latino populations, respectively. While the positive association between BMI and T2D risk is well-known, paradoxically, Singaporean Chinese subjects whose BMI values are considered normal by Western standards also exhibit increased risk and incidence of T2D (20). The data suggested that the Chinese exhibit a phenotype of mild lipodystrophy and limited adipose tissue expansibility (i.e., hypertrophy – increase in cell size) (21, 22), which can predispose them to insulin resistance. There also exist differences in abdominal and visceral adiposity and skeletal muscle IMCL between Chinese, Malay, and South Asian cohorts, which lead to varying insulin sensitivity between the three ethnic groups. While the general inverse trend between percent body fat and insulin sensitivity is maintained (highest in Malays, lowest in South Asians), body fat partitioning itself is not adequate in explaining the differences in insulin sensitivity between the three groups (23). Human genetic studies to date suggest that most of the pathways leading to T2D are shared between ethnic groups (24) and that while the pathophysiology of T2D can be heterogenous, there remains no clear phenotype of T2D that is truly unique to Asia.

Gabriel Shaibi presented on body adiposity and T2D risk in Latino youth, focusing on the

confounding effects of gender, race/ethnicity, and the impact of interventions (25-27). According to 2018 statistics (28), the prevalence of childhood obesity in the United States is ~18%, as defined by a BMI > 95th percentile for age and gender. About 6% have severe obesity, as defined by a BMI > 120% of 95th percentile. Although the prevalence do not significantly differ between boys and girls, there are clear disparities across race/ethnicity. Native-American, Latino, and African American children are disproportionately impacted by obesity in comparison to Non-Hispanic Whites, and girls experience a disproportionate burden compared to boys when it comes to T2D risk (29). Gender differences in the incidence of T2D may, in part, be associated with higher levels of body adiposity among minority girls. Ryder, et al. has shown that percent body fat continues to increase in girls from age 8-20 years, whereas males exhibit a decline in percent fat after about age of 12 years (30). For a given BMI and age, Non-Hispanic Whites and African Americans exhibit similar SAT volumes, whereas the latter have smaller amounts of VAT (31). Latino youths tend to exhibit the most amount of VAT, leading to the TOFI (thin-outside-fat-inside) phenotype (32, 33), similar to the metabolically unhealthy obesity phenotype described by Dr. Machann. Lifestyle intervention was also discussed and differences between boys and girls where adipose tissue volumes are lost and gained were shown. Boys in general lose more VAT and gain more lean mass than girls (34-36) In preventing childhood obesity and lowering T2D risk at an early stage, Dr. Shaibi alluded to the need for individualized precision medicine and easier access to quantitaitve imaging, as there exists tremendous heterogeneities in response to lifestyle intervention (37).

Advances in Water-Fat MRI

Holden Wu, Pernilla Peterson, Stefan Ruschke, and Michael Middleton provided updates on methodological advances in CSE water-fat MRI. The group focused collectively on developments aimed to improve and expand the application of quantitative PDFF

measurements in research and clinical trials (38). Although CSE MRI methods fundamentally relies on the resonance frequency difference between water and fat protons, continued research from the original 2-point method has led to modern implementations with multi-echo acquisitions and advanced signal modeling (39, 40). CSE MRI is an established mainstream method for fat quantification, where voxel-wise PDFF is estimated by acquiring and reconstructing multi-echo spoiled-gradient-echo data using low flip angles to avoid T1 bias between water and fat signals, multi-peak fat spectral modeling, and R2* correction. Additionally, B0 field map estimation and phase error correction due to concomitant field gradients need to be considered (41, 42). While multi-echo CSE MRI increases scan time and often require breath-holds in body applications, advanced techniques such as parallel imaging (43, 44), compressed sensing (45, 46), MR fingerprinting (47), and deep/machine learning (48) have improved CSE-MRI scan time efficiency, making them applicable in patients who can not hold their breath and in children. Emerging respiratory-navigated and motion-robust sequences (49, 50) and non-Cartesian "stack-of-radial" techniques (51, 52) have comparable accuracy and precision in PDFF estimation in comparison to conventional breath-hold techniques.

Existing CSE MRI methods, unlike MRS, are not yet sensitive enough to characterize and detect subtle intra- or inter-individual variations in FAC. Nonetheless, imaging approaches for FAC estimation are attractive in their ability to provide a spatial map of FAC distributions. Significant validation and assessment of reproducibility and repeatability are still needed to make FAC estimation a "push button" technique that provides insights into obesity and health (53-55). Preliminary results from oil phantoms where gas chromatography was used as reference, and more recently in vivo data, are promising (56-58). Dr. Peterson showed that the classic CSE water-fat signal model can be logically expanded to include three descriptive features of FAC: number of double bonds, number of methylene-interrupted double bonds, and chain length, from which unsaturation can be computed. Unlike PDFF estimation that typically

uses six echoes, FAC estimation utilizes longer echo trains (i.e., 12-32 echoes), and the selection of echo spacing requires careful consideration in order to optimize noise performance. While the well-known T1-bias of water and fat impacts PDFF quantification, interestingly, it appears less important in FAC estimation. However, differences in the T2 of water and fat should be considered, especially in water-fat mixtures (59). FAC estimation may be limited to pure adipose tissue and other areas of intermediate to high fat fraction, whilst robust performance in water-fat mixtures of low PDFFs is difficult to achieve.

Brown/Beige/Brite Adipose Tissue

Barbara Cannon, Shigeki Sugii, and Rosa Tamara Branca spoke on brown (BAT), beige, and brite adipose tissue (60). It has been over 50 years since the physiological function of BAT, which is to produce heat through activation of the sympathetic nervous system by the hypothalamus, was realized. The tissue utilizes its dense mitochondrial population and a unique uncoupling protein, termed UCP1. The role of BAT in adaptive non-shivering thermogenesis has also gained general acceptance across multiple disciplines (61). The trend of assessing BAT in *diet* induced, rather than cold induced, thermogenesis has also emerged in popularity (62, 63). Similarly, the process of characterizing the transition of an adipose-derived stem cell to a beige/brite/brown adipocyte by imaging is actively being pursued. In Singapore, significant efforts in developing optical imaging (64) and diffuse reflectance spectroscopy (65, 66) to capture cellular “browning” ex vivo and in vivo have been undertaken, exploiting differences in cell surface markers (66-69).

Human BAT research has however been elevated to a “panacea”-like status in recent years where the potential of BAT to counteract metabolic syndrome and obesity are sought. BAT in the supraclavicular region of humans is most like classical BAT found in mice, rather than

inguinal beige adipocytes. Supraclavicular BAT depots become more WAT-like with age, high-fat diet, and thermoneutrality (70). While the CSE-based PDFF approach remains popular in BAT characterization (71-74), it nonetheless remains not specific enough to differentiate BAT and WAT in adult humans. BAT in humans often mimics WAT, confounding identification and quantification. Although 18F-FDG-PET/CT also remains popular, some concerns over test-retest reliability have been raised (74). Additionally, glucose uptake in BAT reflects the tissue's insulin sensitivity and blood flow rather than cold or diet induced thermogenesis (75, 76). Hyperpolarized ^{13}C MRI has the potential to provide richer metabolic information than 18F-FDG-PET beyond conventional glucose uptake, but applications in human BAT remain unexplored. MR-based thermometry for BAT has emerged as an active area of research. Water exhibits a proton resonance frequency shift of -0.01 ppm/°C. At 3 Tesla, B0 inhomogeneity and motion can however induce significantly larger frequency offsets that render the temperature effect ambiguous. Local hemodynamic changes can also lead to apparent frequency shifts that cannot be decoupled from temperature effect (77). The precision of proton thermometry is also limited to 1-2 degrees Celsius. Since BAT temperature changes are expected to be small, proton-thermometry may therefore, lack the sensitivity for applications in humans. Conversely, ^{129}Xe-based thermometry is a promising alternative. It is highly soluble in adipose tissue and exhibits higher temperature sensitivity (-0.21 ppm/°C) (78).

Imaging the Developing Young and The Barker Hypothesis

Charles McKenzie, Penny Gowland, and Yung Seng Lee highlighted the importance of imaging research during fetal, neonatal, and childhood periods. Placenta anatomy and physiology was first reviewed. It is the primary organ responsible for delivering nutrients and oxygen to the fetus, removing waste product and excessive heat, producing hormones, and providing an immune response (79). Fetal growth restrictions, preeclampsia, and diabetes were

discussed as examples of placental pathology. For fetal growth restriction where birth weight is in the lowest 10th percentile, there exists a ten-fold increase in risk of perinatal mortality, and a 60-90% chance of developing cerebral palsy. In this context, the Barker hypothesis, also known as the developmental origins of adult disease' hypothesis, was introduced (80, 81). It posits that adverse events in early developmental life, particularly in intrauterine life, can result in permanent changes to physiology and metabolism during adulthood and increase one's risk of adult disease. For example, maternal smoking impacts fetal organ growth, resulting in reduced brain, kidney, placenta, and total fetal volume (82). The Dutch famine cohort from World War II was used as an example, where there exists an association between maternal starvation during gestation and increased risk for cardiovascular and metabolic diseases in the offspring (83). Exposure to famine during the first half of pregnancy resulted in higher obesity rates compared to exposure during the last trimester of pregnancy (84).

For preeclampsia, a condition where the pregnant women experience markedly high blood pressure, abnormal immunological response, proteinuria, and reduced blood flow in uterine arteries can be observed, in addition to fetal growth restriction (85, 86). Lastly for diabetes, macrosomia (increased fetal growth) can sometimes be observed, accompanied by maternal and fetal hyperglycemia, along with increased stimulation of pancreatic islet cells, which can further lead to elevated adipose tissue and fat synthesis and accumulation in the fetus and newborn. Downstream risks can include shoulder dystocia, fetal death, premature delivery, respiratory distress, and T2D (87).

MRI methods to assess placental perfusion were reviewed (88-90). Differences in placental perfusion have been reported between fetuses appropriate for gestational age versus those who were small for gestational age. Safety remains paramount for the pregnant mother receiving an MRI (91). Fetal motion remains the biggest hindrance in MRI and while single-shot sequences

remain the workhorse protocols in conjunction with motion-compensated reconstruction algorithms to better visualize fetal anatomy (92), additional efforts are needed for widespread adoption.

To further exemplify the Barker hypothesis, the Growing up in Singapore towards healthy outcomes (GUSTO) study (13, 93), which aims to demonstrate how conditions during pregnancy, infancy, and early childhood influence subsequent health and disease later in life in Asian populations, was highlighted. Of note, maternal fasting glucose exhibited an association with neonatal body fat, and the children's BMI trajectories from birth to 3 years of age showed that the children of mothers with higher fasting glucose had greater BMIs later in life. In a related Singapore Adult Metabolism Study (SAMS), Indian men had the highest amounts of abdominal SAT and IMCL compared to Chinese and Malays. These ethnic differences manifested as early as 4-5 years of age, but were not observed in the neonatal period. Studies like GUSTO and SAMS can potentially provide insights into the evolution of metabolic diseases from fetus to adolescence. The implication is to aid in the prevention of obesity and diabetes by targeting a collection of modifiable risk factors such as pre-pregnancy obesity, maternal diet, gestational weight gain, and gestational diabetes mellitus, age at weaning and diet, and physical activity (94). The challenge is to translate such findings into effective public health policies and strategies, embedding effective intervention components within education and health care systems to achieve long-term sustainable improvements.

Liver Elastogarphy

Claude Sirlin, Meng Yin, and Takeshi Yokoo reviewed state-of-the-art ultrasound and MR-based elastography technology in assessing liver disease and obesity. Obesity can both cause liver disease and worsen preexisting liver disease by accelerating the progression to cirrhosis

and cancer (95-98). It is estimated that 5-10% of adults worldwide have both liver disease and obesity. The liver can be impacted by excessive iron and fat, as well as cell injury, inflammation, and fibrosis. Among these abnormalities, fibrosis is the single most important prognostic factor. Fibrosis can be staged histologically (mild, moderate, severe, cirrhosis), and higher fibrosis stage is associated with incrementally higher mortality (99, 100). As fibrosis worsens, the liver becomes stiffer, and the difference in stiffness becomes more apparent and separated in later stages (101). Liver stiffness measurements by MRE is an established quantitative imaging biomarker of fibrosis, where a recent meta-analysis suggested that a measured change in stiffness of 19% or larger reflects a true change in liver stiffness with 95% confidence (102). In populations at risk for having fibrosis, low liver stiffness measurements provide strong negative predictive value and are clinically useful for excluding patients with advanced fibrosis who may otherwise need treatment. MRE can therefore identify patients who can be managed without biopsy. MRE currently plays a critical role in cohort screening, selection, enrichment, stratification, response prediction, treatment monitoring, and response detection in liver clinical trials, and provide complementary information in epidemiology and radiomics analysis (103).

Skeletal Muscle Adipose Tissue

Chris Boesch reviewed 1H MRS of intramuscular lipids in skeletal muscles and the metabolic aspects of IMCL as an essential part of metabolism in health and disease (104, 105). The number, size, location, and composition of lipid droplets in IMCL play an important role in determining an individual's insulin sensitivity (106-109). Furthermore, diet and exercise can impact an individual's IMCL levels. The differences in IMCL between obese and diabetic populations versus trained athletes (110, 111) were highlighted. In the former, high levels of IMCL is positively correlated with insulin resistance. In the latter, IMCL is uniquely stored as an

energy reservoir for utilization during intense exercise. Quantitative MRS remains the only approach to measure IMCL non-invasively, whereas (extramyocellular lipids) EMCL can and should be quantified by conventional MRI. Magnetic field shimming, careful placement of voxels to avoid major muscle adipose tissue depots (i.e., dominant EMCL signal), fasciae, and blood vessels, and control over leg motion and rotation are critical in IMCL assessments (112). Additionally, variable spectral data fitting constraints (e.g., peak line widths, ppm chemical-shift ranges) used in analysis software can impact metabolite quantification and lead to systematic bias and errors. A consensus statement for best practices of measuring skeletal muscle IMCL and EMCL will appear imminently in the journal NMR in Biomedicine.

Hermien Kan discussed in depth quantitative fat imaging applications in neuromuscular diseases. Unlike muscle biopsy, qualitative scoring, and laboratory muscle function tests, quantitative MRI/S offers an objective and superior approach to assess muscle groups. It is therefore suitable for clinical trials where researchers can track muscles individually, describe disease progression, and characterize disease pathophysiology. Muscle functional loads, muscle cross-sectional area, fat content, T2 relaxometry, diffusion, and metabolism are common surrogate endpoints currently being deployed in research trials (113-124). Dr. Kan specifically discussed the concept of muscle contractile cross-sectional area, defined as the contractile proportion and the non-contractile proportion of the muscle due to the fat replacement. The amount of force that can be generated per contractile cross-sectional area decreases with disease severity (125, 126). Additionally, higher muscle mass is beneficial in developing higher glucose uptake and insulin sensitivity. Standardized imaging landmarks are needed for longitudinal multi-site muscular dystrophy studies, as a shift in a single slice location between time points can lead to apparent changes in PDFF. Along a single muscle, the amount of fat content can differ significantly. Recently, several consensus statements and international

efforts to harmonize efforts and protocols for optimal outcome measures in clinical trials have been published (127-129).

Bone and Bone Marrow Adipose Tissue

Dimitrios Karampinos, Stefan Ruschke, and Roland Krug summarized recent work in bone marrow adipose tissue (BMAT), bone mineral density, bone quality, and implications in health. Bone marrow is composed of white adipocytes, hematopoietic cells, and trabeculae. Red marrow has its characteristic color due to hemoglobin and high levels of vascularization and is active in hematopoiesis. Yellow marrow has its characteristic color due to carotenoids, is minimally involved in hematopoiesis, and is largely composed of triglycerides. BMAT is absent at birth, expands during skeletal development and its volume increases with age and menopause. With age, there is also a constant conversion of red to yellow marrow and bone mass. Differences in BMAT between males and females exist (130-132). Prior to the age of 50, men exhibit higher BMAT PDFF in the vertebral bone marrow than women. However, this trend reverses with aging and in postmenopausal women.

BMAT cells originate from the same mesenchymal stem cells (133, 134) as osteoblasts. Therefore, BMAT plays an important role in growth, development, and healthy aging. While originally thought to simply fill the space in bone marrow cavities occupied previously by hematopoietic cells, BMAT cells are now considered to be involved in bone remodeling and hematopoiesis through their effects on neighboring osteoblasts and hematopoietic cells. Thus, a balance exists between adipogenesis and osteoblastogenesis (135, 136). BMAT and its high PDFF content have also been implicated in osteoporosis (deterioration of the trabecular bone matrix), spondyloarthritis (137), lower back pain, obesity, diabetes and, paradoxically, anorexia

nervosa (138-140), and skeletal health (i.e., fragility, fracture prediction). Interventions that increase bone mass have been shown to coincide with a decrease in BMAT. BMAT is positively associated with vertebral fracture in men (141) and is negatively associated with failure load and bone mineral density (142). Furthermore, FAC of BMAT, specifically unsaturation, decreases with osteoporosis (143) and is negatively associated with the prevalence of fractures (144). Notable differential results of BMAT in subjects with glucocorticoid-induced osteoporosis (71), in postmenopausal women with and without diabetes (145), and in patients with lower back pain as characterized by Modic changes, and Pfirrman grading (146) have been reported.

Conclusion

The imaging community focusing on obesity and metabolic disorders is strong and active. This workshop was successful in fostering collaborations and dialog uniting internationally recognized scientists and clinicians who are developing and applying advanced MRI/S techniques to investigate obesity and metabolic dysfunctions with end-users of imaging including nutritionists, exercise physiologists, and epidemiologists. At the conclusion of the workshop, attendees were asked to work as a group to identify and prioritize challenges and opportunities for future directions of work. Consensus points are summarized in Table 1 as "take-home" messages from the discussion.

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TABLE and FIGURE LEGENDS

TABLE 1:

An abbreviated list of suggested directions of future research discussed during the concluding session of the workshop.

SUPPORTING INFORMATION TABLE S1:

List of countries of origin of the workshop attendees.

SUPPORTING INFORMATION TABLE S2:

List of workshop speakers and their profession.

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TABLE 1: An abbreviated list of suggested directions of future research discussed during the concluding session of the workshop.

• Further validation of joint R2* and PDFF estimation in measuring iron and fat content in brown adipose tissue, pancreas, muscle, and bone marrow adipose tissue are needed, preferably to the degree and rigor with which it has been studied in liver applications.
• A consensus on best practices and protocols beyond the liver is needed for the community.
• MR elastography is challenging in obese patients, where existing mechanical drivers may not yield sufficient wave propagation through the abdomen. Free-breathing MR elastography is desired in obese patients, especially in children.
• Further validation towards MRI methods for characterizing hepatic inflammation, non-alcoholic steatohepatitis, and fibrosis are needed to complement existing PDFF and MRE methods.
• Macro- vs. micro-vesicular organ steatosis cannot be differentiated with existing MRI/S approaches whilst sensitivity towards detection of very small PDFF changes remains limited. This need will be particularly important in BAT imaging.
• Pancreas imaging needs further attention, given the organ's role in diabetes and insulin regulation.
• Novel imaging of adipocyte inflammation and macrophage infiltration needs further development.
• Epicardial / paracardial, renal, perivascular adipose tissue characterization are encouraged.
• Longitudinal studies in human brown adipose tissues are emerging. However, imaging alone cannot provide insight into the implications of this tissue in metabolism, glucose, lipids, hormones, and energy expenditure. The integrated understanding of the tissue's physiology and its therapeutic role in metabolic disorders and obesity, remains largely unanswered. "Big Data -omics" studies are encouraged.
• There is a lack of standardized acquisitions, data-processing pipelines, and reporting templates for both animal and human brown adipose tissue assessment.
• New methods need to be validated by independent groups and made more available across the community, such as MR-based thermometry in adipose tissue, fatty acid composition estimation, etc.
• MRI of the placenta and fetal growth are needed to longitudinally assess impacts of extended bed rest, maternal diet, and drug therapies.
• Motion remains the biggest hindrance in MRI of fetus and neonates. While single-shot sequences remain the workhorse protocols in conjunction with motion-compensated reconstruction algorithms to better visualize fetal anatomy, additional efforts are needed for widespread adoption across platforms.

SUPPORTING INFORMATION TABLE S1
List of countries of origin of the workshop attendees.

Country	Number of Attendees
Australia	2
Austria	1
Belgium	1
Canada	1
China	4
Germany	8
Hong Kong	1
Indonesia	1
Japan	1
Malaysia	3
The Netherlands	2
The Philippines	1
Republic of Korea	6
Singapore	38
Sweden	5
Switzerland	1
United Kingdom	9
United States	21

SUPPORTING INFORMATION TABLE S2
List of workshop speakers and their profession.

Name	Institution, Country	Profession
Fritz Schick, MD PhD	University of Tübingen, Germany	Physician and MRI scientist
Christiani Jeyakumar Henry, PhD	Agency for Science Technology and Research, Singapore	Food and nutrition scientist, physiologist
Tai E. Shyong, PhD	National University of Singapore, Singapore	Endocrinologist, geneticist
Gabriel Shaibi, PhD	Arizona State University, United States	Physiologist, epidemiologist, physical therapist
Holden Wu, PhD	University of California, Los Angeles, United States	MRI scientist
Pernilla Peterson, PhD	Skåne University Hospital and Lund University, Sweden	MRI scientist
Michael Middleton, MD PhD	University of California, San Diego, United States	Radiologist and MRI scientist
Barbara Cannon, PhD	Stockholm University, Sweden	Molecular and cell biologist
Shigeki Sugii, PhD	Agency for Science Technology and Research, Singapore	Molecular and cell biologist
Rosa Tamara Branca, PhD	University of North Carolina at Chapel Hill, United States	MRI scientist
Hermien Kan, PhD	Leiden University Medical Center, The Netherlands	MRI scientist, exercise physiologist
Chris Boesch, MD PhD	Unversity and Inselspital Bern, Switzerland	Physician and MRI scientist
Jürgen Machann, PhD	Institute for Diabetes Research and Metabolic Diseases of the Helmholtz Center Munich at the University of Tübingen, Germany	MRI scientist
Charles McKenzie, PhD	University of Western Ontario, London, Canada	MRI scientist
Penny Gowland, PhD	University of Nottingham, United Kingdom	MRI scientist
Yung Seng Lee, MD PhD	National University of Singapore, Singapore	Physician, pediatrician, nutrition and metabolism scientist
Claude Sirlin, MD	University of California, San Diego, United States	Radiologist and MRI scientist
Meng Yin, PhD	Mayo Clinic, United States	MRI scientist

Takeshi Yokoo, MD PhD	University of Texas Southwestern Medical Center, United States	Radiologist and MRI scientist
Magnus Borga, PhD	Linköping University, Sweden	MRI scientist, medical informatics data scientist
Neerja Karnani, PhD	Agency for Science Technology and Research, Singapore	Systems biologist, biochemist, geneticist
Dimitrios Karampinos, PhD	Technical University of Munich, Germany)	MRI scientist
Stefan Ruschke, PhD	Technical University of Munich, Germany)	MRI scientist
Roland Krug, PhD	University of California, San Francisco, United States	MRI scientist

SUPPORTING INFORMATION

The following sections contain additional excerpts from speaker presentations that did not readily fit into the main manuscript due to space constraints. References are provided for each individual speaker.

Fritz Schick (University of Tübingen, Germany) discussed neural implications of obesity and introduced the "The Hungry Brain" (1). It posits that the non-conscious parts of the brain may drive one to overeat when our conscious behavior attempts to convince us otherwise. He pointed to evidence where prediabetes obese subjects show increased leptin and insulin levels, and yet the brain of obese subjects seems to be resistant to the actions of these hormones in curbing satiety. Furthermore, leptin reduces brain activation to food cues in non-obese subjects, and obese subjects exhibit higher brain activation to food-related cues (2, 3). Sleep deprivation and loss of sleep also promote brain hyperactivity to food cues. Currently there are no concrete approaches to combating these unconscious brain stimulations.

Dr. Schick reviewed pathways linking obesity, adipose tissue, and diabetes. At the cellular level, adipocyte inflammation and macrophage infiltration are hallmark signs of diabetes and insulin resistance, and imaging markers for these signs require further development, including X-nuclei methods, manganese contrast agents, diffusion-weighted MRI/S, and ultra-small superparamagnetic iron oxides (4). He discussed fatty acid composition in adipose tissue depots and that deep subcutaneous depots are more saturated than superficial depots, and that saturation levels in visceral adipose tissue are positively correlated with depot volume.

Dr. Schick encouraged developments in pancreas characterization (5), where organ function and beta cell mass remains difficult to quantify. Recent data in pancreas perfusion imaging have suggested differential perfusion rates in the head, corpus, and tail of the organ (5), and manganese imaging may offer additional insights into the organ's cellular functions (6).

1. Guyenet SJ. The hungry brain. Flatiron Books; 2017.
2. Guthoff M, Grichisch Y, Canova C, et al. Insulin modulates food-related activity in the central nervous system. J Clin Endocrinol Metab. 2010;95:784-755.
3. Grosshans M, Vollmert C, Vollstädt-Klein S. Association of leptin with food cue-induced activation in human reward pathways. Arch Gen Psychiatry. 2012;69:529-537.
4. Luciani A, Dechoux S, Deveaux V, et al. Adipose tissue macrophages: MR tracking to monitor obesity associated inflammation. Radiology. 2017;263:786-793.
5. Schraml C, Schwenzer NF, Martirosian P, Claussen CD, Schick F. Perfusion imaging of the pancreas using arterial spin labeling techniques. J Magn Reson Imaging. 2008;28:1459-1465.
6. Botsikas D, Terraz S, Vinet L, et al. Pancreatic magnetic resonance imaging after manganese injection distinguishes type 2 diabetic and normoglycemic patients. Islets. 2012;4:243-248.

Christiani Jeyakumar Henry (Agency for Science Technology and Research, Singapore) discussed basal metabolic (BMR) rate in depth. Paradoxically, the energy requirements of man and his balance of intake and expenditure are not well known, and that many past attempts to quantify this by investigators have led to inconsistent results (21). About 60-75% of the energy intake is expended and quantifiable as the BMR; 15-30% can be attributed to physical activity; 7-13% to diet-induced thermogenesis (i.e., BAT), and about 2-7% to body growth. BMR can be accurately predicted (2) and it has been shown that for an individual over extended periods of time, the BMR is surprisingly constant, with a coefficient of variation of less than 4%. Historical data suggest that women appear to have more intra-individual variations in BMR (3, 4), and that BMR can decrease significantly with long term fasting (5). He implicated foods with high glycemic index on overeating and obesity (6, 7), reminding the audience that different diet and food composition in the United States, Europe, and Asia play a significant role in influencing disease prevalence (8). His home messages were: (a) Despite continued efforts, our understanding of energy balance remains incomplete; (b) the etiology of obesity in Asians is different than in Europeans and North Americans, and in part this is driven by differences in dietary intake; (c) BMR is the most significant component in energy expenditure; therapeutic and intervention strategies to increase BMR is desirable in combating obesity and metabolic diseases, even if by a small margin (9).

1. Edholm OG, Adam JM, Healy MJ, Wolff HS, Goldsmith R, Best TW. Food intake and energy expenditure of army recruits. Br J Nutr. 1970;24:1091-1107.
2. Henry CJ. Basal metabolic rate studies in humans: measurement and development of new equations. Public Health Nutr. 2005;8(7A):1133-1152.
3. Benedict FG. The factors affecting normal basal metabolism. Proc Natl Acad Sci USA. 1915;1:105-109.
4. Benedict FG. A comparison of the basal metabolism of normal men and women. Proc Natl Acad Sci USA. 1915;1:104-105.
5. Benedict FG. The influence of athletic training upon basal metabolism. Proc Natl Acad Sci USA. 1915;1:102-103.
6. Ma RC, Chan JC. Type 2 diabetes in East Asians: similarities and differences with populations in Europe and the United States. Ann N Y Acad Sci. 2013;1281:64-91.
7. Ludwig DS, Majzoub JA, Al-Zahrani A, Dallal GE, Blanco I, Roberts SB. High glycemic index foods, overeating, and obesity. Pediatrics. 1999;103:E26.
8. Warren JM, Henry CJ, Simonite V. Low glycemic index breakfasts and reduced food intake in preadolescent children. Pediatrics. 2003;112:E414.
9. NCD Risk Factor Collaboration (NCD-RisC). Trends in adult body-mass index in 200 countries from 1975-2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. Lancet. 2016;387:1377-1396.

Jürgen Machann (Institute for Diabetes Research and Metabolic Diseases of the Helmholtz Center Munich at the University of Tübingen, Germany) provided some detailed results ongoing studies in Tübingen and the German Centre for Diabetes Research, such as the *PLIS* - Prediabetes Lifestyle Intervention Study, *PREG* - German Gestational Diabetes Study, and *DDS* - German Diabetes Study. He showed whole-body MRI demonstrating specifically that visceral adipose tissue volume and hepatic fat content can be significantly reduced after 9-24 months of lifestyle intervention (1). These findings allow investigators to predict potential responders from non-responders (2), and possibly tailor a more personalized intervention.

1. NUPREDM: Willmann C, Heni M, Linder K, et al. Potential effects of reduced red meat compared with increased fiber intake on glucose metabolism and liver fat content: a randomized and controlled dietary intervention study. Am J Clin Nutr. 2019;109:288-296.
2. Stefan N, Staiger H, Wagner R, et al. A high-risk phenotype associates with reduced improvement in glycaemia during a lifestyle intervention in prediabetes. Diabetologia. 2015;58:2877-2884.

Magnus Borga (Linköping University, Sweden) differentiated radiomics from another "imiomics" (1). In both instances, large amounts of data are collected from a population-sized cohort. In the former, explicit measurements (i.e., feature extraction) are made from the images and analyzed in conjunction with other available data. In the latter, analysis is performed directly in the image domain, on a voxel-by-voxel basis, without additional feature extraction, similar to BOLD-signal functional MRI analysis over a time course. For whole-body segmentation of adipose tissue and skeletal muscles, the 3D natures of MRI data need to be exploited. He demonstrated that 2D area measurements are a poor proxy for volume and should be avoided. He introduced the concept of continuous segmentation (2). Whereas discrete slice-by-slice segmentation can be resolution dependent, continuous or "fuzzy" segmentation algorithms enables true resolution-independence / invariance in tissue quantification. While classical image processing techniques including morphology are highly transparent but inflexible, emerging deep learning and convoluted neural network algorithms, if trained properly, are highly flexible, but offer little transparency to the user. Atlas-based segmentation approaches offer both high levels of transparency and flexibility.

Dr. Borga differentiated supervised vs. unsupervised machine learning. In the former, predictive models are generated that can be used for segmentation, classification, and regression. In the latter, descriptive models are trained that can be used for dimensionality reduction or clustering. While supervised learning is dependent on labeled data for its training, unsupervised learning uses un-labeled data that is easier to obtain. One example of unsupervised learning that can be used for visualizing high-dimensional data is Laplacian Eigenmaps, which are a non-linear version of principal component analysis, extracting the main modes of variations of the data along a manifold describing the natural anatomical variations. By using the "Adaptive kNN", a virtual control group can be created containing individuals with similar body composition as an investigated individual. The prevalence of different diseases such as coronary heart disease and T2D within the virtual control group can then be used to describe the disease propensities for the investigated individual. This type of analysis has been applied to the UK Biobank study.

1. Strand R, Malmberg F, Johansson L, Lind L, Sundbom M, Ahlström H, Kullberg J. A concept for holistic whole body MRI data analysis, Imiomics. PLoS One. 2017;12:e0169966.
2. Borga M. MRI adipose tissue and muscle composition analysis-a review of automation techniques. Br J Radiol. 2018;91:20180252.

Tai E. Shyong (National University of Singapore, Singapore) also identified and associated obesity, hypertriglyceridemia, high blood pressure, increased insulin resistance, and low high-density lipoprotein cholesterol levels with poor glucose tolerance (1). He also emphasized that most genome wide association studies to date in T2D have been performed mostly in European, Hispanic, and Latin American populations. Studies in Asian, African, and African American, for example, have been scarce (2).

1. Wong MS, Gu K, Heng D, Chew SK, Chew LS, Tai ES. The Singapore impaired glucose tolerance follow-up study: does the ticking clock go backward as well as forward? Diabetes Care. 2003;26:3024-3030.
2. Mills MC, Rahal C. A scientometric review of genome-wide association studies. Commun Biol. 2019;2:9.

Gabriel Shaibi (Arizona State University, United States) additionally emphasized non-alcoholic fatty liver disease in Latino youths (1). While quantitative fat fraction liver MRI is becoming popular (2), broad access to this advanced technology is still limited to many youth groups. The prevalence of non-alcoholic fatty liver disase (3-5) is greater in boys than girls, and recent trends show Latino youth exhibiting more hepatic fat content than Non-Hispanic Whites than African American (6, 7). High hepatic fat content appears to be associated with the PNPLA3 gene and the GG genotype may be more prevalent in the Latinos (8).

1. Schwimmer JB, Ugalde-Nicalo P, Welsh JA, et al. Effect of a low free sugar diet vs. usual diet on nonalcoholic fatty liver disease in adolescent boys: a randomized clinical trial. JAMA. 2019;321:256-265.
2. Browning, Szczepaniak LS, Dobbins R, et al. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. Hepatology. 2004;40:1387-1395.
3. Wang Y, G anger DR, Levitsky J, et al. Assessment of chronic hepatitis. AJR Am J Roentgenol. 2011;196:553-561.
4. Bertot LC, Adams LA. The natural course of non-alcoholic fatty liver disease. Int J Mol Sci. 2016;17:E774.
5. Pavlides M, Banerjee R, Tunnicliffe EM, et al. Multiparametric magnetic resonance imaging for the assessment of non-alcoholic fatty liver disease severity. Liver Int. 2017;37:1065-1073.
6. Toledo-Corral CM, Alderete TL, Hu HH, et al. Ectopic fat deposition in prediabetic overweight and obese minority adolescents. J Clin Endocrinol Metab. 2013;98:1115-1121.
7. Trico D, Caprio S, Rosaria Umano G, et al. Metabolic feature of nonalcoholic fatty liver in obese adolescents: findings from a multiethnic cohort. Hepatology. 2018;68:1376-1390.
8. Bruschi FV, Tardelli M, Claudel T, Trauner M. PNPLA3 expression and its impact on the liver: current perspectives. Hepat Med. 2017;9:55-66.

Michael Middleton (University of California San Diego, United States) reviewed extensively quantitative imaging biomarker usage and analysis in non-alcoholic fatty liver disease and non-alcoholic steatohepatitis clinical trials using proton density fat fraction and MR elastography-based tissue stiffness measures. He re-emphasized the difference between accuracy versus precision of a quantitative imaging biomarker and the need for strict quality control and standardization of acquisition and analysis protocols in multi-site pharmaceutical clinical trials. He stressed that both accuracy and precision should be appropriately stated for the Context of Use (COU), a term that is now defined by the Food and Drug Administration (1). He illustrated how quality control in liver PDFF and stiffness has been addressed through international efforts, such as the Quantitative Imaging Biomarker Alliance of the Radiological Society of North America. Dr. Middleton explained Academic Research Organizations (AROs) and Clinical Research Organizations (CROs), and how partnerships with these entities are critical in supporting pharmaceutical, biotechnology, and medical device industries. AROs and CROs are charged with establishing rigorous quality control metrics and workflow procedures for site qualification and image analysis in large multi-organizational trials.

1. Development and Approval Process | Drugs. https://www.fda.gov/Drugs/DevelopmentApprovalProcess/ Published June 13, 2018. Accessed October 31, 2019.

Barbara Cannon (Stockholm University, Sweden) further noted that beyond its traditional role in cold induced thermogenesis, BAT's role in diet induced thermogenesis has elevated the tissue into an area of intense interest and research in obesity and metabolism. Without UCP1, diet induced thermogenesis cannot occur, and thus in animals kept at thermoneutral temperatures where UCP1 (and BAT) is not activated, excess food intake leads to increased white adipose tissue (WAT) storage and an increase in fat and body mass. The increase does not alter the animal's insulation compared to lean control animals (1). Furthermore, the presence or absence of BAT does not inherently alter the amount of energy an animal expends in a cold environment. Rather, the animal will be more comfortable spending the necessary energy with BAT present (2, 3).

1. Fischer AW, Csikasz RI, von Essen G, Cannon B, Nedergaard J. No insuliatng effect of obesity. Am J Physiol Endocrinol Metab 2016;311:E202-213.
2. Golozoubova V, Hohtola E, Matthias A, Jacobsson A, Cannon B, Nedergaard J. Only UCP1 can mediate adaptive nonshivering thermogenesis in the cold. FASEB J. 2001;15:2048-2050.
3. Meyer CW, Willshäuser M, Jastroch M, et al. Adaptive thermogenesis and thermal conductance in wild-type and UCP1-KO mice. Am J Physiol Regul Integr Comp Physiol 2010;229:R1396-R1406.

Shigeki Sugii (Agency for Science Technology and Research, Singapore) discussed cellular mechanisms for adipocyte maturation and stem cell factors that impact the process of browning. He reviewed SAT and VAT, which are considered healthy versus dysfunctional, respectively (1, 2). The former is lipogenic, insulin sensitive, anti-inflammatory, capable of good adipogenesis and browning. The latter is lipolytic, insulin resistant, pro-inflammatory, and exhibits little potential for adipogenesis and browning. Human adipose-derived stem cells (ASCs) from SAT and VAT also exhibit differences (3). The former has increased potential for adipogenesis and browning, proliferation, and migration. The latter, VAT-ASCs, exhibit high oxidative stress, which causes cellular defects including adipogenesis and browning. SAT-ASCs show properties closer to VAT-ASC during aging and obesity. Novel cell surface markers, CD200 for VAT-ASC and CD10 for SAT-ASC (4, 5), have been identified to elucidate these browning differences (6).

Dr. Sugii described unique optical imaging approaches to detect browning that were developed in Singapore. The Fast Adipogenesis Tracking System is a computational algorithm capable of accurately detecting and quantifying the percentage of cells undergoing adipogenic and browning differentiation in vitro. The tool is suitable for drug screening with hundreds and thousands of cell culture wells (7). For in vivo applications, a label-free optical technique called diffuse reflectance spectroscopy (DRS) has been developed (8). In DRS, the biochemical composition of the tissue is determined based on spectral analysis of the reflected light collected after the tissue is exposed to diffuse white light. WAT and BAT exhibit different profiles in the wavelength range of 500 to 700 nm. Likewise, browning tissues exhibit intermediate DRS profile between WAT and BAT (9). Lastly, a near-infrared fluorescent reporter gene and its detection with photoacoustic tomography were described. Here, the thermo-elastic expansion of a tissue resulting from optical absorption of light (i.e., photoacoustic effect) is detected by ultrasound. The reporter is under the control of a brown/beige-specific UCP1 promoter. By illuminating the tissue with multiple wavelengths, investigators have been able to track the browning process and correlate results with 18F FDG-PET/MR (10). A reporter-free variant of the approach that exploits differences in spectral absorption between oxy- and deoxyhemoglobin was recently demonstrated in mice (11).

1. Després JP, Lemieux I. Abdominal obesity and metabolic syndrome. Nature. 2006;444:881-887.
2. Tran TT, Kahn CR. Transplantation of adipose tissue and stem cells: role in metabolism and disease. Nat Rev Endocrinol. 2010;6:195-213.
3. Ong WK, Sugii S. Adipose-derived stem cells: fatty potentials for therapy. Int J Biochem Cell Biol. 2013;45:1083-1086.
4. Ong WK, Tan CS, Chan KL, et al. Identification of specific cell-surface markers of adipose-derived stem cells from subcutaneous and visceral fat depots. Stem Cell Reports. 2014;2:171-179.
5. Takeda K, Sriram S, Chan XHD, et al. Retinoic acid mediates visceral-specific adipogenic defects of human adipose-derived stem cells. Diabetes. 2016;65:1164–1178.
6. Sriram S, Yuan C, Chakraborty S. Oxidative stress mediates depot-specific functional differences of human adipose-derived stem cells. Stem Cell Res Ther. 2019;10:141.
7. Yuan C, Chakraborty S, Chitta KK, et al. Fast Adipogenesis Tracking System (FATS)—a robust, high-throughput, automation-ready adipogenesis quantification technique. Stem Cell Res Ther. 2019;10:38.

8. Dinish US, Wong CL, Sriram WK, et al. Diffuse optical spectroscopy and imaging to detect and quantify adipose tissue browning. Sci Rep. 2017;7:41357.
9. Dev K, Dinish US, Chakraborty R, et al. Quantitative in vivo detection of adipose tissue browning using diffuse reflectance spectroscopy in near-infrared II window. J Biophotonics. 2018;11:e201800135.
10. Chan XHD, Balasundaram G, Attia ABE, et al. Multimodal imaging approach to monitor browning of adipose tissue in vivo. J Lipid Res. 2018;59:1071-1078.
11. Reber J, Willershäuser M, Karlas A, et al. Non-invasive measurement of brown fat metabolism based on optoacoustic imaging of hemoglobin gradients. Cell Metab. 2018;27:689–701.

Rosa Tamara Branca (University of North Carolina at Chapel Hill, United States) emphasized that PDFF methods alone will not likely be successful in characterizing human BAT. Nonlinear spectroscopy based on intermolecular multiple quantum coherences (iMQCs) (1, 2) are novel yet limited in widespread application. Blood-oxygen-level-dependent (BOLD) (T2/T2*) related contrast (3) in relation to oxygen consumption, perfusion, and thermometry has also been reported. However, whether the BOLD MR signal increases or decreases upon tissue activation remains ambiguous and subject dependent (4, 5). X-nuclei methods, including hyperpolarized ^{13}C (6) and ^{129}Xe (7) have the potential to complement proton-based MRI methods and require additional validation in human studies. The reader is referred to an excellent recent review of MRI methods in BAT characterization (8).

1. Branca RT, Zhang L, Warren WS, et al. In vivo noninvasive detection of brown adipose tissue through intermolecular zero-quantum MRI. PLoS One. 2013;8:e74206.
2. Bao J, Cui X, Cai S, Zhong J, Cai C, Chen Z. Brown adipose tissue mapping in rats with combined intermolecular double-quantum coherence and Dixon water-fat MRI. NMR Biomed. 2013;26:1663-1671.
3. Khanna A, Branca RT. Detecting brown adipose tissue activity with BOLD MRI in mice. Magn Reson Med. 2012;68:1285-1290.
4. Chen YI, Cypess AM, Chen C, Palmer M, Kolodny G, Kahn CR, Kwong KK. Measurement of human brown adipose tissue volume and activity using anatomic MR imaging and functional MR imaging. J Nucl Med. 2013; 54:1584-1587.
5. Van Rooijen BD, van der Lans AAJJ, Brans B, et al. Imaging cold-activated brown adipose tissue using dynamic T2*-weighted magnetic resonance imaging and 2-Deoxy-2-[18F]fluoro-D-glucose Positron Emission Tomography. Invest Radiol. 2013; 48:708–714.
6. Riis-Vestergaard MJ, Breining P, Pedersen SB, et al. Evaluation of active brown adipose tissue by the use of hyperpolarized [1- 13 C] pyruvate MRI in mice. Int J Mol Sci. 2018;19:pii: eE2597
7. Branca RT, He T, Zhang L, Floyd CS, Freeman M, White C, Burant A. Detection of brown adipose tissue and thermogenic activity in mice by hyperpolarized Xenon MRI. Proc Natl Acad Sci USA. 2014;111:18001-18006.
8. Karampinos DC, Weidlich D, Wu M, Hu HH, Franz D. Techniques and applications of magnetic resonance imaging for studying brown adipose tissue morphometry and function. Handb Exp Pharmacol. 2019;251:299-324.

Charles McKenzie (University of Western Ontario, Canada) prefaced the session on fetal and neonatal with historical works where the first images of fetal fat using MRI were reported (1). Expectedly, limitations in technology at the time resulted in poor spatial and spectral resolution, motion artifacts from the fetus, and long acquisition times. Dr. McKenzie provided some background on why MRI of BAT and WAT in the early stages of life is important to study in the context of maternal and fetal health (2-4). Additionally, metabolism during fetal life remains poorly understood, and the use of nuclear medicine modalities is limited (5), whilst access to fetal blood and tissue samples are challenging. Doppler ultrasound measurements of fetal umbilical and cerebral perfusion can be impacted by metabolic abnormalities (6). MRI has been used to assess blood oxygenation in the fetus and placenta (7, 8) and new strategies that can potentially overcome fetal and placental motion (9) are emerging. X-nuclei possibilities of measuring fetal glycolysis and oxidative metabolism using hyperpolarized ^{13}C pyruvate were discussed (10, 11).

1. Deans HE, Smith FW, Lloyd DJ, Law AN, Suntherland HW. Br J Radiol. 1989;62:603-607.
2. Giza SA, Olmstead C, McCooeye DA, et al. Measuring fetal adipose tissue using 3D water-fat magnetic resonance imaging: a feasibility study. J Matern Fetal Neonatal Med. 2018;1-7.
3. Anblagan D, Deshpande R, Jones NW, et al. Measurement of fetal fat in utero in normal and diabetic pregnancies using magnetic resonance imaging. Ultrasound Obstet Gynecol. 2013;42:335-340.
4. Modi N, Thomas EL, Uthaya SN, Umranikar S, Bell JD, Yajnik C. Whole body magnetic resonance imaging of healthy newborn infants demonstrates increased central adiposity in Asian Indians. Pediatr Res. 2009;65:584-587.
5. Stabin MG. Radiation dose and risks to fetus from nuclear medicine procedures. Phys Med. 2017;43:190-198.
6. Chia CC, Huang SC. Overview of fetal growth retardation/restriction. Taiwan J Obstet Gynecol. 2014;53:435-440.
7. Sørensen A, Peters D, Fründ E, Lingman G, Christiansen O, Uldbjerg N. Changes in human placental oxygenation during maternal hyperoxia estimated by blood oxygen level-dependent magnetic resonance imaging (BOLD MRI). Ultrasound Obstet Gynecol. 2013;42:310-314.
8. Schabel MC, Roberts VHJ, Lo JO, Platt S, Grant KA, Frias AE, Kroenke CD. Functional imaging of the nonhuman primate placenta with endogenous blood oxygen level-dependent contrast. Magn Reson Med. 2016;76:1551-1562.
9. Armstrong T, Liu D, Martin T, et al. 3D R2* mapping of the placenta during early gestation using free-breathing multiecho stack-of-radial MRI at 3T. J Magn Reson Imaging. 2019;49:291-303.
10. Friesen-Waldner LJ, Sinclair KJ, Wade TP, et al. Hyperpolarized [1-(13) C] pyruvate MRI for noninvasive examination of placental metabolism and nutrient transport: A feasibility study in pregnant guinea pigs. J Magn Reson Imaging. 2016;43: 750-755.
11. Markovic S, Fages A, Roussel T, Hadas R, Brandis A, Neeman M, Frydman L. Placental physiology monitored by hyperpolarized dynamic 13C magnetic resonance. Proc Natl Acad Sci USA. 2018;115:2429-2436.

Penny Gowland (University of Nottingham, United Kingdom) described the unique phenomenon of involuntary uterine contraction was demonstrated with dynamic MRI (1). These contractions involve a reduction in the volume of the placenta, a contraction and thickening of the uterine wall in the region where the placenta is attached, and an expansion of the remaining uterine wall. The concerted action suggests an active pumping of blood from the placenta and pregnant mothers are unaware of these contractions. The origin and relevance of these contractions and their involvement in venous return flow in the placenta remain unknown.

1. Sinding M, Peters DA, Frøkjaer JB, Christiansen OB, Uldbjerg N, Sørensen A. Reduced placental oxygenation during subclinical uterine contractions as assessed by BOLD MRI. Placenta. 2016;39:16-20.

Yung Seng Lee (National University of Singapore, Singapore) expanded on The Barker Hypothesis (1) and explained that the fetus in utero is hypothesized to anticipate the postnatal environment and prepare itself metabolically for either an energy rich or an energy deficient scenario (2). Dr. Lee showed results where adipose tissue volume differed between children at 4 years of age who were born small for gestational age vs. those appropriate for gestational age and that there is a preferential catch up of body fat accumulation in the former group. Children born preterm also show decreased insulin sensitivity at 4-10 years of age (3).

1. Barker DJ. The development origins of adult disease. J Am Coll Nutr. 2004;23:588S-595S.
2. Gluckman PD, Hanson MA, Mitchell MD. Developmental origins of health and disease: reducing the burden of chronic disease in the next generation. Genome Med. 2010; 2:14. doi: 10.1186/gm135.
3. Hofman PL, Regan F, Jackson WE, Jefferies C, Knight DB, Robinson EM, Cutfield WS. Premature birth and later insulin resistance. N Engl J Med. 2004;351:2179-2186.

Claude Sirlin (University of California San Diego, United States) further emphasized that stiffness is a continuous variable whose value currently carries no clinical meaning by itself unless it is linked to a categorical variable of histological severity. Furthermore, stiffness from imaging has a greater dynamic range than histological fibrosis stage, and it is possible that stiffness may provide greater prognostic value than biopsy. Dr. Sirlin explained that stiffness is not always or entirely due to fibrosis. Edema, cellular swelling, inflammation, biliary pressure, portal pressure, sinusoidal pressure, and myofibroblast contraction can also lead to increased stiffness. Thus, stiffness is most appropriately regarded as an aggregate marker of liver injury and damage rather than fibrosis per se. MRE is challenging in obese patients, where existing MRE mechanical drivers may not yield sufficient wave propagation through the subcutaneous fat layer of an obese subject. A recent study showed a 15% failure rate in MRE in patients with BMI greater than 30 kg/m^2 (1).

1. Wagner M, Corcuera-Solano I, Lo G. Technical failure of MR elastography examinations of the liver: experience from a large single-center study. Radiology. 2017;284:401-412.

Meng Yin (Mayo Clinic, United States) updated on 2D and 3D MRE principles, including single-frequency and multi-frequency approaches (1-3). Elastography can be divided into quasi-static strain imaging and dynamic shear wave stiffness imaging. In the former, both ultrasound and MR-based methods have been developed. Extrinsic vibration using a mechanical driver represents current MRE approaches, while intrinsic vibration, such as acoustic radiation force imaging are ultrasound based. MRE represents a technique that can serve in the early stages of disease diagnosis and stratification, with application to liver, pancreas, kidney, heart, and muscle (4-8).

Tissues have complex and intricate structures and their mechanical properties depend on their microstructure and dynamic environment. Disease states lead to changes in tissue composition and matrix deformation in the environment. While liver MRE is widely accepted, one of the major gaps in clinical practice is the lack of safe and accurate methods to distinguish NASH patients who are at risk of progression to advanced disease from those who have simple steatosis and are less likely to develop liver-related complications. Dr. Yin illustrated recently developed approaches to enhance patient comfort during MRE exams, including flexible and contoured mechanical actuators that better conform to the body, and free-breathing techniques to better accommodate children and obese patients. Automated liver stiffness quantification algorithms that minimize inter-observer variation were also discussed (9). Dr. Yin concluded with emerging multi-parametric 3D MRE, where simultaneous measurement of storage modulus, loss modulus, damping ratio, volumetric strain, in addition to PDFF and global organ stiffness, are made. Collectively, these measures can potentially provide a global and multi-perspective comprehensive view on one's liver health (10-13).

1. Dittmann F, Reiter R, Guo J, et al. Tomoelastography of the prostate using multifrequency MR elastography and externally placed pressurized-air drivers. Magn Reson Med. 2018;79:1325-1333.
2. Dittman F, Hirsch S, Tzschatzsch H, Guo J, Braun J, Sack I. In vivo wideband multifrequency MR elastography of the human brain and liver. Magn Reson Med. 2016;76:1116-1126.
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Takeshi Yokoo (University of Texas Southwestern Medical Center, United States) compared liver elastography between MRI and ultrasound. He reviewed MRE as well as 1D transient elastography, point shear-wave elastography (pSWE), and 2D shear-wave elastography (2D SWE). The source of wave generation differs between the techniques (external piston – transient; acoustic radiation force – pSWE and 2D SWE; and pneumatic paddle – MRE), as does the direction of the traveling shear waves. On ultrasound, the wave speed is converted to the Young's modulus based on elastic model. In MRE the steady-state wavelength is converted to a complex shear modulus based on the viscoelastic model. The quantitative range of stiffness values detected by each modality varies with the Metavir fibrosis F1-F4 stages (1-3), and while all techniques are very good at differentiating higher stages, MRE has better accuracy than ultrasound in detecting lower fibrosis stages (4). Suboptimal wave penetration depth and poor localization of the liver are common failures elastography exams. Central obesity, ascites, small intercostal space, patient claustrophobia, hepatic steatosis and iron overload, also confound measurements. Ultrasound elastography is cheaper than MRE (5, 6), and remains a popular modality of choice for abdominal assessments (7, 8).

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Chris Boesch (University and Inselspital Bern, Switzerland) also reviewed the origins of IMCL and EMCL, differences in their anatomical location and function, and factors that govern the separation of these lipid pools in vivo, including orientation of the muscle fibers and bulk susceptibility effects (1). He underscored the importance of selecting the appropriate muscle compartment for IMCL and EMCL measurements based on the scientific question being addressed and emphasized the need to have appropriate control groups for meaningful comparison studies (2-6). Together, intermuscular adipose tissue (IMAT, the combination of IMCL and EMCL) often behaves in the lower extremity muscle like VAT in the abdomen. An increase in IMAT is positively associated with insulin resistance, poor muscle strength, and frailty (7).

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Hermien Kan (Leiden University Medical Center, The Netherlands) illustrated Duchenne Muscular Dystrophy, where the first clinical signs of muscle weakness appear between birth and 3 years of age. This is followed by the loss of ambulatory capability during the teenage years and leads to cardiac and respiratory dysfunction a few years later. Muscles exhibit a clear increase in fat infiltration over the years (1), both within and across fibers in upper and lower limbs. Additional examples were shown in limb girdle muscular dystrophy, distal myopathy, myotonic dystrophy, facioscapulohumeral dystrophy, and sporadic inclusion body myositis, where muscles are affected depending on the disease. In addition to fat infiltration, Dr. Kan described with histology slides changes in muscle fiber size (e.g., hypertrophy, hyperplasia, atrophy), along with edema, inflammation, fibrosis and necrosis, all of which are common symptoms in these diseases. For future work, there remains a need to overcome the time-consuming manual delineation of muscle groups. Furthermore, decreases in scan time are needed, as muscular dystrophy patients, many of whom are children, are not always comfortable lying supine.

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Dimitrios Karampinos and **Stefan Ruschke** (Technical University of Munich, Germany) and **Roland Krug** (University of California San Francisco) offered a review of current methodologies and applications in assessing BMAT, including T2-corrected MRS (1) and CSE-MRI (2, 3) and common endpoints, such as PDFF, FAC, relaxometry, diffusion and perfusion (4), quantitative susceptibility mapping (5), and magnetization transfer (6). BMAT is a challenging environment for imaging, and that it is effectively a mixture of water and fat (one of the few tissues where a natural fat fraction of 50% can be encountered), with the trabeculae acting to reduce the tissue's T2*. High-resolution MRI for assessing bone microstructure (7, 8) has been reported and visible differences in both morphology, PDFF, and T2* (a surrogate marker of trabecular bone density) between healthy, osteopenic, and osteoporotic subjects can be seen (9). BMAT has been linked to cancer and can potentially represent a therapeutic target in hematopoietic diseases such as multiple myeloma and myeloid leukemia. The newly established Bone Marrow Adiposity Society is a great resource to explore BMAT and its characteristics, function, and origin.

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