Phenotyping cardiometabolic disease with magnetic resonance techniques

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CHAPTER

General introduction and outline

GENERAL INTRODUCTION AND OUTLINE

Over the past decades, the number of individuals with type 2 diabetes has been growing worldwide (1,2), which is largely driven by the increasing prevalence of obesity (3-5). Type 2 diabetes is a major health concern, as it is related to several conditions, including heart failure (6,7) and coronary heart disease (8,9). Despite remarkable advances in cardiovascular prevention and treatment, heart disease remains a common cause of death and an important contributor to health loss globally (10,11).

The aim of the studies in this thesis was to gain more insight into diabetic cardiomyopathy and the cardiometabolic actions of type 2 diabetes medication by using magnetic resonance techniques (Part I). In addition, we aimed to contribute to improving cardiovascular risk stratification in individuals who received hematopoietic stem cell transplantation in childhood, which is associated with cardiometabolic disease later in life (Part II), and in patients with ischemic heart disease, who have an increased susceptibility of ventricular arrhythmia (Part III).

Phenotypic Characterization with Magnetic Resonance Techniques

In this thesis, we used a variety of magnetic resonance methods for the phenotypic characterization of cardiometabolic disease. Whereas the concept 'phenotype' initially referred to the outward appearance of an organism (12), today, this term has also been adopted to describe the manifestation of disease as characterized by radiologic imaging techniques (13). The disease phenotype is the result of a complex interaction between genetic predisposition and environmental conditions, including socioeconomic, occupational and behavioral factors. Starting from the mid-twentieth century, there has been an increasing awareness of the relationship between health behavior and disease, especially in cardiovascular medicine. For example, in 1953, the first study was published on the relation of physical activity to coronary heart disease (14). With the growing evidence of the role of modifiable risk factors (15), contemporary cardiology has expanded its focus beyond treatment to include prevention and early detection of disease. As part of personalized medicine, there is more and more interest in both genotypic and phenotypic characterization, which may help to identify high-risk groups for cardiometabolic diseases and to select appropriate treatment strategies for specific patient populations (16).

Whereas medical research in the fifteenth century was more or less confined to human anatomy (17), the area of physiology started to develop in the mid-ninetieth century (18). In the last hundred years, research in the field of cell and molecular biology has resulted in important insights in human biological processes (18). At present, organ-based but also system-wise thinking is part of medical reasoning (19). Interestingly, in view of the super specialization of medical disciplines, some argue that doctors should also have a generalist approach to medical care (20). For example, obesity and type 2 diabetes are closely related to cardiovascular health

and, in this respect, holistic thinking beyond the highly specialized fields of, for example, internal medicine, cardiology and radiology may be beneficial for patient outcome.

The studies in this thesis were performed in the department of Radiology and were in close collaboration with the department of Internal Medicine. We used several cardiovascular magnetic resonance techniques including 2D and 4D flow imaging, feature tracking cine imaging, T1 mapping and proton-magnetic resonance spectroscopy (^{1}H-MRS). With these methods, it is possible to assess anatomical structures but also organ function and tissue characteristics (21). As such, the thought behind this thesis was that imaging-based phenotyping in radiology might contribute to insights into mechanisms of diseases in the field of internal medicine.

Part I Type 2 Diabetes

Type 2 diabetes has become a major public health challenge, as its prevalence is increasing worldwide due to lifestyle changes related to economic development, rapid urbanization and population aging (2). Whereas type 2 diabetes was affecting 4.7% of the global population in 1980, the world prevalence had risen to 8.5% by 2014 (1).

Although obesity, unhealthy diet and physical inactivity are strong risk factors for the development of type 2 diabetes (22-25), type 2 diabetes is most likely to represent a complex interplay between genetic susceptibility and environmental factors. In the United States, highest prevalences of type 2 diabetes have been reported among Hispanic, Asian and African American individuals (22.6%, 21.8% and 20.6%, respectively, compared with 11.3% in individuals of European descent) (26), whereas in the Netherlands, the highest prevalence of type 2 diabetes has been documented among South Asian Surinamese (16.7% (35-44 years) and 35.0% (45-60 years), as compared with 4.2% and 8.2%, respectively, among ethnic Dutch) (27). Although environmental conditions, for example cultural and socioeconomic factors, vary between ethnic groups, the disparities in type 2 diabetes prevalence may be in part explained by genetic predisposition (28). Proposed mechanisms for the increased risk of type 2 diabetes among South Asian ethnicities comprise a susceptibility to visceral rather than subcutaneous fat storage, a high mitochondrial efficiency, an intrauterine disadvantageous environment and low vitamin D serum levels, in combination with lifestyle factors including a high carbohydrate diet and insufficient physical activity (29).

In the Framingham Heart Study in 1974, for the first time, the association between type 2 diabetes and congestive heart failure, independent of other cardiovascular risk factors, was documented in a large, population-based study (6). The risk of congestive heart failure associated with type 2 diabetes was approximately two to five times increased for men and women, respectively (6). Similarly, other observations have reported rate ratios of incident heart failure of 1.85–2.5 in individuals with compared to those without type 2 diabetes (7,30). Furthermore, a recent study including 1.9 million people has shown that heart failure is a

common initial presentation of cardiovascular disease in type 2 diabetes, accounting for 14.1% of the first cardiovascular manifestations (31). Likewise, another study in older patients with type 2 diabetes has demonstrated that heart failure often develops in the absence of ischemic heart disease (among the individuals who developed heart failure, 27.2% had no preceding of concomitant vascular event and 36.8% had no prior coronary artery disease), and, importantly, heart failure hospitalization in type 2 diabetes patients was associated with high mortality, also in individuals without coronary artery disease (the annual mortality rate after heart failure hospitalization was 21.3% and 24.6% in type 2 diabetes patients with and without preceding vascular disease, respectively) (32). In this context, it has been argued that there should be more attention to heart failure as complication of type 2 diabetes, also in the absence of ischemic cardiomyopathy (33).

Heart failure in type 2 diabetes patients without prior myocardial infarction is characterized by preserved ejection fraction, and is preceded by progressive diastolic dysfunction (34). Heart failure with preserved ejection fraction (HFpEF) in patients with type 2 diabetes is considered to be multifactorial, resulting from coronary atherosclerosis, high blood pressure, extracellular fluid volume expansion and, possibly, diabetic cardiomyopathy (35). The concept 'diabetic cardiomyopathy' has been introduced to refer to the direct detrimental effect of type 2 diabetes on the myocardium, independent of other conditions such as coronary artery disease or hypertension (36), but there is no agreed definition (34). Molecular mechanisms which have been implicated in diabetic cardiomyopathy comprise coronary microvascular dysfunction, chronic inflammation, disturbed insulin and renin-angiotensin-aldosterone signaling, lipotoxicity, altered substrate metabolism, impaired calcium handling, mitochondrial dysfunction, modification of structural proteins by advanced glycation end-products, and perturbations in cell homeostatic processes including apoptosis, autophagy and endoplasmic reticulum stress (37,38).

Although diabetic cardiomyopathy has been recognized as a distinct clinical entity (39), the pathogenesis is still incompletely understood and the phenotypic characterization remains to be elucidated (40,41). Also, until recently, there were no glucose-lowering agents with cardioprotective effects to reduce the risk of heart failure in type 2 diabetes patients (42,43). In Part I, we explored the imaging features of diabetic cardiomyopathy and investigated the effects of an antidiabetic agent with potentially beneficial effects on intrinsic myocardial function.

Chapter 2

The difficulty in characterizing diabetic cardiomyopathy is the strong association between obesity and type 2 diabetes, with approximately 80 percent of the type 2 diabetes patients being obese (44). Therefore, the separation of the cardiovascular effects of type 2 diabetes, obesity or other factors associated with type 2 diabetes and obesity is challenging (45). The population-based Netherlands Epidemiology of Obesity (NEO) study from Leiden was designed

to disentangle the pathways leading to common disease in obesity (46). In Chapter 2, we examined the role of insulin resistance in cardiovascular remodeling in individuals with obesity from the NEO cohort. Strength of this study was the assessment of specific adiposity metrics rather than overall measures of obesity (eg, body weight), which enabled the adjustment for the confounding effects of adipose tissue.

Chapter 3

In the population-based study in Chapter 2, we evaluated standard magnetic resonance parameters of cardiac structure and function. Nonetheless, magnetic resonance also allows for the assessment of myocardial steatosis (47) and diffuse fibrosis (48), as well as cardiac strain as a more sensitive measure of systolic function (49), which were examined in Chapter 3. It has been hypothesized that these myocardial tissue characteristics may be affected in type 2 diabetes, preceding abnormalities in diastolic function (50,51).

Furthermore, there has been limited research on the putative differences in diabetic cardiomyopathy among different type 2 diabetes patient groups, although the pathogenesis of type 2 diabetes and type 2 diabetes-related cardiovascular disease seems different in South Asian compared with other ethnicities (29,52,53). It is known that individuals of South Asian descent have a high risk of developing coronary heart disease, which is not completely explained by excess cardiometabolic risk factors (54). Furthermore, in South Asians, type 2 diabetes increases the mortality of ischemic heart disease nearly threefold, while in Europeans, the excess mortality related to type 2 diabetes estimates 1.5-fold (55). Likewise, previous findings indicate that the etiology of HFpEF in type 2 diabetes may be distinct in South Asian compared with other ethnic groups. For example, it has been demonstrated that the impact of type 2 diabetes on cardiac function is worse in South Asians than in Europeans (56). Furthermore, the population attributable risk of type 2 diabetes for HFpEF appears to be higher among South Asians, as type 2 diabetes is threefold more common in HFpEF patients of South Asian than in those of European origin (56). Also, type 2 diabetes has been reported to have a more adverse impact on heart failure hospitalization and mortality in individuals of South Asian than those of European ethnicity (57). Thus far, it has not been demonstrated that the treatment of type 2 diabetes or the prevention of type 2 diabetes-related cardiovascular disease should be different in South Asians. Nonetheless, because of the disparities in cardiometabolic profile between ethnic groups, current guidelines take ethnicity into account in recommendations for cardiovascular risk management and screening for type 2 diabetes (58). For example, body mass index (BMI) cut points to define overweight are lower for South Asians (BMI >23 kg/m^2 instead of BMI >25 kg/m^2) (59,60). Also, screening for type 2 diabetes is justified above 35 years among South Asians, compared with screening at the age of 45 years and older in other ethnic groups (27).

In the area of The Hague, a large percentage of the type 2 diabetes population is of Surinamese Hindustani descent. In Chapter 3, we aimed to characterize diabetic

cardiomyopathy by using various magnetic resonance techniques, and, additionally, in view of the ethnic differences regarding type 2 diabetes and diabetic heart failure, we compared the cardiovascular remodeling characteristics between Dutch South Asian and Dutch European type 2 diabetes groups.

Chapter 4 and 5

In recent years, several types of antidiabetic agents have been introduced including liraglutide. Liraglutide is a long-acting, glucagon-like peptide 1 (GLP-1) receptor agonist, which, in contrast to native GLP-1, is resistant to degradation by dipeptidyl peptidase 4 (DPP-4) (61). Liraglutide influences blood glucose levels through several mechanisms, including increase of glucose-dependent insulin secretion, decrease of postprandial glucagon, slowed gastric emptying and reduced food intake (62). Because of the excess cardiovascular burden in type 2 diabetes patients and the concerns about potentially higher cardiovascular risks associated with certain antidiabetic agents, since 2008, authorities have mandated cardiovascular safety trials to secure the approval of novel glucose-lowering drugs (63). In the months that we started with the liraglutide study in Leiden, the results of such a cardiovascular safety trial (the LEADER trial) were published. The LEADER trial reported that liraglutide compared to placebo added to standard care is beneficial for cardiovascular mortality in patients with type 2 diabetes and high cardiovascular risk, presumably because of anti-atherosclerotic effects (64). In addition, in prior preclinical and clinical studies, liraglutide proved to exert pleiotropic favorable effects on blood pressure, lipids, inflammation and other metabolic factors (62). However, the effect of liraglutide on intrinsic myocardial function in type 2 diabetes patients with asymptomatic heart failure remained to be addressed.

Previously in Leiden, the effect of the antidiabetic agent pioglitazone on diastolic function has been investigated (65). This thesis reports the results of a similar trial on the effect of liraglutide on diastolic function in type 2 diabetes patients of South Asian descent living in the Netherlands, whereas a parallel study was performed in Dutch European type 2 diabetes patients (66). In Chapter 4, we described the metabolic effects of liraglutide (effects on ectopic fat accumulation and glucose regulation), and in Chapter 5, we assessed the cardiovascular actions of liraglutide (effects on cardiac diastolic and systolic function, aortic stiffness, myocardial triglyceride content and myocardial extracellular volume) in Dutch South Asian type 2 diabetes patients.

Part II Pediatric Hematopoietic Stem Cell Transplantation

Chapter 6

As the long-term survival after pediatric hematopoietic stem cell transplantation has been improved drastically, current research is aimed at enhancing quality of life (67,68). From previous studies it is known that pre-transplant or transplant-related therapies in childhood

are associated with several risks in adulthood, including endocrine and cardiovascular disease (69,70). In Chapter 6, we aimed to find early magnetic resonance-derived features which may be used to select patients at high cardiovascular risk who may require frequent follow-up.

Part III Ischemic Heart Disease

Chapter 7 and 8

In Part I, we examined diastolic dysfunction as complication of obesity and type 2 diabetes. However, metabolically unhealthy individuals have an increased susceptibility of developing HFpEF, but they are also at risk of heart failure with reduced ejection fraction (HFrEF). Although the clinical expression of HFpEF and HFrEF is similar (symptoms of dyspnea, fatigue, exercise intolerance and signs of edema), HFpEF and HFrEF are two separate entities with distinct pathogeneses and epidemiologic differences (71). In general, HFrEF (or systolic heart failure) is caused by coronary artery disease, whereas hypertension, obesity and type 2 diabetes are frequent conditions in HFpEF (or diastolic heart failure) (40,72). In Part III, we addressed ischemic heart disease and heart failure after myocardial infarction.

In Chapter 7, we reviewed the currently available cardiovascular magnetic resonance techniques, with special attention given to the protocols without use of gadolinium-based contrast material. Late gadolinium enhancement (LGE) imaging is an important technique for the clinical evaluation of myocardial scar (73). Interestingly, native T1 mapping may evolve as a non-contrast alternative for myocardial tissue characterization in ischemic heart disease (74).

An important risk in patients with prior myocardial infarction and low ejection fraction is sudden death due to ventricular arrhythmia, but also non-sudden death due to decompensated HFrEF (75). In Chapter 8, we retrospectively evaluated the cardiac magnetic resonance examinations of patients with ischemic heart disease and implantable cardioverter defibrillator (ICD) therapy. We hypothesized that left ventricular function parameters, which are known to be associated with cardiac remodeling, may be used as risk stratifiers for ventricular arrhythmia and decompensated heart failure in post-infarct patients with highly depressed systolic function. In this hypothesis-generating study we assessed the associations between systolic and diastolic strain parameters and the risk of appropriate ICD therapy and all-cause mortality, as surrogate markers of ventricular arrhythmia and decompensated heart failure, respectively.

OBJECTIVES

The general aim of the studies presented in this thesis was to characterize cardiovascular remodeling associated with metabolic disturbances, using various magnetic resonance techniques. It was hypothesized that imaging-based phenotyping may contribute to a better understanding of cardiometabolic disease and help to identify patients at increased cardiovascular risk. We investigated the cardiovascular phenotype in relation to type 2 diabetes and in response to treatment with liraglutide (Part I), after hematopoietic stem cell transplantation (Part II) and in ischemic heart disease (Part III).

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