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Magnetic resonance imaging of obesity and metabolic disorders: Summary from the 2019 ISMRM Workshop

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WORKSHOP SUMMARY

Magnetic Resonance in Medicine

Magnetic resonance imaging of obesity and metabolic disorders: Summary from the 2019 ISMRM Workshop

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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, the 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 multidisciplinary 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 multiparametric 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 the scientific highlights from the workshop and identify future directions of work.

KEYWORDS

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

1 | INTRODUCTION

Research in obesity and metabolic disorders using MRI and MRS has increased significantly in recent years.[1] Magnetic resonance imaging/spectroscopy are used widely to achieve quantitative endpoints such as fat accumulation in subcutaneous adipose tissue (SAT) and visceral adipose tissue (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 (Supporting Information Table S1). Over 40 proffered abstracts were presented, focusing on population findings, developments in the proton density fat fraction (PDFF) imaging biomarker, methodological and technical advances in pulse sequences and machine learning, liver physiology, and brown adipose tissue (BAT). This article summarizes the scientific highlights and insights toward future directions of research from the workshop's invited lectures (see Supporting Information Table S2 for the list of speakers). This overview groups each speaker's contributions into several themes, including precision medicine, big data, and "imaging-omics" in large population studies; nutrition, metabolism, diabetes, and insulin resistance in Asian and Latino cohorts; advances in chemical shift–encoded (CSE) water–fat imaging; BAT imaging; fetal and placenta imaging; liver elastography; and muscle and bone marrow imaging. The reader is referred to online complementary Supporting Information for additional excerpts from speakers.

1.1 | Prelude

Fritz Schick, Christiani Jeyakumar Henry, and Jürgen Machann provided outlines of the obesity and type 2 diabetes (T2D) 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 5 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 show that more than 1.4 billion adults worldwide were overweight (body mass index [BMI] $\geq$ 25 kg/m^2) and obese, whereas 1.2 billion were undernourished, marking the first time in history of this imbalance.

In the context of energy expenditure, the concept of undernutrition and overnutrition 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 $\pm$ 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/MRS-based body composition phenotyping and ectopic fat distribution in subjects with increased risk for T2D. Conventional T_1-weighted 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, in which men and women exhibit dissimilar patterns in SAT and VAT despite similar age and BMI, as well as differential findings of fatty acid composition (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 over 30 kg/m^2, but exhibits adequate insulin sensitivity. In contrast to metabolic healthy obesity, there is also a metabolically unhealthy obesity phenotype, in which subjects have similar BMI but low insulin sensitivity and excess VAT.

1.2 | 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, lipidomics), environment and microbiome data,[12-14] and imaging data are being integrated 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 2 Singapore studies, in which 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 4 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 multicenter trials is critical, so is within-scanner repeatability. Likewise, standardized protocols and postprocessing 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 whom will receive brain, cardiac, and whole-body MRI exams), were shown. To date, over 40,000 participants have been scanned,[18] encompassing 6 distinct propensity clusters that show different risks for metabolic disease depending on their whole-body composition analysis profile.[19]

1.3 | 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] Furthermore, although the general inverse trend between percent body fat and insulin sensitivity is maintained (highest slope in Malays, followed by Chinese, and lowest in South Asians), body fat partitioning itself is not adequate in explaining the differences in insulin sensitivity between the three groups.[21] Differences also exist in abdominal and visceral adiposity and skeletal muscle intramyocellular lipids (IMCL) among Chinese, Malay, and South Asian cohorts. Interestingly, present data raise the possibility that the Chinese may exhibit a phenotype of mild lipodystrophy and limited adipose tissue expansibility (i.e., hypertrophy [increase in cell size]),[22,23] which can predispose them to insulin resistance. Human genetic studies to date suggest that most of the pathways leading to T2D are shared among ethnic groups, and that while the pathophysiology of T2D can be heterogenous, there remains no clear phenotype of T2D that is truly unique to Asia.[24]

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] According to 2018 statistics,[26] the prevalence of childhood obesity in the United States is approximately 18%, as defined by a BMI greater than 95th percentile for age and gender. Approximately 6% have severe obesity, as defined by a BMI greater than 120% of 95th percentile. Although the prevalence does not significantly differ between boys and girls, there are clear disparities across race/ethnicity. Native American, Latino, and African American children are disproportionately affected by obesity in comparison to non-Hispanic whites, and girls experience a disproportionate burden compared with boys when it comes to T2D risk.[27] Gender differences in the incidence of T2D may, in part, be associated with higher levels of body adiposity among minority girls. Ryder and colleagues have 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 the age of 12 years.[28] For a given BMI and age, non-Hispanic whites and African Americans exhibit similar SAT volumes, whereas the latter have smaller amounts of VAT.[29] Latino youths tend to exhibit the most amount of VAT, leading to the TOFI (thin-outside-fat-inside) phenotype,[30,31] similar to the metabolically unhealthy obesity phenotype described by Dr. Machann. Lifestyle intervention was also discussed, and differences between boys and girls in whom adipose tissue volumes are lost and gained were shown. Boys in general lose more VAT and gain more lean mass than girls.[32-34] 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 quantitative imaging, as tremendous heterogeneities exist in response to lifestyle intervention.[35]

1.4 | Advances in water–fat MRI

Holden Wu, Pernilla Peterson, Stefan Ruschke, and Michael Middleton provided updates on methodological

advances in chemical shift–encoded (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.[36] CSE MRI methods fundamentally rely on the resonance frequency difference between water and fat protons and continued research from the original 2-point method has led to modern implementations with multi-echo acquisitions and advanced signal modeling.[37,38] Chemical shift–encoded MRI is an established mainstream method for fat quantification, in which voxel-wise PDFF is estimated by acquiring and reconstructing multi-echo spoiled gradient-echo data using low flip angles to avoid T_1 bias between water and fat signals, multipeak fat spectral modeling, and R_2^* correction. Additionally, B_0 field map estimation and phase-error correction due to concomitant field gradients need to be considered.[39,40] Although multi-echo CSE MRI increases scan time and often requires breath-holds in body applications, advanced techniques such as parallel imaging,[41,42] compressed sensing,[43,44] MR fingerprinting,[45] and deep/machine learning[46] have improved CSE-MRI scan-time efficiency, making them applicable in children and in patients who cannot hold their breath. Emerging respiratory-navigated and motion-robust sequences[47,48] and non-Cartesian "stack-of-radial" techniques[49,50] 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-individual or interindividual 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.[51-53] Preliminary results from oil phantoms, in which gas chromatography was used as reference, and more recently in vivo data, are promising.[54-56] Dr. Peterson showed that the classic CSE water–fat signal model can be logically expanded to include 3 descriptive features of FAC: the number of double bonds, the number of methylene-interrupted double bonds, and the chain length, from which unsaturation can be computed. Unlike PDFF estimation that typically uses 6 echoes, FAC estimation uses longer echo trains (i.e., 12-32 echoes), and the selection of echo spacing requires careful consideration to optimize noise performance. Although the well-known T_1 bias of water and fat affects PDFF quantification, interestingly, it appears less important in FAC estimation. However, differences in the T_2 of water and fat should be considered, especially in water–fat mixtures.[57] The FAC estimation may be limited to pure adipose tissue and other areas of intermediate to high-fat fraction, whereas robust performance in water–fat mixtures of low PDFFs is difficult to achieve.

1.5 | Brown/beige/brite adipose tissue

Barbara Cannon, Shigeki Sugii, and Rosa Tamara Branca spoke on BAT, beige, and brite adipose tissue.[58] It has been over 50 years since the physiological function of BAT, which produces heat through activation of the sympathetic nervous system by the hypothalamus, was realized. The tissue uses its dense mitochondrial population and a unique uncoupling protein, termed UCP1. The role of BAT in adaptive nonshivering thermogenesis has also gained general acceptance across multiple disciplines.[59] The trend of assessing BAT in *diet*-induced, rather than *cold*-induced, thermogenesis has also emerged in popularity.[60,61] 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[62] and diffuse reflectance spectroscopy[63,64] to capture cellular "browning" ex vivo and in vivo have been undertaken, exploiting differences in cell surface markers.[64-67]

Human BAT research has, however, been elevated to a "panacea"-like status in recent years, in which the potential of BAT to counteract metabolic syndrome and obesity is sought. Brown adipose tissue in the supraclavicular region of humans is most like classical BAT found in mice, rather than inguinal beige adipocytes. Supraclavicular BAT depots become more white adipose tissue (WAT)–like with age, high-fat diet, and thermoneutrality.[68] Although the CSE-based PDFF approach remains popular in BAT characterization,[69-72] it nonetheless remains not specific enough to differentiate BAT and WAT in adult humans. Brown adipose tissue 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.[72] Additionally, glucose uptake in BAT reflects the tissue's insulin sensitivity and blood flow rather than cold-induced or diet-induced thermogenesis.[73,74] 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. Magnetic resonance–based thermometry for BAT has emerged as an active area of research. Water exhibits a proton resonance frequency shift of −0.01 ppm/°C. However, at 3 T, B_0 inhomogeneity and motion can 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.[75] The precision of proton

thermometry is also limited to 1-2ºC. Because 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).[76]

1.6 | 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.[77] Fetal growth restrictions, preeclampsia, and diabetes were discussed as examples of placental pathology. For fetal growth restriction, in which birth weight is in the lowest 10th percentile, there exists a 10-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.[78,79] 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 affects fetal organ growth, resulting in reduced brain, kidney, placenta, and total fetal volume.[80] The Dutch famine cohort from World War II was used as an example, in which an association exists between maternal starvation during gestation and increased risk for cardiovascular and metabolic diseases in the offspring.[81] Exposure to famine during the first half of pregnancy resulted in higher obesity rates compared with exposure during the last trimester of pregnancy.[82]

For preeclampsia, a condition in which the pregnant woman experiences markedly high blood pressure, abnormal immunological response, proteinuria, and reduced blood flow in uterine arteries, can be observed, in addition to fetal growth restriction.[83,84] Finally, 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.[85]

Magnetic resonance imaging methods to assess placental perfusion were reviewed.[86-88] 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.[89] 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,[90] additional efforts are needed for widespread adoption.

To further exemplify the Barker hypothesis, the Growing Up in Singapore Toward Healthy Outcomes study,[13,91] 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 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, Indian men had the highest amounts of abdominal SAT and IMCL compared with 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 Growing Up in Singapore Toward Healthy Outcomes and Singapore Adult Metabolism 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 prepregnancy obesity, maternal diet, gestational weight gain, and gestational diabetes mellitus, age at weaning and diet, and physical activity.[92] The challenge is to translate such findings into effective public health policies and strategies, embedding effective intervention components within education and healthcare systems to achieve long-term sustainable improvements.

1.7 | Liver elastography

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.[93-96] It is estimated that 5%-10% of adults worldwide have both liver disease and obesity. The liver can be affected 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.[97,98] As fibrosis worsens, the liver becomes stiffer, and the difference in stiffness becomes more apparent and separated in later stages.[99] Liver stiffness measurements by magnetic resonance elastography is an established quantitative imaging biomarker of fibrosis. 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.[100] 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. Magnetic resonance elastography can therefore identify patients who can be managed without biopsy. Magnetic resonance elastography currently plays a critical role in cohort screening, selection, enrichment, stratification, response prediction, treatment monitoring, and response detection in liver clinical trials, and provides complementary information in epidemiology and radiomics analysis.[101]

1.8 | Skeletal muscle adipose tissue

Chris Boesch reviewed 1H MRS of intramuscular, extramyocellular, and intramyocellular lipids in skeletal muscles and the metabolic aspects of IMCL as an essential part of metabolism in health and disease.[102,103] The number, size, location, and composition of lipid droplets in IMCL play an important role in determining an individual's insulin sensitivity.[104-107] Furthermore, diet and exercise can affect IMCL levels individually. The differences in IMCL between obese and diabetic populations versus trained athletes[108,109] 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 use during intense exercise. Quantitative MRS remains the only approach to measure IMCL noninvasively, whereas extramyocellular lipids 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 extramyocellular lipid signal), fasciae and blood vessels, and control over leg motion and rotation are critical in IMCL assessments.[110] Additionally, variable spectral data fitting constraints (e.g., peak line widths, parts-per-million chemical-shift ranges) used in analysis software can affect metabolite quantification and lead to systematic bias and errors. A consensus statement for best practices of measuring skeletal muscle IMCL and extramyocellular lipids will appear imminently in the *NMR in Biomedicine* journal.

Hermien Kan discussed in-depth quantitative fat imaging applications in neuromuscular diseases. Unlike muscle biopsy, qualitative scoring, and laboratory muscle function tests, quantitative MRI/MRS offers an objective and less subject-motivation-dependent approach to assess muscle groups. It is therefore suitable in providing outcome measures for clinical trials to follow disease progression and to characterize disease pathophysiology. Muscle functional loads, muscle cross-sectional area, fat content, T_2 relaxometry, diffusion, and metabolism are commonly used imaging biomarkers in research studies of neuromuscular diseases.[111-122] Dr. Kan specifically discussed the concept of muscle contractile cross-sectional area, defined as the contractile proportion and the noncontractile proportion of the muscle due to the fat replacement. The amount of force that can be generated per contractile cross-sectional area is often lower in neuromuscular disease.[123,124] Standardized imaging landmarks are needed for longitudinal multisite neuromuscular disease imaging 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.[125-127]

1.9 | 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. The 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.[128-130] Before 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.

The BMAT cells originate from the same mesenchymal stem cells as osteoblasts. Therefore, BMAT plays an important role in growth, development, and healthy aging.[131,132] Although 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.[133,134] The BMAT and its high PDFF content have also been implicated in osteoporosis (deterioration of the trabecular bone matrix), spondyloarthritis,[135] lower back pain, obesity, diabetes and (paradoxically) anorexia nervosa,[136-138] and skeletal health (i.e., fragility, fracture prediction). Interventions that increase bone mass have been shown to coincide with a decrease in BMAT. The BMAT is positively associated with vertebral fracture in men[139] and is negatively associated with failure load and bone mineral density.[140] Furthermore, the FAC of BMAT, specifically unsaturation, decreases with osteoporosis[141] and is negatively associated with the prevalence of fractures.[142]

TABLE 1 Abbreviated list of suggested directions of future research discussed during the concluding session of the workshop

- Further validation of joint R_2^* and proton density fat fraction (PDFF) estimation in measuring iron and fat content in brown adipose tissue (BAT), 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.
- Magnetic resonance elastography (MRE) is challenging in obese patients, in whom existing mechanical drivers may not yield sufficient wave propagation through the abdomen. Free-breathing MRE is desired in obese patients, and especially in children.
- Further validation towards MRI methods for characterizing hepatic inflammation, nonalcoholic steatohepatitis, and fibrosis are needed to complement existing PDFF and MRE techniques.
- Macrovesicular versus microvesicular organ steatosis cannot be differentiated with existing MRI/MRS approaches, while sensitivity toward detection of very small PDFF changes remains limited. This need will be particularly important in BAT imaging.
- Pancreas imaging needs further attention, given its role in diabetes and insulin regulation.
- Novel imaging of adipocyte inflammation and macrophage infiltration needs further development.
- Epicardial/paracardial, renal, and perivascular adipose tissue characterization are encouraged.
- Longitudinal studies in human BAT 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 BAT physiology and its therapeutic role in metabolic disorders and obesity remains largely unanswered. "Big data and imaging-omics" studies are encouraged.
- There is a lack of standardized MR acquisitions, data-processing pipelines, and reporting templates for both animal and human BAT assessment.
- New methods need to be validated by independent groups and be made more available across the community, such as MR-based thermometry in adipose tissue, and fatty acid composition estimation.
- MRI of the placenta and fetal growth are needed to longitudinally assess the effects of extended bed rest, maternal diet, and drug therapies.
- Motion remains the biggest hindrance in MRI of the 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.

Notable differential results of BMAT in subjects with glucocorticoid-induced osteoporosis,[69] in postmenopausal women with and without diabetes,[143] and in patients with lower back pain as characterized by Modic changes, and Pfirrman grading[144] have been reported.

2 | CONCLUSIONS

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/MRS techniques to investigate obesity and metabolic dysfunctions with the 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. The workshop organizers would like to also recognize and congratulate the following travel stipend recipients: Timothy Bray, Yeshe Kway, Sara Saunders, Chuanli Cheng, Hao Peng, Manuel Schneider, Chileka Chiyanika, Naomi Sakai, Lena Trinh, Daniela Franz, Aashley Sardjoe Mishre, and Dominik Weidlich.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

TABLE S1 List of countries of origin of the workshop attendees

TABLE S2 List of workshop speakers and their professions

Supporting Text Additional excerpts from speakers

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