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Diagnostic Imaging in the Management of Patients with Metabolic Syndrome

Seo Rin Kim¹ and Lilach O. Lerman¹

¹Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, USA

Abstract

The metabolic syndrome (MetS) is the constellation of metabolic risk factors that might foster development of type-2 diabetes and cardiovascular disease. Abdominal obesity and insulin resistance play a prominent role among all metabolic traits of the MetS. Because intervention including weight loss can reduce these morbidity and mortality in MetS, early detection of the severity and complications of MetS could be useful. Recent advances in imaging modalities have provided significant insight into the development and progression of abdominal obesity and insulin resistance, as well as target organ injuries. The purpose of this review is to summarize advances in diagnostic imaging modalities in MetS that can be applied for evaluating each components and target organs. This may help in early detection, monitoring target organ injury, and in turn developing novel therapeutic target to alleviate and avert them.

Keywords

metabolic syndrome; diagnostic imaging; abdominal obesity; insulin resistance; target organ injury; computed tomography; magnetic resonance imaging

INTRODUCTION

The metabolic syndrome (MetS) is the constellation of metabolic risk factors that might foster development of type-2 diabetes and cardiovascular disease. According to the NCEP-ATPIII 2005, 3 or more of the following five traits define MetS: 1. Abdominal obesity by waist circumference; 2. Elevated triglyceride levels or drug treatment for elevated triglycerides; 3. Low levels of high-density lipoproteins or drug treatment for low high-density lipoproteins cholesterol; 4. Elevated blood pressure (BP) or drug treatment for elevated BP; and 5. Elevated fasting glucose or drug treatment for elevated blood glucose. These traits might be inter-related, therefore whether MetS merely reflects the additive effects of the individual traits or stratifies distinct risk for cardiovascular disease remains controversial.

Corresponding Author: Lilach O. Lerman, MD, PhD, Division of Nephrology and Hypertension, Mayo Clinic, 200 First St SW, Rochester, MN 55905, Phone: 1-507-206-9376, Fax: 1-507-206-9316, Lerman.Lilach@Mayo.edu.

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Abdominal obesity and insulin resistance play a particularly prominent role among all metabolic traits of the MetS.¹ Duration and severity of obesity are positively associated with incident MetS, as well as increased risk for other MetS components, suggesting that metabolically healthy obesity is a transient state in the pathway to cardiometabolic disease.² Obesity leads to increased morbidity including cardiovascular disease and type-2 diabetes,^{3, 4} and is significantly correlated with increased mortality.^{5, 6} Interventions and life style modifications have been shown to reduce morbidity and mortality in MetS.^{7, 8} Obesity, especially abdominal obesity, can also instigate or worsen insulin resistance in MetS. Excessive fatty acids in MetS increase lipid accumulation, inhibit insulin-mediated glucose uptake, and thereby reduce insulin sensitivity in several organs including adipose tissue, skeletal muscle, and liver.⁹ Additionally, insulin resistance affects sodium reabsorption, sympathetic nervous system activation, and nitric oxide (NO) bioavailability, and is thus implicated in target organ injury.¹⁰ Therefore, the ability to detect and monitor development and progression of abdominal obesity and insulin resistance and their consequences in target organs is important to stratify the risk and apply effective preventive and therapeutic intervention in individuals with MetS.

Recent advances in imaging modalities have provided significant insight into understanding the pathogenesis of two major components of MetS, abdominal obesity and insulin resistance. In addition, diagnostic imaging is essential for early detection of target organ injury and characterization of complications of MetS.

The purpose of this review is to summarize advances in diagnostic imaging modalities in MetS that can be applied for evaluating the features of MetS and its target organs. Timely use of imaging modalities may help in the diagnosis, prediction of target organ injuries, and development of novel therapeutic targets to alleviate and avert them.

EVALUATING COMPONENTS OF METABOLIC SYNDROME

Abdominal obesity

Abdominal obesity is one of the most central factors for the development of MetS.¹¹ Abdominal obesity is often clinically expressed as waist circumferences at the umbilical level,¹² yet this measure cannot discriminate between visceral abdominal (VAT) and subcutaneous adipose tissue (SAT). Visceral obesity is known as a major cause of insulin resistance, and is closely associated with the other four features of MetS through an imbalance between adipokines and insulin.¹² Recent studies have shown that VAT is strongly associated with carotid intima-media thickness (CIMT) and contributes to early development of atherosclerosis.^{13, 14} Ultrasonography (US), computed tomography (CT), and magnetic resonance (MR) imaging have been shown to be useful to assess the VAT (Figure 1). In particular, a previous study using CT to assess MetS reported that accumulation of VAT is the best predictor for MetS in women, and a good predictor for MetS in men.¹⁵

The imaging methods used for quantification of adipose tissue include dual-energy x-ray absorptiometry (DXA). DXA measures the attenuation of two X-ray photon energies to distinguish fat, lean, and bone mineral content measures with low radiation exposure

(~1mSv/scan¹⁶), short scanning time (5–13 minutes), high precision, and low cost.¹⁷ DXA estimation of fat tissue may be somewhat influenced by the degree of hydration or edema.¹⁸ Although it does not discriminate between VAT and SAT, recent studies have developed algorithms for segmenting fat within the torso.^{19, 20} DXA-measured VAT shows a good correlation with CT-measured VAT volume ($r^2=0.89-0.96$ for females and $0.84-0.95$ for males)^{19, 20} and may provide clinically useful information to determine cardiometabolic risk.²¹ However, intra- and inter-instrument reliability of DXA remains imperfect.²²

US has been used to measure VAT and SAT using reflection of sound waves from tissue.²³ While it is safe, noninvasive, applicable, fast, and relatively inexpensive, US requires experienced operators and considerable skill, and lacks standardized and reproducible methods for objective assessment of VAT.²⁴ To measure VAT, intra-abdominal thickness²⁵ and abdominal fat index (ratio of the thicknesses of the pre-peritoneal and subcutaneous abdominal fat)²⁶ have been used. US VAT measurements have been validated against MRI or CT in obese adults and elderly, showing good correlations ($r=0.81-0.82$),^{25, 27} whereas SAT measures showed weaker correlations ($r=0.54-0.68$).^{25, 28} VAT indices measured by US were also correlated positively with serum triglyceride levels and inversely with high-density lipoprotein.²⁹ These results suggest that US may be useful in evaluating intra-abdominal adipose tissue.

CT is considered the reference standard for assessing SAT and VAT (Figure 2A). In CT, x-ray attenuation of tissue is expressed in Hounsfield units (HU), where 0 is assigned to water and -1000 is assigned to air. The values of adipose tissue density conventionally vary from -30 to -190 HU. CT can accurately assess VAT with excellent resolution of adipose tissue and at a relatively high speed.³⁰ To curtail ionizing radiation, VAT can be measured at L4 level in a single slice, which requires only 1 mSV, or 10% of the radiation dose in the standard abdominal-pelvis CT,³¹ and is significantly correlated with the total abdominal VAT measured on a multislice CT scan ($r=0.94$).³² A recent study suggests a single slice CT scan in late expiration for accurate measurement of VAT. The downward movement of the diaphragm during inspiration results in the compression of the abdominal cavity and extension of visceral fat, which cause overestimation of VAT and inclusion of the lower part of the kidney in the slice.³² The importance of CT-based adiposity indices was confirmed in the recent study, which showed a significant correlation between VAT and cardiovascular disease even after adjustment for clinical risk factors and body mass index (BMI), whereas SAT showed no such correlation.³³ Overall, CT shows excellent reproducibility and repeatability of abdominal SAT and VAT measurement.³⁴

Several MR methods can also be used for imaging abdominal obesity, including relaxation-based (T1-weighted fast spin-echo sequence), phase sensitive (chemical shift), and fat selective MRI.^{11, 35} MR offers the advantage of no radiation exposure, but has been used less frequently due to higher cost. Nevertheless, fat assessment using MR is useful for simultaneous evaluation of other cardiovascular risk factors in MetS. Fat and lean tissues have different longitudinal and transverse relaxation times (T1 and T2) in MRI. Fat has the lowest T1 (approximately 300 msec), but comparable T2 to other parenchyma organs (about 1000 msec for most water-containing tissues).^{11, 36} Therefore, T1-weighted fast spin-echo sequence has been applied for quantification of fat, which exhibits high signal intensity.³⁷

This sequence provides a fast and reliable quantification of total body adipose tissue and the distribution of SAT and VAT.³⁷ In phase-sensitive MRI, a frequency difference between water protons and methylene protons (the dominant fat peak) renders phase shift in-phase or opposed phase.¹¹ Fat selective MRI can be performed using suppression of the water signal by a frequency selective prepulse, by frequency selective excitation of the fat signal, or by spectral spatial excitation.¹¹ These images allow discriminations of fat from other tissues. VAT and SAT measures in MR significantly correlate with those of CT.³⁸ In addition, MRI-measured fat volumes showed an associations with various anthropometric and biochemical parameters.³⁹ Given the little associated risk, MRI can also be used for longitudinal monitoring of changes in abdominal compartments during weight loss.⁴⁰

Insulin resistance

Insulin resistance is a key feature in MetS. Skeletal muscle is a primary site for lipid and glucose metabolism responding to insulin, and plays an important role in the pathogenesis of insulin resistance. Excessive fatty acids in MetS increase lipid accumulation, inhibit insulin-mediated glucose uptake, and thereby reduce insulin sensitivity in skeletal muscle,⁹ often preceding hyperglycemia and type-2 diabetes.⁴¹ Therefore, imaging studies in skeletal muscle could be valuable for early detection of insulin resistance in MetS.

In muscle biopsy, intramyocellular lipid (IMCL) contents are inversely correlated with insulin-stimulated glucose uptake.^{42, 43} ¹H-MR spectroscopy (MRS) quantification of IMCL has shown significant correlations with biochemical and electron microscopic measurements of muscle biopsy samples.⁴⁴ ¹H-MRS has shown that IMCL is strongly correlated with insulin sensitivity in childhood and is higher in obese adolescents than those of normal body weight.⁴⁵ Thus, IMCL accumulation and insulin resistance might be related to the natural course of obesity rather than aging.⁴⁵ In healthy adults, IMCL assessed noninvasively by localized ¹H-MRS is a good indicator of whole body insulin sensitivity.⁴⁶ IMCL quantifications using ¹H-MRS distinguish between obese and normal-weight subjects and correlate with body composition and insulin resistance obtained by an oral glucose tolerance test.⁴⁷ However, it is important to note that IMCL is not a direct marker of insulin sensitivity, but may reflect accumulation from increased lipolysis, excess dietary fat, or impaired mitochondrial lipid oxidation.⁴⁸

Several studies utilized positron emission tomography (PET) for assessing insulin resistance. ¹⁸F-fluorodeoxyglucose (FDG) PET imaging demonstrated insulin-stimulated FDG-uptake in skeletal muscle and whole body glucose-uptake.⁴⁹ ¹⁸F-FDG PET imaging in skeletal muscle also showed impaired glucose transport in type-2 diabetes and obesity, and impairment of glucose phosphorylation in type-2 diabetes.⁵⁰ Because these PET studies used compartmental modeling originally designed for brain studies⁵¹, dynamic PET imaging has been subsequently developed to acquire imaging following sequential injections of radioactive ligands to track glucose metabolism in skeletal muscle.^{52, 53} Dynamic triple-tracer PET using ¹⁵O-H₂O, ¹¹C-3-O-methylglucose [3-OMG], and ¹⁸F-FDG quantitatively determined glucose metabolism including delivery, transport, and phosphorylation under insulin-stimulated conditions in lean and healthy volunteers.⁵⁴ Dynamic triple-tracer PET demonstrated insulin resistance in patients with type-2 diabetes, demonstrating impairments

in glucose transport and phosphorylation in skeletal muscle.⁵⁵ Another dynamic PET study discovered that glucose transport defects are strongly correlated with insulin resistance in normal-weight to obese subjects without diabetes, but also found heterogeneity between soleus and tibia anterior muscle in insulin action.⁵⁶ Recently, a PET/MR imaging has been proposed for assessing tissue-specific insulin-mediated ¹⁸F-FDG influx rates, tissue depots, and whole-body insulin sensitivity, which enable individualizing comprehensive metabolic phenotypes in subjects.⁵⁷ However, although quantitative, the use of PET for this purpose is hampered by its limited availability.

EVALUATING TARGET ORGAN DAMAGE

Heart

MetS is associated with a spectrum of cardiovascular complications. In MetS, activated renin-angiotensin-aldosterone and sympathetic nervous systems can lead to elevated heart rates, renal sodium retention, circulating blood volume, ventricular end-diastolic volume, and cardiac output.⁵⁸ Elevated heart rate impairs left ventricle (LV) filling and relaxation, increases myocardial oxygen consumption, reduces coronary perfusion, and deteriorates LV function.⁵⁹ Increased cardiac output gives rise to LV dilation, higher wall stress, and finally compensatory hypertrophy. The thicker heart is stiffer and may have relaxation abnormalities. This diastolic dysfunction induces left atrium enlargement, leading to atrial arrhythmias.⁶⁰ Consequently, diastolic dysfunction in MetS is an early feature and independent predictor of mortality.⁶¹ Indeed, animal studies have demonstrated that heart rate reduction and mineralocorticoid receptor antagonism improve MetS-related LV diastolic dysfunction.^{62, 63} Several studies have linked MetS to LVH regardless of gender.^{64, 65} While hypertension was most strongly related to LVH in both men and women, abdominal obesity and hyperinsulinemia were related to LVH only in women.⁶⁴ This may imply a gender differences in the mechanisms for development of LVH. Obesity affects LV end-diastolic volume in proportion to BMI, but affects LV mass more than volume.⁶⁶ In addition, recent findings have established that most obese subjects develop concentric rather than eccentric LVH.^{58, 66}

Echocardiography is commonly used for assessing cardiac structure and function because of its low cost, availability, temporal resolution, and feasibility of on-line analysis. The type and severity of LVH can be established by assessment of relative wall thickness and LV mass index using M-mode echocardiography, although its accuracy and reproducibility are often unsatisfactory.⁶⁷ Moreover, echocardiographic images of sufficient quality may be hard to obtain in severely obese subjects. Pulsed tissue Doppler imaging is the reference modality to investigate LV dysfunction in the MetS,⁶¹ in which regional LV function is quantified as the myocardial velocity of long-axis motion during systole(S'), early diastole(E'), and late diastole (A').⁶⁸ The calculation of the E/A ratio and the deceleration time of the E peak filling velocity (DT) are useful indices for diagnosis of diastolic dysfunction.⁶⁸ A recent study using tissue Doppler imaging suggested that diastolic dysfunction may develop in patients with MetS even in the absence of hypertension.⁶⁹ Strain and strain rate echocardiographic imaging is also sensitive and feasible for detection of subclinical myocardial functional abnormalities in MetS.⁷⁰ In strain rate imaging, speckle

tracking can assess LV myocardial shortening or strain. MetS is associated with impaired LV circumferential and longitudinal strain assessed by speckle tracking echocardiography,^{71, 72} although several studies have shown an impairment only in longitudinal LV strain in early MetS.^{73, 74} In addition, strain rate echocardiography imaging has shown impaired LA function⁷⁵ as well as impaired LV systolic and diastolic functions in patients with MetS, even in the presence of normal LV ejection fraction.⁷⁶

MRI provides valuable anatomic and functional imaging of the heart. Volume-independent structural measurement using cardiac MRI has been validated using human autopsy and animal specimens.⁶⁷ Cine imaging of the beating heart is important for functional cardiac MRI, and cine MR with steady-state free precession is widely accepted as the reference for assessment of ventricular function as well as mass,⁷⁷ and allows measurement and monitoring of LV mass index in proportion to weight reduction in MetS.⁷⁸ Three-dimensional (D) volume tracking of the mitral annulus with cine MR is useful for assessing diastolic dysfunction, yielding parameters that correlate with tissue Doppler-based variables.⁷⁹ Flow quantification using velocity sensitivity with cardiac MR is also a good technique to quantitatively assess diastolic dysfunction as well as valvular and congenital heart disease,⁸⁰ as validated with tissue Doppler imaging.⁸¹ Tagging can be used to measure myocardial strain in 3D.⁸² Tagged cardiac MR provides information on regional LV function, which includes the slice distance, cardiac deformation, and torsion (twist normalized by slice distance).⁸³ In hypertensive individuals, cardiac torsion is elevated, potentially as a compensatory mechanism to maintain an adequate stroke volume and cardiac output in the face of the progressively reduced LV volumes and myocardial shortening.⁸³ Severely obese adolescents also had increased LV torsional mechanics.⁸⁴ In obese animals, stress cardiac MR has shown supranormal values of LV radial strain and torsion early on diet, followed by later deficits⁸⁵ although obese subjects show lower trends of LV twist and torsion.⁸⁶ Therefore, torsion changes in MetS might depend on the stage of MetS and timing of scanning. Additionally, the complexity of quantitative analysis limits the use of tagging to the evaluation of the wall motion.⁸² Blood oxygen level-dependent (BOLD) MRI can assess myocardial oxygenation using paramagnetic deoxyhemoglobin as an endogenous marker (Figure 2B). Increased deoxyhemoglobin accelerates the magnetic spin of neighboring water molecules, and decreases signal intensity on apparent spin–spin relaxation time-weighted (T2*) images. The rate of magnetic spin dephasing, $R2^*(=1/T2^*)$, reflects the tissue content of deoxyhemoglobin.⁸⁷ Using BOLD-MRI in a swine MetS model we observed obesity-elicited myocardial hypoxia,⁸⁸ but further studies are needed to determine myocardial oxygenation in human subjects with MetS.

Coronary artery atherosclerosis—The association of obesity with atherosclerotic heart disease has been widely known.⁵⁸ MetS is associated with presence and severity of coronary atherosclerosis,⁸⁹ especially with vulnerable lipid-rich plaques.⁹⁰ Intravascular ultrasound (IVUS) and optical coherence tomography (OCT) can assess plaque burden, composition, morphology, and response to therapy, though their use is limited due to the need for invasive intravascular approach. A recent study in patients with MetS and type-2 diabetes has shown that IVUS is useful for diagnosing the degree of coronary artery stenosis,⁹¹ although this may not correlate with the extent of decreased perfusion and metabolism of the affected

myocardial territory. OCT utilize the back-reflection of near-infrared light from optical interfaces in tissue. Although it has a low penetration depth into tissue, OCT can assess plaque morphology with high resolution and thus be used for early diagnosis of coronary artery disease (CAD).⁹² Coronary plaques in MetS contain larger lipid assessed by 3-vessel OCT.⁹² In addition, rupture of the plaque in myocardial infarction is more frequent in patients with MetS and associated with lower cap thickness measured by OCT.⁹³

Using CT, coronary artery calcification (coronary calcium score) can serve as an indicator of the presence of atherosclerosis.⁹⁴ Coronary CT angiography is a noninvasive diagnostic tool that has high diagnostic performance both for detection and exclusion of CAD. Using coronary CT angiography, patients with MetS showed a higher prevalence, extent, and severity of CAD compared to those in patients without MetS.⁹⁵ However, coronary CT angiography has a limited value in assessing the hemodynamics of a given stenosis. Recently, different CT techniques including myocardial CT perfusion imaging have evolved for detecting myocardial ischemia.⁹⁶

Various sequences in cardiac MRI can be used in initial work-up and follow-up evaluation of CAD in MetS. First pass MRI perfusion imaging with exogenous contrast or arterial spin labeling (ASL) MRI evaluate myocardial perfusion and angiogenesis.⁹⁷ ASL-MRI uses the water spins of blood as an endogenous tracer. Perfusion is measured by acquiring a set of labeled (tagged) and non-labeled (control) images⁹⁸ without a need for exogenous contrast media, and thus is useful in patients at a high risk groups for adverse effects of contrast. Delayed contrast enhancement MRI can assess the transmural extent of viable myocardium.⁹⁹ After administration of gadolinium, scar tissue in the infarcted myocardium shows delayed enhancement.⁹⁹ Diffusion MRI assesses cardiac microscopic tissue structure, and diffusion tensor imaging (DTI) can be used for monitoring the process of LV remodeling after myocardial infarction.⁹⁷

Myocardial single-photon emission computed tomography (SPECT) with thallium-201 or technetium-99m labelled tracers is commonly used for evaluating myocardial perfusion, viability, and infarct size as well as ventricular function and intraventricular synchronism.^{100, 101} In patients with MetS, stress-induced reductions in myocardial perfusion measured by SPECT provide an accurate information for near-term risk stratification of CAD.¹⁰² PET can also assess myocardial perfusion, metabolism, and viability,¹⁰³ but is more expensive and less widely-available than SPECT. Semi-quantitative measurement using radionuclide cannot quantify myocardial perfusion in patients with multivessel CAD or non-obstructive atherosclerosis.¹⁰⁴ Contrarily, quantification of myocardial blood flow and flow reserve by PET may improve diagnosis and management of CAD.¹⁰⁴ Furthermore, hybrid imaging-tools, such as cardiac PET/CT and PET/MRI, provide particularly valuable co-registered anatomic information. They can also be helpful for evaluating myocardial infarction by quantifying both vulnerable plaque burden and myocardial scar tissue.¹⁰⁵ Fat-MR-based PET motion correction imaging has shown promise in evaluating vulnerable coronary plaque.¹⁰⁶ In addition to infarction and viability, PET/MR has potential in various cardiac applications including morphology, LV function, perfusion, and molecular imaging.¹⁰⁷

Heart-related fat—Peri- and intra-cardiac fat is elevated in MetS.¹⁰⁸ It is composed of myocardial and pericardial fat, subdivided into epicardial and paracardial fat according to deposition inside or outside pericardium.^{109, 110} For assessing myocardial fat in vivo, ¹H-MRS has proved to be a reliable method in humans.¹¹¹ While myocardial triglyceride content associates with LV diastolic dysfunction in diabetes,^{112, 113} it is not independently related to MetS, thus seems to have a more complex role.¹⁰⁸ Increased pericardial fat, on the other hand, is associated with the severity of structural and functional alterations of the heart in MetS,¹⁰⁸ including coronary artery calcification,¹¹⁴ LV diastolic function,¹⁰⁸ cardiac output, and stroke volume.¹¹⁵ It has been suggested that epicardial fat is a source of inflammatory mediators,¹¹⁶ and paracardial fat may exert a restrictive pressure on myocardial diastolic expansion.¹¹⁰

Pericardial fat can be assessed with echocardiography, CT, and MRI. Echocardiographic assessment measuring linear pericardial lipid thickness could be easy and effective, but 3D volumetric methods using CT and MRI offer higher reproducibility. In echocardiography, epicardial fat thickness appears as an echo-free space that can be measured on the free wall of the right ventricle from both parasternal long- and short-axis views.¹¹⁷ This method showed a strong correlation with MRI-based assessments.¹¹⁷ Additionally, epicardial adipose tissue measured by echocardiography was related to components of MetS.¹¹⁸ CT coronary angiogram studies after contrast administration show infiltrating epicardial fat as low density deposits.¹¹⁹ In MRI, electrocardiographically gated steady-state free-precession short axis cine sequences can measure pericardial fat as well as ventricular function. Manual contour tracing segmentation can be used for image-based volumetric quantification.¹¹⁵ For separating the different pericardial fat, fat-selective imaging is necessary.¹²⁰ These quantitative assessments of pericardial fat using MRI-based volumetric approach are feasible and reproducible, although somewhat laborious.

Peripheral vessels

Hyperglycemia and insulin resistance in MetS decrease production of NO and promote production of endothelin-1, which cause endothelial dysfunction.¹²¹ In addition to insulin, increased leptin and free fatty acids may increase sympathetic activity and its influence over the vascular system,¹²² and vascular smooth muscle cells have blunted vasodilatory responsiveness in MetS.¹²¹ Finally, MetS exacerbates arterial aging, stiffness, and atherosclerosis.¹²³

Vascular stiffness can be indexed as pulse wave velocity (PWV), defined as the velocity of the systolic pressure waves propagating along the vessels.¹²⁴ A higher PWV reflects lower vessel distensibility and higher vascular stiffness,¹²⁴ and is aggravated in MetS, regardless of age and sex.¹²⁵ Applanation tonometry and US are common clinical methods for estimating global PWV by measuring distance and the temporal shift between the carotid and femoral pressure waveforms.¹²⁶ However, they cannot assess the ascending aorta or provide regional information, and distance measurements used in the PWV calculations can be inaccurate.¹²⁶ Additionally, the vessels may have different mechanical and functional characteristics depending on position, aging, and disease.¹²⁷ Therefore, local or regional PWV has been analyzed by echo-tracking, US or MRI. MRI can inform simultaneously on cardiac function,

aortic geometry (diameter and arch length, widening, and curvature) and pliability (distensibility, compliance, elastic modulus, and stiffness index).¹²⁸ Velocity-encoding MRI provides the blood flow velocity by direct imaging of the thoracic and abdominal aorta. This direct measurement of the path length of pulse waves enables to evaluate local or regional PWV in specific vascular segments, as well as global PWV even in the presence of a tortuous vessel.¹²⁴ The distance between measurement sites can be manually or semiautomatically assessed, and the transit time for wave propagation can be automatically determined using time-flow or time-velocity curves.⁸⁰ A recent study demonstrated the association between the presence of MetS and increased carotid PWV using MRI for local PWV in middle-aged subjects.¹²⁹

Perivascular adipose tissue regulates vascular function through paracrine effects¹³⁰ and may directly boost vascular stiffness. Multidetector CT, MRI, and ¹H-MRS can quantify perivascular lipid volume.^{115, 131} Interestingly, periaortic adipose tissue measured by ¹H-MRS is not related to insulin resistance in MetS.¹¹⁵ Similarly, in obese children no association was found between CIMT and insulin resistance,¹³² although CIMT was correlated with other components of MetS, especially increased BP.¹³²

MetS is associated with newly developed carotid plaque, and thus with progression of early atherosclerosis.¹³³ Chronic inflammation in MetS may precipitate atherosclerosis and accelerate acute thrombotic complications.¹³⁴ Therefore, identifying the plaque characteristics using imaging modalities may help direct interventions in atherosclerosis with MetS. CIMT assessed using high resolution B-mode US detects increased CIMT>1mm,¹³⁵ but cannot provide information about the biology of the plaque. Using microbubbles filled with inert gas, contrast-enhanced US identifies microvasculature within the carotid plaque that are associated with plaque rupture,¹³⁶ and IVUS and OCT also allow analyzing the carotid plaque.^{137, 138} CT enables detecting calcium in the arterial wall and differentiating lipid-rich from fibrous plaque, but is limited by ionizing radiation.¹³⁶ MRI might be the most promising method for studying atherothrombotic disease in humans in vivo.¹³⁹ MRI provides information on the plaque volume and composition including lipid core, fibrosis, calcification, and intraplaque hemorrhage deposits.¹³⁹ Vascular inflammation present in some atherosclerotic plaques can be evaluated by ¹⁸F-FDG-PET.¹⁴⁰ High FDG uptake can identify the plaque rich in macrophages, which indicate vulnerability in carotid atherosclerosis. MetS is associated with increased FDG uptake, suggesting increased inflammation.¹⁴¹

Kidney

MetS increases the risk of renal insufficiency and microalbuminuria.¹⁴² Potential mechanisms in kidney of MetS include insulin resistance and adipose tissue expansion. Adipose tissue expansion elicits oxidative stress, chronic inflammation, and exacerbation of insulin resistance, which lead to endothelial dysfunction, activation of renin-angiotensin-aldosterone system (RAAS), and hypertension.¹⁴³ Elevated aldosterone levels promote sodium reabsorption, and in turn, induce the rise in glomerular filtration rate (GFR) through tubuloglomerular feedback.¹⁴³ Thus, early MetS induces renal hyperperfusion and glomerular hyperfiltration. However, sustained hyperfiltration burdens glomerular

capillaries, and microvascular loss is eventually incurred.¹⁴³ A recent systematic review of literature has also described the association of MetS with kidney stone disease.¹⁴⁴ Kidney stones in obese patients are generally composed of calcium oxalate and uric acid.¹⁴⁵ Insulin resistance decreases renal ammoniogenesis and activity of Na⁺/H⁺ exchange channel, and finally causes inappropriate acid urine, which plays an important role in stone formation.¹⁴⁶

Renal US parameters include renal length, renal cortical echogenicity, or distinctness of the corticomedullary boundary.¹⁴⁷ Doppler US is a useful non-invasive imaging to measure pulsatility and resistive indices for detecting alterations in renal vascular resistance,¹⁴⁸ which is increased in subjects with early MetS,¹⁴⁸ indicating renal vasoconstriction and microvascular remodeling.¹⁴³ Renal imaging using radionuclide scintigraphy is infrequently utilized due to the need for an exogenous radioactive tracer, low spatial resolution, and development of alternative imaging modalities.¹⁴⁹ Notwithstanding, the study in patients who underwent renal transplantation showed that MetS was associated with GFR decline assessed by urinary clearance of 99mTc-DTPA.¹⁵¹

CT allows accurate and noninvasive evaluation of renal structure and function including kidney volume, vascular volume fraction, regional perfusion, renal blood flow (RBF), GFR, and tubular function. In dynamic CT analysis, regions of interest and time-attenuation curves are used to obtain measures of RBF and GFR.¹⁵² In our swine study using multidetector CT, early MetS has shown increased GFR and renal cortical perfusion, associated with renal adiposity and microvascular proliferation.¹⁵³ CT has high spatial and temporal resolution, but is limited by radiation exposure and risk for contrast-induced nephropathy, especially in patients with chronic kidney disease (CKD).¹⁵⁴

Renal perfusion can also be measured by dynamic contrast-enhanced (DCE)-MRI and ASL-MRI. DCE-MRI uses exogenous tracers like gadolinium-chelates. DCE-MRI also can estimate single-kidney GFR using multi-compartmental models, although a reference standard needs to be established.⁹⁸ However, gadolinium-based contrast may have a rare but critical adverse effect, nephrogenic systemic fibrosis, particularly in patients with renal insufficiency.¹⁵⁵ In patients with MetS, renal perfusion of a single coronal kidney slice by ASL-MRI was related with renal plasma flow directly measured by para-aminohippuric acid plasma clearance.¹⁵⁶ Furthermore, ASL-MRI enables to approximate changes in kidney perfusion after pharmacological intervention.¹⁵⁶ On the other hand, it does not provide estimates of GFR.

Diffusion-weighted imaging (DWI) allows quantification of water molecule movement which is restricted in a structured environment and not equal in all directions (anisotropic).¹⁵⁷ The average diffusivity of water molecules is quantitated by the apparent diffusion coefficient, and has been proposed to reflect fibrosis. Recently, DWI has been applied for assessing the severity of renal pathology in CKD.¹⁵⁸ However, interpretation of DWI may require special attention in MetS, because renal adiposity confounds calculation of DWI parameters and may lead to underestimation of renal diffusion and pseudodiffusion even at low fractions of the fat signal.¹⁵⁹

BOLD-MRI has demonstrated renal medullary hypoxia in patients with stage-3 diabetic nephropathy.¹⁶⁰ Contrarily, we have found that both cortical and medullary oxygenation is preserved in pigs with early MetS, suggesting that renal oxygenation decreases in more advanced disease.¹⁵³ BOLD-MRI is a non-invasive and promising method for evaluating renal oxygenation, but renal anemia, systemic acid–base disorders, deoxyhemoglobin/total hemoglobin ratio, partial pressure of oxygen in veins, and tissue oxygen levels may interfere with accurate interpretation of BOLD-MRI.¹⁶¹

Kidney-related fat—Para-renal, perirenal, and renal sinus fat accumulation may increase intrarenal pressures, sodium reabsorption, and hypertension via activation of the RAAS.^{143, 162} Perirenal fat thickness is an independent predictor of kidney dysfunction in subjects with type-2 diabetes,¹⁶³ and can exert paracrine effects on the renal circulation through proinflammatory cytokines. We have demonstrated that in pigs with early MetS perirenal fat directly leads to renal artery endothelial dysfunction, partly mediated by tumor necrosis factor- α .¹⁶⁴

Doppler US can be used for measuring para- and perirenal fat from the inner side of the abdominal musculature to the surface of the kidney. In obese subjects, para- and perirenal US fat thickness positively correlates with 24-hour aldosterone urine concentrations and diastolic blood pressure.¹⁶⁵ US measurements of para- or perirenal fat thickness show a good correlation with CT assessments ($r=0.76$).¹⁶³ Renal sinus and perirenal fat in CT can be separated from kidney and other organs based on the attenuation range for fat (Figure 2C), and CT-perirenal fat thickness was demonstrated as a reliable estimate of perirenal fat mass.¹⁶⁶ Perirenal fat can be also expressed as a ratio to the volume of the corresponding kidney.¹⁵³ Importantly, MR can also be used for quantifying intra-renal fat content. A recent study found increased renal lipids in subjects with type-2 diabetes using Dixon-based MRI,¹⁶⁷ although renal fat fraction is estimated at 0.8% in healthy subjects and only 2.38% in type-2 diabetes.¹⁶⁷ MR measured renal sinus fat and intra-renal fat has shown a relation with weight-loss in subjects with abdominal obesity.¹⁶⁸ In addition, ¹H-MRS enables metabolic imaging for detection of cortical triglycerides in human kidneys.¹⁶⁹

Liver

An increase in liver fat is frequently observed in MetS and considered a phenotype of MetS because of its correlation with insulin resistance, dyslipidemia, and obesity.^{170, 171} Hepatic steatosis (>5–10% fat) due to non-alcoholic causes is called non-alcoholic fatty liver disease (NAFLD). MetS is also an important predictor of non-alcoholic steatohepatitis (NASH) and hepatic fibrosis.^{172, 173} In MetS, lipolysis in excessive visceral adipose tissue can increase non-esterified fatty acids, which run into the liver.¹⁷² Adipose tissue can become hypoxic and has increased macrophage infiltration, proinflammatory cytokines, and decreased adiponectin. This inflamed adipose tissue is insulin resistant and promotes synthesis of intrahepatocellular triglycerides and very low-density lipoprotein.¹⁷²

NAFLD—In US, the echogenicity of the normal liver is similar to those of the right kidney and spleen, whereas NAFLD has higher echogenicity using conventional B-mode US. While US is cheap and easily available, it has low sensitivity for mild to moderate steatosis and a

limitation in distinguishing fibrosis and NASH from steatosis.¹⁷⁴ CT enables quantification of hepatic steatosis by determining the difference and ratio between the attenuation values of liver (normal: 50–65 HU, cutoff for steatosis <48 HU) and spleen (normal: 8–10 HU lower than a liver).¹¹⁹ On noncontrast CT, 30% steatosis on microscopy correlates to the findings of hepatic to splenic attenuation ratio less than 0.8 and difference of –10HU.¹⁷⁵ On contrast-enhanced CT, hepatic steatosis can be also diagnosed with hepatic to splenic attenuations difference of –20 to –25 HU.¹¹⁹ Although CT shows high specificity for hepatic steatosis in subjects with MetS,¹⁵ it has low sensitivity and is unable to distinguish fibrosis and NASH from steatosis. MRI and ¹H-MRS seem to be the most accurate techniques to evaluate hepatic steatosis,¹⁷⁶ and are also reliable compared with liver histology in NAFLD.¹⁷⁷ One of MRI method is modified Dixon, based on chemical shift fast gradient between water and fat. It can detect a hepatic fat fraction as low as 15%, and compensate for T2* effect caused by the relatively high iron content in the liver.¹¹⁹ Hepatic fat measured by this method exhibits a good correlation with ¹H-MRS.¹⁷⁸ Fat-selective spectral-spatial gradient echo imaging combines chemical shift selectivity with simultaneous slice-selective excitation in gradient-echo imaging sequences, and can also determine hepatic fat fraction.¹⁷⁹ MRI-proton density fat fraction has been suggested as a good biomarker for steatosis, as it strongly correlates with histological grading of steatosis.^{180–182} In ¹H-MRS, hepatic steatosis can be diagnosed when normally high water peak at 4.2ppm is decreased and lipid peak at 0.9–2.2ppm is markedly elevated.

Inflammation and NASH—NASH is histologically characterized by ballooning necrosis near steatotic hepatocytes, mild inflammation, and possibly fibrosis.¹⁷³ Conventional imaging modalities have limitations to distinguish between NAFLD and NASH and stratify the severity of NASH. A newer technique for differentiate NAFLD and NASH, phosphorus-31 (³¹P) MRS, assesses the ratios of various phosphorus-containing metabolites, including cell membrane precursors (phosphomonoesters), degradation products (phosphodiesteres), and nicotinamide adenine dinucleotide phosphate (NADPH).^{183, 184} In a recent study, ³¹P-MRS has shown distinct biochemical changes in different NAFLD states and a good diagnostic accuracy for NASH.¹⁸⁵

Fibrosis and cirrhosis—NAFLD in MetS has potential to progress to NASH, advanced fibrosis, and cirrhosis due to lipotoxicity and activation of inflammatory and fibrogenic pathways.¹⁸⁶ Hepatic fibrosis is accumulation of excessive collagen fibers responding to chronic inflammation and hepatocyte injury. Existing morphologic assessment on US, CT, and MRI could be subjective and unreliable for detecting early stages of fibrosis. Newer imaging techniques have been used to diagnose liver fibrosis and include US elastography (transient elastography, shear wave elastography, or acoustic radiation force impulse imaging) and magnetic resonance elastography (MRE).¹⁸⁷ US elastography measures the velocity of acoustically induced mechanical shear waves traveling through the liver, which increases in fibrotic livers. However, US elastography may be influenced by inflammation,¹⁸⁸ extrahepatic cholestasis,¹⁸⁹ and central venous pressure,¹⁹⁰ and have limitations in patients of high BMI, ascites, or narrow intercostal space.¹⁹¹ MRE, the currently gold standard for diagnosis and staging of liver fibrosis especially in obese patients, uses continuously generated low frequency mechanical waves in tissue from the vibration source

placed on the body surface.¹⁹² Phase contrast MRI technique gets wave images by micron-level cyclic displacement. Then, these wave images are automatically processed to produce quantitative images about the stiffness of tissue.¹⁹² MRE has shown a strong correlation with the histologic fibrosis score as well as interrater reliability in many studies.^{193–195} However, hepatic MRI signal waves may not be visualized in patients with marked iron deposition, and availability remains comparatively limited.¹⁹¹ Indeed, many noninvasive imaging techniques that await clinical translation include MRI (DWI, hepatobiliary contrast agents, perfusion, and quantitative T1, T2, T1 rho mapping), CT (perfusion, fractional extracellular space, and dual energy), contrast-enhanced US, texture analysis, and direct molecular imaging proves of collagen.¹⁸⁷

Pancreas

MetS is associated with non-alcoholic fatty pancreatic disease (NAFPD).¹⁹⁶ Fat accumulation in pancreas is usually diffuse but can be uneven, showing mainly fat-replacement in pancreatic head.¹⁹⁷ In contrast to liver, NAFPD histologically spares cells and accumulates adipocytes within the pancreatic interstitial septa.¹⁹⁸ Yet, intracellular triglyceride accumulation observed in animal studies may precede adipocytes infiltration.^{199, 200}

NAFPD can be assessed using US, CT, MR, and MRS. Applications of US might be endoscopic or trans-abdominal US, although it is limited by digestive interposition and operators. In US, NAFPD can be assessed through an increased in echogenicity of the pancreatic body compared with the kidney,¹⁹⁶ or in endoscopic US with retroperitoneal fat.²⁰¹ A recent study using trans-abdominal US has shown that NAFPD was associated with each component of MetS.¹⁹⁶ However, fibrotic pancreas is also hyperchogenic in US, and therefore CT or MRI should be used to confirm NAFPD.²⁰² In CT, NAFPD shows hypodense pancreas with low HU compared to the spleen²⁰³ and lobules of acini surrounded by macroscopic fat.¹¹⁹ CT attenuation index between pancreas and spleen was validated with pancreatic fat fraction in histology.²⁰⁴ In MRI, the modified Dixon exhibits a good correlation with ¹H-MRS for assessment of pancreatic fat fraction.¹⁷⁸ Fat-selective spectral-spatial gradient echo imaging can also determine pancreatic fat fraction.¹⁷⁹ Recently, a fat-water 3D imaging technique called IDEAL (Iterative Decomposition with Echo Asymmetry and Least squares estimation) accurately characterized the proportion of fat and water content, and might be better suited for fat quantification in the pancreas compared to MRS.²⁰⁵ Finally, ¹H-MRS can be also used for measuring pancreatic triglyceride content.²⁰⁶ Increasing evidence support the role of pancreatic fat in the development of type-2 diabetes, although its pathogenesis still remains undetermined. Some studies, but not all,²⁰⁷ have shown the correlation between MetS and hyperglycemia or β -cell dysfunction.^{196, 199, 206} Thus, whether fatty pancreas has predictive value for diabetes needs further investigation.

Brain

MetS is known to raise the risk of cognitive dysfunction and dementia²⁰⁸ as well as ischemic stroke.²⁰⁹ The mechanisms underlying brain complications in MetS are likely to be associated with hyperglycemia, insulin resistance, arterial hypertension, and vascular lesions. Hyperglycemia produces free radical, glycation end products, and oxidized lipids,

which can give rise to neurodegeneration.²¹⁰ Insulin resistance induces prolonged peripheral hyperinsulinemia, down-regulated blood-brain barrier insulin receptors, and decreased insulin transport to the brain. This insulin dysregulation decrease cerebral glucose metabolism, neurogenesis, and repair, and increase inflammation, oxidative stress, and vascular dysfunction.²¹¹

Cognitive impairment and dementia—Conventional structural MRI is the most widely used modality for evaluating the brain although brain macrostructure was not associated with MetS,²¹² or correlated with cognition impairment in subjects with MetS.²¹⁰ However, microstructural white matter abnormalities in MetS might be the underlying mechanisms of cognitive impairment.²¹³ Early changes on brain microstructure can be assessed using MRI technique like DTI and magnetization-transfer imaging (MTI). DTI measures water diffusion in the intracellular cytoplasm along the axons, whereas MTI assesses the magnetization exchange between protons bound to water and to macromolecules like the myelin lipids and proteins.²¹⁴ Studies using DTI or MTI have shown microstructural white matter changes in MetS.^{212, 213, 215, 216} Additionally, the area with impaired white matter integrity in MetS is correlated with verbal learning and memory processing^{212, 213}, and components of MetS were independent factors in brain tissue integrity.²¹² Using functional neuroimaging, patients with MetS showed a lower BOLD signal coinciding with development of cognitive impairment.²¹⁷ ¹⁸F-FDG PET suggests effects of insulin dysregulation on the brain glucose metabolism in patients with MetS.²¹⁸ Measurements of regional cerebral glucose metabolism using ¹⁸F-FDG PET can also support the clinical diagnosis for cognitive impairment and dementia,²¹⁹ although the association between MetS severity and regional hypometabolic changes in ¹⁸F-FDG PET at the very early stage of cognitive decline still remains to be clarified.²²⁰ Studies of the correlation between cognitive dysfunction in MetS and functional changes in brain activity are limited. Vascular dementia represents diverse but non-specific abnormalities.²²¹

Ischemic stroke—Previous studies have shown that MetS is an important risk factor for intracranial atherosclerotic stroke,²²² acute ischemic stroke,²²³ and minor ischemic stroke.¹⁴⁵ In acute ischemic stroke with MetS, inflammation and arterial stiffness plays a role,²²³ thus PWV measurement could be helpful for assessing these patients. In addition to conventional CT, MRI, and their angiography, new techniques including vessel wall MRI, transcranial Doppler (TCD), 4D CT angiography, and MR angiography have been widely used for diagnosis of acute ischemic stroke.²²⁴ MetS is associated with lower cerebral vasomotor reactivity, a predictor of increased risk of ischemic stroke.²²⁵ TCD evaluates the intracranial arterial vessels and the cerebral blood flow velocity by placing a low-frequency transducer on the scalp.²²⁶ In addition, TCD is a cost-effective and readily repeatable diagnostic imaging test characterized by high sensitivity and specificity for cerebral artery occlusion.²²⁶

PRACTICAL AND THERAPEUTIC APPROACHES

Imaging modalities have markedly advanced, yet indications of their use in MetS have not been fully established in clinical settings. Evaluation of abdominal obesity and insulin resistance is necessary for assessing severity of MetS. A single slice CT scan at L4 level in

late expiration can be the reference for assessing SAT and VAT, given its accuracy, reproducibility, repeatability, and convenience, allowing follow-up monitoring. For simultaneous evaluation of cardiovascular risk factors, MRI is a good choice for fat assessment. A common method to assess insulin resistance is the homeostatic model assessment, an indirect calculation based on glucose and insulin levels, yet MRS or PET can provide greater insight for better understanding of the pathogenesis. Figure 3 shows a potential diagnostic algorithm based on this review.

It is important to decrease their risk for development of type-2 diabetes and cardiovascular disease in subjects with MetS. Treatment includes life style modification, pharmacological therapy of atherogenic dyslipidemia, hypertension, and hyperglycemia, and possibly surgical approaches. Weight reduction and exercise with patient motivation and adherence is effective.²²⁷ Targets for dyslipidemia in MetS are lowering LDL-cholesterols using statins with or without ezetimibe²²⁸ and triglycerides by fibrates or niacin.²²⁹ To control BP, angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists are considered as first-line therapy, because of their favorable metabolic profile.^{230, 231} In subjects with insulin resistance, metformin can help prevent progression to diabetes, although lifestyle modification may be more effective.²³² Bariatric surgery is also a useful option in patients with severe obesity and cardiovascular comorbidity.²³³

CONCLUSION

MetS leads to increased morbidity and mortality. In early stages of MetS, deleterious changes in each target organ often are subclinical and possibly reversible. Imaging modalities are helpful to stratify risk factors, including abdominal obesity and insulin resistance, and evaluate target organ damages in individual patients with MetS (Figure 1). Non-invasive diagnostic imaging modalities that have been frequently used for this purpose, such as US, CT, and MR, have advantages and limitations. US is a safe, relatively economical, and easily applicable diagnostic tool, but lacks standardized and reproducible methods, and requires experienced operators and considerable skill. CT is faster and less costly than MR, and feasible in patients with some implantable medical devices. However, it is sometimes less sensitive and limited by ionizing radiation. MR offers the advantage of no radiation exposure, and is thus preferable to children and patients requiring simultaneous evaluation of multiple risk factors. In addition, it enables a greater range of soft tissue contrast, as well as more detailed and quantitative studies of anatomy and function. Nevertheless, MR it incurs a higher cost. Nuclear imaging can also investigate target organ function, but is hampered by its limited availability, high cost, and radiation exposure. Conceivably, a combination of techniques might be most useful to illustrate the entire spectrum of alterations associated with MetS, although the cost effectiveness of this approach remains to be determined. Overall, imaging studies in MetS may help diagnosis, predict target organ injuries, and develop novel therapeutic target to alleviate and avert them.

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Abbreviations

ASL	arterial spin labeling
BMI	body mass index
BOLD	blood oxygen level-dependent
BP	blood pressure
CAD	coronary artery disease
CIMT	carotid intima-media thickness
CKD	chronic kidney disease
CT	computed tomography
D	dimensional
DCE	dynamic contrast-enhanced
DTI	diffusion tensor imaging
DWI	diffusion-weighted imaging
DXA	dual-energy x-ray absorptiometry
FDG	fluorodeoxyglucose
GFR	glomerular filtration rate
HU	Hounsfield units
IMCL	intramyocellular lipid
IVUS	intravascular ultrasound
LV	left ventricle
LVH	left ventricular hypertrophy
MetS	metabolic syndrome
MRE	magnetic resonance elastography
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
MTI	magnetization-transfer imaging

NADPH	nicotinamide adenine dinucleotide phosphate
NAFLD	non-alcoholic fatty liver disease
NAFPD	non-alcoholic fatty pancreatic disease
NASH	non-alcoholic steatohepatitis
NO	nitric oxide
OCT	optical coherence tomography
PET	positron emission tomography
PWV	pulse wave velocity
RAAS	renin-angiotensin-aldosterone system
RBF	renal blood flow
SAT	subcutaneous adipose tissue
SPECT	Single-photon emission computed tomography
TCD	transcranial Doppler
US	ultrasonography
VAT	visceral adipose tissue

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Figure 1.

Schematic illustrating evaluation of the metabolic syndrome using imaging modalities.

DXA, dual-energy x-ray absorptiometry; US, ultrasonography; CT, computed tomography; MRI, magnetic resonance; MRS, magnetic resonance spectroscopy; MRE, magnetic resonance elastography; PET, positron emission tomography; SPECT, Single-photon emission computed tomography

Figure 2.

Representative multi-modality images for evaluation of fat content and target organ injury. A. Computed tomography (CT) tomographic images obtained at the fourth lumbar vertebra in lean and obese subjects (body mass index of 19kg/m^2 and 31kg/m^2 , respectively). Both visceral fat (yellow) and subcutaneous fat (red) were elevated in the obese subject. B. Representative R2* maps obtained in lean and obese swine using blood oxygen level-dependent magnetic resonance imaging. Increasing orange and red colors indicate higher R2*, and in turn lower myocardial oxygenation. C. Three-dimensional reconstructed CT images demonstrating increased perirenal fat (yellow) in obese swine.

Figure 3.

Proposed diagnostic algorithm in the metabolic syndrome using imaging modalities. Dotted lines indicate limited availability in the present clinical setting. VAT, visceral adipose tissue; CT, computed tomography; DXA, dual-energy x-ray absorptiometry; US, ultrasonography; MRI, magnetic resonance imaging; CV, cardiovascular; MRS, magnetic resonance spectroscopy; IMCL, intramyocellular lipid; PET, positron emission tomography; CAD, coronary artery disease; CKD, chronic kidney disease; MRE, magnetic resonance elastography; TCD, transcranial Doppler.