MR and CT evaluation of cardiovascular risk in metabolic syndrome

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CHAPTER 1

General introduction and outline of thesis

GENERAL INTRODUCTION

There is a global epidemic of overweight and obesity in many parts of the world. Body mass index (BMI, defined as bodyweight in kilograms divided by the square height in meters (kg/m^2)) is a commonly used measure to classify overweight and obesity in adults. According to the World Health Organization (WHO), a BMI greater than or equal to 25 is overweight; a BMI greater than or equal to 30 is obesity. In 2014, more than 1.8 billion adults were overweight, and 600 million were obese. Worldwide obesity has more than doubled since 1980 (1). Parallel to the increasing prevalence of obesity and physical inactivity, metabolic syndrome has become a major public health problem (2). In most countries throughout the world between 20% and 30% of the adult population can be characterized as having metabolic syndrome (3-9). Patients with metabolic syndrome are at essentially twice the risk for cardiovascular disease compared to those without the syndrome. Furthermore, it raises the risk for type 2 diabetes by approximately 5-fold (10, 11). Metabolic syndrome is a systemic disease with a multifactorial pathogenesis and consists of abdominal obesity, hyperglycemia, dyslipidemia (decreased high-density lipoprotein cholesterol and/or increased plasma triglycerides), and elevated blood pressure (9). Presence of three of any of these factors suffices for the diagnosis of metabolic syndrome (12). Patients with metabolic syndrome are a heterogeneous population with varying risk. Early identification of those patients with subclinical cardiovascular or cerebrovascular disease manifestation is highly relevant as organ damage might still be reversible (13-15). Imaging can be used for risk stratification and optimizing individual prevention and treatment strategies in patients with metabolic syndrome. This thesis evaluates MR and CT imaging techniques for identifying risk factors and subclinical disease in metabolic syndrome, as is summarized in the following paragraphs.

Visceral adiposity and fatty liver

Abdominal obesity is the most prevalent feature of metabolic syndrome. It is generally accepted that excess intra-abdominal fat accumulation is a key correlate and perhaps driver of the health risk associated with overweight and obesity (16). Waist circumference is a simple and inexpensive yet effective clinical measure of abdominal obesity (17). However, waist circumference cannot distinguish between abdominal subcutaneous (SAT) and visceral adipose tissue (VAT). It is known that these fat depots are morphologically and functionally different, and metabolic disturbances are considered greater in visceral adiposity than in subcutaneous obesity (16-18). In addition, it is increasingly recognized that excess visceral adiposity may be a marker of dysfunctional SAT leading to fat accumulation at undesired sites including the liver (16). Increasing evidence suggests that accumulation of fat in the liver is another important determinant of the cardiometabolic complications of obesity (19). For example, it has been shown that fatty liver is associated with dyslipidemia and dysglycemia, also after adjusting for the amount of abdominal visceral fat (20). It is crucial to assess body fat distribution to understand the adverse effects of

obesity as specific fat depots may predispose certain individuals to developing obesity related illnesses. MRI and computed tomography (CT) are commonly used methods for distinguishing and quantifying abdominal fat compartments as well as assessing fatty liver. These imaging biomarkers may help in advanced risk stratification.

Aortic stiffness

Aortic stiffness is an independent cardiovascular risk factor (21). It has been shown that individuals with obesity are likely to have an increase in aortic stiffness, independent of blood pressure, age, and other potential confounding factors (22,23). Aortic stiffness may be an important phenomenon linking obesity to increased cardiovascular risk. Increased aortic stiffness results in deficient absorption of the pulse waves traveling through the vascular system (24). The resultant excessive pulsatile flow is transmitted to the periphery where it may cause damage in end organs such as the brain and kidney, because these organs have low-resistance vascular beds and are passively perfused at high flow throughout the cardiac cycle (24). Pulse wave velocity (PWV), a commonly used surrogate marker of aortic stiffness (25), is defined as the velocity of the systolic wave front propagating through the aorta. Velocity-encoded magnetic resonance imaging (VE-MRI) is a noninvasive and accurate technique for measuring PWV that has been well-validated against invasive pressure measurements (26). Of note, VE-MRI allows for the measurement of regional PWV, also in the aortic arch, whereas ultrasound measurements merely provide and estimation of global aortic PWV (27). Evaluation of the aortic arch may be of particular importance as it has a distinct association with cerebral microvascular disease (28). Increased aortic arch stiffness integrates and reflects the long-term effects of all identified and currently unknown cardiovascular risk factors, and can be assessed at a stage when organ damage may be reversible (25). MRI of aortic arch stiffness provides functional information about vessel compliance that may help determine risk for cardiovascular or cerebrovascular disease (29).

Brain damage

Risk factors associated with metabolic syndrome may accelerate brain disease. MRI can be used to assess imaging evidence of cerebral small vessel disease including white matter hyperintensities and brain atrophy, which in turn have been related to cognitive decline (30). In addition to these overt structural brain abnormalities, novel MRI techniques including magnetization transfer imaging (MTI) and diffusion tensor imaging (DTI) have been used to detect microstructural brain tissue damage that is not visible on conventional structural MRI (31,32). By using these novel imaging techniques, recent studies have shown that changes in brain tissue integrity can be detected in association with risk factors associated with metabolic syndrome (33-35). However, evidence of metabolic syndrome as a risk factor per se is limited (30). In addition, it is unknown whether brain tissue decline is present before MRI evidence of cerebral small vessel disease may become overt. To formulate treatment and prevention strategies, it is crucial to understand the

mechanisms underlying cerebral microvascular disease (29). Using an advanced MRI protocol for combined assessment of aortic arch stiffness and brain tissue integrity may provide insight in the mechanisms underlying subclinical brain disease.

MR and CT imaging techniques

Imaging techniques are available for identifying risk factors and subclinical disease in metabolic syndrome. As mentioned before, it is crucial to assess body fat distribution to understand the adverse effects of obesity. MR and CT can be used to distinguish and quantify abdominal fat compartments as well as assessing fatty liver. VE-MRI has been used as a noninvasive and accurate method for measuring PWV, which is a surrogate marker of arterial stiffness. MRI of aortic stiffness may help determine risk for cardiovascular or cerebrovascular disease. DTI and MTI are relatively new imaging techniques that enable subclinical brain disease to be explored in more detail. DTI probes the direction and magnitude of water diffusion along the axons (36), whereas MTI probes the protons bound to large molecules such as myelin lipids and proteins (37,38). Both DTI and MTI have been used to investigate brain tissue microstructure in normal aging, different disease states, and in association with cardiovascular and metabolic risk factors (39-42).

OUTLINE OF THE THESIS

The studies in this thesis focus on MRI and CT evaluation of cardiovascular risk in metabolic syndrome.

In chapter 2, we evaluate whether regional body fat distribution assessed by CT is different in association with longevity, which in turn has been related to an exceptionally healthy metabolic profile and low prevalence of cardiovascular disease. Chapter 3 describes the extent of liver steatosis in non-diabetic offspring of long-lived siblings and controls by evaluating liver enzymes in plasma and liver to spleen CT attenuation ratio as a measure of liver fat. Chapter 4 reports the association between liver steatosis assessed by CT and brain tissue integrity assessed by MTI in middle-aged to elderly persons. In chapter 5 the relation between aortic arch PWV assessed by VE-MRI and DTI measures of brain tissue integrity is investigated in hypertension patients. Chapter 6 investigates the association between metabolic syndrome and brain tissue integrity assessed by MTI and DTI. In addition, independent associations between the individual metabolic syndrome factors and brain tissue integrity are reported. Chapter 7 shows the association between MTI measures of brain tissue integrity and cognitive test performance in older persons at increased risk for vascular disease. Chapter 8 describes the effect of temporal resolution on the accuracy of aortic arch PWV assessed by VE-MRI in healthy volunteers and patients referred for cardiac MRI.

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