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COMMENTARY

Imaging-based characterization of cardiometabolic phenotypes focusing on whole-body MRI—an approach to disease prevention and personalized treatment

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ABSTRACT

Metabolic syndrome and cardiovascular disorders pose a challenge to global healthcare systems. Too often, patients with metabolic syndrome are diagnosed in advanced disease stages, where disease-associated damage is irreversible and treatment options are limited. Thus, prevention plays an increasingly important role in the management of cardiometabolic disorders. The main challenge of prevention is to identify patient groups who are at risk for developing overt disease and who might benefit from early therapeutic intervention. In this context, imaging-based phenotyping can add significant information to clinical evaluations, revealing anatomical and physiological changes that reflect intrinsic and extrinsic risk factors. The purpose of this review article was to provide an overview of the current state of imaging-based phenotyping of metabolic syndrome and cardiovascular disorders and to discuss current and potential developments in this field.

INTRODUCTION

Metabolic syndrome is defined as a combination of impaired insulin sensitivity, obesity, arterial hypertension, elevated serum triglycerides and reduced high-density lipoprotein cholesterol.¹ The prevalence of metabolic syndrome and of associated cardiovascular diseases, including coronary artery disease, peripheral artery disease and cerebrovascular disease, have increased rapidly over recent decades. The main causes of this development can be found in epidemiological factors and changes in the lifestyle of the general population in developed and developing countries. Current estimates and projections indicate that this trend will continue and pose challenges to healthcare systems globally.^{2,3}

These medical conditions are chronic in nature and are often diagnosed in advanced stages, where clinical symptoms become evident and disease-related damage is irreversible. The focus of research has therefore been directed towards disease prevention and the early detection of pre-clinical stages of disease. The identification of individuals at risk or in the early stages of developing metabolic or cardiovascular diseases may allow for early therapeutic intervention and possibly prevent the transition to clinically overt disease stages.⁴

However, identifying early indicators that precisely predict an individual's predisposition is a difficult task.

The common risk factors used in clinical practice mostly reflect environmental conditions (e.g. habits, lifestyle) without considering intrinsic (e.g. genetic) parameters. As a consequence, these risk factors are statistically predictive for large populations but can fail when applied to individual cases.⁵

Similarly, the ongoing attempt to find genetic markers for disease has led to the identification of certain genotypes that are statistically associated with metabolic or cardiovascular disorders. However, in the context of cardiovascular medicine, these associations are relatively weak and have limited predictive significance in individual cases.⁶

An alternative approach lies in the definition and description of phenotypes that reveal an individual's risk profile. In this context, a phenotype is understood as the set of physical properties of an individual that can be measured objectively. The rationale behind this approach is that an individual's phenotype should reflect both extrinsic, or environmental, and intrinsic, or genetic, predispositions.

Simple phenotypic measures have been successfully used in daily clinical routines for a long time, including blood pressure, body mass index and recently waist-to-hip ratio.⁷ These parameters can be acquired very easily but remain literally superficial. Modern medical imaging technology currently allows a much more detailed and precise phenotypic characterization of individuals. As a logical step, first attempts have recently been made to introduce medical imaging as a tool for the early diagnosis and prediction of disease courses.

This article provides an overview of the technical aspects of medical imaging and the first scientific results obtained by using medical imaging techniques for phenotyping and detection of risk factors for the development of metabolic and cardiovascular disorders.

IMAGING TECHNIQUES AND METHODOLOGY

Certain criteria must be met by an imaging modality in order to be used as a prognostic tool in a clinically healthy population. Most importantly, such a study should be non-invasive and possible adverse side effects should be minimal. In addition, the modality should be widely available and accessible. Measurements should be highly reproducible and quantitative to achieve an optimal result.

None of the currently available imaging modalities fit all criteria perfectly. MRI is the modality that best meets these criteria, and thus the majority of studies on this topic are performed using MRI. Compared with MRI, CT and plain radiography have the disadvantage of being associated with a radiation dose, which is perceived as a form of invasiveness. Sonography, as the third potentially suitable modality, suffers from reduced reproducibility and highly variable image quality.⁸ Still, CT and sonography can be considered for specific applications where MRI has methodological limitations (e.g. CT for the quantification of coronary calcium burden or dual-energy X-ray absorptiometry for measurement of bone density).

Apart from its non-invasive nature, MRI has the advantage of being an intrinsically versatile imaging modality allowing for the imaging of all anatomical regions in great detail and providing additional functional information. For most applications, this methodical versatility comes at the price of lacking standardization and long examination times. Therefore, producing reproducible and comparable results is of the utmost importance to define standardized and time-efficient MR protocols covering the phenotypic features of interest. Such protocols have already been suggested for large epidemiological studies and show similar compositions.^{9,10}

Table 1 shows whole-body MR sequence protocols from two large epidemiological MRI studies focusing on—among others—metabolic and cardiovascular conditions. In these studies, scanners with magnetic field strengths of 1.5 and 3.0 T were used. The 3.0-T system used in⁹ has a relatively large bore size of 70 cm, which is advantageous when examining patients who are obese. As shown in Table 1, the respective MR protocols consist of whole-body sequences followed by organ-specific studies. The acquisition time of these or similar protocols is approximately 1 h.

A central aspect of phenotypic imaging in the context of diabetes and obesity is the quantification and qualitative analysis of adipose tissue compartments. While the first studies on adipose tissue distribution were performed using simple T_1 weighted sequences,¹¹ imaging techniques have rapidly evolved in this field, and in present studies, whole-body multiecho chemical-shift imaging is used for fat quantification. In addition, MR spectroscopy is used to examine the composition of lipids within adipose tissue compartments, providing detailed information about fat metabolism.¹²

The imaging of cardiovascular phenotypes, on the other hand, consists of specific cardiac sequences that allow for anatomic and functional characterization of the heart as well as for angiographic studies that provide information about the vascular

Table 1. Examples of cardiometabolic MR protocols

Application	SHIP	German National Cohort Study
Cardiac imaging	SSFP 2/4-chamber + short axis	Cine 2/3/4 chamber + short axis
	Cine 2/3/4 chamber + short axis + transverse	T_1 mapping (MOLLI short axis)
	PSIR single-shot post-contrast medium	
Vascular imaging	T_1 FLASH 3D head-to-feet pre-contrast/post contrast	3D SPACE STIR angiography of the chest
	Transverse TOF angiography of the head	
Metabolic imaging	Transverse T_1 VIBE chest/abdomen	Whole-body T_1 weighted 2-point Dixon
		Multiecho T_1 weighted gradient-echo sequence of the liver

3D, three-dimensional; FLASH, fast low-angle shot; MOLLI, modified look-locker inversion recovery; PSIR, phase-sensitive inversion recovery; SHIP, Study of Health in Pomerania; SPACE, sampling with application-optimized contrast using different flip-angle evolutions; SSFP, steady-state free precession; STIR, short tau inversion recovery; TOF, time of flight; VIBE, volume-interpolated breath-hold examination.

Excerpts from MRI protocols of the SHIP MRI (1.5-T MR scanner)¹⁰ and the German National Cohort MRI study (3-T MR scanner)⁹ showing dedicated cardiac, vascular and metabolic sequences.

Angiography is performed using gadobutrol as the i.v. contrast agent in the SHIP, whereas no i.v. contrast is used in the German National Cohort MRI study.

system. It should be noted that angiography can be performed with¹⁰ or without⁹ the application of intravenous contrast agents, which has an impact on the invasiveness of the study and associated risks.¹³ Figure 1 shows an example of a possible cardiovascular whole-body MRI protocol using MRI.¹⁴

IMAGING PHENOTYPES IN DIABETES

The recognition of the adipose tissue as a metabolically active endocrine organ has led to extensive research in the field of adipose tissue distribution and the metabolic characterization of adipose tissue compartments. MRI has played a central role in this research effort, providing the methodological basis.

The first studies focused on the phenotypic characterization of fat distribution in patients with pre-diabetes and diabetes.¹⁵ These studies established the concept of ectopic adipose tissue compartments as excessive accumulations of fat in anatomical areas that do not serve as typical fat-storage depots.¹⁶

Further studies revealed that these ectopic fat depots are associated with a higher risk for the development of metabolic syndrome. Specifically, it is now well established that the visceral adipose tissue (VAT) represents an independent risk factor for developing impaired glucose tolerance, diabetes and metabolic syndrome.¹⁵ Similarly, hepatic steatosis (non-alcoholic fatty liver disease) is associated with a higher risk for not only Type 2 diabetes but also the development of cardiovascular complications.¹⁷ The extent of these fat depots has been shown to be independent of simple anthropometric data such as body mass index or waist-to-hip ratios, providing much more differentiated characterization of individual body composition.¹¹

Ectopic adipose tissue depots have furthermore been shown to affect the local metabolism and function of organs. Initial studies revealed the association of pancreatic steatosis, metabolic syndrome and insulin resistance.¹⁸ Similarly, epicardial fat accumulation has been suggested as an independent risk factor for coronary artery atherosclerosis and diabetic cardiomyopathy.¹⁹

Whole-body MRI offers the possibility of studying the pathophysiological associations of different organ systems. A research focus has recently developed on the interplay of metabolic syndrome and brain physiology. Recent studies revealed grey and white matter atrophy in individuals who are obese and higher risk of cerebrovascular disease in patients with visceral fat accumulation.^{20,21}

The high-risk metabolic phenotypes described above can also be found in children, adolescents and young adults. Recent studies in children and adolescents revealed an association of the abundance of VAT and liver fat, with impaired glucose tolerance and dyslipidemia.^{22,23} Increased fat depositions were described in adolescents who were obese with metabolic syndrome.²⁴ Metabolic phenotyping may also play a future role in paediatric patients, paving the way for early intervention and prevention strategies.

As described above, as phenotypic descriptions of at-risk individuals have advanced in recent years, the focus of scientific interest has moved towards the evaluation of possible clinical applications. Initial studies showed that it is possible to monitor the effect of therapeutic interventions on body fat composition using MRI and that interventions such as dietary changes or

Figure 1. Example of a cardiovascular whole-body MRI protocol used for predictive imaging in patients with diabetes on a 3.0-T scanner (reproduced from Bamberg et al¹⁴ with permission from The Radiological Society of North America). Cardiac imaging (a) shows cine sequences (top and middle), revealing focal wall hypokineses (arrows) while late gadolinium enhancement (bottom, arrowhead) reveals scar tissue after myocardial infarction. Cerebrovascular imaging (b) shows no manifestations of cerebrovascular disease in cerebral angiography (top) or T_2 weighted imaging (middle and bottom). In whole-body angiography (c), the arrows indicate discrete variations of the left carotid artery and the abdominal aorta as well as vessel occlusion of the lower right leg. The perceived signal discontinuity of the left femoral artery is artificial and can be attributed to stacking of adjacent acquisition levels.

increased physical activity^{25,26} result in a relevant reduction in liver fat content and somewhat in VAT.

Besides its prognostic value in metabolic syndrome, medical imaging can also be used for the assessment of associated complications. The progression of non-alcoholic fatty liver disease to non-alcoholic steatohepatitis, hepatic fibrosis and cirrhosis is associated with high morbidity and mortality. MR- and ultrasound-based elastography can be used to quantify changes in hepatic stiffness that reflect the development of hepatic fibrosis and cirrhosis and thus enable early therapeutic interventions.^{27,28}

IMAGING PHENOTYPES IN CARDIOVASCULAR DISEASE

Medical imaging plays a central role in the diagnosis of cardiovascular disorders in daily medical practice. Cardiac CT, cardiac MRI, CT- and MR-based angiography are routinely used to characterize the state of the cardiovascular system in patients who are symptomatic. Beyond the imaging of patients who are symptomatic, imaging has also been suggested for risk assessment in individuals who are asymptomatic.

With the development of CT scanner technology, cardiac CT studies have become feasible with reliably high image quality and steadily decreasing radiation exposure.^{29,30} The quantification of the coronary calcium burden by CT is an extensively studied method for assessing an individual's risk for coronary artery disease. A high coronary calcium burden has been shown to be a strong predictor for major cardiac events independent of racial background and conventional risk factors.³¹ Similarly, a recent study revealed a high predictive value of coronary CT angiography for the occurrence of cardiac events in patients who

are asymptomatic and additional negative-predictive value for the presence of coronary artery disease compared with coronary calcium scoring.³²

Strong evidence also exists, supporting the prognostic value of carotid artery intima-media thickness measured by ultrasound as a prognostic test. Increased carotid intima-media thickness has been shown to be associated with higher risk for stroke as well as myocardial infarction in patients who were previously asymptomatic.³³ In contrast to other sonographic studies, measurement of carotid artery intima-media thickness can be performed with high reproducibility.³⁴

Coronary calcium scoring and carotid artery media thickness measurement have both found entrance into the American College of Cardiology Foundation/American Heart Association guidelines for cardiovascular risk assessment in individuals who are asymptomatic.³⁵

With the introduction of whole-body MR protocols, MRI has also been proposed as a tool for detecting and characterizing the pre-clinical stages of disease. The initial studies concentrated on whole-body MR angiography, revealing the feasibility of detecting previously unknown vascular disease and showing a good correlation between MR angiography findings and conventional risk factors.³⁶

More recent studies evaluated the possible additional predictive significance of MRI with respect to the occurrence of cardiovascular events. It could be shown that the presence of peripheral artery disease, as detected by whole-body MR angiography, is associated with a significantly increased risk for coronary artery disease.³⁷ Conversely, a population-based study in a large population drawn from the Heinz Nixdorf Study revealed a high

Figure 2. Predictive power of cardiovascular whole-body MRI for the occurrence of cerebrovascular and cardiovascular events in patients with diabetes patients (reproduced from Bamberg *et al*¹⁴ with permission from The Radiological Society of North America). Patients with imaging-based subclinical manifestations of cardiovascular disease (red curve) were at higher risk for events, while patients without any findings remained event free over the follow-up (blue curve). This difference remained after adjustment for clinical characteristics. These results may possibly result in a therapeutic consequence in the future. For colour image see online.

prevalence of previously unknown cerebrovascular and peripheral artery disease in patients with coronary artery disease.³⁸ These results are also supported by a study in a population of individuals who are diabetic, indicating that whole-body cardiovascular MRI, including cerebrovascular, cardiac and angiographic examinations, provides strong prognostic information concerning the occurrence of major adverse cardiac and cerebrovascular events (Figure 2).¹⁴ Furthermore, MRI was able to predict which patients experienced recurrent events and had therefore a worse clinical course.³⁹ Similar results were found in a study of randomly selected 70-year-old subjects, revealing the prognostic significance of whole-body cardiovascular MRI for the prediction of major adverse cardiovascular events independent of conventional risk factors.⁴⁰

IMAGING OF METABOLIC SYNDROME

As discussed above, medical imaging can contribute to a detailed understanding of the relationship between phenotypic changes and an individual's predisposition for metabolic and cardiovascular disease. It is well established that metabolic syndrome and cardiovascular disorders are strongly associated and share common pathophysiological features and risk factors.⁴¹ This interdependence is also reflected by the strong overlap of metabolic syndrome and cardiovascular phenotypes defined by imaging methods.

The high-risk metabolic phenotype that is characterized by central obesity and ectopic fat accumulation, as described above, is associated with a significantly elevated risk for the development of cardiovascular complications. In a large cohort drawn from the Framingham Heart Study, visceral fat as measured by CT was associated with a significantly elevated risk for cardiovascular events after adjustment of conventional risk factors.⁴² These results are supported by further studies, suggesting increased risk for cerebrovascular events in individuals with visceral adiposity⁴³ and increased risk for coronary artery disease in individuals with mediastinal and epicardial fat accumulation. In a recent large multinational study, abdominal VAT was measured by CT, revealing a significant correlation between VAT abundance and the prevalence of cardiovascular disorders independent of the presence of diabetes.⁴⁴

A recent study of a population of young adults who were obese revealed an association between increased ectopic intramuscular fat, as measured by CT and cardiovascular risk factors and early signs of cardiovascular disease.⁴⁵

CHALLENGES, CURRENT RESEARCH EFFORTS AND OUTLOOK

As summarized above, the technical and conceptual prerequisites for imaging-based phenotyping have been established over the past decade, and the predictive significance of these

phenotypes beyond conventional risk factors has been demonstrated. At this stage of development, predictive imaging is a powerful research tool, contributing to the understanding of pathophysiological processes. Certain challenges, however, must be overcome to introduce this novel concept into clinical reality.

Importantly, the transition from predictive imaging to clinical decision-supporting imaging must be initiated. To this end, interventional studies should be performed in at-risk populations to assess the feasibility of early imaging-guided therapeutic stratification and the possibility of therapy monitoring. Ideally, these studies should be planned with a focus on contributions by multiple imaging centres combined with the necessary expertise from experts in metabolic and cardiovascular medicine.

Equally important, the database of possible phenotypes within a population and their associations with non-imaging parameters should be extended and standardized. To this end, unprecedented efforts have been made in the implementation of imaging in population-based studies, including the SHIP (Study of Health in Pomerania),¹⁰ German National Cohort study⁹ and UK Biobank Imaging study.⁴⁶ Thousands of participants drawn from the general population will be examined by the means of whole-body MRI within the next few years using standardized protocols. The resulting data are expected to give detailed insight into human phenotypes in not only the stages of disease but also the course of healthy ageing.

To efficiently analyse the overwhelming amount of data generated with each imaging study, novel approaches to the analysis of imaging studies are necessary. Automated approaches have been suggested and recently successfully introduced for selected applications; for example, the automated quantification of adipose tissue compartments.⁴⁷ Further developments in this field and a closer cooperation between the medical sciences and computer science are to be expected in the near future. This expansion in methodology might also pave the way for the discovery of more subtle phenotypic features that are difficult for a human observer to perceive.

CONCLUSION

Imaging-based phenotyping, especially using MRI, has evolved into a dynamic and promising field of basic and clinical research over recent decades. Initial studies demonstrated the feasibility of detecting unique subclinical markers of disease and predicting an individual's risk for the development of clinically overt disease stages. The current challenges lie in the standardized acquisition and analysis of imaging data and in the definition of clinical application fields that will benefit from this novel concept of predictive imaging. Imaging-based phenotyping may then become a keystone in disease prevention and personalized treatment.

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