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Faculteit Geneeskunde en Levenswetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

Functional heart remodeling and cardiorespiratory exercise capacity in Type 2 Diabetes Mellitus - a randomized controlled trial

Annelies Backx

Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie, afstudeerrichting revalidatiewetenschappen en kinesitherapie bij kinderen

PROMOTOR :

Prof. dr. Dominique HANSEN

BEGELEIDER :

Mevrouw Lisa VAN RYCKEGHEM

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1 Acknowledgement

Hereby, I want to thank Prof. Dr. Hansen Dominique for his support, especially for his scientific insights, valuable comments and inputs. Thanks to dra. Van Ryckeghem Lisa for the active collaboration and the coaching on the data evaluations.

Thanks also to the people who volunteered to participate in the exercises to get a relevant basis of data input. Only with their active contributions, this study could be made and valuable data could be collected for correlation and scientific evaluation. Thanks to the Jessa Hospital and the University of Hasselt for the accommodation.

2 Research context

This manuscript is written as a master thesis, part of a greater study project (i.e. HITDCM – project about exercise, cardiac function and type 2 diabetes mellitus (T2DM)) at Hasselt University. It can be situated in a wider context of rehabilitation of cardiorespiratory and internal diseases, including cardiorespiratory and metabolic diseases.

Worldwide, a high prevalence of 122.8 million (18.8%) people suffering from diabetes mellitus (DM) is established in a population older than 65 years ("IDF Diabetic Atlas, 8th edn," 2017). T2DM, the most common type of diabetes, is described as a multifactorial disorder characterized by chronic hyperglycemia, dyslipidemia, hyperinsulinemia and related insulin resistance (Scheuermann-Freestone et al., 2003). This metabolic disease is associated with several comorbidities including cardiovascular disease (CVD) (DF Diabetic Atlas, 8th edn," 2017), leading to considerable healthcare expenditures (Cho et al., 2018). Moreover, diabetic cardiomyopathy (DCM) and related heart failure plays a key role in the considerable high rates of mortality and morbidity in this population. More specifically up to 27 out of 1000 persons with T2DM die due to CVD ("IDF Diabetic Atlas, 8th edn," 2017).

This randomized controlled trial focusses to examine the correlation between T2DM and heart functioning using transthoracic echocardiography (TTE). Because of the increasing occurrence of impaired glucose tolerance (IGT), obesity and physical inactivity among children, adolescents and young adults, also the development of T2DM in a younger population must be taken into account (326.5 million people between 20-64 years) ("IDF Diabetic Atlas, 8the edn," 2017). This underlies the importance to optimize the management of T2DM and related complications and to research the benefits of exercise trainings on cardiac remodeling targeting to minimalize the health care expenditure and mortality rates.

The research question of the HITDCM project focusses on the effects of exercise training on cardiac parameters and analyses the difference between moderate intensity training (MIT) and high intensity interval training program (HIIT). This randomized control trial describes the baseline characteristics including the correlation between T2DM, cardiac function and cardiorespiratory

exercise capacity. About this issue, contradictory documentation can be found in literature. Good baseline characteristics are required to evidence some benefits of exercise.
The study design and the research method were determined by the promotor prof. Dr. D. Hanssen and a PhD student L. Van Ryckeghem.

Before using the Dual-energy X-ray absorptiometry (DEXA) scan and the Short-Form-36 questionnaire version 2 (SF-36v2), the psychometric properties including reliability and validity were evaluated by the master student. As evidence (Database PubMed & Web Of Science) about the psychometric properties of the DEXA scan in the T2DM are lacking, studies focusing on obese population were analyzed. In literature, the DEXA scan is described as a reliable method to analyze the body composition of an obese population, with an excellent intra-rater and inter-rater reliability (LaForgia, Dollman, Dale, Withers, & Hill, 2009; Tsang, Briody, Kohn, Chow, & Singh, 2009; von Hurst et al., 2016). Additionally, an acceptable concurrent and predictive validity was evidenced both in an obese as in a type 1 diabetes mellitus (T1DM) population (Paradisi et al., 1999; Rosenfalck, Almdal, Gotfredsen, Hojgaard, & Hilsted, 1995; Tsang et al., 2009).
Also for the SF-36 questionnaire, good psychometric properties are proven. A good reliability of the SF-36 questionnaire to measure the functional status in T2DM and healthy people was evidenced (Brazier et al., 1992; Jacobson, de Groot, & Samson, 1994). The SF-36 questionnaire met also the criteria of validity (Brazier et al., 1992; Jacobson et al., 1994; McHorney, Ware, & Raczek, 1993). Similar results are observed in assessment of the SF-36 version 2 (SF-36 v2) in United Kingdom (Crispin Jenkinson, 1999). In literature, information about the psychometric properties of the Dutch version of SF-36v2 in T2DM population is lacking.

Over a period of five weeks, the master student assisted with the recruitment of participants, including to guide the participants in the reading of het informed consent and the completion of the questionnaires. Further, she helped with the processing of blood samples saved for future research, the performance of TTE exercise assessments and guiding of exercise trainings. The data-acquisition was executed in partnership with a PhD student. The statistical analysis of the obtained data was completed self-employed. Furthermore, the academic writing of the manuscript was performed by the student and reviewed by the PhD student.

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4.1 Abstract

Background: Worldwide, the number of people living with type 2 diabetes mellitus (T2DM) is increasing considerably and the diagnosis is made at younger age. Cardiovascular diseases (CVD), including diabetic cardiomyopathy (DCM), are still a major cause of morbidity and mortality in this population. However, the exact pathophysiology of DCM has not yet been fully clarified.

Objectives: This randomized controlled trial aimed to determine the association of T2DM with heart functioning and the role of N-terminal proBrain natriuretic peptide (NT-proBNP) as biomarker. Besides this, the cardiorespiratory fitness (VO_{2peak}) was examined in T2DM.

Participants: 14 subjects (age 18-81years) with well-controlled T2DM (ADA guidelines), a body mass index (BMI) above 20kg/m^2 and free of chronic disease participated in the study. 23 healthy controls (HC) were included as a basis for benchmark reference.

Measurements: A questionnaire regarding general well-being was completed by each subject to evaluate physical function. Both groups received a DEXA scan and performed a submaximal exercise test accompanied by spirometry and transthoracic echocardiography (TTE) assessment during rest and exercise. In addition, blood samples were collected for the quantification of [blood NT-proBNP].

Results: The baseline characteristics and the global physical function were comparable between both groups, in exception of BMI (*P=0.024*), body weight *(P=0.006),* HbA1C% (*P<0.001),* and gender (*P=0.040*). Unless the E wave, e' lateral and E/e' ratio, significant lower values for TTE parameters including A wave (*P=0.016*), E/A ratio (*P=0.001*) and e' septal (*P=0.039*), were noted in T2DM, indicating LVDD. However, similar [blood NT-proBNP] were measured. The VO_{2peak} remained unchanged. An assessment of pulmonary function suggested a trend to obstructed lungs by lowered Tiffeneau index *(FEV_1/IVCact. P=0.070; FEV_1/IVCact/pred. P=0.001*) in T2DM.

Conclusion: Accompanied by normal [blood NT-proBNP], asymptomatic T2DM patients showed signs of diastolic dysfunction (DD) on TTE, suggesting DCM. An association between T2DM and exercise capacity was not observed.

4.2 Introduction

Today, the metabolic disease Diabetic Mellitus (DM) and its rehabilitation is an emergent topic of interest in the research world. The number of people living with type 2 diabetes mellitus (T2DM), the most common type, is growing fast. From an estimation in 2017, 451 million people, namely 1 in 11 adults, have T2DM worldwide. However, one in two remain undiagnosed. By 2045, a remarkable increase of 54 % is expected (Cho et al., 2018).

Evidence reports DCM as a frequent cardiovascular (CV) complication related to T2DM. However, the underlying mechanisms of DCM remain to be elucidated. Due to myocardial damage, certain structural and functional changes are identified in the diabetic heart, without coronary artery disease, hypertension and valvular disease (Alonso, Moliner, & Mauricio, 2018). In clinical setting, the pathophysiological image of diabetic cardiomyopathy (DCM) is identified by left ventricle (LV) hypertrophy, increased wall fibrosis and decreased LV compliance (Jia, Hill, & Sowers, 2018). In addition, higher rates of oxidative damage plus cardiomyocyte and endothelial cells apoptosis are observed in the T2DM heart, related to an increased activation of the renin-angiotensin system (Boudina & Abel, 2007). This structural concentric remodeling, developing during an asymptomatic subclinical period, is an important predictor of acute heart failure (Levelt, Gulsin, Neubauer, & McCann, 2018). This mechanism underlies the development of left ventricular diastolic dysfunction (LVDD), showed by prior research (Alonso et al., 2018; Levelt et al., 2018). These findings are accompanied by impaired early diastolic filling, increased LV end-diastolic pressure and a prolonged isovolumetric relaxation. In a later stage of DCM, this remodeling can co-exist with systolic dysfunction and reduced ejection fraction, LV chamber enlargement and increased filling pressures (Jia et al., 2018). Altered myocardial energy metabolism including hyperglycemia, insulin resistance, oxidative stress and higher levels of free fatty acid (FFA) are associated with altered molecular pathways in the cardiomyocytes (Alonso et al., 2018; Jia et al., 2018; Levelt et al., 2018). As well as endothelial dysfunction, microvascular disease and autonomic neuropathy are considered to contribute to the development of DCM (Alonso et al., 2018).

Recent data of heart patients (dilated cardiomyopathy) reveal a positive correlation between transthoracic echocardiography (TTE) parameters and Brain natriuretic peptide (BNP). Higher blood N-terminal proBrain natriuretic peptide concentrations ([blood BNP]) are possibly associated with increased LV dimensions, some grade of LVDD (increased E/e' and reduced e') and a reduced LV ejection fraction. In response to myocardial stretch caused by pressure or volume overload, the myocardium will produce a greater amount of BNP (Amorim et al., 2017). Thereby, high [blood BNP] indicate a significant higher risk for acute cardiac events and chronic heart failure (Maisel, Duran, & Wettersten, 2018). Moreover, (Gallagher et al., 2018) showed low evidence that [blood BNP] has even a higher predictive value than LVDD for sudden cardiac death in patients suffering from hypertension, an interesting item for further research.
Because of its fundamental role in the control of CV homeostasis, the measurement of the [blood NT-proBNP] is a meaningful parameter in the diagnosis of heart pathology (Maisel et al., 2018). Given the importance of measuring the [blood NT-proBNP] in the heart rehabilitation, this study focuses on the effect of T2DM on [blood NT-proBNP] to determine a suitable therapy in future.

About the cardiorespiratory fitness of patients diagnosed with T2DM, there is a lack of clear evidence and unambiguity. Study results of (Fringu et al., 2017) reveal an association between functional capacity and glycemic control (Momma et al., 2017). (Fringu et al., 2017) also assumes that individuals living with T2DM have a decreased cardiorespiratory fitness. On the other hand, the results of (Caron et al., 2017) contradict the relation between T2DM and maximal oxygen uptake (VO_{2max}). Basing on contradictions in literature, the conclusion can be made that more research is needed to evidence the correlation between T2DM and VO_{2max} and to detect some possible correlation between diastolic dysfunction and low levels of exercise capacity.

Because of the trend to progressive cardiac remodeling in T2DM patients, the goal of the study is to investigate the effect of T2DM on blood glycated hemoglobin concentration (HbA1C), biomarker [blood NT-proBNP] and the correlation with TTE assessments compared to healthy controls (HC). Besides this, the peak oxygen uptake (VO_{2peak}) is examined in the two groups by performing a single exercise test. The researchers hypothesized to detect signs of LVDD in the T2DM group, together with higher [blood NT-proBNP] and a reduced exercise capacity.

4.3 Methods

4.3.1 Ethical approval:

All test conditions were approved by the Ethical Committee of the Jessa Hospital and the University of Hasselt in Belgium (Abbreviation of the study: HITDCM study, date of approval: 25/09/2017). Prior to participating in the whole test procedure, the participants had to sign a formal informed consent agreement. At the first day of the study, all participants were verbally informed, supported with the written informed consent.

4.3.2 Recruitment of participants:

Various sources have been consulted to find healthy and T2DM volunteers. Patient files of the Jessa hospital were screened. If the patients met five predefined criteria (T2DM diagnosis and related comorbidities, non-insulin dependent diabetes mellitus (NIDDM), absence of coronary artery disease (CAD) and congenital heart disease), an invitation for participation in the study was sent to potential candidates. Also, local general practitioners were informed about the HITDCM project and shared the documentation with potential participants. In addition, an advertisement was handed-over to the senior university of Hasselt and the Flemish Diabetic Association. In case of a positive answer, the volunteers received more detailed information about the research. Prior to participation, a screening of their medical data was made.

4.3.3 Participants characteristics:

See Table 1 Inclusion and exclusion criteria

Subjects with well-controlled T2DM, aged between 18 and 81 years and with body mass index (BMI) above 20 kg/m², have participated in this clinical trial of the University of Hasselt. The diagnosis of T2DM was verified according the ADA guidelines (HbA1c ≥6.5%, fasting blood glucose (FBG) ≥126 mg/dl) ("Standards of Medical Care in Diabetes-2016: Summary of Revisions," 2016). An unchanged medical treatment for at least 3 months was required when not, the participation was postponed for 3 months. Exclusively, patients with NIDDM were eligible for inclusion. The authorization to participate from a physician, based on an electrocardiogram (ECG) analysis, was

mandatory prior to inclusion of T2DM in the study. The presence of known cardiac, neurological, pneumological, orthopedic and any other chronic diseases and related complications, with an exception of T2DM in the experimental group, was a reason for exclusion.

With exception of the T2DM related items, the same inclusion criteria were used for recruitment of the HC group.

Table 1 Inclusion and exclusion criteria

General inclusion criteria	**Inclusion criteria (T2DM group)**	**Exclusion criteria**
- 18 - 81 years - Free of chronic diseases (except T2DM in the T2DM group) - Permission of a physician to perform exercise (ECG analysis) - BMI > 20 kg/m²	- Diagnosis of T2DM as stated in guidelines of ADA ("Standards of Medical Care in Diabetes-2016: Summary of Revisions," 2016) - Non-insulin dependent diabetes mellitus (NIDDM) - Stable medication for at least 3 months ("Standards of Medical Care in Diabetes-2016: Summary of Revisions," 2016)	- Participation in another clinical trial - History of) heart diseases - Neurological/pneumological diseases - Oncological/orthopedic diseases - Pregnant women - Diabetes complications: renal diseases, retinopathy

4.3.4 Measurements

Questionnaire

See Form 1 SF-36v2 questionnaire

When the subjects signed the informed consent, both healthy volunteers and T2DM patients were asked to complete a questionnaire, namely the Short-Form-36 questionnaire version 2 (SF-36v2) in the presence of the researchers.

The SF-36v2 questionnaire was used to collect information about the functional health status (Jacobson et al., 1994). Eight different domains were questioned, including physical functioning, physical health problems, pain, general health perceptions, vitality, social functioning, emotional problems and general mental health. A global image was gathered about the physical and emotional health (Brazier et al., 1992).

Each item of a dimension was separately scored using a Likert scale. The values of eight different dimensions were estimated by taking averages of several items, described in the instructions of the questionnaire.

Summarizing, the SF-36 questionnaire is considered to be sensitive for measuring physical status and it was useful to detect changes in the responses (Jacobson et al., 1994). Physical functioning, pain and role-physical are the dimensions that most obviously describe the physical health. On the other hand, the interpretation of mental health, role limitations due to mental problems and social functioning best describe the mental health. Social functioning, vitality and general health perceptions measure the two dimensions, physical and mental health (McHorney et al., 1993).

DEXA scan

A dual-energy X-ray absorptiometry (DEXA) scan (Hologic - Delphi QDR series), a medical apparatus working with X-radiation, was used to determine the whole-body composition.

Before the administration of the DEXA scan, the subjects were informed about the minimum dose of radiation and the associated health risks. Both HC and T2DM participants received a DEXA scan,

performed in a fasting state. The data of de DEXA scans were used to determine the bone density by T-score, the BMI as well as the total fat %.

Blood samples

Prior to the TTE assessment, blood samples were taken from each participant in a fed state. The obtained material was used for analysis of [blood NT-proBNP] and HbA1c. Blood samples were directly delivered to the clinical lab, in the Jessa Hospital.

For a global image of the glycemic control during the last 8-12 weeks, HbA1c concentrations were measured in both T2DM patients and HC by the technique cation exchange chromatography. The cut-off of ≥ 6.5%, 48 mmol/mol, is used for diagnosing T2DM ("Standards of Medical Care in Diabetes-2016: Summary of Revisions," 2016).

For detecting chronic heart abnormalities, cut-off values of the [blood NT-proBNP] were determined. The predefined threshold values of 125 pg/mL for a participant below 75 years and 450 pg/mL for a participant above 75 years were used in the Jessa hospital. Values exceeding this cut-off value (≥ 125 pg/mL and ≥ 450 pg/mL) are an indication of chronic heart failure. Low concentrations (<125 pg/mL) of the biomarker NT-proBNP make the presence of cardiac dysfunction and heart failure very unlikely (Gustafsson et al., 2005; Ponikowski et al., 2016; Taylor, Rutten, Brouwer, & Hobbs, 2017). In the lab, [blood NT-proBNP] was determined by use of an electrochemiluminescence immunoassay “ECLIA” (Elecsys). The lower limit to measure [blood NT-proBNP] was 50 pg/mL. Concentrations below 50 pg/mL could not accurately be measured thus the outcome was represented as “<50 pg/mL”. In the statistical analysis, the value 50 was used, an important side note to the interpretation of [blood NT-proBNP].

Transthoracic echocardiography

An exercise TTE (General electronics, Vivid E9) is a non-invasive technique based on ultrasound, executed in rest and during a non-maximal single exercise test to assess the heart. During exercise, ECG was made for safety and to detect heart rate arrhythmia. This assessment was executed with a focus on diastolic function, more specifically, for the evaluation of clinical

features related to DCM. Additionally, the exercise TTE was also a tool to measure exercise related changes in cardiac parameters. To maintain a good muscular function during exercise at increasing workload what requires stronger muscle contractions, more oxygen is needed. The heart will take care of this by increasing the cardiac output and the ejection fraction (EF), causing a higher heart workload. This reasoning underlies the performance of the TTE during exercise (Higginbotham, Morris, Coleman, & Cobb, 1984).

Table 2 TTE assessment of DCM

Diastolic function	***Systolic function***
Mitral inflow pattern (E and A)	Ejection fraction (EF)
Mitral annular velocities (e' septal and lateral)	

Spirometry

Before starting the non-maximal cardiopulmonary exercise test (CPET), a spirometry (Schiller, CS-200 Ergo-Spiro) was performed to evaluate the lung function. After a maximal inspiration, the participants were asked to breathe out as powerful and as long as possible (Miller et al., 2005).

Exercise testing

Both T2DM and HC received an echocardiographic assessment during rest and a submaximal CPET, guided by a cardiologist of the Jessa Hospital. On an ergometer, a single exercise test was performed according to a ramp-stage protocol, characterized by a start point of 20W and a 10W/min increase to submaximal load. The test condition consisted of cycling exertion in a semi-supine position (Peteiro & Bouzas-Mosquera, 2010). The global cardiac parameters were recorded. Additionally, the key elements related to diabetic cardiomyopathy, LV and diastolic and systolic function, were analyzed more precisely. An analysis of the CPET measurements allowed to determine the cardiorespiratory fitness by VO_{2peak}. Further, parameters including expiratory volume, peak carbon dioxide output (VCO_{2peak}) and respiratory gas exchange ratio (RER) were also interpreted

4.3.5 Statistical Analysis

SPSS 25.0 (IBM, Chicago, IL, USA) was used for further statistical data analyses. Data was verified for normality with the Shapiro-Wilk test and the Normal Quantile Plot. Homoscedasticity was controlled using Levene's test. In case both conditions, namely normality and homoscedasticity, were met, an unpaired t-test of the parametric, continue data (one-way ANOVA) was performed to detect some relation with T2DM. Non-parametric, continue data, including abnormally distributed data or parameters with unequal variances, were analyzed by the Mann-Witney U test and The Welch test. Categoric data was analyzed by the Pearson Chi-square test. Associations between parameters were determined by Pearson (continuous data) or Spearman (ordinal/nominal data) correlations. A level of significance of 0.05 (2-tailed) was used. Power analyses were performed using G*power.

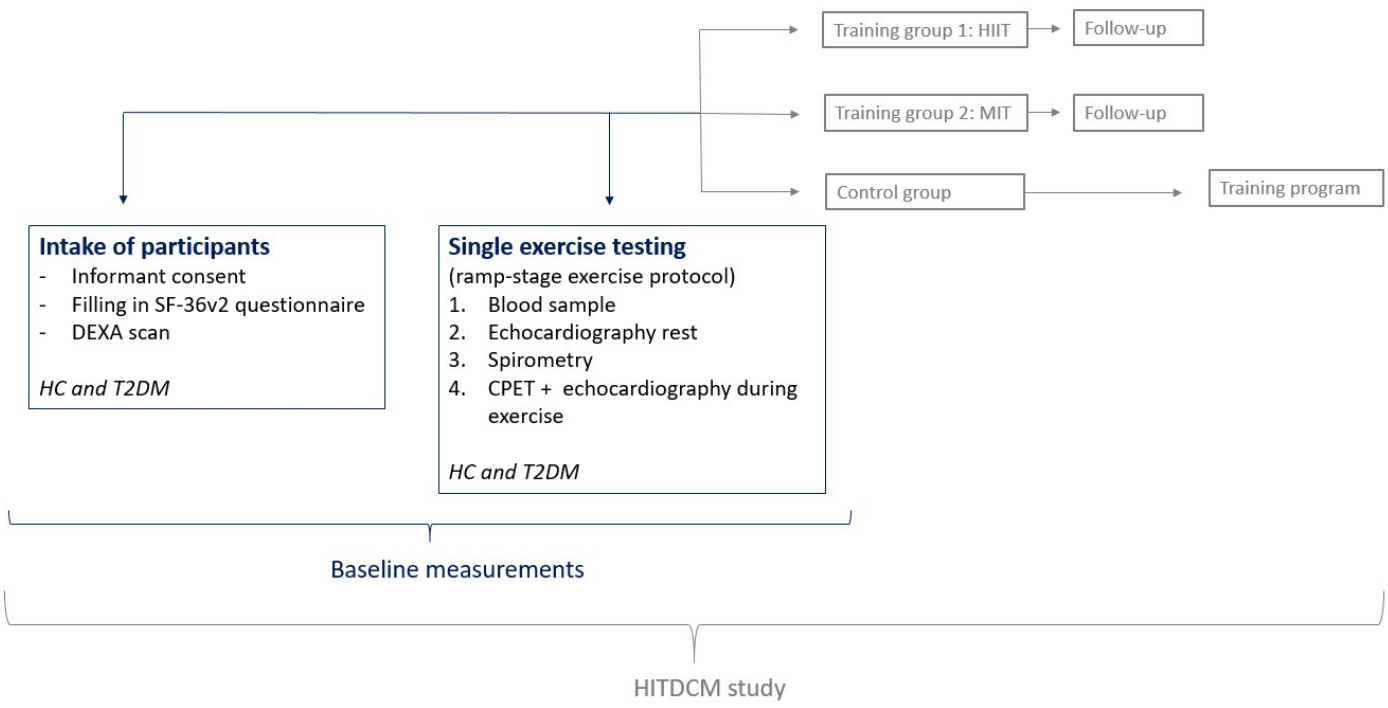

Figure 1 *Study design of Baseline measurements (blue) and HITDCM (gray)*

4.4 Results

Baseline characteristics

See Table 4 Baseline characteristics

In the HC group, 29 volunteers were checked for participation. Based on TTE assessment, heart abnormalities including aneurysm or severe valvular heart disease were registered in four subjects. Because of this finding, these persons could not be considered as healthy and needed to be excluded. In addition, the data of two HC participants were not analyzed because of poor image quality of TTE. Finally, the study enrolled 14 T2DM patients and 23 HC.

11 women and 12 men were included in the study as HC (n=23). Concerning the T2DM group (n=14), the majority of the participated T2DM patients were male (n=12). About the number of smokers in the study, one T2DM patient smoked weekly one to two cigars and one HC was a daily smoker. Besides, seven participants, where of three in the T2DM group, were known as an ex-smoker. No significant difference was found between T2DM and HC.

In general, the T2DM and HC were comparable in terms of age and anthropometric data, including bone density (T-score), height and total fat percentage (total fat %). However, in the T2DM group, BMI (25.10 ± 3.14 vs. 28.99 ± 6.53; *P=0.024*) and body weight (72.92 ± 13.12 vs. 89.73 ± 21.49; *P=0.006*) were significantly higher compared to HC *(Figure 2* Box plot body weight*, Figure 3* Box plot BMI). Additionally, a significant difference was observed for the HbA1C % (5.32 ± 0.30 vs. 6.64 ± 0.48, *P<0.001*) in T2DM vs. HC, explicable by an impaired glycemic control in the T2DM group. All the T2DM participants used anti-diabetic drugs *(P<0.001)* and 50 % of them statins *(P=0.043).* Anti-depressive drug was used by two T2DM patients. Drug use of fibrates, anti-hypertension and anti-thrombotic was low in both groups.

The occurrence of a known family history of DM was not different between the T2DM and HC groups. Nine T2DM patients had at least one parent suffering from this metabolic disorder. Regarding the family history of heart and CV diseases, the data did not reveal a significant difference. Only two HC and three T2DM patients exhibited cardiac complaints like shortness of breath or heart palpitations.

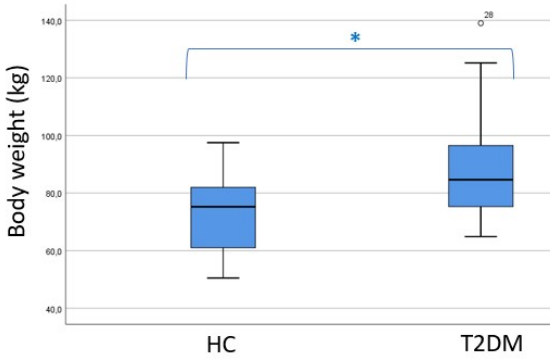

Figure 3 Box plot body weight

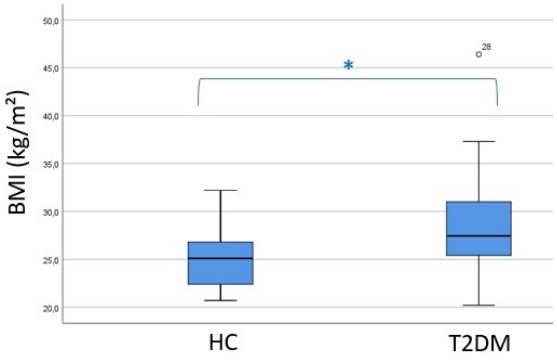

Figure 2 Box plot BMI

Impact of type 2 diabetes mellitus on functional status and related exercise capacity

See Table 5 SF-36v2 questionnaire and Table 9 CPET

An analysis of the SF-36 Questionnaire did not reveal a statistical significance, regarding the functional health status. Although, a trend to lower quantification of the general health was observed in the T2DM group compared to the scores of HC. (73.26 ± 12.58 vs. 63.93 ± 15.59; *P=0.053*).

The results of this questionnaire were confirmed by a non-significant different cardiorespiratory capacity (VO_{2peak}) in the T2DM group. However, VCO_{2peak} (1.29 ± 0.65 vs. 1.62 ± 0.57; *P=0.033*) was significant higher in T2DM compared to HC. A statistical analysis of parameters including heart rate (HR), ventilation and oxygen pulse (O2 pulse) did not reveal a powerful difference. All the other data of the CPET were similar between both groups.

Impact of type 2 diabetes mellitus on cardiac parameters

See Table 4 Baseline characteristics ([blood NT-proBNP] value), Table 7 TTE assessment and Table 8 Classification of diastolic function

T2DM patients showed significant lower values for the following parameters: early diastolic mitral annular velocity (e' septal) (0.07 ± 0.03 vs. 0.05 ± 0.02; *P=0.039*), the ratio of the peak velocity in the early diastole (E wave) to the peak velocity in the late diastole (A wave) by atrial contraction

(ratio E/A) (1.15 ± 0.51 vs. 0.70 ± 0.18; *P<0.001)* and the A wave (0.67 ± 0.23 vs. 0.85 ± 0.17; *P=0.016) (*Figure 6*,* Figure 4*,* Figure 5*)*. However, the values of the E wave, e' lateral and the E/e' ratio were comparable in the two groups. Blood analysis did not indicate a relation between T2DM and [blood NT-proBNP] value.

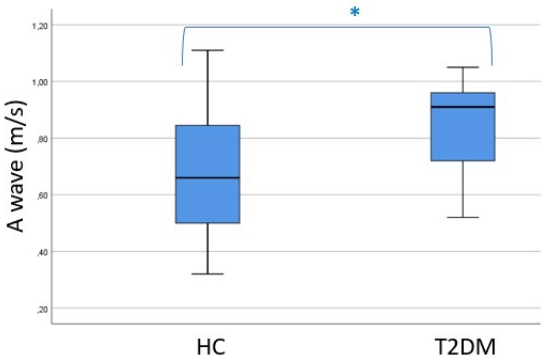

Figure 4 Box plot A wave

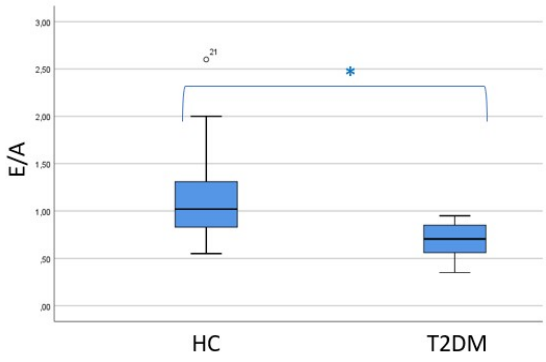

Figure 5 Box plot ratio E/A

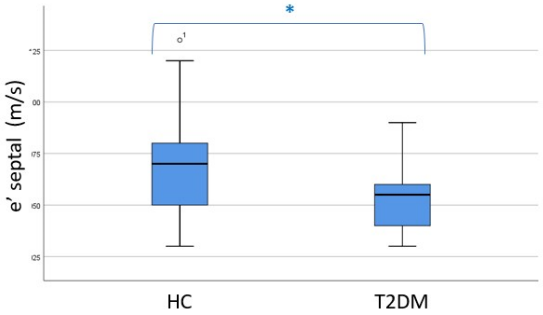

Figure 6 Box plot e' septal

The classification of (Nagueh et al., 2016) was used to describe the diastolic function of the T2DM heart. The TTE results of only seven T2DM patients could unambiguously be assigned to a category in line with that classification schedule (Nagueh et al., 2016). T2DM patients could be categorized as follows: three with grade 1 LVDD (E/A ≤ 0.8, E/e' <10), one with grade 2 LVDD (E/A >0.8 and <2, E/e' = 10-14) and three with a normal diastolic function profile. In the control group, the diastolic function of 17 HC could be described according to this classification and 11 subjects had a normal diastolic function profile. The category grade 1 LVDD included one HC and five HC could be assigned to the category grade 2 LVDD.

Impact of type 2 diabetes mellitus on pulmonary parameters

See Table 6 Spirometry

The spirometry of the T2DM did not show a clinically relevant difference towards the inspiratory vital capacity (IVC) compared to HC. Additionally, the forced expiratory volume in one second (FEV_1) and the peak expiratory flow (PEF) in the T2DM group were also not significantly different from the results of the HC. The T2DM group showed significant lower percentages of the predicted Tiffeneau index, expressed by FEV_1/IVC act/pred, compared to HC (119.23 ± 29.23 vs. 87.38 ± 18.34; *P=0.001)*. However, only a trend to lower values of the actual Tiffeneau index (FEV_1/IVC act) was observed by comparing both groups (0.93 ± 0.26 vs. 0.77 ± 0.12; *P=0.070*).

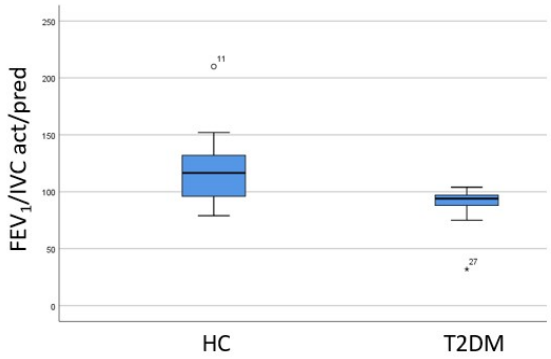

Figure 7 Box plot Fev1/IVC act/pred

Correlations between parameters

See Table 10 Correlations between parameters

BMI of T2DM patients was related to total fat % *(r=0.574, P=0.032).* This significant correlation was not observed in the HC group. Only in the HC group, gender and total fat % were correlated (*r=0.667, P=0.001).*

In T2DM group, the cardiac function showed no significant correlation with HbA1C % and [Blood NT-proBNP]. Furthermore, the pulmonary function was not associated with parameters including the glycemic control or smoke behavior. About the correlation between the cardiac function and

parameters of CPET, the E wave was correlated with VO_{2peak} *(r=0.660, P=0.020)* and VCO_{2peak} *(r=0.693, P=0.012).* The VCO_{2peak} was also correlated with e' septal *(r=0.612, P=0.034).* In addition, the VO2peak and VCO2peak were related to IVC *(r=0.754, P=0.005; r=0.699, P=0.011),* FEV_1act *(r=0.838, P=0.001; r=0.799, P=0.002)* and PEF *(r=0.670, P=0.017; r=0.614, P=0.034).*

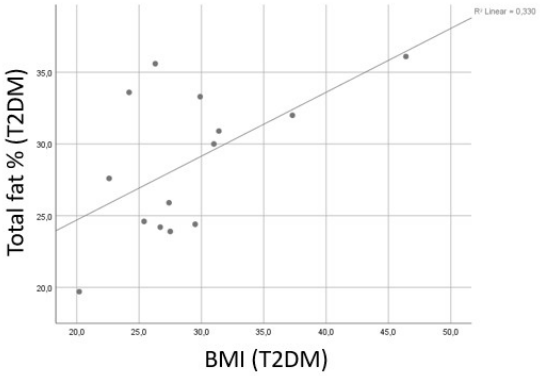

Figure 9 Correlation Total fat % and BMI

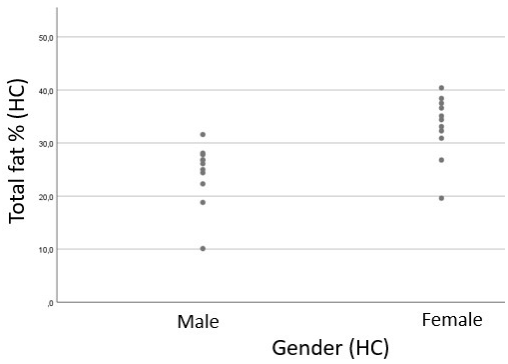

Figure 8 Correlation of total fat % and gender

4.5 Discussion

The objective of this study was to investigate the potential relation between T2DM and heart function and the functional exercise capacity in T2DM patients compared to HC. Prior to the statistical analyses, the baseline characteristics were verified.

Baseline characteristics

The majority of the patients with T2DM enrolled in the experimental group were male (12:2) compared to the HC group in which the ratio men versus women was comparable (15:13). This finding can be explained by a variety of potential reasons. A selection bias occurred in this study. Some of the T2DM patients had already participated in prior studies, such as the LIDE study and EXTIDI study, performed at the Hasselt University. The participants in those studies were exclusively men, because it was one of the inclusion criteria, and these were contacted again to participate in this new study. On the other hand, it could also be explained by a potential higher prevalence of T2DM in male, both on younger and older age, perceived in some previous research (Kautzky-Willer, Harreiter, & Pacini, 2016; Nordstrom, Hadrevi, Olsson, Franks, & Nordstrom, 2016; Rothney et al., 2013) . Gender differences, including different sex hormones and a larger amount of visceral fat, may be linked to an increased male vulnerability to develop the metabolic disease. However, the review of (Kautzky-Willer et al., 2016) and (Pucci et al., 2017) questions the higher prevalence with different female risk factors including higher waist circumference, lower levels of physical activity, a number of psychologic stress factors (low income, occupation and education) and lower testosterone levels. Because consensus on this item is lacking, more research is needed to justify this argument.

Body composition

In the T2DM group, the BMI and body weight were higher compared to the HC group. Nevertheless, T2DM was not correlated to the outcome total fat %. This finding was contradictory with the basic assumption of the study.

In the T2DM group, BMI and total fat % were positively correlated, but a similar correlation was not observed in the HC group. And, only in the HC group, a positive correlation between total fat % and gender was observed. This associations can underlie the higher values for BMI and weight in the T2DM patients and similar values for total fat %. A higher number of women was included in the HC group, with a high average total fat % as possible result. Because of the high values of total fat % (cut off value for men <25; women <30) in the HC, these correlations can indicate why the analysis revealed no relation between T2DM and total fat % (Okorodudu et al., 2010). However, the study of (Maryam Abolhasani1, 2013) also suggests some correlation between BMI and total fat % in a healthy population, contradictory with the findings of the present study. The performance of weekly moderate to vigorous physical activity, related to increased fat-free mass, can also result in high values of BMI in the T2DM group.

To confirm this reasoning, an analysis of the fat-free mass would be required, what is missing in this study. More research could clarify the potential relation between T2DM and total fat % and the inclusion of fat-free mass and skeletal structures is suggested to incorporate as outcomes. Also important in the interpretation of these data, low power was found for the results of BMI and total fat %.

SF-36v2 questionnaire

The SF-36v2 questionnaire was used to acquire some general impression about the functional health status. The answers to the different items gauges to the physical activity for the past four weeks. The responses depended on the time of the year, they entered the study. Specifically, the activity intensity made differ from winter to summer. In addition, the scoring in a questionnaire is subject to personal interpretation. In general, the T2DM group judged their general health, a subscale of the questionnaire, lower compared to healthy controls, but the physical functioning did not differ between both groups of the present study. Possibly, the lower scores of general health in T2DM can be declared by the diagnosis of T2DM. In addition, two subjects of T2DM group used anti-depressive drug compared to zero HC participants. The observation of similar values of physical functioning may suggest that the included T2DM patients achieve sufficient physical activity weekly. Accelerometers should be used to have accurate measurements of daily

physical activity of T2DM. Similarly, the conclusion of the study of (Thiel, Sayah, Vallance, Johnson, & Johnson, 2017) confirms that adults with T2DM who weekly perform the recommended proportion of moderate to vigorous physical activity, show a better physical functioning. However, literature of (Fagour et al., 2013) demonstrates lower levels of physical activity in T2DM population. Moreover, a sedentary lifestyle is a key risk factor to develop T2DM and obesity, at itself a risk factor for T2DM (Hamilton, Hamilton, & Zderic, 2014; Hu, 2003).

Again, for this outcome, a selection bias was present. The more sedentary T2DM patients could not be reached with this study as candidates were obtained through a variety of organizations, including senior university of Hasselt, an organization for elderly people, with members being per default more engaged to be active. Furthermore, the data in this study is part of a research, the HITDCM study, in which it was expected to perform a six-month exercise program, with a frequency of three times of exercise training per week. The data were extracted from the baseline measurements of the HITDCM study, focusing on the effect of two different types of exercise training on DCM. For six-months, the T2DM participants performed an exercise training program. Thus, every patient who responded to participate, was motivated to exercise.
In addition, the participants sourced from prior studies had already performed some exercise program. Their daily physical activity can be changed after the participation in the prior supervised exercise program.

Exercise capacity

In this study, a negative correlation between T2DM and exercise capacity was assumed at the beginning. However, a statistical analysis of the present CPET data revealed no meaningful difference between T2DM and HC, except of an increased VCO_{2peak} in T2DM group. A low power was observed for the results of the CPET. Contradictory, previous research indicates a reduced VO_{2peak} in T2DM population. (Fang, Sharman, Prins, & Marwick, 2005) and (Awotidebe et al., 2014) suggest that the observed lower values of exercise capacity are correlated to an increase of age, higher BMI and obesity, high fasting blood glucose levels and the duration of T2DM. Remarkable, both studies tested the exercise capacity at maximal load, namely the VO_{2max}. An important side

note to the data of the present study, the participants did not achieve the maximal workload. About a RER of 1.03 the cycling work load was stabilized and an exercise TTE assessment was performed.

Because of a preserved VO_{2peak} in the T2DM group, contradictory with the hypothesis, the spirometry and the TTE results were analyzed to reveal possible compensations in the pulmonary and cardiovascular system.

Left ventricular diastolic dysfunction

TTE, an accurate method available in the Jessa Hospital to investigate the heart function, was used to detect heart abnormalities. Although, with an intraobserver variability of 1-13% and an interobserver variability of 1-14%, this medical apparatus is sensitive to erroneous measurements because excellent skills and trained operators are required to achieve an ideal image quality for an accurate, statistical interpretation of the parameters (Muraru, Niero, Rodriguez-Zanella, Cherata, & Badano, 2018).

In the T2DM group, signs of DCM can be derived from the outcome of the rest TTE assessment. These findings suggest some potential relation between T2DM and the development of LVDD, described as a mark for DCM. However, the cardiac parameters were not correlated to glycemic control. A trend to a higher number of LVDD was observed in T2DM subjects compared to HC. It was impossible to categorize all participants according to classification of (Nagueh et al., 2016). Hence, the analysis of the number of LVDD in HC group and T2DM was performed only on a small part of the total sample size (n HC: 17; n T2DM: 7). As described in the study of (Jorgensen et al., 2016; Ofstad et al., 2015), significant lower values of E/A ratio (power 0.91) were measured in the asymptomatic T2DM patients of the present study. The non-significant different values of E wave, low power, may indicate the preservation of a good LV relaxation in the T2DM group. However, the researchers (Veeranki et al., 2016) and (Jorgensen et al., 2016) evidenced an impaired cardiomyocyte relaxation in a T2DM heart.

Additionally, previous research performed on mice and humans demonstrate a calcium (Ca^{2+}) dysregulation, including lower levels of Ca^{2+} during systole and diastole, what can be related to a

slower relaxation of the cardiomyocytes (Li et al., 2016; Stolen et al., 2009). Future research with a greater sample size is required to estimate this finding.

An increase in E wave value with the duration of T2DM was suggested by (Jorgensen et al., 2016). The duration of T2DM can be meaningful to explain the similar value of E wave in both groups. Data about the duration of the metabolic disease were not incorporated in the present study, which forms a possible limitation for our interpretation of the echocardiographic parameters. Conversely, the increase of A wave with a power of 0.72 revealed an impaired heart compliance. Research of (van Heerebeek et al., 2008) also ascertains LV wall stiffness in diastole and describes some association with excessive cardiomyocyte fibrosis and hypertrophy. The observation of wall stiffness and lower values of e' septal suggest an increased filling pressure in LV and some relation with DCM, but no significant difference was observed for the E/e' ratio and e' lateral (low power). It is assumed that the duration of T2DM can be some root cause or the occurrence of faulty measurements (Jorgensen et al., 2016). However, the study of (Ommen et al., 2000) describes tissue doppler imaging as a good method to estimate LV filling pressures. Besides, the non-significant e' lateral values could be explained by following reasoning. The parameter e' septal measured the velocity of the septum at the insertion of the Mitral valve during diastolic phase. Thereby, the lower values of e' septal in T2DM group are possibly related to wall stiffness of the right heart side. The parameter e' lateral is possibly less dependent of the mobility of the right heart wall because this was measured at the other insertion of the mitral valve, namely the LV wall. This phenomenon can be related to the duration of T2DM, accompanied with increased wall fibrosis. However, the study of (Jorgensen et al., 2016) showed increased filling pressures by lowered values e' septal, as well as e' lateral and higher values of E/e' ratio. To confirm the assumption of increased filling pressures, a more detailed evaluation of parameters related to the outcome LV filling pressure is recommended in further research.

Another limitation of the present study is the missing data of EF. Previous research describes the relation between T2DM and systolic dysfunction, namely a reduced EF (Dodiyi-Manuel, Akpa, & Odia, 2013; Jia et al., 2018). Also, (van Heerebeek et al., 2008) emphasized the importance to consider the EF in the interpretation of the mechanism underlying the LVDD.

Next, through the close association between the heart function and structure, some evaluation of potential heart remodeling is needed to achieve a complete image of altered heart function and structure related to T2DM. A structural analysis is recommended to incorporate in further research.

Compensation mechanisms for preserved VO_{2peak}

Although the evidence of impaired diastolic heart function in the T2DM group, the cardiorespiratory exercise capacity was preserved in T2DM group. Except of the E wave, no correlation was observed between VO_{2peak} and the altered cardiac parameters. Although, a greater value of E wave did not mean a better EF. Through this observation, an accurate analysis of the lung function was performed. Measured by spirometry, only a trend to lowered Tiffeneau index was observed in the T2DM group. This finding indicates some susceptibility to obstructive changes in the lung structure and suggest some risk to develop COPD, an obstructive lung disease, in T2DM population. However, the ventilation and FEV_1 remained unchanged. About the Tiffeneau index, no correlation was found with the smoking behavior, glycemic control or exercise capacity of the participants. In literature, the recent study of (Hsu et al., 2018) demonstrated equal results, indicating a higher incidence of COPD in the T2DM population. (Aparna, 2013) questions this observation with rather an increase of the Tiffeneau index in T2DM population, signaling of restrictive lung disease. More research with the focus on lung function in T2DM disease is required to make a statement about the association between pulmonary function and T2DM.

Correlation between parameter of transthoracic echocardiography and exercise testing

A negative correlation was observed between E wave and VCO_{2peak}. The higher values of VCO_{2peak} can be declared by the altered energy metabolism in T2DM population. In literature, an overload to fatty acid metabolism in T2DM is described as some potential mechanism of impaired cardiac functioning. Thereby, a higher VCO2peak was expected to be associated with a higher E wave, thus a positive correlation. In the present study, the finding of a negative correlation can not be explained. The negative correlation of VO_{2peak} and E wave shows that a reduced exercise capacity accompanies with a severe clinical picture.

Blood NT-proBNP concentration

In addition to the TTE heart assessment, blood analyses were performed to figure out the correlation between T2DM and [blood NT-proBNP]. In contradiction to previous research in T2DM and heart failure population, no significant correlation was found between the [blood NT-proBNP] and glycemic control or TTE findings (Amorim et al., 2017; Kristensen et al., 2017; Ohkuma et al., 2017). Prior studies used a bigger samples size to investigate the relation between T2DM and this biomarker. Higher [blood NT-proBNP] were supposed because of the changed heart parameters in the T2DM group. Because of cardiac stress, the LV wall will release a greater amount of BNP in blood circulation (Alter et al., 2007). The equal values of [blood NT-proBNP] (low power of 0.19) contradict with the impression of increased filling pressure. Probably, the LV wall stress was not yet high enough to influence the [blood NT-pro BNP] or measurement errors lead to incorrect interpretations of the TTE parameters. Also for this outcome, the duration of T2DM disease should have been taken into account. On the other hand, the [blood NT-proBNP] were measured from blood samples taken before the TTE assessment during single exercise testing, similarly to previous research about T2DM patients and patients with chronic heart failure. Possibly, after exertion accompanied by an increased heart workload, other phenomena including an extreme elevation of [blood BNP] could be observed (Win et al., 2005). The influence of a single exercise testing on the [blood NT-proBNP] in T2DM population is an interesting question for further research.

Pulmonary function

Again, a lowered Tiffeneau index was observed, accompanied with a preserved exercise capacity. Parameters including IVC, FEV1 act and PEF were not different between the two groups, but positively correlated to VO_{2peak}. Therefore, this remarkable finding suggests that T2DM people may compensate in other system for the DCM and the trend to changed lung function. To detect whether they compensate and how, more detailed analysis of the exercise capacity including muscle structure and energy metabolism is needed. Maybe, a metabolic dysregulation can also explicate the preserved exercise capacity at non-maximal load. The metabolic disease T2DM impairs glucose metabolism. This means that a great amount of ATP is synthetized from fatty acids, because the glucose mechanism of a patient with T2DM is not efficient (Bays, Mandarino, & DeFronzo, 2004; Rynders, Blanc, DeJong, Bessesen, & Bergouignan, 2018). This underlies the importance of achieving a maximal load. Producing a maximal load requires an efficient working glucose metabolism which is not guaranteed in patients with T2DM. Presumably, the T2DM patients did not achieve that point in the present exercise testing what requires a total shift to glucose metabolism. An investigation of exercise capacity by exercise testing on maximal load and related metabolism is recommended for further research.

Conclusion

In conclusion, T2DM is possibly correlated with the development of LVDD, described as a phenomenon related to the pathophysiology of DCM. More detailed heart assessment with a greater sample size and the incorporation of the duration of T2DM is recommended for further research. Any correlation between T2DM and cardiorespiratory fitness (VO_{2peak}) was not observed. A single exercise testing to maximal workload can be needed to detect differences.

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6 Appendix

Table 3 List of abbreviations

A wave	Peak velocity in the late diastole by atrial contraction
BMI	Body mass index
CPET	Cardiopulmonary exercise test
CV(D)	Cardiovascular (Disease)
DCM	Diabetic cardiomyopathy
DM	Diabetes Mellitus
DEXA	Dual energy X-ray absorptiometry
E wave	Peak velocity in the early diastole by atrial contraction
e' septal/lateral	Early diastolic mitral annular velocity
EF	Ejection fraction
FBG	Fasting blood glucose
FEV_1	Forced expiratory volume in one second
FFA	Free fatty acid
HbA1C	Blood glycated hemoglobin concentration
HC	Healthy controls
HIIT	High intensity interval training
HR	Heart rate
IGT	Impaired glucose tolerance
IVC	Inspiratory vital capacity
LVDD	Left ventricular diastolic dysfunction
MIT	Moderate intensity training
NIDDM	Non-insulin dependent Diabetes Mellitus
NT-proBNP	N-terminal pro Brain natriuretic peptide
RER	Respiratory exchange ratio
PEF	Peak expiratory flow
SF-36v2	Short form 36 questionnaire version 2

T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TTE	Transthoracic echocardiography
VE	Ventilation

Table 4 Baseline characteristics

Parameters	HC (n=23)	T2DM (n=14)	P value	Power
Age (Years)	54.77 ± 15.62 [47.89;61.65]	62.00 ± 8.68 [56.99;67.01]	0.083	
Gender			***0.038****	
Female (n)	11	2		
Male (n)	12	12		
T-score[1]	0.07 ± 1.36 [-0.55; 0.69]	0.31 ± 1.25 [-4.42;1.03]	0.607	
Height (cm)[2]	170.88 ± 9.98 [166.34;175.42]	175.87 ± 8.54 [170.94; 180.81]	0.135	
Weight (kg)[3]	72.92 ± 13.12 [67.11;78.74]	89.73 ± 21.49 [77.32;102.14]	***0.006****	0.77
BMI (Kg/m²)[4]	25.10 ± 3.14 [23.67;26.53]	28.99 ± 6.53 [25.22;32.76]	***0.024****	0.19
Total fat (%)[5]	28.77 ± 7.27 [25.55;31.99]	28.70 ± 5.07 [24.78;31.63]	0.976	0.05
HbA1C (%)	5.32 ± 0.30 [5.19;5.45]	6.64 ± 0.48 [6.36;6.91]	***<0.001****	1.00
HbA1C (mmol/mol)	34.74 ± 3.32 [33.30;36.17]	48.79 ± 5.19 [45.79;51.78]	***<0.001****	1.00
NT-proBNP (pg/mL)	60.87 ± 27.69 [48.90;72.84]	75.50 ± 46.21 [48.82;102.18]	0.283	0.19
Family history of DM (n)			0.081	
Yes (n)	7	9		
No (n)	16	5		
Family history of CVD (n)[6]			0.365	
Yes (n)	9	4		

No (n)	14	10	
Smoke status			0.445
Smoker (n)	1	1	
Ex-smoker (n)	3	4	
No smoker (n)	20	9	
Cardiac complaints[7]			
Yes (n)	2	3	0.272
No (n)	21	11	
Drug use (n)			
Anti-diabetic	0	14	***<0.001****
Statins	4	7	***0.043****
Fibrates	0	2	0.068
Anti-thrombotic	0	2	0.068
Anti-hypertension	1	2	0.116
ACE inhibitor	2	2	0.629
Stomach acid inhibitor	0	3	***0.023****
Anti-depressive	0	2	0.068
Uric acid inhibitor	1	2	0.303

**p<0.05; Mean ± SD – T2DM: type 2 Diabetes Mellitus; HC: healthy controls; T-score: bone density; BMI: body mass index; HbA1C: Blood glycated hemoglobin concentration; NT-proBNP: N-terminal proBrain natriuretic peptide; DM: diabetes mellitus; CVD: cardiovascular disease*

[1]: 1 missing value in T2DM (n) because of incorrect measurement of T-score by the presence of orthopedic material in hip + 1 missing value in HC group because a dexa scan was not performed on one subject

[2,3,4,5]: 1 missing value in HC group because a dexa scan was not performed on one subject.

[6]: cardiovascular disease including cardiac arrest, atherosclerosis and stents, pacemaker, aneurysm, aorta valve replacement

[7]: cardiac complaints: shortness of breath, heart palpations, pain, acute loss of consciousness.

Table 5 SF-36v2 questionnaire

Parameters	***HC (n=23)***	***T2DM (n=14)***	***P value***	***Power***
Physical function	90.10 ± 9.92 [85.81;94.39]	87.14 ± 10.14 [81.29;93.00]	0.316	0.13
Role limitations (physical health)	90.33 ± 19.49 [81.90;98.75]	83.93 ± 33.41[64.64;103.22]	0.983	0.10
Role limitations (emotional problems)	95.65 ± 15.26 [89.05;102.25]	90.48 ± 27.51 [74.59;106.36]	0.581	0.10
Energy/fatigue	72.39 ± 17.51 [64.82;79.96]	68.21 ± 18.46 [57.56;78.87]	0.495	0.10
Emotional well-being	81.04 ± 15.03 [74.55;87.54]	78.29 ± 16.66 [68.77;87.90]	0.717	0.08
Social functioning	94.02 ± 9.88 [89.75;98.29]	88.39 ± 14.26 [80.16;96.63]	0.160	0.25
Pain	84.35 ± 17.67 [76.71;91.99]	78.39 ± 19.55 [67.10;89.68]	0.336	0.15
General health	73.26 ± 12.58 [67.82;78.70]	63.93 ± 15.59 [54.93;72.93]	0.053	0.47
Health change	58.70 ± 17.85 [50.98;66.42]	58.93 ± 15.83 [49.79;68.07]	0.720	0.05

**p<0.05; Mean ± SD - T2DM: type 2 Diabetes Mellitus; HC: healthy controls.*

Table 6 Spirometry

Parameters	HC (n=22)[1]	T2DM (n=13)[2]	P value	Power
IVC (L)	3.03 ± 1.25 [2.48;3.59]	3.54 ± 1.05 [2.90;4.17]	0.230	0.23
FEV_1 act (L)	2.64 ± 0.75 [2.31;2.97]	2.71 ± 0.80 [2.23;3.19]	0.790	0.06
FEV_1 act/pred (%)	91.05 ± 16.86 [86.57;98.52]	88.46 ± 17.43 [77.93;98.99]	0.946	0.07
FEV_1/IVC act (L)	0.93 ± 0.26 [0.82;1.05]	0.77 ± 0.12 [0.69;0.84]	0.070	0.57
FEV_1/IVC act/pred (%)	119.23 ± 29.23 [106.27;132.18]	87.38 ± 18.34 [76.30;98.47]	***0.001****	0.94
PEF (L/s)	6.77 ± 2.18 [5.81;7.74]	6.49 ± 2.46 [5.01;7.98]	0.728	0.06

**p<0.05; Mean ± SD - T2DM: type 2 Diabetes Mellitus; HC: healthy controls; IVC: inspiratory vital capacity; FEV_1: Forced expiratory volume in one second; FEV_1/IVC: Tiffeneau index; PEF: pulmonary expiratory flow.*

[1]: 1 missing value in HC group, spirometry was not performed because of dyskinesia in rest TTE.

[2]:1 missing value in T2DM group, the body weight of one subject exceeded the maximum weight (125 kg) allowed for the bicycle used for CPET.

Table 7 TTE assessment

Parameters	HC (n=23)	T2DM (n=14)	P value	Power
E wave (m/s)	0.64 ± 0.16 [0.57;0.71]	0.58 ± 0.14 [0.50;0.66]	0.258	0.21
A wave (m/s)	0.67 ± 0.23 [0.58;0.77]	0.85 ± 0.17 [0.75;0.95]	***0.016****	0.72
E/A	1.15 ± 0.51 [0.93; 1.38]	0.70 ± 0.18 [0.60;0.80]	***0.001****	0.91
E/e'	9.62 ± 3.08 [8.29; 10.95]	10.71 ± 2.17 [9.45; 11.98]	0.258	0.22
e' septal (m/s)	0.07 ± 0.03 [0.06;0.08]	0.05 ± 0.02 [0.05; 0.06]	***0.039****	0.61
e' lateral (m/s)[1]	0.09 ± 0.03 [0.07;0.10]	0.08 ± 0.02 [0.06;0.09]	0.365	0.19

**p<0.05; Mean ± SD - T2DM: type 2 Diabetes Mellitus; HC: healthy controls; E wave: Peak velocity in the early diastole by atrial contraction; A wave: Peak velocity in the late diastole by atrial contraction; e': Early diastolic mitral annular velocity (septal and lateral view).*

[1]: 2 missing value in HC and 1 missing value in T2DM group because of poor image quality to measure e' lateral.

Table 8 Classification of diastolic function

Parameters	HC (n=17)	T2DM (n=7)	P value	Power
Normal diastolic function (n)	11	3		
LVDD (n)			0.085	0.05
Grade 1 (n)	1	3		
Grade 2 (n)	5	1		

**p<0.05 - T2DM: type 2 Diabetes Mellitus; HC: healthy controls, LVDD: left ventricular diastolic dysfunction*

Table 9 CPET

Parameters	HC (n=22)[1]	T2DM (n=12)[2]	P value	Power
VO_2 (L/min)				
Rest	0.22 ± 0.13 [0.16;0.27]	0.28 ± 0.13 [0.20;0.36]	0.204	0.24
AT	1.30 ± 0.65 [1.01;1.59]	1.32 ± 0.50 [1.00;1.64]	0.843	0.05
Max load	1.47 ± 0.65 [1.18;1.76]	1.52 ± 0.56 [1.17;1.88]	0.824	0.06
VCO_2 (L/min)				
Rest	0.18 ± 0.10 [0.13;0.23]	0.24 ± 0.01 [0.17;0.32]	0.117	0.63
AT	1.29 ± 0.65 [1.01;1.58]	1.31 ± 0.49 [0.99;1.62]	0.843	0.05
Max load	1.29 ± 0.65 [1.01;1.58]	1.62 ± 0.57 [1.26;1.98]	***0.033****	0.30
RER max load	1.05 ± 0.03 [1.04;1.07]	1.06 ± 0.06 [1.03;1.10]	0.393	0.09
VE				
Rest	6.38 ± 3.75 [4.71;8.04]	8.74 ± 4.41 [6.03;11.64]	0.096	0.34
AT	35.04 ± 17.24 [27.39;42.68]	36.47 ± 12.83 [28.31;44.62]	0.803	0.06
Max load	43.35 ± 19.15 [34.86;51.84]	46.85 ± 16.94 [36.09;57.61]	0.599	0.08
VO_2/Kg (mL/min/kg)				
Rest	2.73 ± 1.25 [2.17;3.28]	3.31 ± 1.37 [2.44;4.18]	0.219	0.22
AT	16.93 ± 6.96 [13.84;20.02]	16.32 ± 6.54 [12.16;20.47]	0.803	0.06
Max load	19.37 ± 7.27 [16.15;22.60]	18.66 ± 6.55 [14.50;22.82]	0.779	0.06

VCO_2/Kg (mL/min/kg)				
Rest	2.73 ± 1.09 [1.79;2.75]	2.89 ± 1.27 [2.08.3.70]	0.145	0.07
AT	16.84 ± 6.92 [13.77;.19.91]	16.15 ± 6.23 [12.20;20.11]	0.775	0.06
Max load	20.39 ± 7.73 [16.96;23.82]	19.80 ± 6.41 [15.73;23.87]	0.823	0.06
HR (beats/min)				
Rest	68 ± 13 [62;73]	72 ± 9 [66;79]	0.284	0.16
AT	123 ± 19 [114;131]	119 ± 16 [109;129]	0.546	0.09
Max load	131 ± 24 [121;142]	121 ± 27 [104;138]	0.289	0.18
O_2 pulse (mL/beat)				
Rest	3.40 ± 2.47 [2.30;4.49]	3.83 ± 1.68 [2.76;4.90]	0.321	0.08
AT	10.49 ± 4.36 [8.55;12.42]	10.96 ± 3.26 [8.88;13.03]	0.746	0.06
Max load	11.35 ± 4.37 [9.41;13.29]	12.96 ± 4.77 [9.93;15.99]	0.327	0.16
PET O_2 (mmHG)	107.46 ± 3.59 [105.87;109.06]	109.53 ± 6.54 [105.38;113.69]	0.240	0.19
PET CO_2 (mmHG)	41.58 ± 13.63 [35.54;47.62]	37.63 ± 4.28 [34.91;40.36]	0.264	0.18

**p<0.05; Mean ± SD - T2DM: type 2 Diabetes Mellitus; HC: healthy controls; VO_2: oxygen uptake; VCO_2: carbon dioxide output; HR: heart rate; RER: respiratory exchange ratio; VE: ventilation; VO_2/kg: relative oxygen uptake; VCO_2/kg: relative carbon dioxide output; O2 pulse: oxygen pulse; PET O_2: end-tidal oxygen; PET CO_2: end-tidal carbon dioxide.*

[1]: 1 missing value in HC group, one subject did not perform a CPET because of dyskinesia in rest TTE.

[2]:2 missing values in T2DM group, one subject did not perform a CPET because of dyskinesia in rest TTE and the body weight of one subject exceeded the maximum weight (125kg) allowed for the bicycle used for CPET.

Table 10 Correlations between parameters

Parameters		Correlation coefficient	P value	Power
[Blood NT-proBNP]	E (m/s)	-0.154	0.598	0.08
	A (m/s)	0.298	0.301	0.19
	E/A	-0.365	0.199	0.27
	e' septal (m/s)	-0.383	0.176	0.30
	e' lateral (m/s)	-0.379	0.201	0.29
	E/e'	0.421	0.134	0.36
	HbA1C %	0.376	0.185	0.29
HbA1C %	E (m/s)	0.192	0.510	0.10
	A (m/s)	-0.168	0.566	0.09
	E/A	0.339	0.236	0.24
	e' septal (m/s)	0.039	0.896	0.05
	e' lateral (m/s)	-0.318	0.281	0.21
	E/e'	0.316	0.270	0.21
	IVC (L)	0.110	0.708	0.07
	FEV_1 act	-0.081	0.783	0.06
	FEV_1/IVC	0.457	0.100	0.39
	PEF	-0.116	0.692	0.07

	VO_{2peak}	-0.244	0.445	0.13
	VCO_{2peak}	-0.190	0.553	0.10
Smoke behavior	IVC (L)	0.021	0.944	0.05
	FEV_1 act	-0.115	0.696	0.07
	FEV_1/IVC act	0.305	0.289	0.18
	PEF	-0.312	0.278	0.19
$VO_{2\ peak}$	E (m/s)	-0.660	***0.020****	0.82
	A (m/s)	-0.129	0.609	0.07
	E/A	-0.448	0.144	0.38
	e' septal (m/s)	-0.524	0.081	0.53
	e' lateral (m/s)	-0.181	0.593	0.09
	E/e'	-0.127	0.694	0.0.7
	IVC	0.754	***0.005****	0.93
	FEV_1 act	0.838	***0.001****	1.00
	FEV_1/IVC act	0.001	0.998	0.05
	PEF	0.670	***0.017****	0.84
$VCO_{2\ peak}$	E (m/s)	-0.693	***0.012****	0.88
	A (m/s)	-0.192	0.550	0.10
	E/A	-0.428	0.165	0.34
	e' septal (m/s)	-0.612	***0.034****	0.72

	e' lateral (m/s)	-0.148	0.665	0.08
	E/e'	0.012	0.971	0.05
	IVC	0.699	**0.011***	0.89
	FEV_1 act	0.799	**0.002***	0.99
	FEV_1/IVC act	0.120	0.710	0.07
	PEF	0.614	***0.034****	0.72
BMI[1]	Total fat %[1]	0.299	0.199	0.26
BMI	Total fat %	0.574	***0.032****	0.67
Gender[1]	Total fat %[1]	0.667	***0.001****	0.98
Gender	Total fat %	0.506	0.065	0.52

[1]: These correlations are analyzed in HC group. All the other correlations are tested in T2DM group.

Form 1 SF-36v2 questionnaire

SF-36 GEZONDHEIDSTOESTAND VRAGENLIJST

INSTRUCTIE: Deze vragenlijst gaat over uw standpunten t.a.v. uw gezondheid. Met behulp van deze gegevens kan worden bijgehouden hoe u zich voelt en hoe goed u in staat bent uw gebruikelijke bezigheden uit te voeren.

Beantwoord elke vraag door het antwoord op de aangegeven wijze te markeren. Als u niet zeker weet hoe u een vraag moet beantwoorden, geef dan het best mogelijke antwoord.

1. Hoe zou u over het algemeen uw gezondheid noemen? (omcirkel één cijfer)

Uitstekend	1
Zeer goed	2
Goed	3
Matig	4
Slecht	5

2. Hoe beoordeelt u nu uw gezondheid over het algemeen, vergeleken met een jaar geleden? (omcirkel één cijfer)

Veel beter nu dan een jaar geleden	1
Wat beter nu dan een jaar geleden	2
Ongeveer hetzelfde nu als een jaar geleden . . .	3
Wat slechter nu dan een jaar geleden	4
Veel slechter nu dan een jaar geleden	5

3. De volgende vragen gaan over bezigheden die u misschien doet op een doorsnee dag. Wordt u door uw gezondheid op dit moment beperkt bij deze bezigheden? Zo ja, in welke mate? (omcirkel één cijfer op elke regel)

BEZIGHEDEN	Ja, ernstig beperkt	Ja, een beetje beperkt	Nee, helemaal niet beperkt
a. Forse inspanning, zoals hardlopen, tillen van zware voorwerpen, een veeleisende sport beoefenen	1	2	3

b. Matige inspanning, zoals een tafel verplaatsen, stofzuigen, zwemmen of fietsen	1	2	3
c. Boodschappen tillen of dragen	1	2	3
d. Een paar trappen oplopen	1	2	3
e. Eén trap oplopen	1	2	3
f. Bukken, knielen of hurken	1	2	3
g. Meer dan een kilometer lopen	1	2	3
h. Een paar honderd meter lopen	1	2	3
i. Ongeveer honderd meter lopen	1	2	3
j. Uzelf wassen of aankleden	1	2	3

4. Heeft u in de afgelopen 4 weken, een van de volgende problemen bij uw werk of andere dagelijkse bezigheden gehad, ten gevolge van uw lichamelijke gezondheid?

(omcirkel één cijfer op elke regel)

	JA	NEE
a. U besteedde minder tijd aan werk of andere bezigheden	1	2
b. U heeft minder bereikt dan u zou willen	1	2
c. U was beperkt in het soort werk of andere bezigheden	1	2
d. U had moeite om uw werk of andere bezigheden uit te voeren (het kostte u bv. extra inspanning)	1	2

5. Heeft u in de afgelopen 4 weken, een van de volgende problemen ondervonden bij uw werk of andere dagelijkse bezigheden ten gevolge van emotionele problemen (zoals depressieve of angstige gevoelens)?

(omcirkel één cijfer op elke regel)

	JA	NEE
a. U besteedde minder tijd aan werk of andere bezigheden	1	2
b. U heeft minder bereikt dan u zou willen	1	2
c. U deed uw werk of andere bezigheden niet zo zorgvuldig als gewoonlijk	1	2

6. In hoeverre hebben uw lichamelijke gezondheid of emotionele problemen u gedurende de afgelopen 4 weken gehinderd in uw normale omgang met familie, vrienden of buren, of bij activiteiten in groepsverband? (omcirkel één cijfer)

Helemaal niet 1

Enigszins 2

Nogal 3

Veel 4

Heel erg veel 5

7. Hoeveel lichamelijke pijn heeft u de afgelopen 4 weken gehad? (omcirkel één cijfer)

Geen 1

Heel licht 2

Licht 3

Nogal 4

Ernstig 5

Heel ernstig 6

8. In welke mate bent u de afgelopen 4 weken door pijn gehinderd in uw normale werk (zowel werk buitenshuis als huishoudelijk werk)? (omcirkel één cijfer)

Helemaal niet 1

Een klein beetje 2

Nogal 3

Veel 4

Heel erg veel 5

9. Deze vragen gaan over hoe u zich voelt en hoe het met u ging in de afgelopen 4 weken. Wilt u a.u.b. bij elke vraag het antwoord geven dat het best benadert hoe u zich voelde. Hoe vaak gedurende de afgelopen 4 weken

(omcirkel één cijfer op elke regel)

	altijd	meestal	vaak	soms	zelden	nooit
a. Voelde u zich levenslustig?	1	2	3	4	5	6
b. Was u erg zenuwachtig?	1	2	3	4	5	6
c. Zat u zo in de put dat niets u kon opvrolijken?	1	2	3	4	5	6
d. Voelde u zich rustig en tevreden?	1	2	3	4	5	6
e. Had u veel energie?	1	2	3	4	5	6
f. Voelde u zich somber en neerslachtig?	1	2	3	4	5	6

g. Voelde u zich uitgeput?	1	2	3	4	5	6
h. Was u een gelukkig mens?	1	2	3	4	5	6
i. Voelde u zich moe?	1	2	3	4	5	6

10. Hoe vaak hebben uw lichamelijke gezondheid of emotionele problemen u gedurende de afgelopen 4 weken gehinderd bij uw sociale activiteiten (zoals vrienden of familie bezoeken, etc)? (omcirkel één cijfer)

Altijd 1

Meestal 2

Soms 3

Zelden 4

Nooit 5

11. Hoe JUIST of ONJUIST is elk van de volgende uitspraken voor u? (omcirkel één cijfer op elke regel)

	volkomen juist	grotendeels juist	weet ik niet	grotendeels onjuist	volkomen onjuist
a. Ik lijk wat gemakkelijker ziek te worden	1	2	3	4	5
b. Ik ben even gezond als andere mensen	1	2	3	4	5
c. Ik verwacht dat mijn gezondheid achteruit zal gaan	1	2	3	4	5
d. Mijn gezondheid is uitstekend	1	2	3	4	5

Form 2 overview of consultations with PHD student

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KNOWLEDGE IN ACTION

VOORTGANGSFORMULIER WETENSCHAPPELIJKE STAGE DEEL 2

DATUM	INHOUD OVERLEG	HANDTEKENINGEN
27/10/18	Opstart Masterproef 2. - verdeling onderwerp - Bespreking Metingen	Begeleider: Copromotor: Student(e): Student(e):
13/02/18 tot 20/03/18	Maandag- vrijdag helpen bij Metingen Meerdere heren samengezeten voor bespreking en feedback ITPR'	Begeleider: Copromotor: Student(e): Student(e):
9/05/18	Bespreking statische analyse	Begeleider: Copromotor: Student(e): Student(e):
31/05/18	Bespreking eindversie + laatste aanpassingen	Begeleider: Copromotor: Student(e): Student(e):
		Promotor: Copromotor: Student(e): Student(e):
		Promotor: Copromotor: Student(e): Student(e):
		Promotor: Copromotor: Student(e): Student(e):
		Promotor: Copromotor: Student(e): Student(e):
		Promotor: Copromotor: Student(e): Student(e):
		Promotor: Copromotor: Student(e): Student(e):

* Begeleider: Dra. Lisa Van Rycheghem

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Jaar: **2018**

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Voor akkoord,

Backx, Annelies

Datum: **5/06/2018**