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Multiorgan, Multimodality Imaging in Cardiometabolic Disease

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Abstract

Cardiometabolic disease, spanning conditions such as obesity to type 2 diabetes mellitus with excess cardiovascular risk, represents a major public health burden. Advances in preclinical translational science point to potential targets across multiple organ systems for early intervention to improve cardiometabolic health. Validation in clinical trials and translation to care would benefit from *in vivo* diagnostic techniques that facilitate therapeutic advancements. This review provides a state-of-the-art, multi-modality perspective spanning the multiple organ systems (Figure) that contribute to cardiometabolic disease.

Journal subject terms

imaging; cardiovascular disease; metabolic syndrome

Introduction

Historically, cardiometabolic disease (CMD) has been defined as disorder that encompasses a spectrum of risk factors strongly associated with the development of type 2 diabetes mellitus (T2DM) and that ultimately leads to cardiovascular disease[1]. The burden of CMD is high, affecting more than 30% of US adults[2], and this number is rising in parallel with rates of obesity. Morbidity and mortality due to CMD are ultimately caused by complications associated with cardiovascular disease and T2DM, which together are the leading causes of death in the United States[3]. While aggressive management of risk factors can improve prognosis in CMD[4], ongoing discovery of novel mechanistic pathways across various organ systems emphasizes the need for diagnostics that interrogate across relevant systems. Such approaches would facilitate *in vivo* targeting of multiple organs simultaneously to guide therapeutic development and personalize treatment. This review summarizes the pathophysiology of cardiometabolic disease in skeletal muscle, liver, pancreas, adipose tissue, and the microcirculation that collectively impact the heart, forming the basis of multiorgan imaging to assess CMD. Pathogenesis and non-invasive examination of atherosclerosis is excluded from the present discussion, and covered in detail elsewhere.

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Skeletal Muscle

Pathogenesis

Skeletal muscle is the major site of glucose disposal in the body, and plays a crucial role in the development of CMD via: 1) metabolic inflexibility (i.e. inability to use multiple fuel sources) and insulin resistance, 2) intramuscular fat accumulation and 3) impaired mitochondrial oxidative capacity.

Normal skeletal muscle has the potential to draw from both carbohydrate and lipid pools for fuel depending on availability. In metabolically healthy individuals storage and oxidation of glucose is significantly higher in hyperinsulinemic, non-fasting conditions than in fasting states[5]. Furthermore, insulin exposure reduces fatty acid oxidation in healthy individuals. Insulin resistance, due to impaired insulin signaling and glucose transport under abnormal metabolic conditions such as obesity, contributes to inflexibility and increasing reliance on fatty acids as a primary energy substrate. Known CMD causes like chronic over-nutrition and insufficient physical activity adversely affect insulin sensitivity and metabolic flexibility of skeletal muscle[5].

Metabolic inflexibility and insulin resistance can lead to aberrant mitochondrial oxidative function and ectopic lipid accumulation, including toxic ceramides and diacylglycerol. Increased intra- and extramyocellular lipids (IMCL, EMCL) are associated with CMD, and may indicate an imbalance between fatty acid availability and maximum oxidation potential. Interestingly, ectopic lipid accumulation is not always a pathologic phenomenon. The “athletes paradox” occurs when certain highly trained, metabolically healthy individuals exhibit increased levels of IMCL compared to normal subjects. However, the skeletal muscle of these athletes maintains higher oxidative capacity and is more insulin sensitive than lean, untrained or obese counterparts. Thus, imaging must be interpreted in the context of an individual’s history, physical examination, and other testing[6]. In metabolically-unhealthy individuals, intracellular accumulation of fatty acid oxidation byproducts impairs insulin signaling. The combined effects of insulin resistance and increased reliance on fatty acids leads to mitochondrial uncoupling, an adaptive process that ultimately reduces oxidative phosphorylation capacity[7]. Furthermore, insulin resistant muscle exhibits a greater proportion of glycolytic fibers compared to oxidative, mitochondria-rich fibers[8].

Mitochondrial Oxidative Capacity

Magnetic resonance spectroscopy tuned to phosphorous (^{31}PMRS), an endogenous nucleus found in various high-energy substrates within cells throughout the body, has been used to quantify mitochondrial oxidative capacity and uniquely illuminate biochemistry *in vivo*[9].

Skeletal muscle^{31}PMRS measurements performed *in vivo* with exercise-recovery protocols yield noninvasive quantification of oxidative phosphorylation capacity[10]. Such protocols produce an energy imbalance for which increased demand for adenosine triphosphate (ATP) is met through the enzymatic breakdown of phosphocreatine (PCr) through the creatine kinase reaction. Upon cessation of exercise performed to fatigue, the rate of ATP production is dominated by oxidative phosphorylation and represents the maximum *in vivo* capacity of the mitochondria. The post-exercise recovery of PCr can therefore be quantified by the

fitting of an exponential time constant (τ_{PCr}), with shorter values of τ_{PCr} representing greater capacity for oxidative ATP synthesis[10].

Creatine kinase flux

The creatine kinase- catalyzed ATP hydrolysis reaction is fundamental to the production of energy through oxidative phosphorylation. Recently developed magnetization transfer (MT) techniques, which saturate the signal of a nuclei-of-interest and observe the transfer of this saturated signal through chemical exchange, may provide additional insight into skeletal muscle bioenergetics[11]. Compared to ^{31}PMRS methods, MT techniques allow for localized acquisition with relatively high spatial resolution. Furthermore, MT experiments do not require exercise and therefore may be more easily standardized. MT techniques, however, require long scan times and sacrifice feasibility at low field. Long repetition times are required to allow for complete relaxation of the ^{31}P nucleus. Incomplete saturation and radiofrequency spillover are issues that are more apparent at low field, although corrections can be introduced into the modified Bloch equations to account for this. However, the combination of low SNR from the low availability of ^{31}P in biological systems, combined with saturation and signal homogeneity issues makes the use of high-field systems preferable for MT techniques[11].

Metabolite quantification

Carbon 13 (^{13}C) MRS offers *in vivo* measurement of various metabolites and their kinetics. To overcome the low natural abundance of ^{13}C (~1%) hyperpolarization techniques have emerged to generate ^{13}C-tagged metabolites for use as an exogenous contrast agent, increasing SNR by several log-fold[12]. Pyruvate, lactate and alanine are important intermediaries in anaerobic and aerobic metabolic pathways that can be examined using hyperpolarized ^{13}C MRS. Recent work has demonstrated the feasibility of *in vivo* investigations of skeletal muscle lactate and pyruvate kinetics. However, further work is required to translate these techniques into humans[13].

Recent advancements in hydrogen MRS (^{1}HMRS) techniques have enabled quantification of intramuscular metabolites that may change in response to the progression of CMD. Acetylcarnitine (ACC) is an important factor that maintains pyruvate oxidation in the mitochondria. Recent work has demonstrated the feasibility of using long echo time to suppress the lipid signal and detect ACC using ^{1}HMRS even in overweight/obese subjects[14]. Preliminary studies have been completed using ^{1}HMRS techniques at ultra-high field to quantify skeletal muscle carnosine, an endogenous dipeptide that may improve insulin sensitivity, in response to exogenous supplementation[12].

Fat Quantification

Ectopic intramuscular fat can be quantified non-invasively by ultrasound, computed tomography (CT) or MR. Ultrasound techniques may also identify differences in echogenicity between fat and lean muscle tissue[15]. However, intramuscular fat and connective tissue have similar echogeneic properties, a significant limitation of this technique[16]. The characteristic hypoattenuation of fat by CT signal intensities of -190 to -30 Hounsfield units[17] offers a reliable and simple method for intramuscular fat quantification.

While CT-based fat quantification requires exposure to ionizing radiation, many technical strategies can help minimize dose. Resolution and technique limitations presently preclude CT-based distinction between intra- and extracellular lipids.

MR techniques demonstrate a distinct advantage over other non-invasive fat quantification methods by its breadth. ^{1}HMRS methods, the current gold-standard for *in vivo* fat quantification, can distinguish between intra- and extracellular fat deposits due to the difference in chemical shift between fat deposits inside and outside of the cell membrane. Fat-water MR imaging methods can quantify and map intramuscular fat. The classic Dixon method of capturing images when fat and water are in-phase and out of phase has been refined for more precise fat quantification.[18]

Liver

Pathogenesis

There is a strong link between non-alcoholic fatty liver disease (NAFLD), particularly nonalcoholic steatohepatitis, and CMD. NAFLD, affecting approximately 20% of American adults, describes a range of conditions from ectopic triglyceride accumulation to non-alcoholic steatohepatitis, and is an increasingly common cause of cirrhosis[19].

The precise mechanistic links between NAFLD and CMD remain to be fully elucidated; however, increasing evidence indicates a symbiotic relationship between the two conditions. NAFLD is a known risk factor for T2DM, as it causes hepatic insulin resistance[20]. Visceral fat accumulation, another characteristic of CMD, contributes to increased hepatic fatty acid levels and intracellular fat accumulation. Furthermore, considerable evidence implicates even simple hepatic steatosis as a predecessor of CMD[21]. Chronic fatty liver, in combination with metabolic syndrome, promotes the development of nonalcoholic steatohepatitis leading to hepatic fibrosis[22]. Deranged hepatic glucose and lipid metabolism result in increased oxidative stress and potentially disordered mitochondrial function[23]. The liver's central role in optimal cardiometabolic health is evident from recent definitions of "metabolically healthy" obese individuals that are predicated on absence of NAFLD[24].

Imaging applications

Fat Quantification—Ultrasound is a widely available non-invasive technique for detection of hepatic fat. Steatotic liver demonstrates increased scatter and attenuation sound waves compared to normal liver and produces characteristic qualitative markers such as hyperintense liver, blurry hepatic vessels and poor resolution of the diaphragm. US is the most common method for hepatic fat quantification although its use is limited by low sensitivity and poor penetration in obese individuals[25].

CT can be rapidly acquire images to quantify liver fat. However, CT requires exposure to ionizing radiation making it less appealing for serial quantification, and sensitivity may be limited for fat detection below 30%[26].

MR can quantify total fat content using imaging methods, and spectroscopy methods can further assay the intracellular fraction. Spectroscopy is typically less widely available both in

instrumentation and expertise. Imaging techniques leverage the difference between in and out-of phase water and fat signals and can produce fat fraction maps[25].

Fibrosis quantification—Ultrasound detection of fibrosis with B-mode methods qualitatively assess the liver surface; detection of a nodular liver surface has relatively low sensitivity and is considered reliable for detection of cirrhosis only. Preliminary data suggest high reproducibility and good correlation to histological measures using dual energy CT acquisition and multi-material decomposition to quantify liver fibrosis[27]; further validation of this technique in prospective trials are warranted. Magnetic resonance elastography is an emerging method involving external placement of a pneumatic driver to generate low-frequency waves. MR elastography techniques may different between fibrotic and non-fibrotic liver in the context of simple steatosis or steatohepatitis[28]. However, MR elastography is extremely sensitive to the confounding effects hepatic iron[29]. Recent improvements to non-contrast multiparametric techniques include T2* correction, which accounts for the T1-shortening effect of hepatic iron that allows for more accurate fibrosis quantification[30].

Metabolic quantification—Hepatic glucose utilization can be investigated with positron emission tomography (PET) techniques. ^{18}F-FDG PET in combination with euglycemic hyperinsulinemic clamp protocols have been used to assess liver glucose utilization. Iozzo et al. demonstrated that in the fasted state hepatic glucose uptake is similar in obese diabetic and normal, healthy-weight individuals. However, glycemic control is inversely related to insulin-stimulated hepatic glucose uptake[31].

Phosphorous MRS and saturation transfer techniques demonstrate changes in hepatic energetics due to T2DM and obesity. Baseline levels of ATP and inorganic phosphate are lower and rate of ATP turnover slower in individuals with metabolic abnormalities compared to healthy controls[32]. ^{13}C MRS with infusion of labeled acetate can be used to quantify the rate of tricarboxylic acid flux, which is crucial for hepatic fatty acid oxidation[33]. Further investigation is required to evaluate this technique in the context of CMD, and to quantify changes due to disease.

Pancreas

Pancreatic beta cell dysfunction is central to a range of metabolic disorders. In type 2 diabetes, hyperglycemia, fatty acids, and oxidative stress cause beta-cell demise so that individuals with impaired fasting glucose have lost 50% of beta cell mass, while around 65% of beta cell mass is lost in frank type 2 diabetes[34]. Pancreatic fat accumulation impairs beta cell mass and function; intriguing pilot data from Lim *et al.* using MRI-based quantification suggests that marked, short-term calorie restriction lowers pancreatic triglyceride content, normalizes beta cell function, and restores hepatic insulin sensitivity[35]. Novel molecular probes for use with nuclear imaging techniques, like single photon emission computed tomography (SPECT) and PET, show promise for noninvasive quantification of beta cell mass[36]. Glucagon-like peptide 1 receptor (GLP-1R) is a protein specifically expressed by pancreatic beta cells, and is a common target for molecular imaging probes. An indium-111 labeled GLP-1R agonist (^{111}In-labelled exendin) for use with SPECT imaging has been

developed to quantify beta-cell mass in animals, healthy individuals, and human subjects with beta cell dysfunction[37]. PET techniques may be preferable to SPECT if increased sensitivity can be offered with lower radiation exposure. However, preliminary PET studies in a large animal diabetes model using a radiolabeled synthetic GLP-1 analog raise toxicity concerns[38]. Magnetic nanoparticle-tagged GLP-1R agonists have been images with MRI, and demonstrate reduced signal in mouse models of diabetes[39]. Non-invasive quantification of beta cell mass requires further optimization before effective translation to clinical trials.

Adipose Tissue

Pathogenesis

Adipose tissue is the primary caloric reservoir in the body, and it is responsible for maintaining energy homeostasis through regulation of lipid storage and lipolysis in response to environmental requirements. Changes in the ability of adipose tissue to maintain energy homeostasis (i.e. inability to properly store lipids, abnormal signaling or impaired thermoregulation) may precede CMD and further distinguishes metabolic health/disease from normal weight/obesity[40]. The two major types of adipose tissue in humans are: white (WAT) and brown (BAT). The physiological role of WAT is thought to be an insulator and energy reservoir, although recent evidence suggests its role as an endocrine organ as well. A majority of WAT is located in the abdomen, both inside the cavity (visceral) and subcutaneously. Adipokines, adipocyte-secreted cytokines, are secreted by WAT and play a key role in the regulation of energy homeostasis. BAT is highly metabolically active and plays an important role in thermoregulation. Interestingly, while obesity, or excess accumulation of WAT, is associated with CMD it is not necessarily a marker of disease. In fact, a subset of obese individuals are considered “metabolically healthy” because they do not exhibit any other cardiometabolic risk factors, like increased blood pressure or insulin resistance, and do not demonstrate increased risk of CMD compared to normal weight individuals. Interestingly, a primary feature of the metabolically healthy obese subpopulation is the absence of visceral WAT accumulation, which may point to potential mechanisms responsible for CMD[41].

Imaging applications: white adipose tissue

Subcutaneous and visceral WAT mass can be quantified using abdominal imaging techniques such as fat-water MRI, CT, US and dual-energy x-ray absorptiometry[42]. Pathophysiological changes that may occur in subcutaneous WAT include increased inflammation, insufficient tissue oxygenation, and dysregulated endocrine function. Diffuse optical spectroscopy has demonstrated the potential to quantify physiologic changes of subcutaneous WAT (e.g. tissue water fraction and deoxyhemoglobin concentration) during weight loss in obese human subjects[43]. The phenotype of subcutaneous WAT in CMD, as well as potential changes due to treatment of risk factors, is yet to be investigated.

Imaging applications: brown adipose tissue

BAT is a highly metabolic, insulin sensitive tissue and is therefore well suited to quantification with ^{18}F-FDG PET. An important caveat to note is that glucose uptake occurs in mainly activated BAT and low FDG uptake may indicate either an absence of BAT or lack

of tissue activation. Cold-induced activation, using cooling vests or rooms, has been used to overcome this limitation although this method is still prone to intra-subject variability. FDG detection of BAT has demonstrated a blunted response in obese subjects compared to lean individuals[44]. Additional PET tracers have been developed for imaging of both active and inactive BAT. Accumulation of radiolabelled tribenzyl phosphonium (^{18}F-FBnTP) in BAT, which targets changes in mitochondrial membrane potential and proton flux, is inversely proportional to tissue activation. Interestingly, dynamic imaging of ^{18}F-FBnTP has been used to assess changes due to activation in real-time preclinical models[45]. Further investigation is required to establish the consequences of CMD on BAT function and to evaluate the potential of novel PET tracers in humans.

More recently, MR techniques have been developed for BAT quantification and characterization. BAT, due to differences in lipid storage, vascularity and mitochondrial content, has increased intracellular water content compared to WAT. Dixon MRI techniques can be used to distinguish between BAT and WAT in humans. Franssens et al. demonstrated increased BAT fat fraction in a cohort of patients with CMD using Dixon MRI[46].

Microcirculation

Pathogenesis

The microcirculation encompasses vessels <150 um in diameter that support the supply of oxygen and nutrients to tissue as well as stabilize changes in hydrostatic pressure. Altered microcirculatory morphology and function occur in the context of CMD, and accompany pathologies like insulin resistance and hypertension[47]. As insulin exerts a local vasodilatory effect on microvasculature, reduced insulin delivery due to microvascular dysfunction contributes to decreased glucose uptake in skeletal muscle. Furthermore, insulin signaling enhances capillary recruitment promoting more homogenous perfusion and increased glucose uptake in target tissues. Microvascular rarefaction, vessel reduction that significantly increases vascular resistance, occurs with insulin resistance, and hypertension incurs symbiotic detrimental effects on microvascular structure and function[48].

Imaging applications

CMD-associated microvascular dysfunction can occur in many organs including the eye, skeletal muscle, and heart[49, 50]. Cutaneous microvasculature may be a particularly appealing target to image the response to cardiometabolic risk-reducing interventions[51]. Capillary video microscopy is an optical imaging technique that uses green-spectrum light to illuminate superficial micro vessels in the nail beds. Detectors capture backscattered light and images are reconstructed producing images of capillaries[52]. Contrast-enhanced ultrasound can be used to quantify microvascular recruitment in deeper tissues, like skeletal muscle. Disruption of bubbles with the ultrasound beam and recovery of steady-state can be used to calculate microvascular blood volume and vessel resistance. Meijer *et al.* used such an approach to correlate skin and skeletal muscle microvascular recruitment in healthy individuals to whole-body glucose uptake[53]. Progressively worse microvascular function has been shown to occur with increased severity of insulin resistance[54].

Myocardial microvascular function can be accurately quantified with PET[55]. ^{82}Rb PET imaging has been used to demonstrate impaired coronary microvascular function in diabetics without overt cardiovascular disease[56].

Cardiac Consequences of CMD

Pathogenesis

Across the range of CMD, a number of mechanisms ensue to incur cardiac dysfunction. Aberrant insulin signaling in CMD, both systemic and myocardial, contributes to cardiac dysfunction via altered substrate use, increased oxidative stress and insufficient myocardial perfusion. Subsequent dysregulation of remodeling processes, like cellular hypertrophy, collagen deposition, accumulation of advanced glycemic end products and ectopic lipid accumulation lead to cell damage, impaired contractile function and diastolic dysfunction[57]. Mitochondrial dysfunction ensuing from CMD affects myocardial energetics may ultimately result in heart failure[58].

Imaging applications

Echocardiography is the most commonly used technique for non-invasive evaluation of DD[59]. Standard echocardiography techniques quantify the ratio of mitral inflow velocities in early/passive (E) and late/active (A) phases of LV relaxation. A low E:A ratio indicates a greater dependence on active filling to overcome impaired myocardial relaxation. Additionally, lower E′ velocity of the mitral annulus during early filling indicates impaired diastolic function. A higher E:e′ ratio infers higher LV filling pressures. Increased LV filling pressure and greater dependence on atrial contraction during diastole result in left atrial hypertrophy[60]. Thus, left atrial volume is an additional marker of DD with established prognostic value.

Cardiac magnetic resonance may be used to similarly estimate mitral inflow and annular velocities, whereas unique methods such as tissue tagging offer more direct quantification of myocardial relaxation. Tagged cine superimposes saturation lines or grids onto the imaging plane; their deformation in myocardium over the cardiac cycle is used to calculate systolic and diastolic strain in various directions and components. Cardiac MRS is uniquely capable of quantifying myocardial lipids and interrogating *in vivo* myocardial energetics, which are abnormal in CMD. Wei *et al.* have observed significantly increased myocardial triglycerides in women with CMD using ^{1}HMRS techniques[61]. Using phosphorus spectroscopy, Rider *et al.* demonstrated significantly lower ratio of phosphocreatine to adenosine triphosphate (PCr:ATP) at rest in obese vs. normal-weight individuals, a deficit that improved with weight loss as did measures of LV diastolic function[62]. Using 13C cardiac MRS in a rat diabetic cardiomyopathy model, therapy with a pyruvate mimetic has been shown to improve myocardial substrate selection and diastolic function[63]. 13C MRS techniques are also capable of quantifying the effects of anti-diabetic agents on cardiac and hepatic metabolism in preclinical models[64]. Coupled with the distinct capabilities for magnetic resonance-based quantification of myocardial fibrosis, lipid, and energetics, CMR holds significant appeal in the multidimensional, multi-organ characterization of cardiometabolic disease sequelae.

Myocardial substrate utilization varies across the spectrum of CMD, and cardiac PET is uniquely able to visualize glucose uptake *in vivo*. Mobely *et al.* used this modality to demonstrate that a 13-hour infusion of glucagon-like peptide 1 (GLP-1) increases myocardial glucose uptake in lean subjects but not in obese type 2 diabetics[65].

Multiorgan Approaches in Clinical Trials

Several groups have implemented multiorgan imaging to serially evaluate *in vivo* the effects of therapeutic interventions. Scheuermann-Freestone and colleagues demonstrated one of the earliest multi-organ approaches to detect subclinical metabolic abnormalities in diabetic individuals without evident cardiovascular disease, incorporating exercise ^{31}PMRS in skeletal muscle with multimodality cardiac imaging and spectroscopy[66]. Gallagher *et al.* showed reduced mass of the liver and spleen in obese T2DM subjects using whole body T1-weighted MRI in a prospective lifestyle intervention trial, though tissue characterization was not performed to know if mass reduction was effected via reduced fat in these organs[67]. Combining phosphorus and hydrogen cardiac MRS with PET and dobutamine stress echocardiography in a randomized clinical trial of pioglitazone vs. metformin, van der Meer *et al.* demonstrated the potential of a multimodality, multiorgan approach to refine therapeutic strategies for CMD[68].

Emerging Techniques for CMD Imaging

As insights into CMD mechanisms and therapeutic approaches continue to evolve, emerging imaging techniques offer potential utility in translating these insights to *in vivo* studies in humans. Noninvasive measurement of skeletal muscle oxygen consumption from magnetic susceptibility-based oxygen extraction fraction and arterial spin labeling-based blood flow computations[69]. In the liver, ultrasound-based elastrography holds appeal for fibrosis quantification in children and adolescents with nonalcoholic steatohepatitis[70]. Coupled with thermogenic capsaicin-like compounds, near infrared time-resolved spectroscopy holds appeal as a low-cost method to quantify supraclavicular brown adipose tissue[71]. Noninvasive interrogation of the cutaneous microcirculation with optical coherence tomography may be enhanced with topical solutions that increase light penetration depth[72]. And in the heart, chemical exchange saturation transfer (CrEST) hold the promise of noninvasive quantification of myocardial creatine kinase metabolism[73].

Conclusions

Advances in the non-invasive assessment of cardiometabolic disease across multiorgan sequelae may facilitate earlier detection and improved outcomes. Currently, there are a number of imaging modalities that can be used to detect and quantify various aspects of the disease. With hypothesis-driven approaches targeting key organs, contemporary cardiometabolic imaging affords quantitative, noninvasive, and serial *in vivo* evaluation of disease mechanisms and treatment response. Appropriate techniques warrant greater integration into clinical trials and evidence-guided management of patients with cardiometabolic disease.

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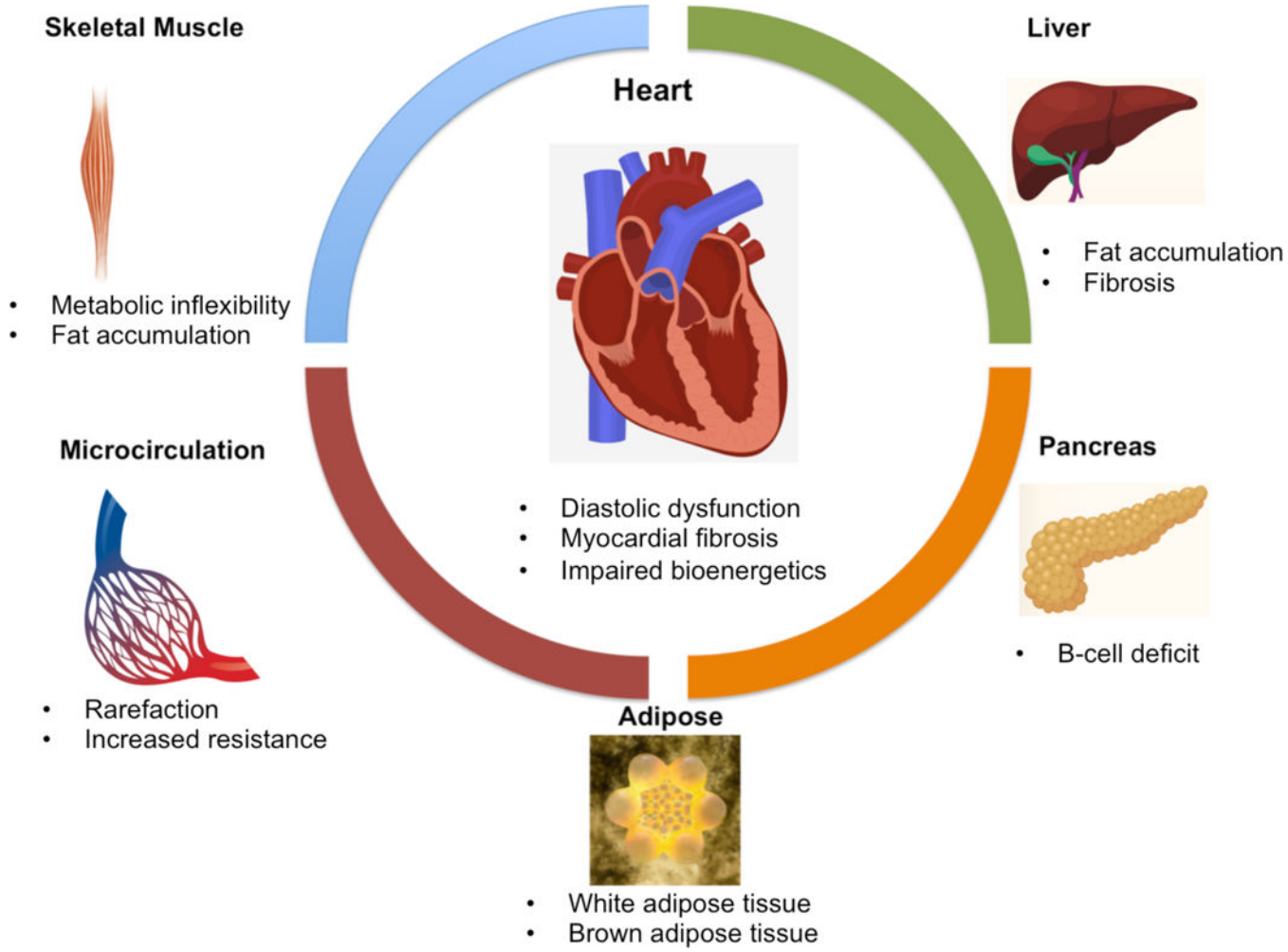

Figure.

The cardiac consequences of cardiometabolic disease ensue from functional and structural alterations in multiple organ systems, including skeletal muscle, liver, the pancreas and microcirculation. Primary imaging targets for non-invasive investigation of CMD are listed. Multiple imaging modalities are used in the evaluation of organ systems involved in CMD. Skeletal muscle investigation typically involves multinuclear MR spectroscopy and MR imaging. Liver is non-invasively interrogated using CT, elastography (both MR and US) and PET for fat quantification, fibrosis quantification and glucose utilization, respectively. Pancreatic beta cell deficit is measured in humans using novel SPECT and PET techniques and in preclinical models with magnetic nanoparticles and MR imaging techniques. Adipose tissue can be quantified using MRI, CT, US and dual-energy x-ray absorptiometry. Brown adipose tissue can be quantified using FDG-PET techniques. Microcirculatory rarefaction and resistance can be evaluated with optical imaging techniques and PET. Finally, the heart in CMD can be investigated using US, MRI and multinuclear MR spectroscopy.