Metabolic and functional evaluation of diabetic cardiomyopathy using MR Spectroscopy and MR Imaging

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Chapter 1

General introduction and outline

General introduction

Type 2 diabetes mellitus (T2DM) affects almost half a billion people worldwide, and prevalence has been estimated to increase by 25% in 2030 and 51% in 2045[1]. This rise in prevalence is largely caused by increasing obesity rates worldwide. The severity of this pandemic is signified by a two-fold increased risk of cardiovascular disease (CVD) and cardiovascular death in patients with T2DM[2]. Overall, about half of T2DM patients die from CVD[2].

The increased risk of cardiovascular (CV) complications in T2DM is partly caused by the co-existence of "traditional" CV risk factors such as obesity, hypertension and dyslipidemia (the metabolic syndrome). These conditions drive the process of atherosclerotic disease leading to coronary artery disease (CAD) and myocardial infarction. As compared to other patients with myocardial infarction, T2DM patients with myocardial infarction have a two to five times increased mortality risk, even when other CV risk factors are absent[3]. This suggests that T2DM encompasses an additional adverse CV risk, that goes beyond the traditional CV risk factors. In addition to increased risk of CAD and myocardial infarction, T2DM is associated with a two to three-fold increased risk of heart failure. Of all heart failure patients, approximately 25-40% have diabetes[4]. A large proportion of these patients have ischemic cardiomyopathy, predominantly characterized by heart failure with reduced ejection fraction (HFrEF)[4]. Interestingly, in T2DM patients without CAD there is an increased prevalence of heart failure. In literature, the term diabetic cardiomyopathy has been used for this clinical condition[5]. Although strict criteria to diagnose diabetic cardiomyopathy are currently lacking[5], the cardiac phenotype has been characterized in detail. Diabetic cardiomyopathy is marked by concentric left ventricular (LV) remodeling with diastolic dysfunction, i.e. heart failure with preserved ejection fraction (HFpEF)[6]. The mechanism behind this increased risk is not fully understood, but may involve insulin resistance, impaired myocardial energy metabolism, myocardial steatosis and fibrosis[5]. In light of the high prevalence of heart failure in T2DM patients, heart failure has been suggested to be a forgotten diabetes complication that can no longer be ignored in large CV outcome trials[7].

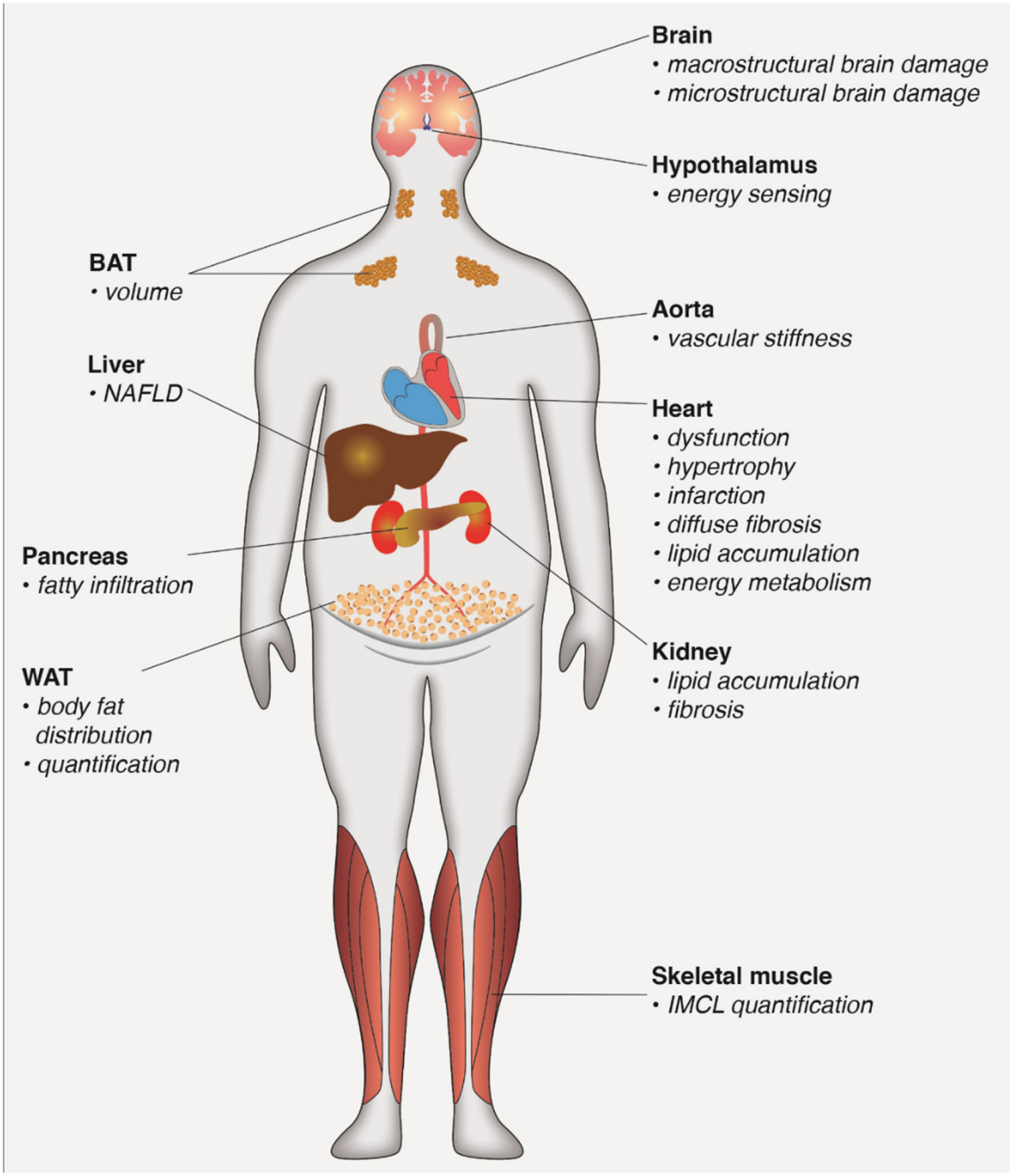

Figure 1. Overview of MRI and MRS assessment of multi-organ involvement in T2DM. MRI accurately assesses the distribution of body which is deposited in the visceral adipose tissue and ectopically in and around orans. Hepatic steatosis, may play a central role T2DM pathophysiology and can progress into nonalcoholic steatohepatitis, fibrosis, and cirrhosis. Cardiovascular MR detects focal (eg, myocardial infarction) or global (eg, diabetic cardiomyopathy) pathology. Diabetic cardiomyopathy is characterized by left ventricular dysfunction, hypertrophy, diffuse fibrosis and myocardial steatosis. Various other organs and tissues, such as the brain, kidneys, pancreas, and skeletal muscle, undergo pathologic alterations in T2DM. Figure reference: M.B. Bizino et.al. Magn Reson Imaging Clin N Am. 2015 Feb;23(1):41-58.

Magnetic Resonance Imaging (MRI) is a non-ionizing imaging modality that has proven useful to characterize CV complications in T2DM patients[8], of which an overview is represented in figure 1. Cardiovascular MR (CMR) has the ability to combine high spatial resolution imaging with superior image contrast. As such, CMR is the gold standard for the quantitative assessment of cardiac morphology, for example LV volume and LV hypertrophy. MR cine imaging enables to assess LV systolic function with high reproducibility. MR phase contrast imaging with velocity encoding is a robust technique to quantitatively assess blood flow to evaluate LV diastolic function with high reproducibility (see figure 2). MR angiography can be used for example to image coronary arteries to evaluate atherosclerotic stenosis. When a gadolinium contrast agent is used, myocardial infarction can be assessed and quantified with high precision (late gadolinium enhancement MR imaging). CMR can be combined with Magnetic Resonance Spectroscopy (MRS) in one single exam. MRS is a unique tool to gain insight into cardiac energy metabolism, for example by assessing myocardial steatosis with ^{1}H-MRS, see figure 3. Myocardial steatosis is defined as an increased abundance of intracellular triglyceride depositions, i.e. ectopic fat accumulation. Myocardial steatosis has been linked to adverse cardiac morphology[9] and left ventricular diastolic function[10] in T2DM As such, an integrated morphological, functional and metabolic assessment of CV (dys)function can be performed using a single MR exam. In light of its non-ionizing properties and high reproducibility, MR is a suitable imaging modality to evaluate efficacy of therapeutic interventions to treat or prevent various CV complications in T2DM.

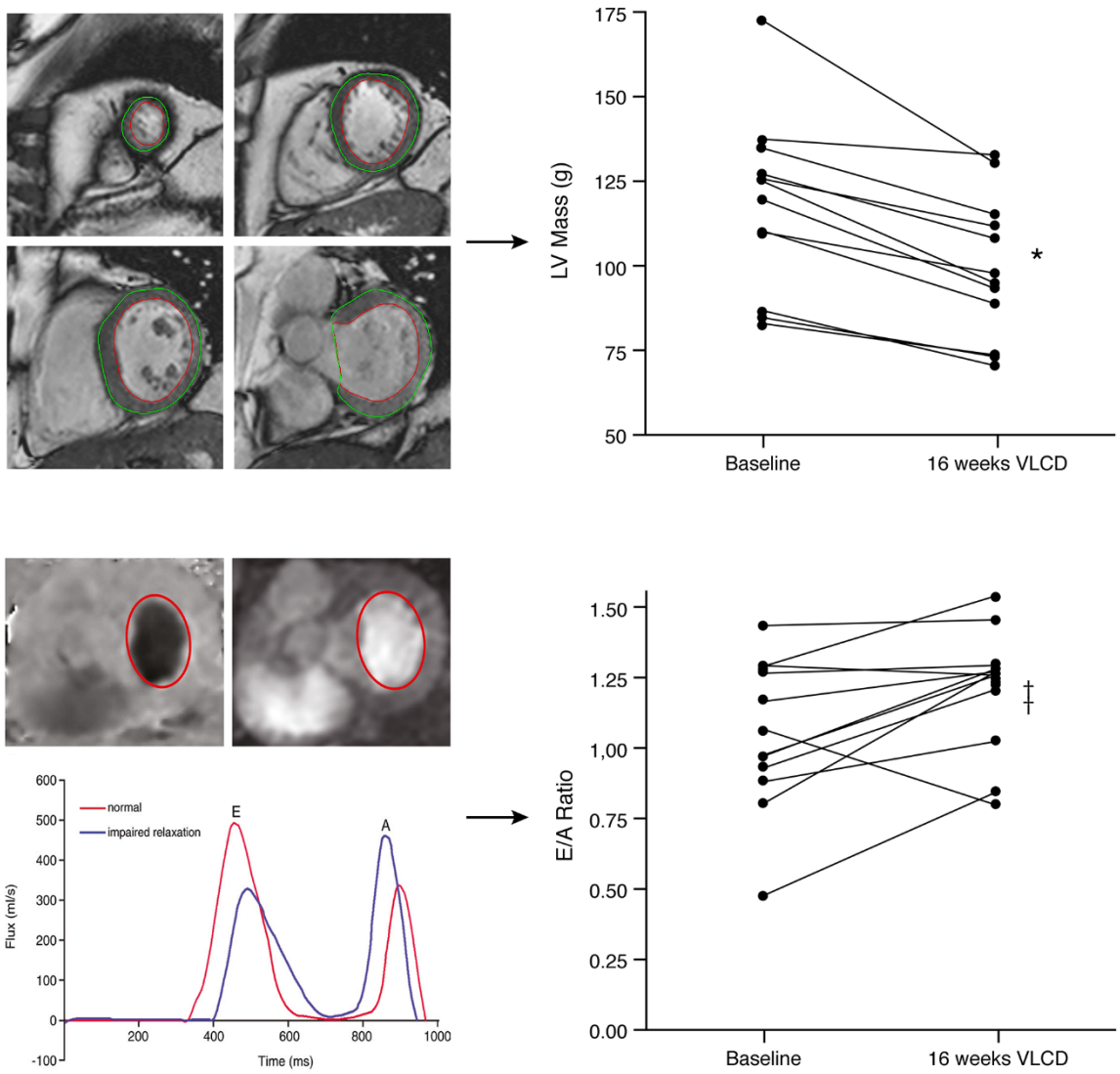

Figure 2. This figure represents reversible cardiac manifestations associated with T2DM: left ventricular hypertrophy and diastolic dysfunction. MR measures left ventricular (LV) mass and diastolic function with high precision and reproducibility. The upper left panel shows short axis views - as required with MR cine imaging of the LV - enabling accurate determination of LV mass. In this particular example, LV mass diminished in T2DM patients after a 16-week very lowcalorie diet, upper right panel. By combining cine imaging with transmitral phase contrast imaging with velocity encoding, LV diastolic function can be assessed within the same MR examination (lower left panel). LV diastolic function is reflected by the E/A ratio (E = early filling phase, A = atrial late filling phase). In T2DM the E/A ratio is frequently diminished (< 1.0). As shown in the lover right panel, LV diastolic function can be improved in association with decreased LV mass. * P<0.001; y P<0.05. Figure reference: M.B. Bizino et.al. Magn Reson Imaging Clin N Am. 2015 Feb;23(1):41-58. This figure is based on [Left lower panel] van der Meer RW, Lamb HJ, Smit JW, et al. MR imaging evaluation of cardiovascular risk in metabolic syndrome. Radiology 2012;264(1):31 and [Right panel] Hammer S, Snel M, Lamb HJ, et al. Prolonged caloric restriction in obese patients with type 2 diabetes mellitus decreases myocardial triglyceride content and improves myocardial function. J Am Coll Cardiol 2008;52(12):1011.

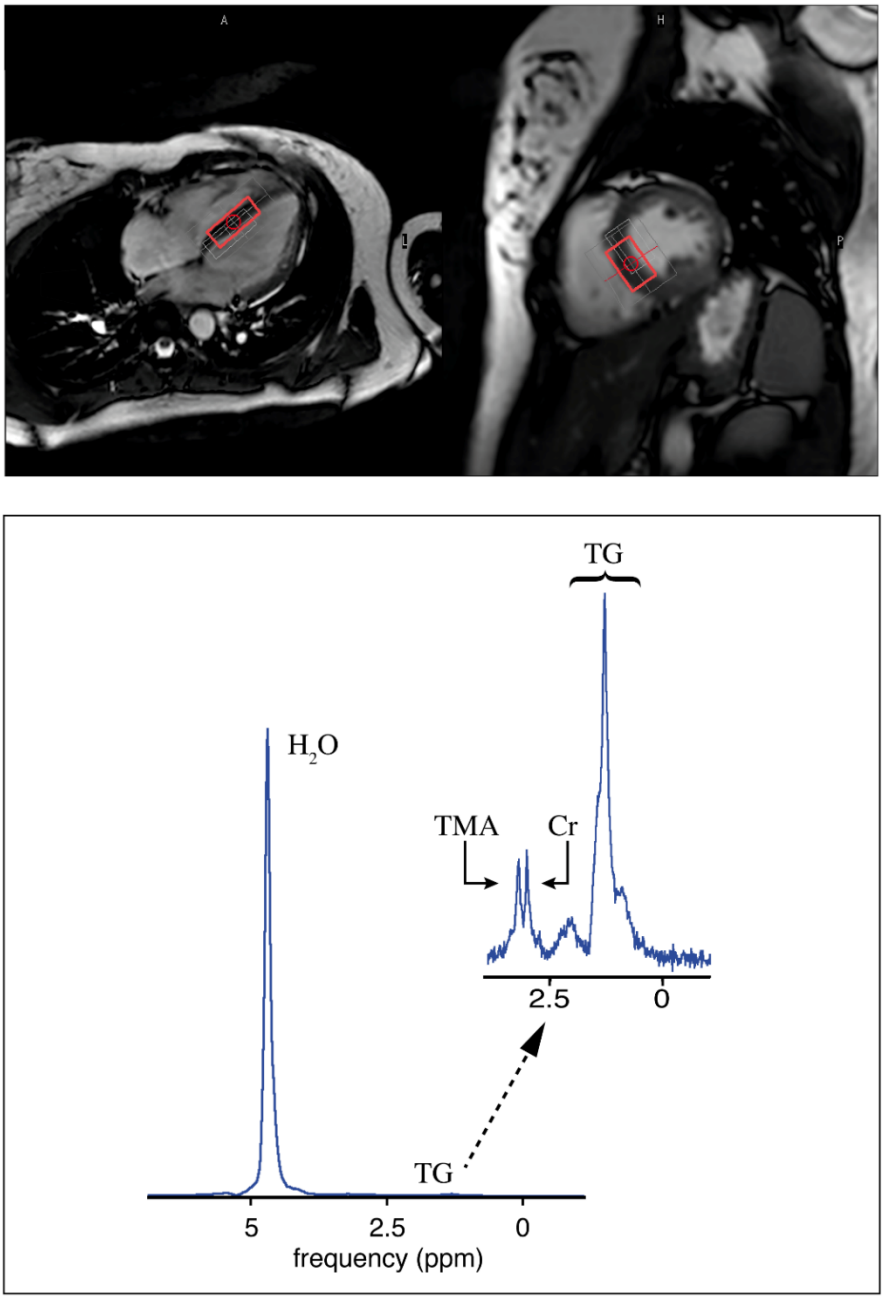

Figure 3. Cardiac proton magnetic resonance spectroscopy (^{1}H-MRS) to quantify myocardial steatosis can be performed on 1.5 and 3 T MR systems using commercially available transceiver coils. Cardiac ^{1}H-MRS is subject to motion artifacts owing to contraction and breathing. To overcome these issues, cardiac ^{1}H-MRS is usually performed with electrocardiographic gating and either breath-holding or free-breathing with respiratory motion triggering/compensation. To prevent contamination of pericardial fat, the voxel of interest (VOI) is placed in the interventricular septum. The low abundance of the various metabolites requires water suppression and acquisition of multiple averages resulting in relatively long scan duration. The water-suppressed spectrum displayed in the lower panel shows signals from creatine (Cr), triglycerides (TG) and trimethyl ammonium (TMA). In this example, 16 non–water-suppressed and 48 water-suppressed averages were acquired at 3 T from a VOI of 15 mL. Figure reference: M.B. Bizino et.al. Magn Reson Imaging Clin N Am. 2015 Feb;23(1):41-58

Diabetes care aims to prevent diabetes-related complications, of which CV complications are the most important threats[11]. In general, CV outcome can be improved by controlling hyperglycemia and by modifying CV risk factors such as smoking, obesity, hypertension and dyslipidemia. However, despite all efforts that have been pursued in clinical practice, CV risk remains high in the T2DM population[12]. So to further improve CV prognosis of T2DM patients, therapeutic interventions to reduce ischemic heart disease and diabetic cardiomyopathy are warranted. On an individual level, MR could help identify subjects with subclinical stages of ischemic heart disease and diabetic cardiomyopathy. Such patients, who are at increased risk for future clinical CV complications could be offered intensive therapy. On a population level, MR could be used to detect efficacy to improve CV risk. When heart failure has progressed into a symptomatic stage, mortality rates are even higher. Therefore, early detection of asymptomatic CVD in T2DM might be a worthwhile strategy to detect patients at high risk for adverse CV outcome. Subsequent therapeutic interventions should halt or even reverse subclinical CVD, thereby preventing irreversible damage.

Within T2DM management, two entities of therapeutic interventions are important. First, lifestyle medicine has been traditionally designated as a first-line intervention[11]. By promoting healthy diet and physical exercise, type 2 diabetes can be reversed[13]. To what extent lifestyle interventions are effective in long-standing diabetes requiring insulin-treatment has been less well investigated. Secondly, pharmacologic treatment of T2DM has shown to improve CV outcome in recent years[11]. Most trials have been performed in T2DM patients with very high CV risk, i.e. those with previous myocardial infarction. The glucagon-like-peptide-1 receptor agonist (GLP-1RA) liraglutide lowers the risk of CV events[14]. To what extent this therapy might improve the CV prognosis of T2DM patients without prior CVD, and how liraglutide affects diabetic cardiomyopathy remains to be established.

Outline of thesis

This thesis is the result of collaborative work performed within the departments of Radiology and Internal Medicine (Division of Endocrinology). As such, the studies described in this thesis are related to investigations to optimize MR technology and apply MRI and MRS in the evaluation of lifestyle and pharmacologic interventions aiming to reverse key (early) features of diabetic cardiomyopathy in T2DM patients.

Part 1. Technical Advances in MRS and MRI to Evaluate Diabetic Cardiomyopathy

Cardiovascular MRI has earned its place in the field of clinical cardiac imaging. Regularly used techniques include anatomical imaging, functional imaging, perfusion, and delayed enhancement (DE). The discrimination between non-viable (scarred) and viable (hibernating or stunned) myocardium is of clinical importance to determine the potential benefit of revascularization interventions.

Chapter 2 Clinical application of cardiac magnetic resonance spectroscopy

MRS can be performed using the same MR systems used for routine clinical MRI scans, making it suitable to add MRS to routine clinical MR examinations. MRS in itself generates a spectrum by using the gyromagnetic properties of protons (^{1}H, ^{31}P, ^{13}C and ^{23}Na are suitable). In a predefined voxel of interest, the abundance of metabolites can be quantified as such, as represented in figure 3. In case of ^{1}H-MRS, excitation of hydrogen protons in water and triglycerides (TG) give rise to a unique spectrum at a given frequency. Using dedicated software, the relative abundance of triglycerides is quantified as a ratio against water. As such, ^{1}H-MRS can be used to determine the fat fraction of organs and tissues.

Myocardial triglyceride content as assessed with ^{1}H-MRS reflects the triglyceride pool that is located in cardiomyocytes (i.e. intracellularly). Pre-clinical studies have shown that increased TG stores in the myocardium reflect abundance of toxic lipids (such as diacylglycerol and ceramide)[15,16] that disrupt cardiac energy metabolism. In T2DM

patients increased MTGC is an independent predictor of asymptomatic left ventricular diastolic dysfunction[17]. Importantly, diabetic cardiomyopathy has been shown to be reversed by dramatic weight loss induced by a very low calorie diet[18]. In light of the enormous ATP requirement of the heart, it is not surprising that cardiac energy metabolism and function are so tightly linked[19].

Although aforementioned studies exhibit the widespread use of cardiac ^{1}H-MRS in research settings, the performance of ^{1}H-MRS is generally limited to specialized centers due to technological challenges. One of these challenges is that the voxel of interest is constantly moving due to myocardial contraction and breathing, which challenges acquisition of a reliable spectrum. In conjunction with a low TG content in the myocardium (approximately 0.5% in healthy individuals), the acquisition of a cardiac proton spectrum is challenging and time-consuming. Despite technological solutions that have improved the success rate and quality of cardiac ^{1}H-MRS[20], one of the drawbacks limiting widespread adaptation in clinical cardiac MR examinations is the fact that it remains time-consuming. The aim in **chapter 2** is to review the current standings of application of MRS in cardiac diseases such as ischemic heart disease, diabetic cardiomyopathy, valvular heart disease and heart transplantation. Moreover, the review aims to describe the technological hurdles that need to be addressed to allow further optimization and clinical application of cardiac MRS.

Chapter 3 Cardiac proton magnetic resonance spectroscopy using high permittivity pads

A major technological challenge of ^{1}H-MRS of the heart is the low signal-to-noise ratio (SNR). Low SNR is caused by several factors including low intrinsic signal of myocardial triglycerides, and fluctuations in the main magnetic field (B_0) and in the transmit field (B_1^+). Low SNR can be overcome by acquiring multiple signal averages (between 32 and 128) of which the signals are added up. A drawback of acquiring multiple signal averages is that it is time-consuming: acquisition of a cardiac proton spectrum usually takes over ten minutes. Obviously, that hinders assessment of MTGC in a clinical cardiac MR protocol. Therefore, one important aspect of improving cardiac

^{1}H-MRS is to increase SNR. A recent study using high permittivity material containing a suspension of barium titanate (placed on the subject's chest) has shown that cardiac imaging could be improved by favoring transmit field homogeneity[21]. We hypothesized that a high permittivity pad could also be applied in ^{1}H-MRS. Therefore, the aim in **chapter 3** was to investigate whether high permittivity pads could increase SNR of cardiac ^{1}H-MRS, allowing shorter acquisition time.

Chapters 4 and 5 Improving MR assessment of ischemic heart disease

One strategy to improve CV outcome in patients with T2DM could be to better detect (subclinical) coronary artery disease and previous (silent) myocardial infarction[22]. In high risk patients, therapeutic management could then be intensified, for example by initiating treatment with sodium-glucose cotransporter 2-inhibitors and/or glucagon-like peptide-1 receptor agonists. These agents have shown to exert beneficial effects on major CV outcomes[14,23]. The non-invasive, non-ionizing properties make MR a suitable imaging modality for CV risk assessment in T2DM. Coronary magnetic resonance angiography (MRA)[24-26] and late gadolinium contrast enhancement cardiac MR (LGE-CMR)[27] have been shown to be able to detect coronary artery stenosis and myocardial infarction, respectively. In fact, LGE-CMR is the gold standard for assessment of myocardial viability[27]. However, both coronary MRA and LGE-CMR have some technical challenges that need to addressed.

One technical challenge of coronary MRA is that high spatial resolution is required due to the small size of coronary arteries. Imaging with high spatial resolution decreases SNR and contrast-to-noise ratio (CNR) thereby compromising vessel conspicuity and diagnostic accuracy of stenosis. A previous study has shown that SNR and CNR of coronary MRA could be ameliorated by using a 3 T instead of 1.5 T MR system[28]. Therefore, ultrahigh field (7 T) MR could potentially further boost SNR and CNR thereby enabling high spatial resolution coronary imaging. A previous study had already shown that SNR, CNR and vessel edge sharpness improved at 7 T as compared with 3 T[29]. In **chapter 4**, we aimed to investigate whether high spatial resolution coronary MRA at 7 T had enough image contrast to conserve vessel conspicuity while improving sharpness of the vessel borders.

The traditional method for LGE-CMR is performed in 2D using an inversion recovery gradient echo sequence with manual depiction of the inversion time (applied approximately fifteen minutes post-contrast administration) to null signal of healthy myocardium[27]. During acquisition, patients need to hold their breath repeatedly which can be challenging, especially for patients suffering from heart failure[30]. Another limitation of the traditional LGE-CMR acquisition is that spatial resolution is low, and that image quality highly depends on correct manual depiction of inversion time. Therefore, an LGE-CMR sequence that allows for high spatial resolution 3D acquisition during free-breathing was developed. This sequence also allowed phase sensitive inversion recovery (PSIR) image reconstruction, making images less susceptible to wrong inversion time[31]. Both the traditional and newly developed sequences were performed in the clinical cardiac MR exams of patients referred for LGE-CMR imaging in the past years. In **chapter 5**, the aim was to validate and compare scar mass and image quality of the free-breathing 3D PSIR LGE-CMR images with the traditional breath-hold sequence.

Part 2. Clinical Application of MRS and MRI in Diabetic Cardiomyopathy

In the study of diabetic cardiomyopathy, it is important to acknowledge the complex pathophysiology of T2DM that involves ectopic fat accumulation, metabolic alterations and low grade inflammation. As such, diabetes complications occur in a wide variety of organs and tissues ranging from the CV system to abdominal organs and to the brain. A comprehensive study of these complications, i.e. phenotyping the T2DM patient, is important for two reasons. First, on a patient level it provides in risk assessment on an organ level thereby guiding therapeutic interventions. Second, on a population level, it gains insight into the mechanisms of diabetes complications. For example, hepatic steatosis has been shown to be associated with left ventricular diastolic dysfunction in obese patients[32]. Another example is the association between aortic stiffness and LV systolic function[33]. MR has the unique ability to acquire images of high resolution and with superior image contrast allowing for imaging these various

organs and tissues. Combined with ^{1}H-MRS, the connection between ectopic fat accumulation and organ damage can be investigated.

Chapters 6, 7 and 8 The MAGNA VICTORIA study

Liraglutide (Victoza®) is a glucagon-like peptide-1 receptor agonist (GLP-1-RA) approved for the treatment of T2DM. Liraglutide lowers blood sugar levels by promoting insulin secretion, suppressing glucagon production and by inducing moderate weight loss. In addition to these beneficial glycemic effects, pre-clinical studies provided evidence for a direct cardioprotective effect of GLP-1RA (reviewed in[34]), in terms of improved myocardial contractility. In addition, liraglutide-induced improvement of diabetic cardiomyopathy in mice was associated with reduced cardiac lipotoxicity[35,36]. Therefore, it was hypothesized that – in humans with T2DM – liraglutide could improve diabetic cardiomyopathy in terms of amelioration of left ventricular diastolic dysfunction, in relation to reduction of myocardial steatosis. To test this hypothesis, the MAGNetic resonance Assessment of VICTOza efficacy in the Regression of cardiovascular dysfunction In type 2 diAbetes mellitus (MAGNA VICTORIA) study was designed. The MAGNA VICTORIA study was a randomized placebo-controlled trial that aimed to include 50 Western European patients with T2DM and BMI > 25 kg/m^2 that had inadequate glycemic control despite the use of metformin and/or sulphonylurea derivatives and/or insulin. The aim was to include patients without (symptoms of) prior CVD.

In **chapter 6**, we describe the primary analysis of the MAGNA VICTORIA study: the effect of liraglutide on left ventricular diastolic and systolic function as assessed by CMR.

In **chapter 7**, a combination of MRI and MRS techniques was used to investigate the effect of liraglutide on ectopic fat accumulation: visceral fat, hepatic steatosis, myocardial steatosis and epicardial fat. These were secondary endpoints of the MAGNA VICTORIA study.

In addition to the aforementioned primary and secondary endpoints, we studied the effect of liraglutide on glycemic endpoints. Although the effect of liraglutide has been studied in the randomized placebo-controlled LEAD trials that included patients with T2DM with various background medication settings[37], patients

using multiple daily insulin injections (MDI) were not included in these studies. In the MAGNA VICTORIA study, a large proportion of participants were on MDI. Although MDI can be regarded as a last-resort treatment in T2DM, most patients on MDI do not reach glycemic target[38]. MDI is also associated with significant (further) weight gain and risk of hypoglycemia[39], which makes it very difficult to treat these patients satisfactorily. In light of the reduced risk of hypoglycemia and its effect on body weight, add-on therapy with liraglutide seems an interesting option for MDI-treated patients. In **chapter 8**, we aimed to investigate the effect of add-on therapy with liraglutide on patients on MDI. In this study we also included South Asian participants that were enrolled in a separate MAGNA VICTORIA trial. A separate study in South Asians was performed because of their disparate body composition with relatively high amount of visceral fat, low lean body mass and predisposition to develop T2DM often early in life.

Chapter 9 eSupported lifestyle intervention in insulin-dependent T2DM

Despite all pharmacological agents available, promotion of a healthy lifestyle remains the major pillar of T2DM management[11]. Traditionally, lifestyle advise was a first-line strategy that was applied before the initiation of blood glucose lowering drugs. When lifestyle coaching failed to reach glycemic targets, and drugs were initiated, further lifestyle advices were often not considered worthwhile. However, a paradigm shift has occurred due to the results of recent lifestyle intervention trials that have shown that T2DM can be reversed obese patients using oral blood glucose lowering drugs[13]. Interestingly, diabetes remission was paralleled by dramatic reductions in hepatic[40] and pancreatic steatosis[41] as assessed using MR. However, these studies excluded patients requiring insulin therapy. In the context of the progressive nature of T2DM, with deteriorating beta cell function over time[42], it is therefore questionable to what extent aforementioned studies can be extrapolated to insulin-dependent T2DM patients. In addition, when T2DM is in such a advanced state, and potentially complicated by CV alterations, it remains to be established whether diabetes and diabetic cardiomyopathy can still be reversed. Therefore, in

chapter 9 we aim to investigate the effect of a lifestyle intervention on glucose metabolism in relation to ectopic fat accumulation and cardiac function in patients with insulin-dependent T2DM.

Thesis objectives

The general aims of this thesis were to improve MR techniques to characterize diabetic cardiomyopathy and, by using these MR techniques, study the relationship between ectopic fat accumulation and diabetic cardiomyopathy in response to pharmacological and lifestyle interventions in patients with T2DM.

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