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Rijzewijk, L.J.

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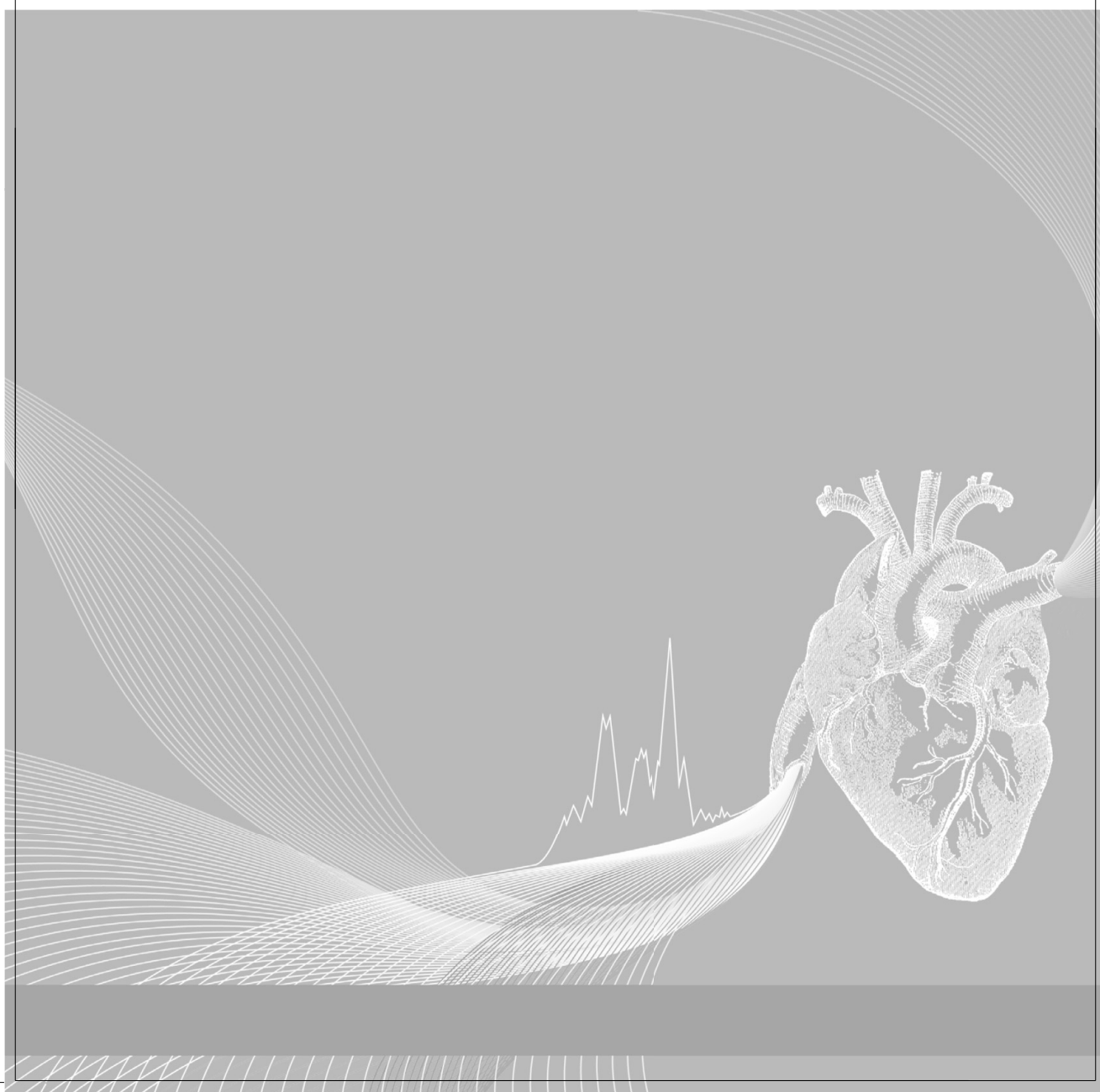
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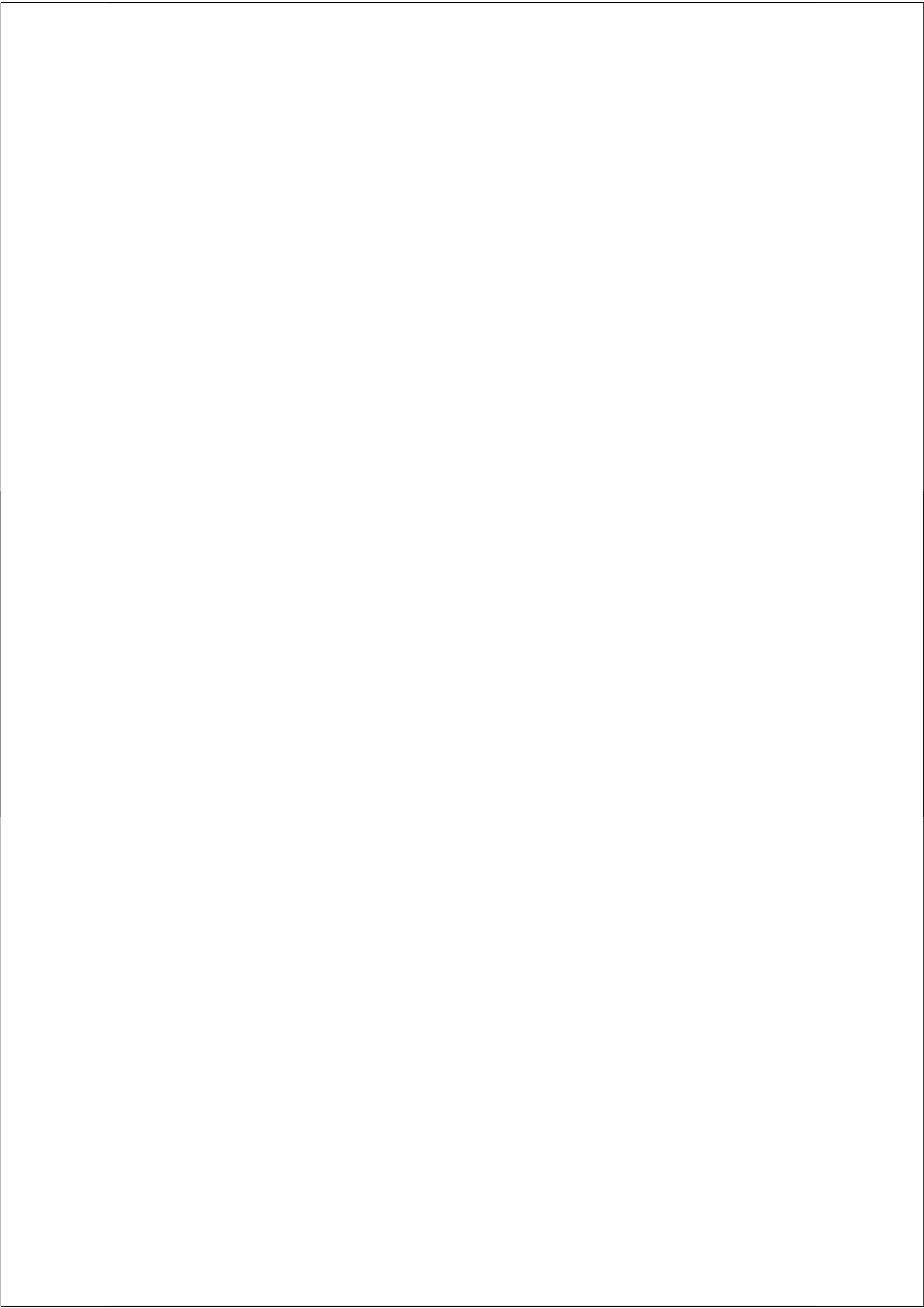
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Summary





Type 2 diabetes mellitus (T2DM) has reached epidemic proportions worldwide. Mortality rates in T2DM patients are increased and cardiovascular disease, in particularly heart failure, is a prominent cause. Although coronary artery disease and hypertension are the main causes leading to heart failure, a significant group of T2DM patients develops heart failure without being affected with coronary artery disease and hypertension, a condition denominated as diabetic cardiomyopathy (DCM). Various mechanisms leading to DCM have been proposed. Most data have been derived from animal models, as studies in humans are limited due to obvious limitations and ethical considerations. However, with the introduction of dedicated non-invasive imaging modalities, including positron emission tomography (PET), tissue Doppler echocardiography and magnetic resonance imaging (MRI) and spectroscopy (MRS), noninvasive research of the human heart has become possible. This is in particular relevant as it has been proposed that one of the main causes leading to DCM is altered myocardial substrate metabolism leading to gluco-lipototoxicity. Gluco-lipototoxicity refers to the harmful effects of altered glucose and fatty-acid metabolism, leading to unfavorable metabolic events, including steatosis, the formation of toxic intermediates, oxidative stress, mitochondrial dysfunction, resulting in apoptosis and eventually organ damage and dysfunction.

Gluco-lipototoxicity is not restricted to the heart, but is suggested to involve many other organs including the liver, skeletal muscle and the pancreatic islets, resulting in decreased whole-body and hepatic insulin sensitivity and β -cell dysfunction. Indeed, hepatic steatosis in insulin resistant states and diabetes is associated with many cardiometabolic abnormalities known to affect cardiovascular disease risk unfavorably. Additionally, hepatic steatosis also increases the risk of non-alcohol fatty liver disease (NAFLD), non-alcoholic steato-hepatitis (NASH), cryptogenic fibrosis, cirrhosis, liver failure and hepatocellular carcinoma.

The gluco-lipotoxic hypothesis originates from work in animal models and often is extrapolated to the human situation, even though many differences between species exists and direct evidence from humans is limited. Therefore, the present thesis aimed to phenotype myocardial and hepatic metabolism in non-ischemic patients with uncomplicated T2DM disease and additionally, to relate myocardial metabolism to LV function. The choice for non-ischemic T2DM patients with uncomplicated T2DM disease was made, since co-morbidities such as ischemia and autonomic neuropathy per se are known to affect metabolism and LV function. In addition, the effect of the blood-glucose lowering agents pioglitazone versus metformin on myocardial and hepatic metabolism, triglyceride content and LV function and geometry were studied. Pioglitazone is a thiazolidinedione and acts via activation of specific nuclear receptors, i.e. peroxisome proliferator-activated receptor γ (PPAR γ). Pioglitazone has insulin sensitizing and antisteatotic properties. Concerns about its safety were raised as the large-scaled prospective PROACTIVE study, in which pioglitazone versus placebo were administered to high-risk T2DM patients, showed an increased incidence of non-fatal heart failure. Metformin is a biguanide which supposedly acts via AMP-activated protein kinase (AMPK) and inhibits hepatic gluconeogenesis and increases insulin sensitivity. The UK Prospective Diabetes Study (UKPDS) showed that metformin reduced cardiovascular risk, however, data on the mechanism of action of AMPK in the myocardium in diabetes are scarce. Therefore the PIRAMID (Pioglitazone Influence on tRiglyceride Accumulation in the Myocardium In Diabetes) study was designed, a 24 weeks prospective randomized double-blind double-dummy trial with active comparator, 2-center parallel-group intervention. Besides T2DM patients, healthy controls were included, the latter only undergoing baseline assessments. Before and at 24 weeks of intervention PET was used to measure myocardial and hepatic perfusion using [^{15}O]H $_2$ O, rate of glucose uptake using [^{18}F]-2-fluoro-2-deoxy-D-glucose ([^{18}F]FDG) and fatty acid uptake using [^{11}C]palmitate. β -oxidation (MFAO) and esterification (MFAE) using [^{11}C]palmitate was only determined in myocardium and not in liver as reliable mathematical models remain to be developed for the liver.

In **chapter 1** the concept of DCM was introduced, with a focus on metabolic alterations leading to heart disease. The role of altered substrate metabolism, lipotoxicity, glucose toxicity and oxidative stress, and altered calcium homeostasis were covered in addition to functional changes in the diabetic heart and non-invasive methods for measuring metabolism and function in humans. It was argued that few and inconsistent data on human myocardial metabolism exist and that there is a lack of studies investigating to what extent (altered) metabolism and myocardial function relate to each other. Another point made was that at present no treatment is advised, apart from a healthy life style and adequate glucose regulation, as no hard data on metabolic approaches are available for the treatment of DCM.

In **chapter 2** myocardial triglyceride content and function are compared between T2DM patients and healthy controls with a similar body-mass index and age, and the association between myocardial triglyceride content and function was assessed. Myocardial triglyceride content was significantly higher in T2DM patients compared with controls. In addition, indices of LV diastolic function, but not systolic parameters, were impaired in T2DM patients relative to controls. Multivariable analyses indicated that myocardial triglyceride content was independently associated with indices of LV diastolic function. A causal relationship between increased myocardial triglyceride content and reduced LV function, however, could not be established.

In **chapter 3** myocardial substrate and high-energy phosphate (HEP) metabolism in T2DM and age-matched control subjects were assessed. In addition, associations between LV function and metabolism were evaluated. Patients had impaired LV diastolic filling dynamics and reduced glucose uptake. Myocardial fatty-acid uptake and oxidation, on the other hand, were increased. No differences in myocardial HEP metabolism or perfusion were found and no associations were found between LV diastolic function and cardiac substrate or HEP metabolism. This was the first human non-invasive study to combine myocardial perfusion and metabolism measurements, thereby phenotyping myocardial metabolism in T2DM patients relative to age-matched controls. In contrast to expectations based on animal data, no associations were found between myocardial metabolism and any parameter of LV function in T2DM patients.

In **chapter 4** results of 24 weeks of treatment with pioglitazone 30 mg/day versus metformin 2000 mg/day were described. A total of 78 Caucasian men were included and 71 patients completed the study. No patient developed heart failure. Both therapies similarly improved glycemic control, whole-body insulin sensitivity and blood pressure. Pioglitazone versus metformin improved both diastolic function and LV compliance. Pioglitazone versus metformin increased myocardial glucose uptake, but pioglitazone related diastolic improvements were not associated with changes in myocardial substrate metabolism or LV functional changes. Because changes in myocardial metabolism and function in the pioglitazone treated patients were not related, it is unlikely that the improvement in diastolic function is due to altered metabolism. Metformin did not affect myocardial function, but decreased cardiac work relative to pioglitazone, paralleled by a reduced myocardial glucose uptake and fatty-acid oxidation, but increased plasma lactate levels. Observed decreases in cardiac glucose and NEFA metabolism in the metformin group might be linked to increased myocardial lactate utilization or treatment related reduction in cardiac work, as less ATP needs to be generated to maintain adequate high-energy phosphate levels. Neither treatment affected cardiac high-energy phosphate metabolism or triglyceride content. Only pioglitazone reduced hepatic triglyceride content. From this study it was concluded that treatment with pioglitazone in patients

with uncomplicated, well-controlled T2DM and absence of cardiac ischemia might be beneficial, as demonstrated by improved LV diastolic function and compliance, in the presence of unaltered myocardial high-energy phosphate metabolism.

In **chapter 5** the first two parts of this thesis were bridged. Hepatic steatosis is related to increased risk of heart disease. In this chapter effects of hepatic triglyceride content on myocardial metabolism and function in T2DM patients was assessed. Patients were divided into low (T2DM-low) and high (T2DM-high) liver triglyceride groups, based on a hepatic triglyceride content of 5.56%. In addition to decreased whole body insulin sensitivity, T2DM-high patients had reduced myocardial perfusion, glucose uptake and PCr/ATP ratio compared with T2DM-low patients, whereas cardiac fatty-acid metabolism and LV function were not different. Hepatic triglyceride content correlated inversely with whole body insulin sensitivity, myocardial glucose uptake and PCr/ATP. Insulin sensitivity correlated positively with myocardial glucose uptake and borderline with myocardial PCr/ATP, whilst a positive association was found between cardiac glucose uptake and PCr/ATP. The long-term clinical implications of this association between increased liver triglyceride content and altered cardiac metabolism requires further study in T2DM.

In **chapter 6** the relation between hepatic triglyceride content and hepatic perfusion and metabolism was assessed. Both healthy controls and T2DM patients were included, the latter again divided in high and low triglyceride groups. T2DM-high patients had the highest BMI, worst glycemic control, and lowest whole body insulin sensitivity. Compared with control subjects and T2DM-low patients, T2DM-high patients had the lowest hepatic parenchymal perfusion and insulin stimulated hepatic glucose uptake. The observed decrease in hepatic fatty acid influx rate constant, however, only reached borderline significance. Significant inverse associations were found between hepatic triglyceride content and hepatic perfusion, glucose and fatty-acid uptake. Results of this study suggested a potential modulating effect of hepatic steatosis on hepatic physiology.

In **chapter 7**, effects of 24 weeks of treatment with pioglitazone 30 mg/day versus metformin 2000 mg/day on hepatic triglyceride content, parenchymal perfusion and metabolism were evaluated. Both therapies similarly improved glycemic control and whole body insulin sensitivity. Only Pioglitazone reduced hepatic triglyceride content. Pioglitazone, but not metformin, increased insulin mediated hepatic glucose uptake and liver parenchymal perfusion from baseline. Neither treatment affected the hepatic fatty-acid influx rate constant.

Chapters 8 & 9 are two methodology based chapters and comprise the third part of this thesis. In **chapter 8** various kinetic models for analyzing myocardial [^{11}C]palmitate were evaluated. This study was undertaken, as the use of several models to describe and quantify [^{11}C]palmitate kinetics have been reported, but no systematic analysis had been performed to define the most suitable model. In this study a total of 21 plasma input models comprising one to three compartments and up to 6 free rate constants were compared using statistical analysis of clinical data and simulations. To this end, 14 healthy volunteers were scanned using [^{11}C]palmitate, whilst myocardial blood flow was measured using [^{15}O]H₂O. Models including an oxidative pathway, representing production of [^{11}C]CO₂, provided significantly better fits to the data than other models. Model robustness was increased by fixing efflux of [^{11}C]CO₂ to the oxidation rate. Based on accuracy of data description, number of free parameters and generality, the 3-tissue compartment model with 3 free rate constants was chosen as the model of choice for describing [^{11}C]palmitate kinetics in terms of oxidation and fatty acid accumulation in tissue.

In **chapter 9** initial stroke volume measurements with first pass dynamic PET were compared with cardiovascular magnetic resonance in 59 subjects with a varying degree of cardiac function using [¹⁵O]H₂O. This comparison was performed for both right and left ventricle against aorta velocity encoded phase contrast cardiovascular MRI. PET estimated SV was higher for RV than for LV, and both were higher than values obtained by MRI. Although significant, correlations between PET and CMR were only moderate for both RV and LV. Bland-Altman analysis revealed progressive overestimation with increasing SV measured in either ventricle. It was concluded that first-pass dynamic [¹⁵O] H₂O PET for assessment of forward SV is feasible. Although values are progressively overestimated with increasing SV, particularly when the RV is used, and correlations with aorta velocity-encoded phase-contrast CMR are moderate, probably related to protocol-dependency.

Chapter 10 is a review in which the question was asked whether gluco-lipototoxicity exists as a major mechanism by which LV function is finally compromised in non-ischemic hearts from patients with uncomplicated T2DM. This chapter was therefore primarily a critical discussion, integrating the results of chapters 2 to 5 in the context of the present literature. In this review a human perspective was chosen with a focus on functional, structural and metabolic aspects of the diabetic heart. Current ideas on the pathology of DCM were critically reviewed and put into perspective using data from animal studies and traditional views on DCM, taking into account gender and race specific data. The review ended with a description of currently available drugs in T2DM and specifically their effects in DCM.

Future perspectives

In the present thesis, we describe phenotyping of the non-ischemic human T2DM heart and liver, and the effect of pioglitazone versus metformin on myocardial and liver metabolism and myocardial function. As the obesity and diabetic pandemic progresses, diabetes-related morbidity and mortality from cardiovascular and hepatic disease increases simultaneously. Effective and safe treatments are therefore mandatory. The development of these dedicated treatments can only be initiated with a thorough understanding of the pathophysiology leading to human DCM and liver disease in diabetes, as surrogate animal models of diabetes have their major limitations. Although the present study is valuable as it has provided detailed phenotypic data of resting human heart and liver metabolism in middle aged Caucasian males, the inclusion of only this population limits generalizability. Thus, other relevant populations, including female patients with T2DM, male and female patients with T1DM, T2DM patients of different ethnic origins, pre-diabetic individuals and patients in more advanced stages of diabetes and cardiac disease still need to undergo similarly thorough investigations. Also, the effect of interventions including lifestyle, i.e. diet and exercise, as well as the impact of cardiac (pharmacological) stress on myocardial function and metabolism requires further study. A largely unexplored area of research is whether diabetes duration influences myocardial metabolism and how these changes relate to myocardial function during the course of the disease, with the additional interaction of developing complications and co-morbidities. Future research should address these questions and hopefully finally result in the development of targeted treatments aimed at patient groups across different stages of diabetic disease.