Master's thesis

NTNU
Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
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Sex differences in exercise response in type 2 diabetes

Master's thesis in Exercise Physiology
Supervisor: Professor, MD, Dr. Charlotte Björk Ingul
May 2019

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Kunnskap for en bedre verden

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Abstract:

Background: Type2 diabetes (T2D) is a global health problem, which increases the risk of cardiovascular disease (CVD). Aerobic capacity is lower in T2D individuals compared to healthy, and women with T2D have even lower aerobic capacity compared to men with T2D. These sex disparities could lead to increased CV morbidity and mortality in women compared with men with T2D. However, the same exercise recommendations are given to women and men.

Objectives: To compare the cardiometabolic training response in women and men with T2D following the same exercise interventions. We hypothesized that women with T2D would have a reduced exercise response compared to men.

Methods: Twenty-nine individuals with T2D (15 women, 14 men), were randomized and stratified by sex to either supervised training group (STG) or active control group (ACG) for 12 weeks. The STG performed aerobic and resistance training three days a week, whereas the ACG was advised to use a Mio Slice heart rate watch and reach 100 PAI (Personal activity intelligence) each week. Changes in cardiac function, glycosylated hemoglobin (HbA_{1c}), insulin resistance, aerobic capacity (VO_{2peak}) and heart rate recovery were measured.

Results: Both STG and ACG showed significant improvements in cardiac function and aerobic capacity with no significant difference between groups. In the STG, men improved more than women in VO_{2peak} (25%, $p < 0.001$ vs. 15%, $p = 0.001$) and stroke volume index (15%, $p = 0.10$ vs. 11%, $p = 0.04$). Whereas, only women significantly improved heart rate recovery (after 1min, 48%, $p = 0.04$), insulin resistance (25%, $p = 0.03$), insulin C-peptide (27%, $p = 0.02$) and right ventricular systolic function (TAPSE, 21%, $p=0.04$). Both sexes in the ACG showed improvements in cardiac function and aerobic capacity.

Conclusions: Women had less improvement in left ventricular cardiac function and aerobic capacity compared to men after 3 months of supervised training. However, women had a greater response in insulin resistance and heart rate recovery. Moreover, a weekly activity index PAI can be an effective strategy to motivate and increase the exercise adherence for both women and men. Further research is needed to investigate the sex differences in training response to potentially develop sex specific training programs to optimize the effects of training.

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List of abbreviations:

A- Late diastolic filling by mitral doppler flow

ACG- Active control group

CVD- Cardiovascular disease

E- Early diastolic filling by mitral doppler flow

E’- Early peak diastolic tissue Doppler velocity

HbA_{1c}- Glycosylated hemoglobin

HOMA-IR-Homeostasis model assessment for insulin resistance

HRM- Heart rate maximum

LV- left ventricle

LVOT VTI- Left ventricle outflow track velocity time integral

S’- Peak systolic tissue Doppler velocity

STG- Supervised training group

SV- Stroke volume

TAPSE- Tricuspid annular plane systolic excursion

T2D- Type 2 diabetes

VO_{2peak}- Peak oxygen consumption

1 Introduction:

The global prevalence of T2D is continuing to rise over time. According to the World Health Organization, T2D was the seventh leading cause of mortality in 2016 [1]. Physical inactivity, obesity, and aging are the most important risk factors for the development of T2D. T2D predispose individuals to develop diabetic cardiomyopathy and atherosclerotic CVD, that leads to the development of heart failure [2, 3]. There is a two to four-fold higher rate of mortality from CVD in the diabetic population, as compared to non-diabetic population. Moreover, individuals diagnosed with T2D have a two times higher risk of developing heart failure [3]. Left ventricular remodeling and impaired systolic and diastolic function are the key mechanisms involved in the development of heart failure in T2D. Reduced diastolic function is evident even in asymptomatic individuals with T2D and could be an early sign of development of heart failure [4, 5].

Exercise training has been shown to be an effective treatment for the management of T2D and its complications [6]. Data suggest that aerobic training especially high intensity interval training can improve echocardiographic indicators of systolic and diastolic function [7]. Recommendations for exercise training in T2D includes both aerobic and resistance training because studies in T2D favors the superior effect of combined training protocol in managing the risk factors for CVD [6].

There is emerging evidence suggesting that there are sex/gender related differences in the course and treatment of T2D [8]. Women with T2D present with more impaired cardiac function [3, 9]. Moreover, greater abnormality in cardiac exercise performance has been seen in women with T2D [10]. Currently, there is a lack of data on the prevalence of sex-related differences in response to training in T2D. Thus, it is uncertain whether women with T2D will respond differently to the same training program.

1.1 Aim, hypothesis and outcome variables:

The main aim of the current study was to investigate if women and men with T2D respond differently to the same exercise interventions. The secondary aim was to gain knowledge about how women with T2D should train to reduce the cardiometabolic risk factor load. We hypothesized that women with T2D would have a reduced exercise response compared to men.

The primary outcome measure was cardiac function. In cardiac function we focused on the variables of left ventricular systolic function (stroke volume (SV), global strain, peak systolic tissue doppler velocity (S'), left ventricle outflow track velocity time integral (LVOT VTI)),

right ventricular (RV) systolic function (Tricuspid annular plane systolic excursion (TAPSE), RV S') and LV diastolic function (Early peak diastolic tissue Doppler velocity (E'), Early diastolic filling by mitral doppler flow and E/A ratio). Our secondary outcome measures were VO_{2peak}, HbA_{1c}, insulin resistance and heart rate recovery.

1.2 Background of T2D:

The global prevalence of diabetes is estimated to increase from 400 million in 2017 to 600 million in 2045 [11]. According to World Health Organization 60 million people are living with diabetes (all types) in Europe [1]. T2D is the major sub-category of diabetes accounting for approximately 90% of all diabetic cases [11].

Diabetes Mellitus is a group of metabolic disorders characterized by high glucose levels due to either a defect in the insulin production, insulin action or both [12]. Insulin is an important hormone produced by the β-cells of the pancreatic islets of Langerhans for intracellular transport of glucose to maintain normal glucose level. An inadequate production of insulin leads to a high blood sugar i.e. hyperglycemia. Insulin resistance is the insensitivity of the body to insulin and it is an important hallmark of T2D. Due to insulin resistance, excess glucose is not sufficiently absorbed by the cells even in the presence of insulin, causing an increase in the blood glucose level. Moreover, there is an increased production of glucose from the liver in response to insulin [13]. Therefore, T2D is characterized by high blood sugars. One of the criteria presented in Figure 1 must be fulfilled for the diagnosis of T2D.

Diagnosis criteria for T2D , (American diabetes association, 2010)	
Test	Threshold
HbA_{1c}	≥6.5% ≥48mmol/mol
Fasting plasma glucose (At least 8h no caloric intake)	≥7.0mmol/L ≥126 mg/dL
2-h plasma glucose	≥11.1 mmol/L ≥200 mg/dL
Random plasma glucose (Repeat tests 1-3, if unequivocal hyperglycemia is absent)	≥11.1 mmol/L ≥200 mg/dL

Figure 1: Diagnosis criteria for T2D.

HbA_{1c} is a marker of chronic glycemia and represents the average blood glucose levels over the past two to three months [12].

The risk factors for T2D include genetic susceptibility, sedentary lifestyle and most importantly, obesity. There is a casual link between obesity and excess free fatty acids, hyperglycemia and hyperinsulinemia [14]. These factors can lead to increased oxidative

stress causing mitochondrial dysfunction, which alter energy production and decrease glucose transporter 4 (GLUT 4), a protein that facilitate glucose transport [15]. Oxidative stress is an imbalance between the production of reactive oxygen species and the body's antioxidant defense mechanism, resulting in tissue damage [16]. Oxidative stress leads to an increased production of inflammatory proteins that impair insulin signal transduction causing insulin resistance [15].

T2D has long been recognized as a major risk factor for CVD. According to the American Heart Association, CVD mortality rate is two to four folds higher in individuals with T2D compared to non-diabetic individuals. A Chinese study found more than 50% mortality cases in newly diagnosed T2D during 23 years of follow-up, in which CVD was the dominant cause of death [17]. Both CVD and T2D have common genetic and environmental risk factors such as obesity, inactivity, dyslipidemia, hypertension, high triglycerides, abnormal cholesterol, making a strong association between these two conditions, also known as common soil hypothesis (Figure 2) [18]. More specifically T2D increases the risk of each component of CVD, namely coronary artery disease, heart failure and stroke [3]. With every 1% increase in HbA_{1C}, the risk of death with CVD is raised by 7.5% in T2D [19].

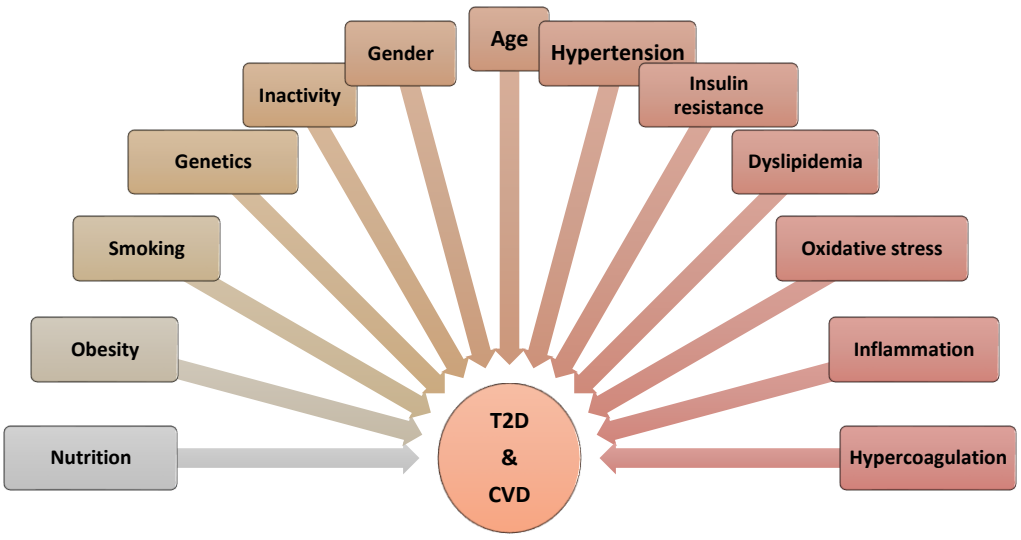


Figure 2: Illustration of common soil hypothesis; T2D and CVD springs from common soil.

1.3 T2D and cardiac dysfunction:

Cardiac subclinical dysfunction is an early manifestation of heart failure and other CVD in T2D [20]. The central pathological mechanism involved in macrovascular complications is atherosclerosis caused by metabolic abnormalities in T2D. Along with other metabolic

abnormalities, insulin resistance and hyperglycemia induce a series of events that leads to endothelial dysfunction with reduced bioavailability of nitric oxide as the main cause [21-23]. Atherosclerosis also increases the risk of coronary artery disease as well as hypertension, which are the common comorbidities in T2D and are primary risk factors for systolic and diastolic dysfunction [4, 5, 24]. Subclinical evidence of diastolic dysfunction in T2D can be found in more than 50% of individuals with T2D [25]. Diastolic dysfunction could lead to diastolic heart failure (heart failure with preserved ejection fraction) [20].

Diabetes cardiomyopathy is defined as diabetes-associated changes in the structure and function of the myocardium, which are not related to coronary artery disease, hypertension or other valvular disease [26]. The development of diabetic cardiomyopathy is multi-factorial and several pathophysiological mechanisms have been proposed. Possible mechanisms are altered free fatty acid metabolism, copper metabolism, left ventricular hypertrophy, increased apoptosis, necrosis and fibrosis of myocardium, lipotoxicity, impaired insulin signaling, mitochondrial dysfunction, increased glycation end products and reactive oxygen species, down regulation of glucose transporter proteins and endothelial dysfunction [20, 26]. HbA_{1c} is considered as an independent risk factor for development of heart failure [27]. Most pathways involved in heart failure development are related to hyperglycemia like up-regulation of renin-angiotensin-aldosterone system, impaired calcium handling and oxidative stress.

Both early systolic and diastolic dysfunction [5, 20] can be detected by sensitive measurements of cardiac function like strain, strain rate, and myocardial tissue doppler velocity using echocardiography [28].

1.4 Cardiac function:

Cardiac output is the amount of blood ejected from the heart per minute and a product of stroke volume (SV) and heart rate (CO= SV x HR). SV is the amount of blood ejected during ventricular contraction. Each component is regulated according to energy demands of the body. To maintain a normal cardiac function is a challenge for the T2D individuals [29].

The cardiac cycle is mainly divided into ejection of the blood (systole) and filling of the heart (diastole).

1.4.1 Diastolic function:

At the start of the cycle, both atria's and ventricles are in a relaxed state i.e. diastole. Diastole is usually divided into four phases.

First phase is known as the "Isovolumic relaxation" and starts right after systole when the semilunar valves i.e. aortic and pulmonary valve closes. The pressure within the ventricles starts dropping due to the expansion of volume in ventricles by the relaxation and untwisting of myocardium. The energy stored in the elastic elements of myocardium while they were compressed and twisted, is released during the elastic recoil. This cause a rapid drop in the pressure in the left ventricle.

When the pressure drops below atrial pressure, the atrioventricular valves opens. Blood rapidly starts flowing into the ventricles due to energy dependent ventricular suction and the pressure gradient created by the expansion of myocardial tissue (compliance). This phase is called rapid filling and it is represented by early (E) wave on ultrasound. This phase is manifested by active suction of blood into the ventricles, and almost 70% of the blood is filled in the ventricles during this phase.

Due to the rapid filling of the ventricle along the pressure gradient, the pressure of blood in the ventricles equilibrates the pressure of atrium. This phase is known as "diastasis". The atrioventricular flow is almost stopped.

The final phase of diastole is atrial contraction, which is the final kick of atria to push the remaining blood into the ventricles. With the increasing age its contribution increases steadily [30]. This atrial systole is represented by the active (A) wave on ultrasound. After atrial contraction, atria relax which decreases their pressure compared to ventricles. This will begin the closure of atrioventricular valves and the start of systole.

During periods of high energy demand for example during exercise, heart rate increases to meet body energy requirements thus reducing the diastolic period as less time is available. A higher resting heart rate represents a more inefficient cardiovascular system. Higher resting heart rate is observed in people with T2D moreover it increases the risk of CVD in T2D [31].

1.4.2 Systolic function:

The second main part of the cardiac cycle is systole, the ejection of blood from the ventricles. The increase in pressure in the ventricles at the start of systole closes the atrioventricular valves and ends diastole. The volume of blood present in the ventricles at the end of diastole is known as "end diastolic volume". Systole has two phases.

First the muscles (myocardium) in the ventricle contract. This will increase the pressure in the ventricles, but it's not high enough to open the semilunar valves. Therefore, no blood is ejected and the volume of blood in the ventricles remain the same. This is known as the

isovolumic contraction. The second phase is the ventricular ejection. In this phase the pressure of blood in the ventricles exceeds the pressure in aorta and pulmonary trunk due to ventricular contraction. This pressure opens the aortic and pulmonary valve and blood is ejected from the heart. The same amount of blood is ejected from the left and right ventricle i.e. average 70-80 ml known as SV. However, LV must contract more forcefully due to higher existing pressure in aorta. Afterload is the tension developed in the LV wall to eject the blood.

The left side of the heart is usually more focused as this side supplies blood to the whole body whereas the right side only supply blood to lungs. That's why the left side ventricle has more thickened myocardial walls. Moreover, mostly cardiac dysfunctions are related to the abnormalities of LV. Thus, the assessment of cardiac dysfunction mainly concerns performance of LV [32].

The LV performance is affected by preload, afterload and contractility of the LV. As defined above, preload is the volume of blood in the ventricle at the end of diastole. Preload can be determined by the left ventricular filling pressure or the end diastolic volume. End diastolic volume and force of contraction are related through "Frank starling relationship". According to Frank starling mechanism, the SV increases in response to an increase in the end diastolic volume. Increase volume of blood in the ventricles, stretches the cardiac muscle fibers thus leading to an increase in the force of contraction.

On the other hand, afterload is the pressure against which heart must work to push blood during systole and it can be measured by pressure in arteries as well as by the LV volume and thickness.

LV contractility is independent of preload and afterload. It is the inherited property of myocardium to contract depending on availability of chemical components e.g. calcium, troponin and efficiency of forming cross bridges [33, 34].

The assessment of cardiac function can be done by echocardiography, cardiac magnetic resonance imaging, angiography and other imaging modalities. In this study we used echocardiography which will be discussed further.

1.5 Echocardiographic analyses of systolic and diastolic dysfunction:

1.5.1 Systolic dysfunction and analysis:

Systolic dysfunction is the reduced ability of ventricles to eject blood. Systolic performance depends on myocardial contractility as well as on load and ventricle configuration. So, it is

possible to have impaired systolic function with normal myocardial contractility when afterload is high like in hypertension and to have nearly normal systolic function with despite reduced contractility when afterload is low for example in mitral regurgitation [32]. Ejection fraction is the mostly used parameter to quantify LV function. It is the percentage of blood ejected by LV in each heartbeat.

Other parameter that is important to quantify systolic function is peak systolic tissue doppler velocity, S' which is the velocity at which myocardium moves during systole (Figure 3). It is measured at the base of the walls of the mitral annulus. The mean of septal and lateral wall is mostly used. Reduced S' can be an indicator of myocardial dysfunction [30]. Blood flow across the left ventricular outflow tract (LVOT) is determined by velocity time integral abbreviated as LVOT VTI. LVOT VTI represents how far the blood is pushed through the aorta i.e. distance traveled by the blood through aorta in each heartbeat. If we consider aorta as a cylindrical tube, the height of the tube is VTI and the volume of that tube will then be SV [35].

Recent data suggest that global strain is a more reliable technique to assess the contractile properties of heart. It represents the deformation of LV myocardium and calculated as the relative change in length of LV myocardium between end systole and end diastole [35]. The global strain value more than -20% is usually considered abnormal. Global strain is derived from speckle tracking from all three apical planes (4-chamber, 2-chamber and apical long-axis views) (Figure 4) [36].

Tricuspid annular plane systolic excursion (TAPSE) is a measure of longitudinal movement of tricuspid annulus between end-diastole and peak systole and is a good indicator of right ventricular systolic function [35, 36]. TAPSE value is good correlated with right ventricular ejection fraction [37]. The TAPSE value of >17mm is considered normal [36].

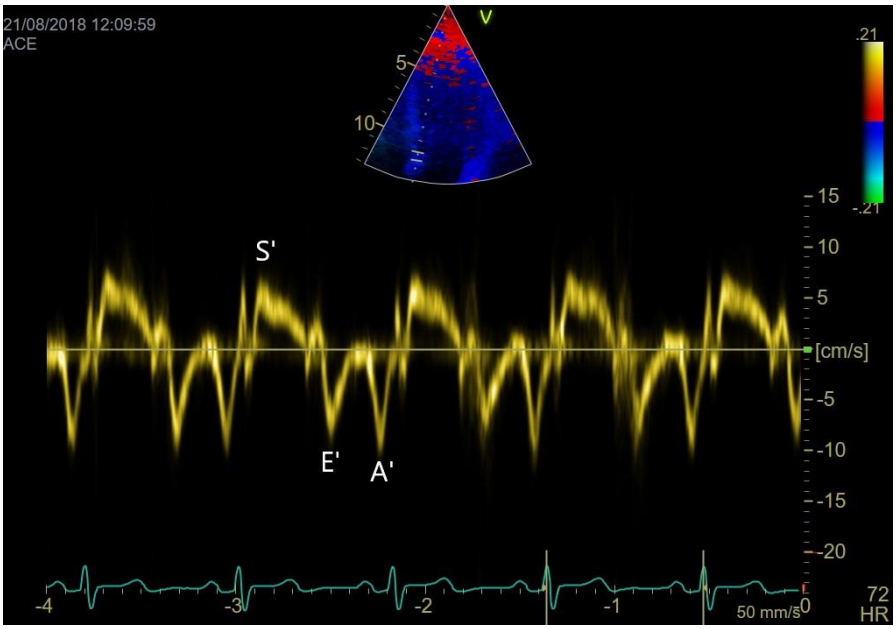


Figure 4: Echocardiogram of a study participant illustrating pulsed wave tissue doppler velocities. Abbreviations: S'= Peak systolic tissue doppler velocity; E'= Early diastolic tissue doppler velocity; A'= Late diastolic tissue doppler velocity

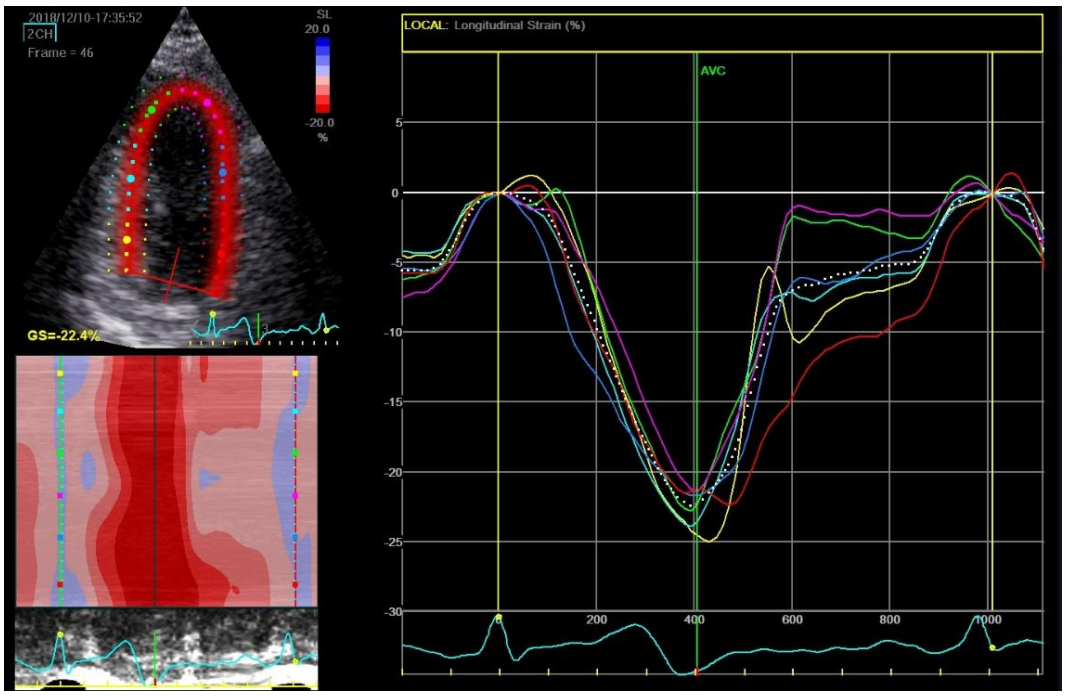


Figure 3: 2D strain image in a normal individual presenting peak longitudinal systolic strain. The right graph represents the strain traces for each segment and a global value for the six segments. The top left image represents parametric color overlay and global strain value (-22.4%). The low left image represents the colorization of the entire muscle according to a scale where dark red represents high negative peak strain values and blue positive strain values.

1.5.2 Diastolic dysfunction and analysis:

Diastolic dysfunction is defined as impaired left ventricular relaxation with increased left ventricular stiffness and high filling pressure. Assessment of diastolic dysfunction includes myocardial relaxation and ventricular compliance. Reduced compliance and impaired relaxation can cause increased filling pressures. Echocardiography is an important non-invasive tool for the measurement of different parameters in different modes from which we can analyze the diastolic pressures, LV-relaxation and compliance [34].

1.5.2.1 *Mitra inflow velocities measurement:*

Impaired relaxation can be measured by mitral inflow velocities. The primary measurements recorded by mitral inflow contains peak early rapid filling velocity (E), late diastolic filling velocity (A), the deceleration time of E wave (DT) and the E/A ratio. In the normal functioning heart, the blood is more rapidly filled in early phase and thus the E velocity is higher than the A velocity. This filling pattern is altered with diastolic dysfunction. E/A ratio is a good indicator of diastolic dysfunction, but it is also affected by the age and load [30].

With age and disease, there is impaired LV relaxation causing impaired rapid filling, which results in reduced E wave velocity ($\leq$ 50cm/sec) and a longer time to open the mitral valve. Thus, to compensate a decreased early filling more blood is transported during atrial contraction. This will cause decreased E/A ratio (E/A $\leq$ 0.8cm/s) and increased deceleration time known as grade 1 diastolic dysfunction [30]. In grade 1, filling pressure is normal or mildly increased.

With the progression of disease, LV filling pressure increases which again causes increase of E velocity and decrease of deceleration time due to higher pressure difference. This filling pattern looks like a normal pattern and is therefore known as pseudo-normal filling pattern. In advance stages, filling pressure are markedly elevated resulting even higher E, shorter deceleration time and small, narrow A wave (E/A $\geq$ 2) called restrictive inflow pattern or grade 3 diastolic dysfunction [38]. According to new American society of Echocardiography recommendations changes in mitral inflow velocities should be measure with Valsalva maneuver. As Valsalva maneuver can unmask the elevated filling pressure and can help to distinguish the pseudo-normal filling from normal filling and if restrictive filling is reversible or not [30].

1.5.2.2 Tissue doppler imaging measurements*:*

Tissue doppler imaging uses a high-amplitude, low-velocity signal to measure myocardial tissue movement. It can be performed in color mode and pulsed-wave mode. Mitral annular

motion is analyzed to measure LV contraction and relaxation as apex stays relatively still during the cardiac cycle. E' represents the ascending of mitral annulus during early rapid filling phase of diastole and A' is the late diastolic annular motion (Figure 3). They are measured by pulse wave doppler in apical 4-chamber view at lateral and septal regions of mitral annulus. Usually the average of septal and lateral is used for analysis. E' is the more sensitive measurement to assess diastolic function as it is less load dependent than mitral inflow velocities [39]. Its value is dependent on age and sex. E' is even more reduced than age related decrease with reduced myocardial relaxation [38].

Neri et al. found lower values of end diastolic volume, E/A ratio, SV and higher heart rate in T2D compared to non-diabetic individuals [40].

1.6 Physical Activity:

Physical inactivity or sedentary lifestyle is considered as a central modifiable risk factor for T2D and CVD. There is a strong association between sedentary behavior, abnormal plasma glucose and clustering of metabolic risk factors [41, 42]. Apart from medication and diet, physical activity is an important keystone in prevention and management of T2D. Lifestyle intervention programs which incorporate increase physical activity are recommended by the American Diabetes Association as well as all Diabetes associations for individuals at risk of T2D development. These interventions are designed with the goal of preventing or delaying the onset of T2D [43].There is a vast empirical literature that demonstrates the efficacy and effectiveness of these intervention [44]. The main aims of treatment of T2D is to maintain normal blood glucose, lipid, blood pressure level and to manage obesity [43]. Increased physical activity is an important strategy to achieve these goals. Physical activity can reduce HbA_{1c}, and could have an effect on body weight, blood pressure and other CVD risk factors [6, 45, 46]. Therefore, according to current guidelines individuals with T2D should perform both endurance and resistance training in order to get optimal health benefits. American Diabetes Association recommends aerobic exercise of moderate-to-vigorous intensity 150 minutes per week or minimum 75 minutes of vigorous-intensity interval training per week with no more than two consecutive days without activity. Resistance training should be included two to three times per week on nonconsecutive days [6].

1.6.1 Resistance training:

Resistance training has been defined as any activity that uses muscular strength to move a weight or work against a resistive load [6]. Eight to ten exercises with the resistance machines, resistance bands, free weights or body weights are recommended. Training should be started with moderate intensity (10-15reps) with a progressive increase in

resistance or repetitions. T2D is related to a loss of muscle mass and muscle strength [47]. Apart from increasing muscle mass and strengthening of muscles resistance training enhances muscle to capillary ratio and mitochondrial oxidative capacity. The increase in muscle mass and quality improves skeletal muscle glucose uptake and insulin sensitivity [48]. Increase in glucose transport proteins i.e. GLUT4 and insulin receptors after resistance training are also involved in improving insulin action in T2D [48]. Some studies also show the positive effect of resistance training on metabolic factors like reduction of inflammatory cytokines [49], oxidative stress [50], total cholesterol and blood pressure [51] which may help to reduce the adverse cardiovascular outcomes in T2D.

Resistance training increases plasma adiponectin; a protein hormone that regulates glucose levels and breakdowns fatty acid, which enhances the insulin sensitivity [52]. Reduction in inflammation could also be related to increase of adiponectin as they have anti-inflammatory response [52]. The up regulation of anti-oxidative enzymes by training is related to the reduction of oxidative stress [50].

There are documented benefits to adding resistance training to aerobic training. These benefits include improvements in glycemic control, inflammation, body composition, bone density, muscle mass, and strength increasing overall exercise capacity of individuals [53].

1.6.2 Aerobic Training:

Aerobic training is the physical activity that primarily depends on aerobic energy. During aerobic exercise, there is an increased workload on the heart and lungs to meet the energy demands of working muscles, which improve the cardiorespiratory fitness of an individual. Cardiorespiratory fitness reflects the functional capacity of a person to transport oxygen from atmosphere to mitochondria. Maximal oxygen uptake (VO_{2max}) is the best measure of cardiorespiratory fitness and an important marker of cardiovascular health. VO_{2max} is measured during a graded exercise protocol. VO_{2max} is reached when there is no longer increase in oxygen uptake despite an increase in workload. If the plateau of oxygen uptake is not achieved, the term VO_{2peak} is used instead of VO_{2max}. Respiratory exchange ratio (RER) is used as one of the criteria to reach VO_{2max}. Different cutoff values have been used, but a cutoff value of ≥1.05 is widely used [54]. The value above one indicates that carbohydrates are being the dominant fuel for energy.

VO_{2peak} is a strong early predictor of CVD and all-cause mortality [55]. Lower cardiorespiratory fitness has been associated with impaired insulin sensitivity and fasting

glucose and it can be an early indicator of insulin resistance and T2D [56, 57]. Many studies have shown 10-30% lower VO_{2peak} in T2D compared to healthy individuals [10, 56, 58].

Aerobic exercise can improve cardiorespiratory fitness by inducing changes in the whole cycle from oxygen supply to its utilization by cells. According to Fick equation [59, 60]:

$VO_2 = CO * a\text{-}vO_2$ diff

(CO= cardiac output, a-vO_2 diff= arteriovenous oxygen difference)

Cardiac output represents the circulation of oxygen and a-vO_2 is the amount of oxygen diffused into the alveoli and the cells. The changes in VO_{2peak} after exercise are mostly attributed to changes in cardiac output [61, 62]. SV is reduced in T2D [63]. Aerobic exercise can improve the SV by improving the function of the heart through increased myocardial contractility, cardiomyocyte hypertrophy, and physiological left ventricular hypertrophy [64]. The mechanism behind increased cardiomyocyte contractility is an enhanced calcium (Ca^{2+}) handling and sensitivity [65]. Moreover, improvements in preload and afterload by enhanced endothelial function, reduced vascular resistance, and increased blood volume also increase SV and overall cardiac function [66, 67]. Regular training is also linked with improved insulin signaling, plasma lipid profile, antioxidative protection of myocardium, reduction of insulin resistance and inflammation [46].

However, intensity seems to be important component in initiating these results. Growing evidence reveals the superior effect of high intensity interval training in improving VO_{2peak}, HbA_{1C}, cardiac function and other cardiometabolic risk factors compared to moderate training [45, 61, 64, 68]. Increased insulin signaling, enhanced production of glucose transporter proteins (GLUT4) and improvement in muscle oxidative capacity are important mechanisms behind increase glucose uptake after aerobic exercise. Though the improvement in insulin sensitivity lasts only for a period of hours to days depending on the intensity and duration of exercise [43].

High intensity interval training produces more stress on physiological systems involved in aerobic exercise. It continuously challenges cardiac and vascular function, so these systems get adapted to meet the metabolic demands of working muscle. Recent studies showed higher effect of high intensity interval training on VO_{2max}, physiological hypertrophy, calcium handling and cardiomyocyte contractility than moderate training [64]. Hafsdal et al. found changes in substrate utilization i.e. increase in glucose utilization and a decrease in fatty acid oxidation only with high intensity in mice. High intensity interval training also improves cardiac maximal mitochondrial respiratory capacity. These factors improve the efficiency of

the heart. [69]. A study in heart failure patients revealed superior effect of high intensity in improving systolic, diastolic and endothelial function in 12 weeks [68].

A recent study on T2D with diastolic dysfunction compared high and moderate intensity exercise found that the study participants in the high intensity group experienced significantly greater improvements in diastolic function (E velocity, E/e' and E/A ratio) and systolic function (S' and global strain %) compared to study participants in the moderate intensity group [7]. Another study in T2D found no significant improvements in diastolic function with moderate training [70]. These results show that high intensity aerobic training is an important component to gain maximum benefits from exercise and combining resistance training could add positive effects.

1.7 Sex and gender differences:

Sex and gender differences can be relevant to the development, pathophysiology, diagnosis, treatment and prevention of any disease and this also applies toT2D. Sex differences are defined as the differences in the biology of women and men due to sex chromosomes, sex hormones, their expression and the effect on the body. Gender differences are caused by environmental and economic factors, and how we respond to these factors. Both sex and gender differences are interlinked. Sex hormones have great influence on body composition, energy breakdown, vascular function, and inflammatory responses [8].

In the general population, there is a high prevalence of CVD in men but, in the diabetic population, women are at a higher risk of developing CVD than men [71, 72]. Both sex and gender differences can be attributed to this increased risk in women [73]. T2D is associated with a reduction of the protective effect of estrogen on vascular walls. Moreover, some risk factors for T2D including obesity, metabolic risk factors, no leisure time activity, previous gestational diabetes, low sex hormone-binding globulin levels, endothelial response, psychosocial stress, sleep deprivation and depression are more pronounced in women and maybe the cause of a more adverse outcome [8]. Yetkin et al. found diabetes and female gender, independent risk factors for poor collateral vessel development in individuals with advance coronary artery stenosis [74].

Furthermore, women with T2D are more susceptible to subclinical cardiac dysfunction with greater wall thickness and left ventricular mass [2, 3]. Gori et al, found more pronounced diastolic dysfunction with impaired left ventricular relaxation and left ventricular filling pressure in women particularly due to the impact of sex hormones [9]. Higher hypercoagulative profile with denser fibrin clots and compromised fibrinolysis have been

observed in women with T2D which can also explain the higher risk of diabetic cardiopathology in women [75].

Impaired fasting glucose is more frequent in men and impaired fasting glucose is usually associated with insulin resistance. Whereas, impaired glucose tolerance dominates in women, which is more closely related to impaired beta-cell function [72]. The diagnosis based on fasting glucose measurements misses the early diagnosis of diabetes in women which delays management and could cause more complications [73].

There are also sex and gender differences in the cardiovascular function during rest and submaximal exercise. In general, women have lower SV, hemoglobin and higher heart rate at rest as well as present limitations in aerobic exercise performance. Lower sympathetic response with greater vasodilation during exercise reduces the venous return and cardiac contractility, thus lowering the SV in women. Therefore, to compensate for this, women rely on increasing heart rate and more peripheral oxygen extraction, whereas men have higher SV, blood pressure, and show more reliance on Frank-starling mechanism [76].

Impaired cardiac exercise performance has been seen in T2D; however, women with T2D present with greater abnormality in exercise performance (VO_{2peak}) than men which could be a reason of increase CVD in them [10]. Howden et al. showed different cardiovascular response of women and men to the same one-year endurance training. Men showed progressive increase in VO_{2max} and LV mass while, in women, the majority increment in VO_{2max} and LV mass occurred in the first three months. Moreover, LV hypertrophy and increase in VO_{2max} were blunted in women compared to men. Both groups improved ventricular compliance and distensibility, but men had greater enhancement in Frank-Starling mechanism [77].

Some studies also find different response of women and men to medical treatment suggesting consideration of sex in the management of T2D [73, 78]. Despite these well-documented sex and gender differences, current treatment and exercise guidelines do not differentiate between sexes and no study, to our knowledge, has investigated sex differences in response to training in T2D.

2 Methods:

2.1 Study design:

The study was a randomized controlled trial with two parallel intervention groups. The study protocol was approved by the regional ethics committee (REK number 2018/454). Randomization procedures were carried out by the unit of Applied Clinical Research at the Norwegian University of Science and Technology (see figure 6).

2.2 Participants:

Participants were recruited from the advertisement on Facebook and through the diabetic outpatient clinic at the University Hospital in Trondheim (St. Olavs Hospital).

Inclusion criteria were age 30-60 years and the diagnosis of T2D. Participants were excluded from the study if they were currently receiving insulin treatment or if they had a diagnosis of liver dysfunction, renal dysfunction, heart failure, myocardial ischemia or major cardiovascular event history.

Participants were also excluded if they engaged in greater physical activity than current guidelines i.e. 150 minutes per week for T2D or if they were unable to perform exercise thrice a week. After careful screening 29 individuals with average age 53 ±5 years were included. All included participants reviewed and signed an informed consent before participating in the study. All testing and training were conducted during the period of August 2018 - December 2018 at the Department of Circulation and Medical Imaging, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim.

2.3 Initial assessment:

All individuals were asked about the medical history, family history of CVD and risk factors including smoking, alcohol and physical inactivity. Patients' medications were compared pre- and post-test to discover any changes. The participants were asked not to change their antidiabetic medications during the study period.

2.4 Habitual physical activity:

Participants were given an activity tracking watch i.e. Mio Slice (SLICE 60P, Mio Global, Vancouver, Canada). Study participant wore the activity tracker throughout the duration of the study. Further, to record a baseline of physical activity preceding the intervention, participants were asked to wear the tracker for one week prior to the start of the study. This device measures steps, calories burnt and weekly PAI (personal activity intelligence). PAI is

a number calculated from scientifically proved algorithm based on HUNT study. It takes account heart rate and personal profile (like age, sex etc.) of a person and gives a score from 1-100. All study participants were given a specific group code which they entered in the "PAI" app on their mobile phones. So, all the activity data was directly collected from their mobile phones.

2.5 Height, weight and waist circumference:

Body weight (SECA, Germany) was measured without shoes, but with clothes. An average of three height measurements was taken from a wall mounted scale (SECA). Waist circumference was measured using a measuring tape at midway between lowest rib and the iliac crest with the participant standing. Three measurements were taken by the same researcher in all individuals to reduce measurement variability.

2.6 Echocardiographic Measurements:

Echocardiographic examinations (Vivid E95 scanner, phased-array (M5S transducers), GE Vingmed Ultrasound AS, Horten, Norway) were performed according to the recommendations of ASE and European Society of Echocardiography. Any physical activity and caffeine consumption were restricted for 2 hours before the echocardiographic measurement. The same cardiologist performed the echocardiography in all participants both in pre- and post-testing. The detailed procedure was published before [79]. Ejection fraction and LV volumes were determined by biplane (apical 4-and 2-chamber) modified Simpsons method. Mitral inflow velocities i.e. peak early (E) and late (A) and deceleration time of early filling were measured using pulsed-wave Doppler imaging at the leaflet tips. SV was calculated by pulsed-wave Doppler imaging of the aortic outlet in the 4-chamber view. Peak mitral annular tissue velocities at early (E'), late (A') diastolic and peak systolic (S') were measured in pulsed-wave Doppler mode. The mean of septal and lateral points was used.

Offline echo analysis (Echopac version 202) was performed by the same cardiologist blinded to the randomization group.

2.7 Electrocardiographic measurement:

Before the cardiopulmonary tests an ECG was recorded in lying position (PageWriter Trim iii, Philips). All ECGs were analyzed by a cardiologist. All participants that were analyzed met the inclusion criteria.

2.8 Blood pressure measurements:

Blood pressure was taken before or after echocardiography with the same restriction of caffeine and physical activity. In total, three consecutive measurements were taken, with two minutes time lapse between measurements (Casmed 740). All measurements were taken with study participants in the sitting position with feet resting on the floor. Blood pressure cuff of size 25-34 cm was placed on the right arm. Participants were instructed to relax the arm and asked not to speak while the measurements were being taken. The average of the last two readings were used for later analysis.

2.9 Blood sample analysis:

Blood sample was taken with 8 hours of fasting. At the pre-test, HbA_{1C}, insulin C-peptide, triglycerides, cholesterol, fasting glucose, LDL, HDL, GFR est/1.73m2, creatinine and hemoglobin were analyzed. At the post-test, only HbA_{1C}, fasting glucose and insulin C-peptide were analyzed. Standardized procedure of blood analyzation was used at St. Olav Hospital, Trondheim. Homeostatic model assessment (HOMA-IR) were used to analyze β-cell function and insulin resistance.

2.10 Cardiorespiratory fitness:

Cardiorespiratory fitness was measured with incremental running and walking protocol on a treadmill (Woodway PPS 5, Woodway, Weil am Rheim, Germany). The procedure was fully explained to all participants and they were asked to consent to all increases in level of inclination or speed. The participants were instructed to run/walk to their maximal effort, but to immediately stop if they felt any chest discomfort. First all participants warmed-up for 10 minutes with the inclination set at 2%. The speed was individualized according to their fitness level. After warm-up participants wore the mask for metabolic measurements. The test started with the same speed as warm-up and at 4% inclination. Afterwards every 2-minutes, the inclination level was increased by 2%. After 10% inclination, the speed was increased by 1km/h every second minute until exhaustion.

Metalyzer 2 (CORTEX, Leipzig, Germany) was used to measure oxygen consumption. VO_{2peak} was used as not all the participants reached the criteria for maximal oxygen consumption. VO_{2peak} was calculated from the average of three highest consecutive values and it was expressed as ml/kg/min.

2.11 Maximal heart rate and heart rate recovery:

Heart rate was continuously monitored during the VO_{2peak} test by Polar H10 and F6 heart rate monitors (Polar Electro, Kempele, Finland). The maximal heart rate (HRM) was calculated by adding five beats to the highest value recorded during the test.

Heart rate recovery is the reduction of heart rate after stopping the exercise test. It is calculated as the difference between the maximal pulse recorded at the end of test and pulse at one and two minutes when test stopped while participants were standing still.

2.12 Intervention:

Participants were randomized and stratified by sex into the supervised training group (STG) and the active control group (ACG) (Figure 5). The ACG followed standard training recommendations for people with T2D [6]. They were given an activity tracking watch and encouraged to gain 100 PAI every week to keep them motivated. General diet recommendations for diabetes given by Helsenorge were sent to both groups. For a period of 12 weeks, the STG trained three days a week. The training consisted of two supervised high intensity interval sessions at the exercise lab and one moderate intensity workout at home. Participants in the STG group also engaged in supervised resistance training twice a week. The resistance training occurred after the aerobic training sessions. Participants alternated between six different exercise modes each of which is described below:

1. 4-min high intensity intervals (4x4 minutes)
   Participants started with 10 minutes warm-up at 70% of HRM followed by 4 minutes work bouts four times at 90% to 95% of HRM with 3 minutes active recovery between work bouts at 70% of HRM. Training ends at 5 minutes of cool-down.
2. Two 4-min high intensity intervals (2x4 minutes)
   Training starts with 3-min warm-up at 70% of HRM continued by two sets of 4-min high intensity at 90-95% with 2-min recovery in between and 1-min cool down.
3. Ten 1-min high intensity intervals (10x1 minutes)
   This protocol includes 3-min warm-up at 70% of HRM and ten sets of 1-min high intensity training with recovery period of 75sec at 70% of HRM between each interval. Cool down was 2-min.
4. Five 1-min high intensity intervals (5x1 minutes)
   The exercise starts with warm-up of 3-min at 70% of HRM followed by five sets of 1-min high intensity at 90-95% of HRM with 75-sec of active recovery at 70% between intervals and one minute of cool down.

5. Moderate intensity training
   Every week STG performed one home session of 30 minutes continues training at 70% of HRM.
6. Resistance training
   Four different resistance exercises were included in the study that are squats, hip lift and rowing with dumbbells and push-ups. They did the three rounds of these exercise with 10-20 repetitions. Participants were instructed to increase the weight every time they managed to do 10 repetitions but if they couldn't add weight repetitions were added. Participants which were not able to do full push-ups, they did half push-up advancing to the full push-up.

In the first week, one day they performed a combination of 1 and 6 and the other day, they performed the combination of 4 and 6. The moderate intensity training (number 5, as described above) was completed independently by participants in their home. In the second week, they did combination of 2 and 6 on the first day and combination of 3 and 6 on the second day. As in the first week, participants also completed a third day of moderate intensity training at home (Figure 5).

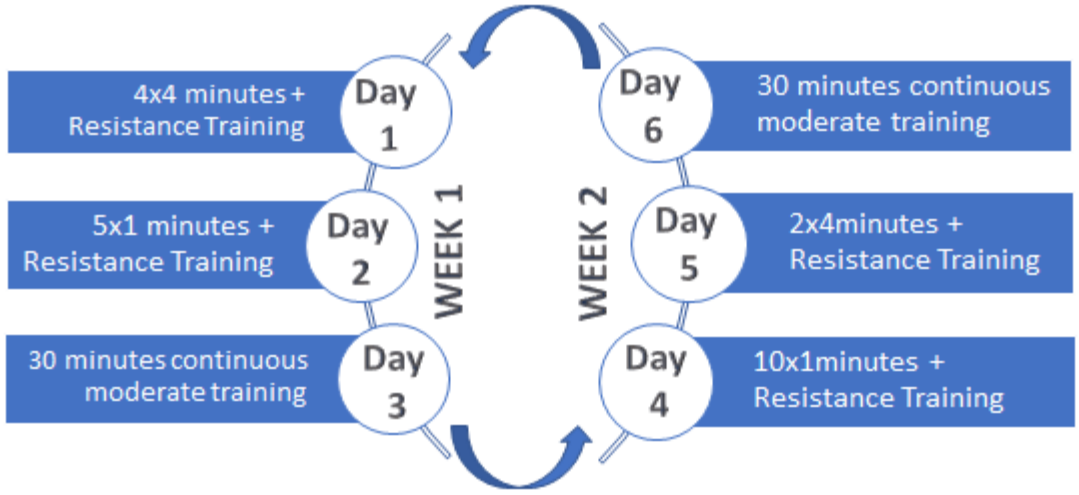


Figure 5: Illustration of training intervention held in 12-weeks

All participants in the STG received these programmed weekly sessions alternatively every week. The sessions were planned so that there was no more than two days gap between the two training sessions. Almost all sessions were supervised unless a participant couldn't attend the training but, still the training was monitored by the Mio Slice to ensure the required exercise intensity was achieved. Walking, running were preferred exercise modalities. A stationary bicycle was used only four times. The latter was used by one

participant due to knee pain and by another participant due to problems in the participant's feet.

Exercise intensity was calculated from HRM measured during the exercise test. Heart rate monitors Polar H10 and F6 were used during all exercise sessions to ensure required intensity was reached and maintained. If the participant achieved higher value of heart rate during the training, then intensity of training was adjusted by adding five beats to new highest recording.

2.13 Post-testing:

Post-testing was started after a week from the last exercise session to avoid acute effects of exercise and same procedures and modalities were used.

2.14 Statistical analysis:

Data analyses were carried out using standard statistical software (SPSS version 25, IBM corp., Armonk, NY). Data was checked for normal distribution with quantile-quantile (Q-Q) plots. All data was found normally distributed. To identify within group improvements from baseline to post-test, paired sample t-test was used while between group differences were identified from independent t-test. Same tests were used to detect changes in the female and male group from baseline to post-test and for between group differences and changes. Graphs were created using Prism (GraphPad software, Version 8.1.0, Inc., La Jolla, CA, USA). Intention-to-treat analysis was used and all participants regardless of their compliance to intervention were included in the analysis.

3 Results:

3.1 Baseline Characteristics:

Baseline data is presented in Table 1. There were significant baseline differences in insulin C-peptide, LDL, HDL, waist circumference and HOMA-IR between STG and ACG. No recent history of smoking was reported. Previous history of CVD included hypertension (n=9), high cholesterol (n=7), Wolff-Parkinson-White syndrome (n=1) and atrial fibrillation (n=1).

Participants:

The recruitment period was from May 2018 until August 2018. The follow-up period was 12 weeks. Figure 6 explains the enrollment procedure. In total 29 participants were included and 8 were lost to follow-up. The total training sessions for the supervised training group and compliance are shown in Table 2. All participants in this group completed more than 90% of the sessions except two. Two participants reported change in medication, one reduced the dosage of metformin (500mg) and one reduced lipitor (20mg).

Of those 29 included in the study, diastolic dysfunction was found in one individual, a small mitral regurgitation in two and LV hypertrophy in one at the baseline measurement.

Table 1: Baseline characteristics of the study participants.

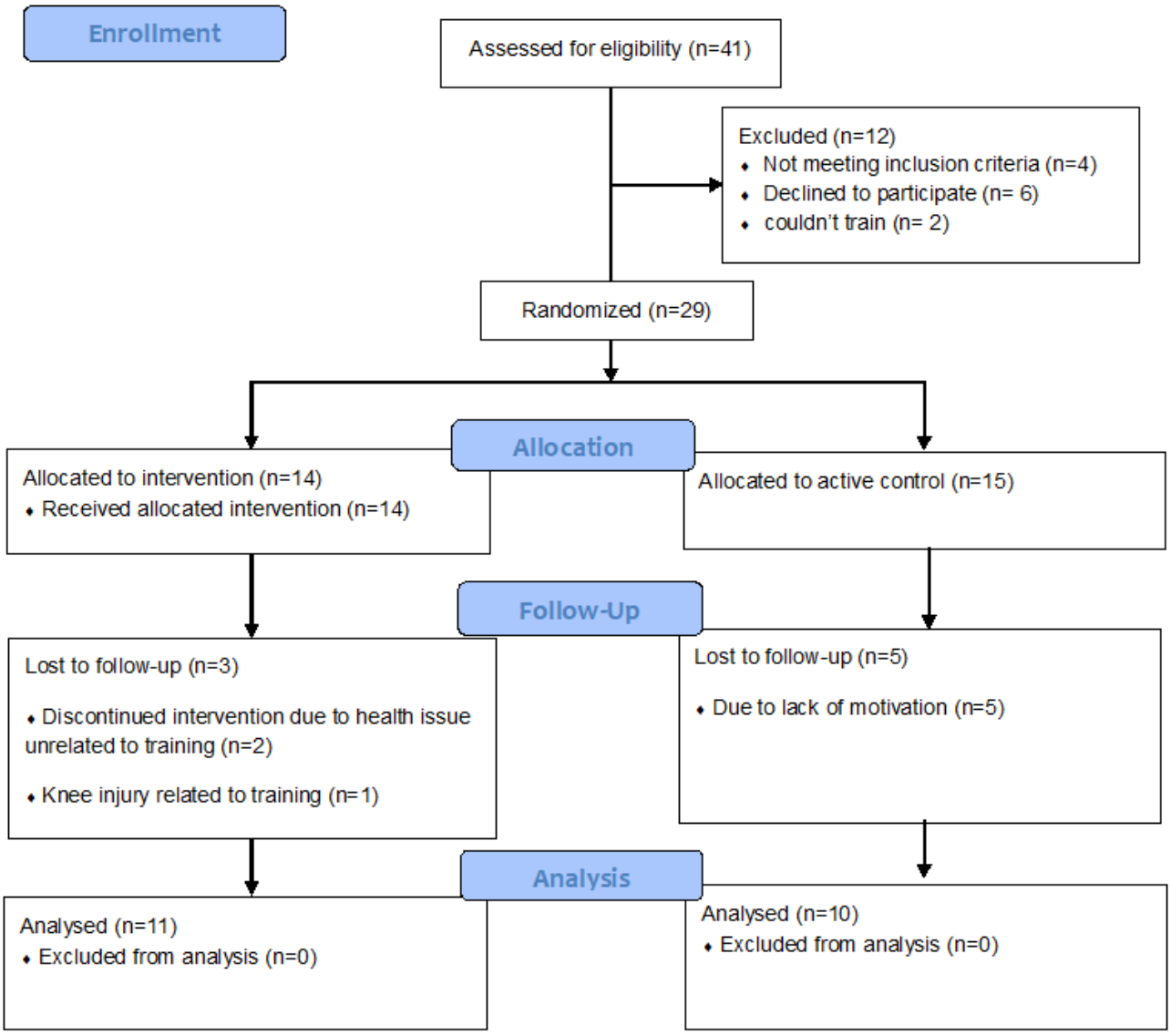
Characteristics	Supervised Training Group (N=14)	Active Control Group (N=15)	P-value
Age (years)	51.6 ± 5.0	54.1 ± 5.0	0.20
Men/Women	7/7	7/8	0.86
BMI (kg/m²)	32.3 ± 4.4	31.3 ± 9.6	0.72
Waist circumference (cm)	109.2 ± 13.8	99.2 ± 6.2	0.02
Diabetes duration (years)	6.0 ± 4.0	6.1 ± 5.5	0.97
Systolic blood pressure (mmHg)	134.9 ± 13.6	130.0 ± 14.1	0.35
Diastolic blood pressure (mmHg)	90.9 ± 11.4	88.3 ± 10.8	0.52
B-HB (g/dL)	14.4 ± 1.4	14.4 ± 1.0	0.92
Creatinine (µmol/L	68.2 ± 13.0	62.0 ± 11.4	0.19
Insulin C-peptide (nmol/L)	1.1 ± 0.5	0.8 ± 0.3	0.05
Cholesterol (mmol/L)	4.7 ± 0.8	4.5 ± 0.9	0.47
LDL (mmol/L)	3.0 ± 0.7	2.4 ± 0.7	0.02
Triglyceride (mmol/L)	2.1 ± 1.0	1.5 ± 1.0	0.16
HDL (mmol/L)	1.1 ± 0.2	1.4 ± 0.4	0.03
Fasting glucose (mmol/L)	8.4 ± 1.6	7.6 ± 1.7	0.21
HOMA-IR	2.9 ± 1.2	2.0 ± 0.8	0.05
HbA_{1c} (%)	7.1 ±1.1	6.6 ± 0.6	0.16
HbA_{1c} (mmol/mol)	54.3 ± 11.6	49.0 ± 6.4	0.16

Baseline data is presented in mean ± standard deviation. P-value show group difference between Supervised training group and active control group. BMI= Body mass index, LDL=low density lipoproteins, HDL= High density lipoproteins, HOMA IR= Homeostatic model assessment of insulin resistance, HbA_{1C}= Glycosylated hemoglobin

Table 2: Presents the total training sessions performed by the participants.

Participant No.	Resistance training (total 24 sessions)	Aerobic training (total 36 sessions)	Sessions in right heart zone	Missing sessions
1	24	36	35	0
2	24	36	35	0
3	23	34	29	2
4	24	36	35	0
5	24	36	36	0
6	24	36	34	0
7	24	35	35	1
8	24	36	35	0
9	24	36	33	0
10	13	20	19	16
11	3	4	4	32

Figure 6: Flow chart of the study.



3.2 Cardiac function in supervised training group vs. active control group:

Systolic function:

After 12 weeks of intervention both groups improved systolic function (Table 3). In the STG, LV systolic function was improved by an increase in SVi (stroke volume indexed for body surface area) by 13% ($p = 0.01$), global strain improved 6% ($p = 0.02$), and LVOT VTI increased 12% ($p = 0.02$). Heart rate was reduced by 12% ($p = 0.02$). Whereas in the ACG, SVi increased 22% ($p=<0.001$), and global strain improved 15% ($p < 0.001$). Heart

rate was reduced by 13% (p=0.01). Only global strain (p = 0.02) was significantly different between the groups.

Right ventricle peak systolic tissue doppler velocity (RV S') was improved by 6% in the STG and 12% in the ACG with no significant difference between the groups (see Table 3).

Diastolic Function:

Diastolic function was only significantly improved in the STG, E velocity increased by 12% (p = 0.02), and E' mean by 13% (p = 0.02). A similar insignificant increase in E' was also observed in the ACG (13%, p = 0.11). No significant difference between groups was found (see Table 3).

3.2.1 Sex differences observed in STG:

Systolic function:

In the STG, SVi increased by 15% (p = 0.10) and resting heart rate reduced by 13% (p = 0.05) in men. While in women, SVi increased by 11% (p = 0.04) and heart rate was reduced by 10% (p = 0.22) (Table 4, Figure 7E). Men tended to improve LV systolic function by a greater improvement in global strain compared to women (7%, p = 0.11 vs. 4%, p = 0.12, respectively) (Table 4, Figure 7C) with no difference in S' where both women and men improved by 7%. Women had the tendency to increase more in LVOT VTI (9% vs. 14%, p > 0.05) and ejection fraction (6% vs. -2%, p > 0.05).

Women improved more in right ventricular systolic function measured by TAPSE (21%, p = 0.02) and. RVS' by 10% (p = 0.07). TAPSE was significantly different between the sexes (p = 0.04) (see Table 4).

Diastolic function:

Diastolic function was more improved in men measured by the increase in mitral E velocity by 14% (p = 0.02) and E' by 13% (p = 0.058). Women resulted in insignificant increase of E velocity by 13% and E' by 14% (Table 4, Figure 7G). No significant sex differences were found (see Table 4).

3.2.2 Sex differences observed in ACG:

Systolic function:

In the ACG, no improvement in systolic function for women was observed after 12 weeks. However, men increased SVi by 28% (p = 0.008) (Table 5, Figure 7F), global strain by 18% (p < 0.001) (Table 5, Figure 7D), and ejection fraction by 15% (p < 0.001). Resting heart

rate was decreased by 16% in men (p = 0.01). Only SVi was increased by 16% (p = 0.05) in women.

Diastolic function:

E/A ratio which was significantly increased in women (p = 0.01). (see Table 5).

3.3 Cardiorespiratory fitness:

A significant increase in VO_{2peak} by 20% (p < 0.001) in the STG and 11% (p = 0.005) in the ACG was observed after 12 weeks of intervention with no significant difference between the intervention groups. Heart rate recovery after 2-min significantly improved in STG (14%, p = 0.02), which significantly differed from the ACG group (p=0.04) (Table 6).

Sex differences:

In the STG, men improved VO_{2peak} by 25% (p < 0.001) and women by 15% (p = 0.001) with a significant difference (p = 0.01) between sexes (Table 7, Figure 7A). Heart rate recovery after 1-min and 2-min improved by 48% (p = 0.04) and 16% (p = 0.01) respectively in women. No significant change in heart rate recovery was found in men (Table 7).

In the ACG, women improved VO_{2peak} by 17% (p = 0.11) and men improved by 8% (p = 0.03) (Table 8, Figure 7B). A significant between group interaction was found in heart rate recovery after 2-min (p = 0.01). Women improved heart rate recovery after 2-min by 9%, whereas in men it was reduced by 5% (p > 0.05) (Table 8).

3.4 Blood variables:

No significant change from the baseline was found in HbA_{1c} between STG and ACG, neither between women and men (see Table 6). Eleven participants had a higher HbA_{1C} value (≥48mmol/mol) at baseline and 7 of these reduced HbA_{1C}. There was a tendency for a higher reduction of HbA_{1C} in the STG in the men (Table 7 & 8).

In the STG, significant decrease in insulin-c peptide by 27% (p = 0.02) and HOMA-IR by 25% (p = 0.03) in women was observed, which were significantly different from the men (p = 0.01 and p = 0.02, respectively). No changes in the ACG was found (Table 7 & 8).

Table 3: Pre and post results for Doppler Echocardiographic Variables in supervised training group vs. active control group.

	Supervised Training Group (N=11)						Active Control Group (N=10)						ACG vs. STG
	Pre		Post				Pre		Post		Interaction		
	N	Mean	N	Mean	Δ Mean	P-value	N	Mean	N	Mean	Δ Mean	P-value	P-value
HR (bpm)	11	77.1 ±11.8	11	68.2 ±7.7	-8.9 ±11.0	0.02	10	78.3 ±13.8	10	68.4 ±9.8	-10 ±9.5	0.01	0.81
Blood Pressure (mmHg)													
Systolic	11	131.9 ±12.6	11	140.1 ±15.3	8.2 ±14.0	0.08	10	128.5 ±13.7	10	131.1 ±11.3	2.6 ±10.1	0.44	0.31
Diastolic	11	88.5 ±9.9	11	88.7 ±7.8	0.2 ±7.5	0.94	10	89.4 ±11.4	10	88.9 ±8.3	-0.5 ±8.4	0.85	0.85
Systolic function													
Left Ventricle													
SV (ml)	11	76.1 ±12.8	11	85.5 ±14.3	9.4 ±9.0	0.01	10	64.5 ±16.3	10	79.7 ±12.7	15.2 ±9.0	<0.001	0.16
SVi (ml/m²)	11	35.6 ±6.2	11	40.2 ±6.9	4.6 ±3.9	0.003	10	32.6 ±10.8	10	39.9 ±8.8	7.3 ±4.2	<0.001	0.14
CO (L/min)	11	5.8 ±0.8	11	5.8 ±1.1	0.1 ±0.9	0.81	10	5.3 ±1.5	10	5.4 ±0.1	0.1 ±1.1	0.74	0.89
Cardiac index (L/min/m²)	11	2.7 ±0.4	11	2.8 ±0.5	0.05 ±0.4	0.680	10	2.7 ±1.0	10	2.7 ±0.7	0.03 ±0.5	0.871	0.92
EDV (ml)	11	103.6 ±24.5	11	106.5 ±30.3	2.9 ±18.1	0.61	10	102.4 ±23.1	10	108.5 ±34.3	6.1 ±14.2	0.21	0.91
EDVi (ml/m²)	11	48.2 ±10.7	11	49.9 ±13.8	1.7 ±8.1	0.50	10	50.7 ±10.3	10	53.3 ±13.7	2.3 ±6.5	0.23	0.78
GS (%)	11	-18.1 ±2.8	11	-19 ±2.3	-1.0 ±1.1	0.02	10	-17.0 ±3.0	10	-19.5 ±2.6	2.5 ±1.6	<0.001	0.02
S' mean (mm/s)	11	92.8 ±15.1	11	99.1 ±11.8	6.3 ±10.2	0.07	10	102.7 ±22.9	10	109.0 ±19.0	6.3 ±10.9	0.87	0.99
LVOT VTI (cm)	11	23.3 ±4.7	11	26.0 ±4.0	2.7 ±3.4	0.02	10	20.5 ±4.6	10	22.5 ±3.4	2.0 ±3.7	0.12	0.66
EF (%)	11	55.5 ±7.5	11	56.7 ±4.6	1.2 ±6.6	0.57	10	52.3 ±5.4	10	59.1 ±5.4	6.8 ±4.4	0.00	0.91
Right Ventricle													
TAPSE (mm)	11	25.3 ±4.3	11	27.9 ±3.7	2.6 ±4.3	0.07	10	26.0 ±3.7	10	26.7 ±4.1	0.7 ±2.9	0.47	0.25
RV S' (mm/s)	11	136.6 ±26.3	11	144.7 ±24.1	8.1 ±11.3	0.04	10	132.3 ±28.9	10	148.3 ±24.5	16.0 ±17.9	0.02	0.24
Diastolic function													
E' mean (mm/s)	11	91.9 ±20.5	11	104.1 ±23.0	12.2 ±15.2	0.02	10	106.4 ±35.4	10	120.7 ±20.6	14.3 ±25.5	0.11	0.66
E velocity (m/s)	11	0.8 ±0.2	11	0.9 ±0.1	0.1 ±0.1	0.02	10	0.7 ±0.2	10	0.7 ±0.1	0.0 ±0.1	0.26	0.28
E/A- ratio	11	1.0 ±0.2	11	1.1 ±0.2	0.1 ±0.2	0.21	10	1.2 ±0.9	10	1.1 ±0.3	-0.1 ±1.0	0.86	0.62

Data is presented as mean ± SD. Abbreviations: GS, Global strain; TAPSE, Tricuspid annular plane systolic excursion; E, Peak early diastolic mitral inflow velocity; A, Peak late diastolic mitral inflow velocity; DT, Deceleration time; HR, Heart rate; SV, Stroke volume; SVi, Stroke volume index; CO, Cardiac Output; RV S', Right ventricle peak systolic tissue doppler velocity; LVOT VTI, Left ventricle outflow track Velocity time integral; EF, Ejection fraction; EDV, End diastolic volume; EDVi, End diastolic volume index; S', Left ventricle peak systolic tissue doppler velocity; E', Left ventricle peak early diastolic tissue doppler velocity; P-value: Differences within group, P-value interaction: Difference between the groups.

Table 4: Pre and post results for Doppler Echocardiographic Variables in men vs. women in the supervised training group

Supervised Training Group (N=11)												
	Men (N=5)						Women (N=6)					Men vs. Women Interaction
	Pre		Post				Pre		Post			
	N	Mean	N	Mean	ΔMean	P-value	N	Mean	N	Mean	ΔMean	P-value	P-value
HR (bpm)	5	77.8 ±3.7	5	67.4 ±10.9	-10.4 ±8.5	0.05	6	76.5 ±16.3	6	68.8 ±4.7	-7.7 ±13.4	0.22	0.70
Blood Pressure (mmHg)													
Systolic	5	132.8 ±14.4	5	137.0 ±9.7	4.2 ±16.1	0.59	6	131.2 ±12.3	6	142.7 ±19.4	11.5 ±12.4	0.07	0.42
Diastolic	5	90.6 ±8.7	5	90.6 ±7.9	0.0 ±9.0	1.00	6	86.8 ±11.2	6	87.2 ±8.0	0.3 ±7.0	0.91	0.95
Systolic function Left Ventricle													
SV (ml)	5	77.8 ±12.6	5	88.6 ±16.3	10.8 ±11.5	0.10	6	74.7 ±14.1	6	82.8 ±13.3	8.2 ±7.2	0.04	0.65
SVi (ml/m²)	5	34.8 ±6.4	5	40.0 ±9.1	5.2 ±5.0	0.08	6	36.3 ±6.5	6	40.3 ±5.3	4.1 ±3.2	0.03	0.66
CO (L/min)	5	6.0 ±1.0	5	5.9 ±1.4	-0.1 ±1.0	0.84	6	5.6 ±0.5	6	5.8 ±1.0	0.2 ±0.7	0.54	0.59
Cardiac index (L/min/m²)	5	2.7 ±0.6	5	2.7 ±0.8	-0.02 ±0.4	0.94	6	2.7 ±0.2	6	2.8 ±0.4	0.1 ±0.4	0.51	0.63
EDV (ml)	5	123.4 ±21.2	5	119.4 ±34.3	-4.0 ±19.8	0.67	6	87.2 ±11.2	6	95.8 ±24.4	8.7 ±15.9	0.24	0.51
EDVi (L/min/m²)	5	55.2 ±10.8	5	53.9 ±17.5	-1.3 ±8.5	0.76	6	42.5 ±6.9	6	46.6 ±10.4	4.1 ±7.5	0.23	0.30
GS (%)	5	-17.6 ±4.0	5	-18.9 ±3.1	1.3 ±1.4	0.11	6	-18.4 ±1.6	6	-19.2 ±1.6	0.7 ±1.0	0.12	0.46
S' mean (mm/s)	5	96.5 ±12.6	5	103.0 ±12.5	6.5 ±13.1	0.33	6	89.8 ±17.5	6	95.8 ±11.1	6.1 ±8.4	0.14	0.30
LVOT VTI (cm)	5	22.3 ±3.5	5	24.2 ±4.2	1.9 ±2.8	0.21	6	24.2 ±5.7	6	27.5 ±3.3	3.3 ±3.9	0.09	0.95
EF (%)	5	59.4 ±9.3	5	58.2 ±5.8	-1.2 ±8.3	0.76	6	52.3 ±3.9	6	55.5 ±3.4	3.2 ±4.7	0.16	1.00
Right Ventricle													
TAPSE (mm)	5	27.0 ±5.2	5	26.9 ±2.9	-0.2 ±3.5	0.92	6	23.9 ±3.3	6	28.9 ±4.4	4.9 ±3.7	0.02	0.04
RV S' (mm/s)	5	143.0 ±27.4	5	145.8 ±23.8	2.8 ±6.3	0.37	6	131.3 ±26.5	6	143.8 ±26.6	12.5 ±13.2	0.07	0.17
Diastolic function													
E' mean (mm/s)	5	95.7 ±28.1	5	107.9 ±29.9	12.2 ±10.3	0.06	6	88.8 ±13.3	6	100.9 ±17.9	12.2 ±19.4	0.19	0.27
E velocity (m/s)	5	0.7 ±0.2	5	0.9 ±0.2	0.1 ±0.1	0.02	6	0.8 ±0.2	6	0.9 ±0.1	0.1 ±0.2	0.24	0.79
E/A- ratio	5	1.0 ±0.3	5	1.1 ±0.3	0.1 ±0.3	0.52	6	0.9 ±0.2	6	1.0 ±0.1	0.1 ±0.2	0.31	0.88

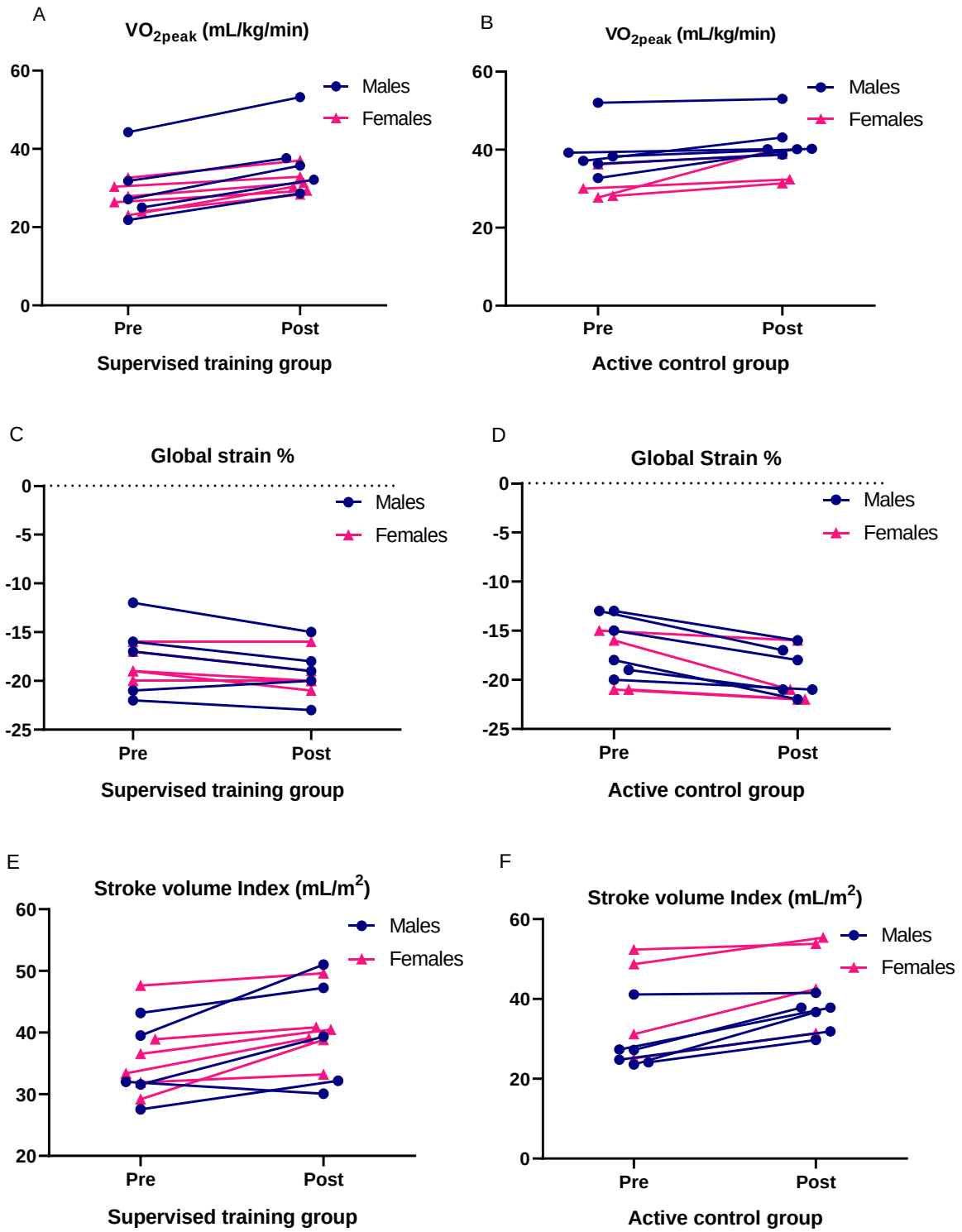
Data is presented as mean ± SD. Abbreviations: GS, Global strain; TAPSE, Tricuspid annular plane systolic excursion; E, Peak early diastolic mitral inflow velocity; A, Peak late diastolic mitral inflow velocity; DT, Deceleration time; HR, Heart rate; SV, Stroke volume; SVi, Stroke volume index; CO, Cardiac Output; RV S', Right ventricle peak systolic tissue doppler velocity; LVOT VTI, Left ventricle outflow track Velocity time integral; EF, Ejection fraction; EDV, End diastolic volume; EDVi, End diastolic volume index; S', Left ventricle peak systolic tissue doppler velocity; E', Left ventricle peak early diastolic tissue doppler velocity; P-value: Differences within group, P-value interaction: Difference between women and men.

Table 5: Pre and post results for Doppler Echocardiographic Variables in men vs. women in the active control group.

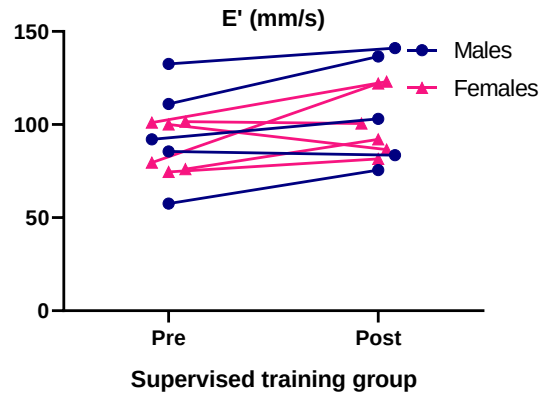
Active Control Group (N=10)												
	Men (N=6)						Women (N=4)				Men vs. Women	
	Pre		Post				Pre		Post			Interaction
	N	Mean	N	Mean	ΔMean	P-value	N	Mean	N	Mean	ΔMean	P-value	P-value
HR (bpm)	6	80.8 ±14.6	6	66.7 ±10.0	-14.2 ±9.3	0.01	4	74.5 ±13.7	4	70.8 ±10.0	-3.8 ±6.0	0.30	0.09
Blood Pressure (mmHg)													
Systolic	6	135.2 ±11.3	6	131.5 ±13.7	-3.7 ±6.1	0.20	4	118.5 ±11.4	4	130.5 ±8.3	12.0 ±7.1	0.04	0.01
Diastolic	6	94.7 ±10.7	6	90.7 ±10.3	-4.0 ±5.5	0.14	4	81.5 ±7.6	4	86.3 ±3.8	4.8 ±10.0	0.41	0.11
Systolic function													
Left Ventricle													
SV (ml)	6	59.2 ±10.5	6	76.3 ±8.2	17.2 ±9.9	0.008	4	72.5 ±21.7	4	84.8 ±17.8	12.3 ±7.9	0.054	0.43
SVi (ml/m²)	6	28.0 ±6.6	6	35.9 ±4.3	7.9 ±4.6	0.008	4	39.4 ±13.3	4	45.8 ±11.2	6.4 ±4.1	0.050	0.62
CO (L/min)	6	4.7 ±0.7	6	5.1 ±0.6	0.3 ±1.2	0.49	4	6.2 ±2.0	4	6.0 ±1.2	-0.2 ±1.1	0.69	0.45
Cardiac index (L/min/m²)	6	2.2 ±0.5	6	2.4 ±0.2	0.1 ±0.6	0.56	4	3.4 ±1.3	4	3.2 ±0.9	0.1 ±0.6	0.66	0.46
EDV (ml)	6	109.0 ±27.4	6	120.0 ±39.7	11.0 ±13.8	0.11	4	92.5 ±11.7	4	91.3 ±15.0	-1.3 ±12.8	0.86	0.14
EDVi (L/min/m²)	6	51.1 ±12.2	6	56.1 ±16.7	4.9 ±5.6	0.08	4	49.9 ±8.4	4	49.0 ±7.4	0.1 ±6.7	0.79	0.17
GS (%)	6	-16.3 ±3.1	6	-19.2 ±2.5	2.9 ±1.2	<0.001	4	-18.1 ±3.0	4	-20.0 ±3.0	1.9 ±2.1	0.17	0.38
S' mean (mm/s)	6	106.1 ±26.1	6	116.2 ±19.7	10.0 ±11.6	0.09	4	97.5 ±19.4	4	98.0 ±13.0	0.5 ±7.8	0.91	0.19
LVOT VTI (cm)	6	19.0 ±3.4	6	22.3 ±2.0	3.3 ±4.2	0.12	4	22.9 ±5.7	4	22.9 ±5.2	0.1 ±1.9	0.94	0.20
EF (%)	6	53.0 ±6.2	6	61.1 ±5.9	8.1 ±3.7	<0.001	4	51.3 ±4.7	4	56.0 ±2.9	4.8 ±5.1	0.16	0.86
Right Ventricle													
TAPSE (mm)	6	26.1 ±1.0	6	27.6 ±2.1	1.5 ±1.9	0.10	4	25.8 ±6.3	4	25.2 ±6.1	-0.5 ±4.1	0.81	0.30
RV S' (mm/s)	6	147.2 ±19.8	6	162.8 ±17.0	15.7 ±15.8	0.06	4	110.0 ±27.2	4	126.5 ±16.3	16.5 ±23.3	0.25	0.95
Diastolic function													
E' mean (mm/s)	6	106.6 ±41.0	6	126.1 ±25.2	19.5 ±21.1	0.07	4	106.0 ±30.9	4	112.5 ±8.5	6.5 ±32.8	0.72	0.20
E velocity (m/s)	6	0.7 ±0.2	6	0.8 ±0.1	0.0 ±0.1	0.31	4	0.7 ±0.2	4	0.7 ±0.2	0.0 ±0.1	0.67	0.80
E/A- ratio	6	1.4 ±1.1	6	1.2 ±0.3	-0.2 ±1.2	0.70	4	0.9 ±0.2	4	1.1 ±0.2	0.2 ±0.1	0.01	0.57

Data is presented as mean ± SD. Abbreviations: GS, Global strain; TAPSE, Tricuspid annular plane systolic excursion; E, Peak early diastolic mitral inflow velocity; A, Peak late diastolic mitral inflow velocity; DT, Deceleration time; HR, Heart rate; SV, Stroke volume; SVi, Stroke volume index; CO, Cardiac Output; RV S', Right ventricle peak systolic tissue doppler velocity; LVOT VTI, Left ventricle outflow track Velocity time integral; EF, Ejection fraction; EDV, End diastolic volume; EDVi, End diastolic volume index; S', Left ventricle peak systolic tissue doppler velocity; E', Left ventricle peak early diastolic tissue doppler velocity; P-value: Differences within group, P-value interaction: Difference between women and men.

Figure 7: A-H, Echocardiographic data men vs. women in supervised training group and active control group



G



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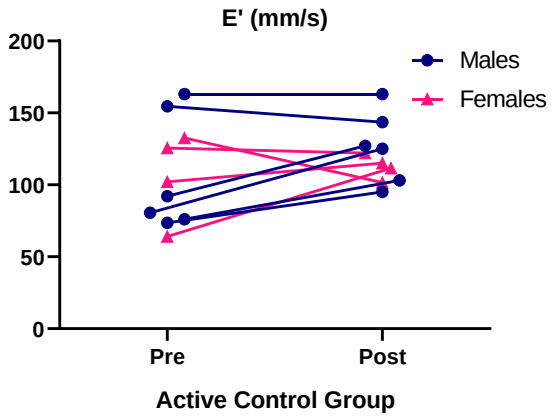

Table 6: Pre and post results for cardiovascular risk factors in supervised training group vs. active control group.

	Supervised Training Group (N=11)						Active Control Group (N=10)					STG Vs. ACG	
	Pre		Post				Pre		Post			Interaction	
	N	Mean	N	Mean	Δ Mean	P-value	N	Mean	N	Mean	Δ Mean	P-value	P-value
VO_{2peak} (ml/kg/min)	11	28.6 ±6.3	11	34.2 ±7.1	5.6 ±2.3	<0.001	10	35.8 ±7.1	10	39.7 ±5.9	4.0 ±3.4	0.005	0.20
Heart Rate Recovery (beats/min)													
1-minute	10	25.1 ±9.0	10	30.7 ±5.1	5.6 ±8.9	0.08	9	35.0 ±6.7	9	34.7 ±10.7	-0.3 ±11.2	0.93	0.22
2-minutes	9	42.6 ±10.3	9	48.3 ±9.7	5.8 ±6.2	0.02	9	53.0 ±4.6	9	52.9 ±6.4	-0.1 ±4.6	0.94	0.04
Blood variables													
HbA_{1C} (mmol/mol)	11	53.8 ±11.8	11	51.5 ±9.8	-2.4 ±5.8	0.21	10	48.5 ±7.0	10	48.5 ±5.8	0.0 ±2.4	1.00	0.24
HbA_{1C} (%)	11	7.1 ±1.1	11	6.9 ±0.9	-0.2 ±0.5	0.21	10	6.6 ±0.6	10	6.6 ±0.5	0.0 ±0.2	1.00	0.24
Insulin C-peptide (nmol/L)	11	1.2 ±0.5	11	1.0 ±0.5	-0.1 ±0.2	0.09	10	0.7 ±0.3	10	0.7 ±0.3	-0.1 ±0.2	0.24	0.43
Fasting glucose (mmol/L)	11	8.4 ±1.6	11	8.2 ±1.8	-0.3 ±1.8	0.65	10	7.7 ±2.0	10	7.8 ±1.6	0.03 ±0.9	0.92	0.66
HOMA-IR	11	3.0 ±1.3	11	2.7 ±1.4	-0.3 ±0.6	0.10	10	1.8 ±0.8	10	1.6 ±0.7	0.2 ±0.5	0.30	0.53
Waist Circumference (cm)	11	110.4 ±12.2	11	108.6 ±11.4	-1.8 ±4.4	0.21	10	97.5 ±6.3	10	98.2 ±7.1	0.7 ±2.6	0.42	0.14

Data is presented in Mean ±SD. Abbreviations: VO_{2peak}, Peak oxygen consumption; HbA_{1C}, Glycosylated hemoglobin; HOMA IR; Homeostasis model assessment of insulin resistance. P-value: Differences within group, p-value interaction: Difference between the groups.

Table 7: Pre and post results for cardiovascular risk factors in men vs. women in the supervised training group.

Supervised Training Group (N=11)												
	Men (N=5)						Women (N=6)					Men Vs. Women
	Pre		Post				Pre		Post			Interaction
	N	Mean	N	Mean	ΔMean	P-value	N	Mean	N	Mean	ΔMean	P-value	P-value
VO_{2peak} (ml/kg/min)	5	30.0 ±8.8	5	37.4 ±9.5	7.4 ±1.3	<0.001	6	27.4 ±3.7	6	31.5 ±3.1	4.15 ±1.7	0.001	0.01
Heart Rate Recovery (beats/min)													
1-minute	5	28.2 ±10.4	5	28.8 ±5.1	0.6 ±7.5	0.87	5	22.0 ±7.0	5	32.6 ±4.8	10.6 ±7.7	0.04	0.07
2-minutes	5	40.4 ±11.9	5	45.0 ±9.8	4.6 ±8.4	0.29	4	45.3 ±8.8	4	52.5 ±8.9	7.3 ±2.2	0.01	0.56
HbA_{1C} (mmol/mol)	5	52.2 ±16.3	5	49.2 ±11.4	-3.0 ±7.1	0.40	6	55.2 ±7.9	6	53.3 ±8.8	-1.8 ±5.2	0.42	0.76
%	5	6.9 ±1.5	5	6.7 ±1.0	-0.3 ±0.6	0.40	6	7.2 ±0.7	6	7.0 ±0.8	-0.2 ±0.5	0.42	0.76
Insulin C-peptide (nmol/L)	5	1.3 ±0.7	5	1.3 ±0.6	0.04 ±0.1	0.48	6	1.1 ±0.4	6	0.8 ±0.2	-0.3 ±02	0.02	0.01
Fasting glucose (mmol/L)	5	8.3 ±2.4	5	7.7 ±1.5	-0.6 ±1.2	0.36	6	8.5 ±0.8	6	8.5 ±2.2	0.01 ±2.2	0.99	0.61
HOMA-IR	5	3.3 ±1.8	5	3.4 ±1.7	0.1 ±0.3	0.44	6	2.8 ±0.9	6	2.1 ±0.7	-0.7 ±0.5	0.03	0.02
Waist Circumference (cm)	5	112.0 ±15.6	5	108.8 ±12.9	-3.3 ±3.4	0.10	6	109.0 ±9.9	6	108.5 ±11.2	-0.5 ±5.0	0.80	0.33

Data is presented in Mean ±SD. Abbreviations: VO_{2peak}, Peak oxygen consumption; HbA_{1C}, Glycosylated hemoglobin; HOMA IR; Homeostasis model assessment of insulin resistance. P-value: Differences within group, P-value interaction: Difference between women and men.

Table 8: Pre and post results for cardiovascular risk factors in men vs. women in active control group.

Active Control Group (N=10)													
	Men (N=6)						Women (N=4)						Men vs. Women Interaction
	Pre		Post				Pre		Post				
	N	Mean	N	Mean	ΔMean	P-value	N	Mean	N	Mean	ΔMean	P-value	P-value
VO_{2peak} (ml/kg/min)	6	39.3 ±6.6	6	42.5 ±5.3	3.3 ±2.8	0.03	4	30.5 ±3.9	4	35.6 ±4.2	5.1 ±4.5	0.11	0.45
Heart Rate Recovery (beats/min)													
1 minute	6	35.7 ±6.9	6	34.7 ±13.1	-1.0 ±12.3	0.85	3	33.7 ±7.6	3	34.7 ±5.0	1.0 ±10.8	0.89	0.82
2 minutes	6	53.5 ±5.2	6	51.0 ±6.3	-2.5 ±3.1	0.10	3	52.0 ±3.6	3	56.7 ±5.9	4.7 ±3.1	0.12	0.01
HbA_{1c} (mmol/mol)	6	45.2 ±5.2	6	45.7 ±4.0	0.5 ±1.8	0.52	4	53.5 ±6.8	4	52.8 ±5.7	-0.8 ±3.3	0.68	0.45
HbA_{1c} (%)	6	6.3 ±0.5	6	6.3 ±0.4	0.04 ±0.2	0.52	4	7.0 ±0.6	4	7.0 ±0.5	-0.1 ±0.3	0.68	0.45
Insulin C-peptide (nmol/L)	6	0.6 ±0.3	6	0.6 ±0.3	-0.1 ±0.1	0.30	4	0.8 ±0.3	4	0.8 ±0.3	-0.1 ±0.2	0.55	0.81
Fasting glucose (mmol/L)	6	6.9 ±1.4	6	7.1 ±1.4	0.2 ±0.8	0.65	4	8.9 ±2.2	4	8.8 ±1.5	-0.2 ±1.2	0.82	0.64
HOMA-IR	6	1.6 ±0.7	6	1.4 ±0.7	-0.1 ±0.3	0.37	4	2.2 ±1.0	4	2.0 ±0.6	-0.2 ±0.7	0.55	0.70
Waist Circumference (cm)	6	97.7 ±7.8	6	97.5 ±8.6	-0.2 ±1.7	0.75	4	97.1 ±4.1	4	99.2 ±5.0	2.1 ±3.2	0.29	0.17

Data is presented in Mean ±SD. Abbreviations: VO_{2peak}, Peak oxygen consumption; HbA_{1C}, Glycated hemoglobin; HOMA IR; Homeostasis model assessment of insulin resistance. P-value: Differences within group, P-value interaction: Difference between women and men.

4 Discussion:

The main finding from this study was that there was a sex difference in training response in the supervised group with women having an improvement in autonomic function, right ventricular systolic function and insulin resistance compared to the men, while the men improved left ventricular cardiac function and aerobic fitness more.

Both the supervised training group and the active control group showed cardiac improvements and increased aerobic fitness in both women and men after 12 weeks of intervention.

However, the sex-based results should be interpreted with caution due to low sample size in the analysis between women and men.

A novel and important finding was the improvement in both cardiac function and cardiorespiratory fitness in the active control group that were only advised to reach 100 PAI each week by themselves.

4.1 Cardiac function:

Greater enhancement in left ventricular systolic function variables of stroke volume, ejection fraction and global strain were observed in the ACG, whereas the STG resulted in the augmentation of peak systolic tissue doppler velocity (S') and LVOT VTI. Right ventricular systolic function (RV S') was also improved in both groups with a higher increase in the ACG. The lower baseline value of RV S' in the ACG could be a reason for a higher increase in this group. LV diastolic function was only significantly improved in the STG, which explains the higher increase in VO_{2peak} in the STG (STG=20% vs. ACG=11%). The same percentage increase in E' was seen in ACG, but without significance.

Recently, Hollekim et al. studied the effect of high intensity interval training on the cardiac function in T2D individuals. Results from their study is comparable with our findings in the STG with an improvement in global strain of 6%. However, LV systolic tissue velocity S' increased more in their study (13%) compared to 7% of increase in our study [7]. Overall the cardiac adaptations were lower in our study. The reason for the discrepancy between the results could be due to the lower baseline values observed in their study. Other reason could be the difference in the training programs with more time spent in the high intensity zone in the other study.

Kemi et al. demonstrated that intensity of the training is important to induce physiological cardiomyocyte hypertrophy, increase contractility and Ca^{2+} handling [64]; important mechanisms involved in the improvement of cardiac function [65]. The improvements in the myocardial contractility and diastolic filling in T2D individuals in the present study are of clinical importance and might prevent heart failure in the future [4, 20].

The positive effects of exercise in individuals with T2D are well established. However, the mode and intensity of the exercise should be targeted to the individuals´ cardiometabolic profile as well as wish [53]. To improve aerobic fitness, high intensity interval training could be a promising strategy [62] whereas, combined aerobic and resistance would be preferable for the improvement in glucose uptake [80]. As T2D is the end result of various metabolic, structural and functional consequences, different parameters should be targeted to gain optimal health benefits [53]. Therefore, both aerobic and resistance training are recommended in T2D [6]. Moreover, the study participants in the present study found different training protocols combined with resistance very motivating and exciting, which adds to the value of combined training programs.

Data shows that the adherence to physical activity in T2D individuals is surprisingly low. Only 9% of individuals with T2D follow the physical activity recommendations [81], and lack of motivation is the main reason [53]. The improvements found in the ACG of our study is an interesting finding in regard to increase the compliance to physical activity in this population. These results suggest that the use of wearable technology giving a weekly index could be a powerful tool to motivate the individuals with T2D, which is a major obstacle to the exercise engagement in this population.

4.1.1 Sex related response to training:

Diastolic function:

Diastolic dysfunction is the most common cardiac impairment in T2D that can lead to heart failure. Almost half of the population with asymptomatic T2D have diastolic dysfunction [82]. Out of 21 participants that were included in the analysis, 14 had reduced diastolic function compared to age-matched healthy individuals. More men in our study had reduced diastolic function (8 men, 6 women) but, the values were more pronounced in women, which is consistent with the findings from previous studies [9]. The impact of sex hormones, higher burden of risk factors and differences in the course of disease are reasons behind more impaired diastolic function in women [8].

In the STG, although men significantly improved LV diastolic function (E'), the same percentage of improvement by 13% was observed in women, however not significant. Similarly, in the ACG, both sexes presented improvement in diastolic function. Previously, a study in postmenopausal women with T2D found no changes in diastolic filling patterns after exercise training. However, compared to our study they targeted elderly women. Moreover, the intervention period was short (10 weeks) and only moderate intensity training on cycle ergometer was performed [83]. In contrary to these results, Egelund et al. found diastolic improvements in premenopausal and postmenopausal women after 12 weeks of high intensity interval training [84]. The findings of these studies in addition to the findings in men with T2D [70] suggest that intensity play an important role in initiating diastolic adaptations in both women and men.

Systolic function:

In left ventricular systolic function, men showed greater increase in global strain whereas, women in LVOT VTI and ejection fraction in the STG. Systolic tissue doppler velocity (S'), was equally improved in women and men. However, women in our study had lower mean value of S' (93mm/s) at baseline compared to the normal mean value in this age group (i.e. 101mm/s) whereas, men had the normal baseline value (102mm/s). Gori et al. also observed lower value of S' in women compared to the male counterparts in heart failure patients [9].

Global strain is an early indicator of subclinical cardiac dysfunction and a more sensitive measure compared to ejection fraction [85]. A lower absolute value of global strain is generally observed in men [86] which was the case in our study at baseline (men= 16.9% vs. women= 18.3%) and even after more improvement in men, the absolute post-value (men = 19.05% vs. women = 19.50%) was still higher in women. Less improvement in global strain in women could be due to higher blood pressure and lower value of SV.

Men in both groups (STG=15%, ACG=28%) showed higher improvement in the SVi compared to the women (STG=11%, ACG=16%). A higher afterload in women could be a reason. No change in cardiac output was found due to the reduction of resting heart rate in both sexes.

Sex-related differences in right ventricular systolic function have been mentioned before both in healthy and diseased populations with higher values for right ventricular systolic function being observed in women [87]. We observed a greater improvement in right ventricular systolic function in women. A study with healthy women found no changes in right ventricular systolic function in response to exercise training, which is possibly due to

lower exercise intensity (85% of maximal heart rate) and difference in exercise modality (cycle ergometer). Moreover, the baseline values were lower in our population. The augmentation of right ventricular systolic function enhances the exercise capacity of individuals and could predict a better prognosis of heart diseases [88].

Our study is the first to date to evaluate sex-related response to cardiac adaptations in T2D. Women and men in both groups showed cardiac adaptations after 12 weeks of training. However, sex differences in exercise response were observed with men improving more in LV cardiac function and women in right ventricular systolic function. Reduced LV cardiac function (E' and S') at baseline was observed in women. Deteriorating LV cardiac function and less improvement by exercise in women with T2D highlights the need for sex specific exercise program.

4.2 Cardiorespiratory fitness:

We observed lower VO_{2peak} values at baseline in both sexes compared to average values for their age group [89]. Prior studies have also observed the impaired cardiorespiratory fitness in T2D [10, 58, 82]. After 12 weeks intervention period, an increase in VO_{2peak} was seen in both ACG and STG. However, the increase was more pronounced in the STG (20%) than the ACG (11%) which could be related to the greater enhancement of LV diastolic function in the STG [90]. The improvement of 20% in VO_{2peak} in the STG was more than that observed in study by the Hollekim et al. by 13%, which is possibly due to a lower VO_{2peak} at baseline in the STG of our study. Stoa et al. found similar improvements in VO_{2peak} (21%) as our STG after 12 weeks of high intensity interval training in T2D individuals [45].

Lower value of VO_{2peak} in women is usually observed compared to men due to difference in body mass, hemoglobin content and heart dimensions [91]. Diabetic women have even lower $VO2_{peak}$ compared to their non-diabetic counterparts [10]. The greater increase in VO_{2peak} in men was seen with same training program, which is in line with prior findings [10, 91]. The increase in VO_{2peak} is related to the increase in SV. This is also supported by our study as men increased more in SV and thus in VO_{2peak} as compared to women [61]. Howden et al. found 22% and 15% increase respectively in men and women after 1-year endurance training, which is comparable to 25% and 16% increase in our study. Slightly increased results in our study could be due to the higher intensity of endurance training. Sex-related difference in VO_{2peak} was still observed after adjusting by body mass in prior studies [77].

In contrast to the STG, women in the ACG presented greater improvement in VO_{2peak}, which is possibly due to the women being more active or training harder than men.

These findings suggest that women with T2D should train harder to gain similar benefit in aerobic fitness as men. Moreover, the use of PAI seems to motivate women to exercise by themselves as well as men, which is a great achievement as fewer women than men engage in recommended level of physical activity [92].

4.3 Resting heart rate and heart rate recovery:

A significant decrease in heart rate was observed in both groups (STG=12%, ACG=13%). People with T2D generally have higher resting heart rate than normal individuals and every 10 bpm increase in resting heart rate cause 15% increase risk of deaths in T2D [93].

Sex differences in improvement of resting heart rate was found with men reducing more than women. (STG=13% vs. 10%, ACG=16% vs 5% respectively).

Heart rate recovery is a decrease in heart rate immediately after exercise, associated with activation of vagal tone and withdrawal of sympathetic activity. Lower heart rate recovery is caused by cardiac autonomic dysfunction and can lead to cardiovascular morbidity and mortality. Reduced heart rate recovery is observed in individuals with T2D [94]. Autonomic dysfunction in T2D is reflected by higher resting heart rate. Exercise training has a positive effect in the improvement of heart rate recovery, which is indicated by the finding in the STG.

In our study, women significantly improved heart rate recovery after 2-min in both groups than men (STG=16% vs. 11%, ACG=9% vs. 5%). This is in contrast with the finding by MacMillan et al. that found the same improvement of 14% (after 1-min) in both sexes after a cardiac rehabilitation program [95]. Whereas, we found a large increase in heart rate recovery after 1-min by 48% in the STG. Firstly, the discrepancy between our results could be due to the difference in the method of measurement. They measured heart rate recovery after 2 minutes of cool down. Secondly, the population in MacMillan et al.'s study was cardiac patients with more pronounced impairment in autonomic function and thirdly, the discrepancy could be due to the difference in training programs (i.e. lower intensity training in their study would have led to lesser improvement). However, a study with healthy individuals found faster heart rate recovery in women which supports our finding [96]. Higher parasympathetic drive in women could be associated with this faster recovery compared to men.

Abnormalities in autonomic function are observed in T2D [94] and may contribute to the development of diastolic dysfunction [97]. Our finding suggest that exercise training is effective in improving autonomic function in individuals with T2D.

4.4 HbA_{1C}:

We found no significant improvements in HbA_{1C} in any group, only a tendency in the STG (-0.2%). In contrast, Hollekim et al. found significant improvement in HbA_{1C} (-0.4%) in the high intensity interval group with the baseline level similar to our STG. Less improvement in our study could be explained by the difference in the training program. In contrast to our finding, the combined aerobic and resistance training have been shown to have greater effect in reducing HbA_{1c}. Moreover, Umpierre et al. proposed that the volume of the exercise is more important than exercise intensity for the improvement of HbA_{1c} in T2D [80].

There was a trend in the men to reduce HbA_{1C} more than the women in the STG, which could be related to the decrease in fat mass in men. We did not directly measure fat mass, but a decrease in the waist circumference of the men was noticed and improvements in body composition are associated with enhanced glucose homeostasis [98].

Improvement in long term glycemic control is highly important in T2D-patients as it is an independent risk factor for heart failure [27]. Exercise intervention has been shown to be more effective in the patients with higher HbA_{1c} value at baseline [99]. Decrease in HbA_{1c} reduces the risk of developing coronary heart disease by 5-17% and all-cause mortality by 6-15% within a time frame of 10 years [100].

4.5 Insulin resistance:

The homeostasis assessment model (HOMA-IR) is a common reliable measure used to assess the insulin resistance in individuals with T2D and it is well correlated with highly invasive and time-consuming glycemic clamp technique [101]. Although results did not reach significance, improvement in both STG and ACG in insulin resistance (10% and 11%) was observed. Hollekim et al. found no improvement in insulin resistance after 12 weeks of HIIT [7]. Improvements observed in the present study can be explained by the superior effect of combined aerobic and resistance training on insulin sensitivity [44]. Moreover, repeated bouts of high intensity induce greater glucose transporter proteins (GLUT4) improving sensitivity to insulin [101].

A significant sex differences in the improvement of insulin resistance and insulin C-peptide was found in the STG. Women decreased HOMA-IR by 25%, whereas men increased by 3%. The improvement in women was related to the significant decrease in insulin C-peptide

(25%). Similarly, in the ACG women showed more decrease in HOMA-IR (9% vs. 6%). In contrast to our finding Metcafle et al. found 28% improvement in insulin sensitivity in men whereas no significant improvement in women after 3 weeks of sprint intervals [102].

Insulin resistance is a hallmark of T2D and the improvement in insulin sensitivity is important to reduce the clustering of metabolic and CVD risk factors like dyslipidemia, hypertension and endothelial dysfunction [21].The physiological mechanisms that are involved in the improvement in insulin sensitivity include an increase in insulin receptors, GLUT4, muscle oxidative capacity, reduction in free fatty acids and inflammation proteins [101]. Greater improvements in women suggest that they had better enhancement in one or more of these mechanisms. However, exercise should be planned differently (maybe short bouts of HIIT) to improve insulin resistance in men.

4.6 Limitations and strengths:

Comparison of the exercise response between the women and men was affected by the small sample size. The diabetes group studied is a heterogenous group with different diabetes duration, and possibly different degree of inflammation as well as genetics.

Part of the improvement of VO_{2peak} could have been caused by the individuals having performed a VO_{2peak} test at baseline, and at post-testing they were more familiar with the procedure.

The blood pressure was not measured at the same time. The risk of random bias was reduced by the usage of same apparatus and cuff size. Moreover, the same investigator took all the measurements and the same procedure was followed.

Another limitation of the study was that information about the menstrual cycles in women was not gathered. As sex hormones has an impact on sex related difference. However, most of the women were in menopause.

An important strength was the continuous documentation of the intensity and duration of all training sessions.

Conclusions:

Women and men with T2D showed different cardiovascular and metabolic adaptations in response to 12-weeks of exercise training. Women had a greater improvement in autonomic function and insulin resistance, whilst men showed a greater improvement in left ventricular cardiac function and aerobic capacity. The present study indicates that while designing a training program for individuals with T2D one should consider the individual target parameter as well as sex.

However further research is needed to investigate the sex differences in training response to potentially develop sex specific training programs to optimize the effects of training.

A novel finding was that a heart rate watch providing a personal weekly activity index was an effective approach to motivate and increase the activity levels in both women and men with T2D. Both cardiorespiratory fitness and cardiac function were improved.

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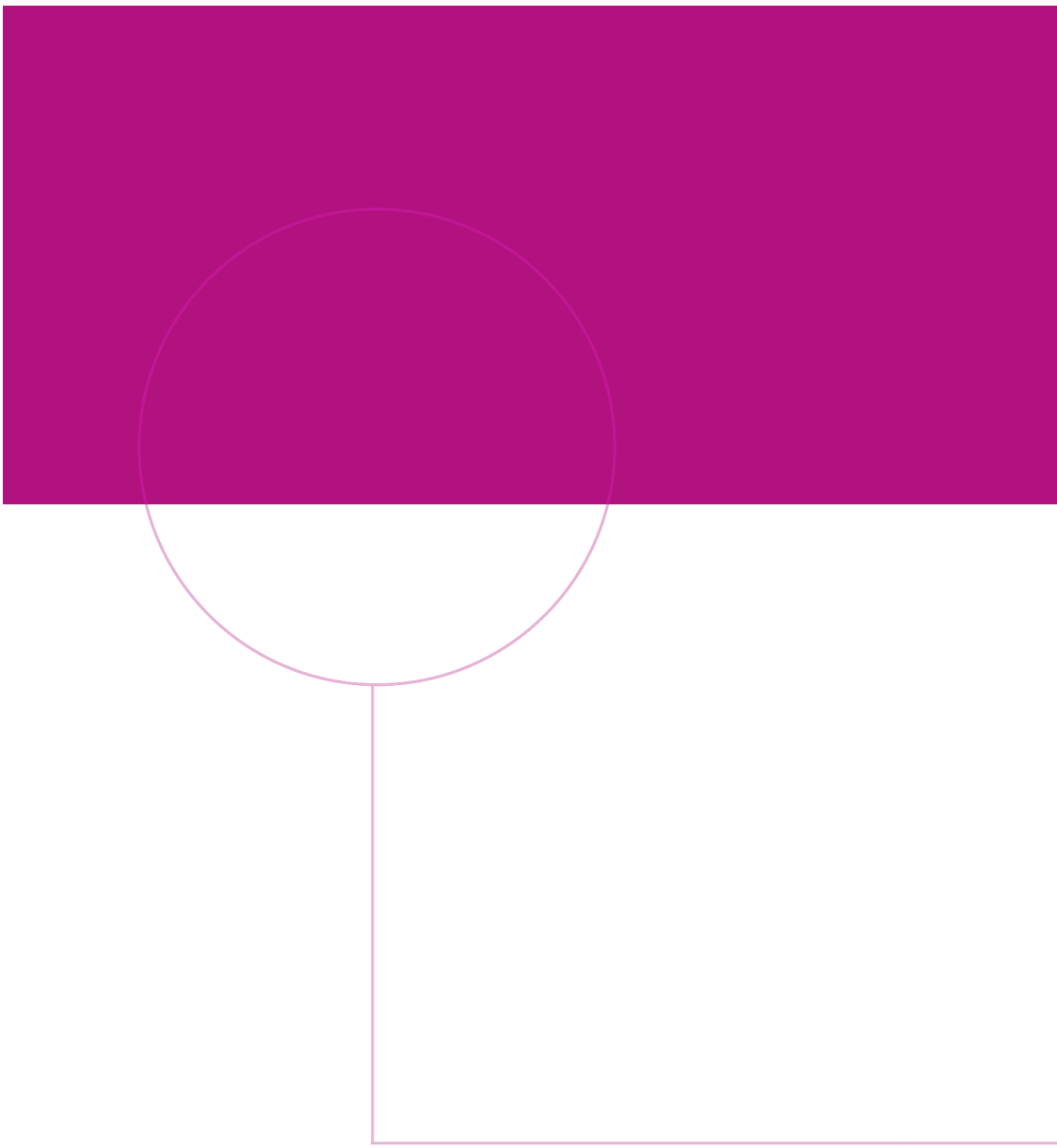

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