2013•2014
FACULTEIT GENEESKUNDE EN LEVENSWETENSCHAPPEN
*master in de revalidatiewetenschappen en de kinesitherapie*

# Masterproef

## Impaired glucose tolerance in chronic heart failure: prevalence, explanatory factors and the impact of exercise therapy

Promotor :
Prof. dr. Bert OP 'T EIJNDE

Copromotor :
Mevrouw An STEVENS

Jef Lettens
*Proefschrift ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie*

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universiteit hasselt
KNOWLEDGE IN ACTION

## Voorwoord

Deze masterproef is het eindwerk van mijn opleiding in de kinesitherapie en revalidatiewetenschappen aan de Universiteit Hasselt. Allereerst wil ik mijn promotor Prof. Dr. B. Op't Eijnde en co-promotor Dra. A. Stevens oprecht bedanken voor het mogelijk maken van deze masterproef. Zij hebben mij bijgestaan in het schrijven van dit eindwerk en hebben me veel bijgebracht over het onderwerp. Ik kon altijd bij hen terecht met vragen en ze maakten altijd tijd vrij om verbeteringen aan te brengen.

Ik wil ook een dankwoord richten aan de deelnemers die dit onderzoek hebben mogelijk gemaakt. Zij dragen bij aan een evolutie in de gezondheidszorg.

Tot slot wil ik mijn ouders bedanken voor de steun in mijn 5-jarige opleiding. Dankzij hun heb ik deze opleiding kunnen verwezenlijken en hier ben ik hen eeuwig dankbaar voor.

Te Hasselt, mei 2013 J.L.

## Background

During the last years, the western population is characterized by an increased prevalence of chronic heart failure (CHF). CHF is defined as the inability of the heart to pump blood in a forward direction at an amount to reach the body's metabolic needs despite a normal pressure (forward heart failure) or only at the expense of increased pressures (backward heart failure) [1].

The combination of CHF and insulin resistance is a common problem [2]. The prevalence is estimated to be over 30%. During the last decade, investigations have found that physical training does not only affects exercise tolerance and quality of life, but it also decreases mortality and hospitalization rates [3] Therefore, increased physical activity is considered to be very important [4].

The primary objective of this master thesis was to describe the prevalence of impaired glucose tolerance and to investigate the effects of exercise therapy on glucose tolerance in patients with chronic heart failure. Exercise therapy is an important strategy in other insulin resistant populations, such as obese and diabetes mellitus type 2. Unfortunately, the effects of exercise therapy on insulin resistance were not enough investigated in this population. We have investigated this comparing a training group with a control group in a randomized controlled trial. Before this trial an observational cohort study was described comparing three groups: patients with normal glucose regulation, patients who were pre – diabetes and patients with diabetes.

This master thesis is part of PhD project 'Influence of exercise therapy on insulin resistance in patients with chronic heart failure' of dra. An Stevens. The study investigates the effect of exercise therapy on glucose tolerance, body composition, exercise tolerance, skeletal muscle strength, heart function and quality of life within the frame of REVAL, research rehabilitation centre of Hasselt University and the Heart Centre of the Jessa Hospital. This master thesis focuses on the influence of exercise therapy on glucose tolerance, skeletal muscle strength and body composition in chronic heart failure patients. My contribution in this project was supervising and coaching patients during training sessions. In addition, data processing and data analysis was performed.

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# Impaired glucose tolerance in chronic heart failure: prevalence, explanatory factors and the impact of exercise therapy

Drawn up according the guidelines of The European Journal of Cardiovascular Prevention & Rehabilitation except for figures and tables.

## Abstract

**Background:** Patients with chronic heart failure are prone to develop impaired glucose tolerance. However, evidence about the prevalence and the effect of exercise therapy in this population is scarce. The aim of this study was to investigate the prevalence, explanatory factors and the effect of exercise therapy on glucose tolerance in patients with chronic heart failure.

**Patients and Methods:** An observational cohort study was set up. Patients underwent a 2 h oral glucose tolerance test (OGTT), isometric strength testing of the upper leg and dual energy x-ray absorptiometry. Health-related quality of life and physical activity level were assessed by questionnaire. Thereafter, 27 clinically stable patients with CHF (NYHA I-III) were randomly (2:1) assigned to a 12-week supervised combined exercise and strength program. Glucose tolerance, cardiopulmonary endurance, muscle strength and body composition were evaluated.

**Results:** OGTT revealed that 12 patients (21%) had a normal glucose regulation, 22 patients (39%) were diagnosed pre – diabetic and 23 patients (40%) were diabetic. 22 patients completed the training study. No significant training effects were found regarding glucose. Fasting insulin levels remained unchanged in EG and increased in CG ($p<0,05$) and was significant different between groups ($p<0,05$). Exercise tolerance: $VO_2$ at peak exercise and $VO_2$ at the second ventilatory threshold increased compared to CG ($p<0,05$). Isokinetic muscle endurance: average power and total work increased was significantly increased compared to CG ($p<0,05$). Body composition did not change.

**Conclusion:** The prevalence of IGT in people with CHF is alarming. A combined exercise training program increased exercise tolerance and isokinetic muscle endurance in patients with CHF who were stable for three months. It stabilized fasting insulin and fasting HOMA – IR. However the effect of training on glucose tolerance remains unclear.

**Keywords:** Chronic heart failure, glucose tolerance, exercise therapy, oral glucose tolerance test.

## Introduction

Chronic heart failure (CHF) is a major health issue in the Western world.(ref?) It can be defined as the inability of the heart to pump blood forward at a sufficient rate to meet the metabolic demands of the body (forward failure), or the ability to do so only if the cardiac filling pressures are abnormally high (backward failure), or both [1]. The disease is defined as a syndrome with the following symptoms: shortness of breath at rest or during exertion, fatigue, signs of fluid retention such as pulmonary congestion or ankle swelling and wheezing [5]. The Rotterdam study in the Netherlands showed a prevalence of 7% of the population in 1999, which increased over time and with age, from 0,9% in those aged 55-64 years to 17.4 in those aged 85 years or more in 1998 [6].

CHF is a syndrome which not only comprises a heart problem, but also affects organs over the entire body. Next to the cardiac problem, CHF is a complex syndrome with many aspects: neurohormonal alterations, endothelial dysfunctions, renal dysfunctions, pulmonary complications and peripheral muscle wasting [5]. Furthermore, insulin resistance (IR) has also been related to CHF. IR is a status of pre-diabetes, which is characterized by an impaired glucose tolerance (IGT) [2, 7, 8]It is an important risk factor for developing CHF, but it is also often developed in CHF patients [7]. The exact prevalence of diabetes in CHF is not clear yet. The prevalence differs between studies from 8 up to 44% in patients with CHF [2]. Also, the prevalence of IGT in patients with CHF without diabetes is not yet known [9, 10].

Exercise therapy is an important aspect in the therapy of CHF. Exercise therapy not only improves exercise tolerance, life expectancy and quality of life, it also reduces hospitalization rates in CHF [5]. According to the European Association for Cardiovascular prevention and Rehabilitation an aerobic exercise training combined with resistance training is the most effective training model for patients with CHF [3].

Not much is known about the effect of exercise therapy on insulin resistance in patients with CHF. There are only few exercise intervention studies in this population and there was no consistency in results [11-19]. This can be explained by differences in training programs and glucose tolerance measurements between studies. There is only one research group that presented positive results on whole-body insulin mediated glucose uptake after exercise training [15, 16], but this study was not randomized nor could the results be confirmed by other studies [13, 14, 18, 19]. Therefore, more research is necessary to support these results for this population.

Based on the above line of reasoning, the first aim of this study was to describe glucose tolerance in a general CHF population. Second, we aimed to investigate the influence of exercise therapy on glucose tolerance in patients with chronic heart failure. We hypothesized that a combined exercise program has a positive effect on glucose tolerance.

## Methods

*Patients*

Inclusion criteria were subjects diagnosed with CHF for longer than 6 months, clinically stable in the last 3 months without hospitalization and a NYHA classification I-III. Exclusion criteria were glucose lowering medication, participation in a training program for the last 3 months and major adjustments of medication or surgical interventions during the training study. Subjects were informed about the nature and risks of the procedures and an informed consent was obtained. All patients gave their written informed consent. Ethical approval of the study was obtained from the committees of the Jessa hospital and Hasselt University. The investigation conforms with the principles outlined in the Declaration of Helsinki.

*Study design*

The observational cohort study consisted of one testing day. An oral glucose tolerance test (OGTT) was performed after an overnight fast of 8 hours, Dual Energy X-ray Absorptiometry (DEXA) for body composition and isometric muscle strength was assessed. In the training study patients were randomly assigned in a training group or control group in a 2:1 ratio. Randomization was based on age, sex, OGTT and type of heart failure. The randomized controlled trial consisted of two testing days. The first day an OGTT, DEXA and isometric and isokinetic muscle strength was assessed. On the second day the cardiopulmonary exercise test and the ultrasound scan of the heart were performed. The total research period consisted of 12 weeks of training intervention and 2 test weeks. The study design is presented in figure 1.

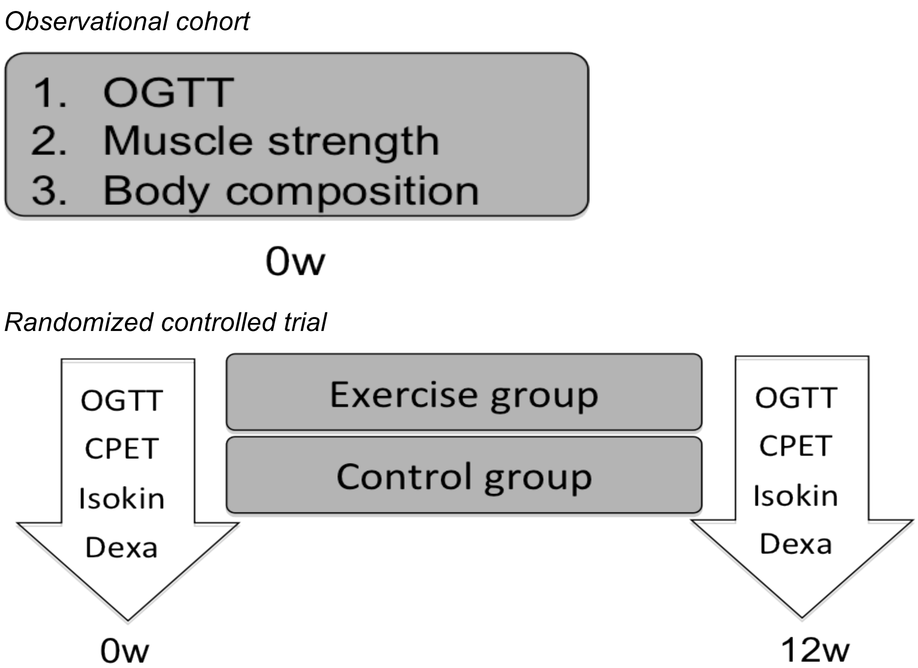



**Figure 1: Study design**

OGTT: Oral glucose tolerance test; CPET: cardiopulmonary exercise test; Isokin: Isokinetic dynamometry (BIODEX).

*Oral glucose tolerance test*

After a fasting period of 8 hours, blood samples from an antebrachial vein was taken before, 1h and 2h after intake of 75g glucose dissolved in 200mL water. Blood samples for glucose and insulin (collected in serum separation tubes) and BNP (collected in EDTA tubes) were maintained at room temperature for 30min, centrifuged, and the collected serum and plasma were frozen at −80°C until assays were performed. Blood samples for HbA1c (collected in EDTA tubes) were processed on the test day. All analyses were performed in the clinical laboratory of the Jessa hospital. Patients were classified into three groups according to the American Diabetes Association 2013 criteria, which are presented in table 1. When patients had a plasma glucose value of ≥ 11,1 mmol/L during the 2h oral glucose tolerance test, they were classified as diabetic. Total area under the curve (AUC) of glucose and insulin were calculated with the trapezoidal rule. The AUC from 0 to 60 minutes, from 60 to 120 minutes and the total AUC were evaluated.

**Table 1: Criteria of the American Diabetes Association**

| | Normal glucose regulation | Pre - diabetes | Diabetes |
|---|---|---|---|
| **HbA1c** | ≤ 5,6% | 5,7 – 6,4% | ≥ 6,5% |
| | AND | OR | OR |
| **2-h PG in the 75-g OGTT** | ≤ 7,7 mmol/L | 7,8 – 11,0 mmol/L | ≥ 11,1 mmol/L |
| | AND | OR | OR |
| **FPG** | ≤ 5,5 mmol/L | 5,6 – 6,9 mmol/L | ≥ 7,0 mmol/L |

*Body composition*

Body composition was determined by Dual Energy X-ray Absorptiometry (DEXA) (Hologic Series Delphi-A Fan Beam X-ray Bone Densitometer). Quality control tests were performed. After the completion of the scan total body weight, lean mass and fat mass were obtained together with a whole body visual display. To determine body composition in different segments, the following areas were selected: legs, trunk, gynoid and android region. From these findings the waist – to – hip ratio and trunk – leg ratio were also determined. DEXA is a valid method to assess body composition [20].

*Skeletal muscle strength*

Skeletal muscle strength was evaluated on an isokinetic dynamometer (System 3; Biodex Medical Systems, New York, USA). Patients were seated on a backward inclined (5°) chair with upper leg, hips and shoulders stabilized with safety belts. In order to evaluate to evaluate the upper leg the rotational axis of the dynamometer was aligned with the transverse knee-joint axis and connected it to the distal end of the tibia. This lever could be adjusted according to the patients needs. Maximal isometric strength was evaluated by two maximal isometric contractions performed by knee extensors and flexors at knee angles of 45° and 90°. Maximal contractions (during 4 seconds) were interspersed by 90-second rest intervals. Maximal isokinetic muscle strength, only performed by patients in the training study, was measured using 20 maximal isokinetic knee extensions at a velocity of 180°/s after three sub-maximal trial contractions. The knee extensions were initiated at a joint angle of 90° towards an angle of 160. The total work (J) and average power (Watts) were calculated. The Biodex is a reliable instrument to measure muscle strength [21].

*Quality of life*

The Minnesota Living with Heart Failure questionnaire and the EQ5D questionnaires were used to inventory health-related quality of life. The Minnesota Living with Heart Failure questionnaire consists of 21 items asking how much the disease and its treatment have affected the patient's life in the previous month. Available responses for each question range from 0 (no effect) to 5 (very much). The total score is calculated by adding ratings from all 21 items and can range from 0 to 105 points, with higher scores indicating poorer health related quality of life.

The EQ5D Health Questionnaire is a widely used generic quality of life scale. It is a standardized instrument for use as a measure of health outcome. The EQ5D comprises five questions on mobility, self-care, pain, usual activities, and psychological status. In addition, there is a visual analogue scale to indicate the general health status with 100 indicating the best health status (The EuroQoL group).

***Additional methods used in the training study***

*Cardiopulmonary exercise testing*

Maximal cardiopulmonary exercise tests on bicycle ergometer (Ergoline GmbH, Ergometer EBIK COMFORT) were performed. After 1 min of rest, 1min of unloaded cycling was performed. Thereafter the resistance was increased to 20W for 1 minute and increased every 2 minutes by 10W or 20W, based on previous exercise tests, until exhaustion. This test entailed an individualized rate to yield a test duration between 8 and 15 minutes. Standardized verbal encouragement was used to stimulate the patient to persevere till exhaustion. A respiratory – exchange ratio (RER) higher than 1.05 ensured that all patients had performed a maximal exercise test.

An electrocardiogram (cardiosoft 6.6) and respiratory data through breath-by-breath analysis (Jaeger masterscreen CPX) were registered continuously. Heart rate was calculated from the electrocardiogram. Gas analyzers and flow meter were calibrated before each test. Oxygen uptake ($VO_2$) and carbon dioxide output ($VCO_2$) were determined from the continuous measurement of oxygen and carbon dioxide concentration in the inspired and expired air. Peak $VO_2$ was defined as the highest 10-s average of $VO_2$ in the last minute of the test. The first and second ventilatory threshold (VT) were determined by the nadir of $VE/VO_2$ as the first VT, whereas the nadir of $VE/VCO_2$ is the second VT [22].

*Intervention*

Patients randomized to the training group participated in a supervised, facility-based training program that consisted of combined exercise training with both an aerobic endurance and a resistance training component. The training period was 12 weeks with 2 training sessions one week and 3 training sessions the other week from 40 to 60 min.

Every session started with a warming up of 5 min on a cycle ergometer (Gymna, Ergo-fit Ergo Cycle 157, Belgium) at a low intensity (0-25 Watt), followed by 2 sets of cycling and 2 sets of walking on a treadmill (Gymna, trac 3000 S Alpin, Belgium). Set duration progressively increased from 6 to 10 min. The exercise intensity was determined by an incremental cardiopulmonary exercise test. During the first training session the intensity was set at the power output and heart rate just before the second

ventilatory threshold. The following training sessions, power output was adapted to heart rate and ratings of perceived exertion (Borg 14-16). Heart rate and patient reactions were monitored. Heart rate was registered and adjusted at rest and during exercise with a Polar heart rate transmitter and by manual control in such a way that critical power was achieved (highest training intensity that could be maintained with constant heart rate during the exercise).
Resistance-training consisted of leg press, leg extension, vertical arm traction and chest press (Technogym and Fysioplus, Belgium). After two training sessions, 3-5 repetition maximum was determined and 1RM was calculated. Then, the workload was set at 50 - 70% of 1-RM. Training loads started at 2x10 and increased to 3x15 repetitions.

*Statistics*

At baseline, normal distribution was investigated using the Shapiro-Wilk test. Due to small patient samples and no normality of variables, we decided to use non – parametrics statistics. A Fisher exact test was used to compare frequencies. For comparison of the three ADA groups a one – way ANOVA was used.

In the intervention study, The Mann-Whitney U test was used to determine differences between groups in continuous variables, and for comparison of changes (pre-post delta scores). Changes within groups were evaluated with the Wilcoxon signed – ranks test. The threshold for statistical significance was set at $P < 0,05$. Statistical analyses was performed with SPSS (MAC version 22).

## Results

### *Observational cohort study*

*Patients*

From March 2011 to March 2012, hospital files of a total of 480 patients were screened. Of these, 99 patients were diagnosed diabetics with glucose lowering medication and 218 patients met other exclusion criteria. From 163 patients who were contacted by telephone, 61 patients were willing to participate in the study. 61 patients were screened at baseline. This process is presented in figure 2. From the results of the OGTT, 12 patients (21%) showed a normal glucose regulation, 22 patients (39%) were diagnosed pre – diabetic and 23 patients (40%) were diabetic. Diabetics showed a significant higher Hba1c compared to NGR and pre – diabetics (p<0,05). Mean fasting insulin was comparable between groups but after 2 hours glucose load, insulin curves did not decrease in pre - diabetics and diabetics (figure 3).

Age, NYHA score, ejection fraction and BNP were comparable between groups. Fat trunk/fat limb ratio was significantly higher in patients who were diagnosed diabetic (p<0,05). Patient characteristics of the observational cohort study are presented in table 2. Maximal isometric strength was comparable between groups (figure 4).

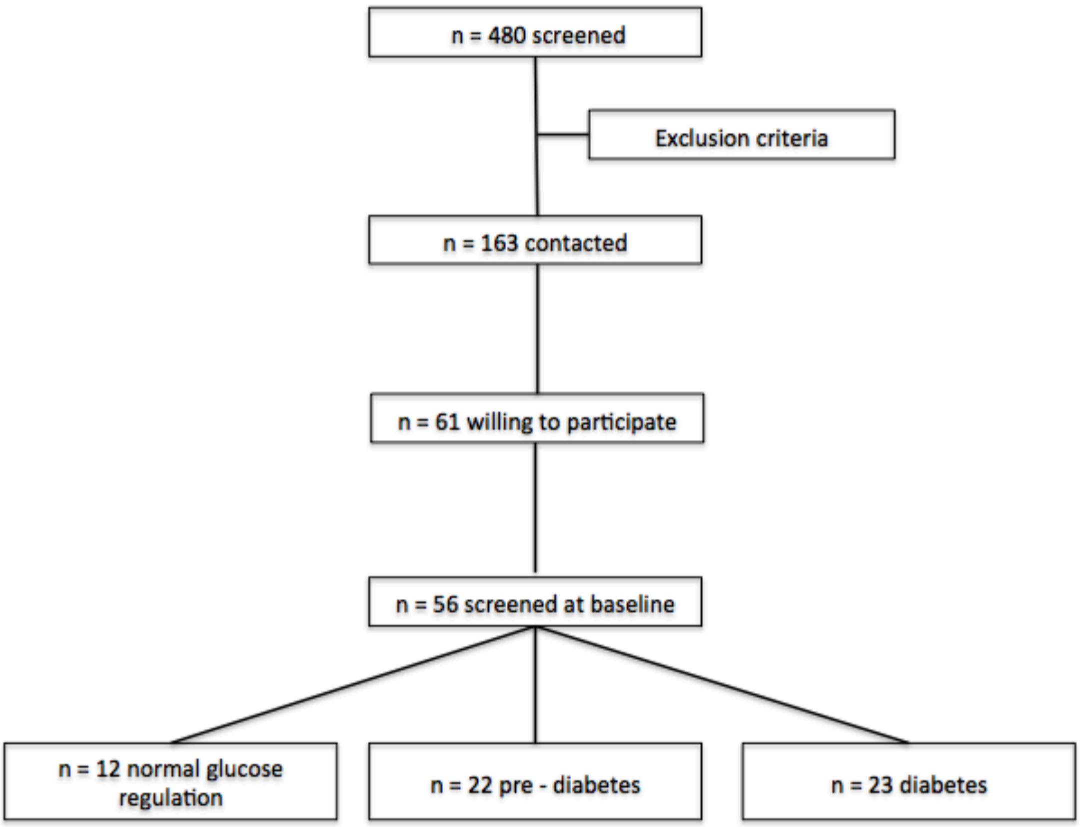



**Figure 2: flowchart of patient inclusion of the observational cohort study**

**Table 2: Patient characteristics of the observational cohort study**

| | NGR (n=12) | Pre - diabetes (n=22) | Diabetes (n=23) | P-value |
|---|---|---|---|---|
| Age | 66 ± 16,9 | 68 ± 10,5 | 70 ± 10,5 | 0,85 |
| Sex | | | | 0,08 |
| Women | 1 (5,3%) | 10 (52,6%) | 8 (42,1%) | |
| Men | 11 (28,9%) | 12 (31,6%) | 15 (39,5%) | |
| NYHA | 1,7 ± 0,8 | 2,1 ± 0,7 | 2 ± 0,7 | 0,29 |
| I | 6 (37,5%) | 4 (25%) | 6 (37,5%) | |
| II | 4 (14,3%) | 11 (39,3%) | 13 (46,4%) | |
| III | 2 (15,4%) | 7 (53,8%) | 4 (30,8%) | |
| BMI | 25,1 ± 3,9 | 27,9 ± 6,2 | 29,6 ± 8,1 | 0,15 |
| Ischemia | 3 (13,6%) | 7 (31,8%) | 12 (54,5%) | 0,21 |
| Hba1c (%) | 5,4 ± 0,2 | 5,7 ± 0,3 | 5,9 ± 0,3 | **0,000** |
| BNP | 181 ± 145 | 149 ± 169 | 233 ± 327 | 0,50 |
| Fat (kg) | 23,2± 87,6 | 28 ± 11,4 | 29,3 ± 16,4 | 0,62 |
| Fat (%) | 30,3 ± 7,2 | 36,6 ± 9,6 | 34,3 ± 8,2 | 0,22 |
| Trunkal fat (%) | 30,9 ± 7,8 | 37,1 ± 8,2 | 37,0 ± 8,8 | 0,20 |
| Fat on legs (%) | 29,9 ± 8,7 | 35,0 ± 9,4 | 30,2 ± 8,1 | 0,17 |
| Fat trunk/Fat limb ratio | 1,31 ± 0,39 | 1,32 ± 0,23 | 1,62 ± 0,33 | **0,006** |

NYHA: New York Heart Association functional class; BMI: body mass index; BNP: B-type natriuretic peptide; Fat (kg): fatmass; Fat (%): Fat percentage; Trunkal fat (%): Trunk fat percentage; Fat on legs (%): Legs fat percentage; Continuous variables are presented as means ± SD; Categorical variables are presented as number and percentage. P<0,05 for differences between groups.

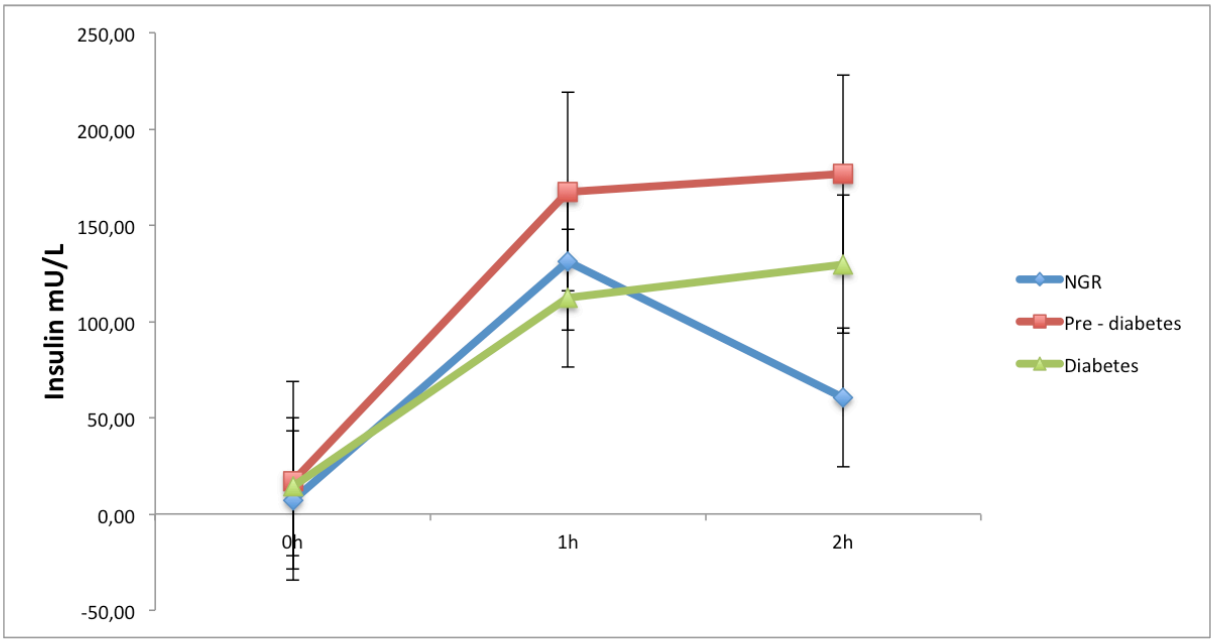
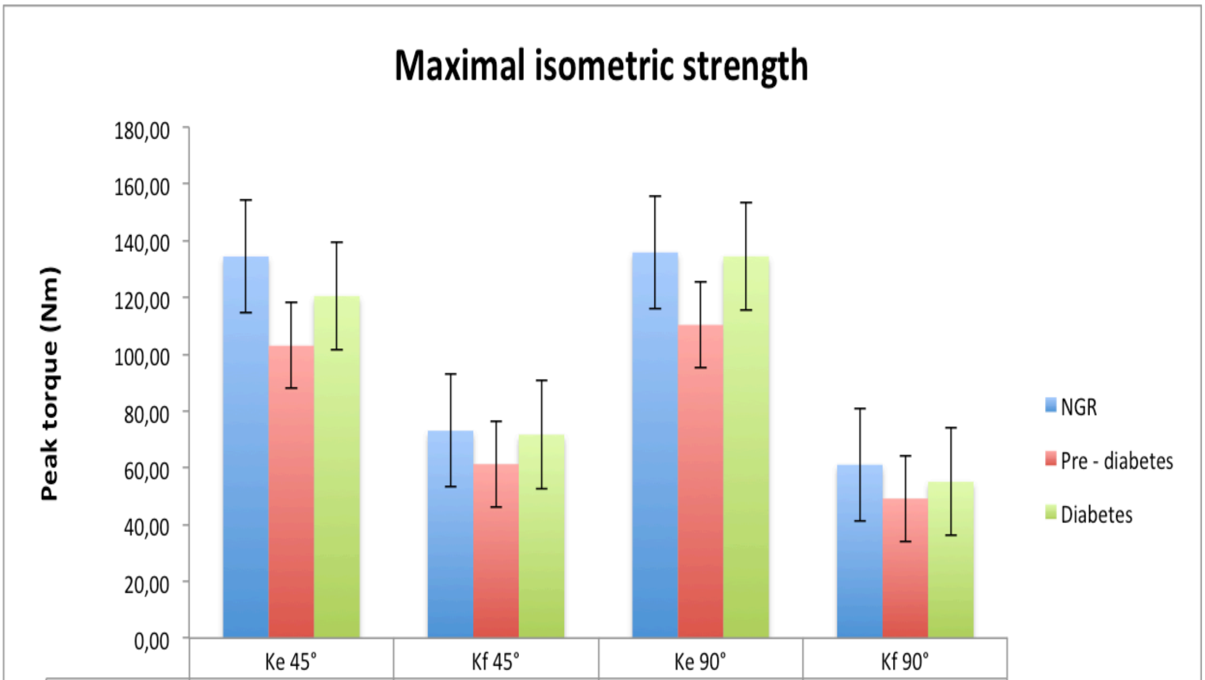



**Figure 3: Insulin concentrations during 2h OGTT of the observational cohort study**

Data are presented as mean ± SE. NGR: normal glucose regulation.




| | Ke 45° | Kf 45° | Ke 90° | Kf 90° |
|---|---|---|---|---|
| NGR | 134,44 | 73,06 | 135,88 | 61,08 |
| Pre - diabetes | 103,00 | 61,30 | 110,31 | 49,16 |
| Diabetes | 120,51 | 71,67 | 134,48 | 55,07 |

**Figure 4: Maximal isometric strength of the observational cohort study**

Ke: knee extension; Kf: knee flexion; Data are presented as mean ± SE. NGR: normal glucose regulation. Differences were not statistically significant.

### *Training study*

*Patients*

27 patients from the cohort study were randomized in a training group (n=18) and a control group (n=9). In the training group, 3 patients were excluded during the study for the following reasons: In 1 person, it was impossible to draw venous blood samples, one received a pacemaker and another suffered from an exacerbation of heart and kidney failure. One person was excluded from the control group because it was also impossible to draw venous blood samples. Another person was excluded after 6 weeks due to musculoskeletal problems with cortisone treatment. Fifteen persons of the intervention group and 7 persons of the control group completed the study. The flowchart of patient inclusion is presented in figure 3.

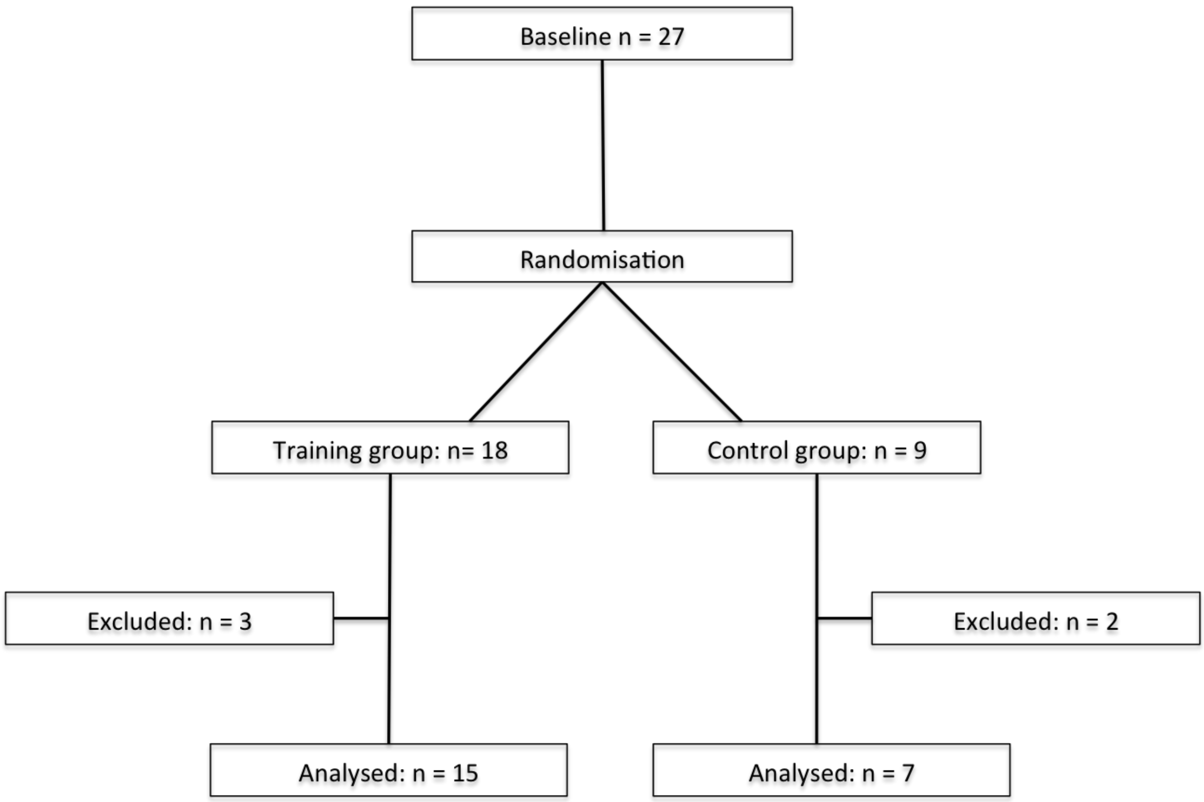



**Figure 5: flowchart of patient inclusion of the training study**

Baseline patient characteristics of the training study are presented in table 3. The NYHA and BMI values were not significant between the two groups. Age, gender and height were comparable between groups. Although there were more smokers in the control group and body weight was higher in the exercise group, there were no significant differences between groups.

**Table 3: Baseline patient characteristics of the training study**

| | Exercise group (n=15) | Control group (n=7) | P-value |
|---|---|---|---|
| Age | 66,5 ± 14,2 | 65 ± 15,6 | 1 |
| Sex | | | 0,62 |
| Women | 33% | 14% | |
| Men | 67% | 86% | |
| NYHA | 1,87 ± 0,7 | 2,25 ± 0,7 | 0,27 |
| I | 5 | 1 | |
| II | 7 | 4 | |
| III | 3 | 3 | |
| BMI | 28,8 ± 8 | 24,3 ± 4 | 0,053 |
| Smokers | 13% | 57% | 0,054 |

The total patient group (n=22) consisted of 50% pre – diabetic and 23% diabetic patients. Baseline measurements are presented in table 4 and 5. Fasting insulin was significantly higher in the exercise group at baseline. Baseline muscle strength and body composition were comparable between groups.

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**Table 4: oral glucose tolerance test responses**

| OGTT | 0 weeks | | 12 weeks | | |
|---|---|---|---|---|---|
| | Exercise group | Control group | Exercise group | Control group | P - value |
| Glucose | | | | | |
| Fasting (Mmol/L) | 5,8 ± 0,6 | 5,4 ± 0,5 | 5,7 ± 0,7 | 5,0 ± 2,1 | 0,08 |
| 1h (Mmol/l) | 9,6 ± 2,3 | 9,7 ± 3,2 | 8,7 ± 2,9 | 8,4 ± 3,9 | 0,36 |
| 2h (Mmol/l) | 7,9 ± 3,0 | 8,7 ± 3,2 | 6,9 ± 3,1 | 5,8 ± 2,8 | 0,62 |
| AUC | 17832 ± 4179 | 18977 ± 4176 | 16318 ± 5068 | 17109 ± 2952 | 0,78 |
| Insulin | | | | | |
| Fasting (mU/L) | 14 ± 8 | 8 ± 5 | 15 ± 10 | 25 ± 25* | **0,04** |
| 1h (mU/L) | 147 ± 166 | 93 ± 56 | 115 ± 70 | 116,0 ± 64,0 | 0,43 |
| 2h (mU/L) | 102 ± 48 | 115 ± 69 | 74 ± 35 | 80 ± 35 | 0,93 |
| AUC | 12289 ± 10448 | 9206 ± 5197 | 9558 ± 4413 | 10092 ± 4933 | 0,46 |
| Homa index | | | | | |
| Fasting | 3,8 ± 2,3 | 1,6 ± 1,1 | 4 ± 3,3 | 6,6 ± 7,7* | **0,05** |

p <0,05 for pre-post effects between groups; *p<0,05 for pre-post effects within a group.

**Table 5: muscle strength, muscle endurance and body composition test responses**

| Variabele | 0 weeks | | 12 weeks | | |
|---|---|---|---|---|---|
| | Exercise group | Control group | Exercise group | Control group | P - value |
| **Isometric muscle strength** | | | | | |
| Knee extension 45° (Nm) | 124 ± 34 | 138 ± 48 | 136 ± 33 | 139 ± 45 | 0,41 |
| Knee flexion 45° (Nm) | 73 ± 23 | 78 ± 24 | 78 ± 24 | 81 ± 17 | 0,73 |
| Knee extension 90° (Nm) | 136 ± 34 | 141 ± 45 | 139 ± 29 | 145 ± 33 | 0,14 |
| Knee flexion 90° (Nm) | 58 ± 16 | 60 ± 21 | 60 ± 15 | 65 ± 15 | 0,96 |
| **Isokinetic muscle endurance** | | | | | |
| Total work 180°/s (J) | 1087 ± 423 | 1157 ± 485 | 1202 ± 391* | 1054 ± 389 | **0,03** |
| Average power 180°/s (Watts) | 90 ± 37 | 107 ± 52 | 106 ± 36* | 97 ± 41 | **0,001** |
| **Body composition** | | | | | |
| Total mass (kg) | 82,2 ± 22,2 | 69,2 ± 10,7 | 83,3 ± 22,9 | 69,4 ± 11 | 0,25 |
| Fat free mass (kg) | 52,5 ± 9,5 | 48,6 ± 5,9 | 53,7 ± 9,7 | 48,8 ± 6,4 | 0,13 |
| Fat mass (kg) | 29,7 ± 15,9 | 20,6 ± 8,8 | 29,7 ± 16,4 | 20,6 ± 8,6 | 0,94 |
| Fat (%) | 34,8 ± 8,2 | 28,9 ± 9 | 34,2 ± 8,5 | 29 ± 8,8 | 0,45 |
| **$VO_2$** | | | | | |
| At Peak exercise (ml/min) | 1464,5 ± 410,8 | 1227,0 ± 583,3 | 1494,2 ± 512,2 | 1141,7 ± 570,0 | **0,04** |
| At 1st VT | 806,1 ± 163,9 | 716,0 ± 269,4 | 814,9 ± 243,7 | 649,5 ± 303,2 | 0,22 |
| At 2nd VT | 1132,8 ± 324,2 | 900,8 ± 331,9 | 1222,2 ± 423,6 | 784,0 ± 283,4 | **0,03** |

p <0,05 for pre-post effects between groups; *p<0,05 for pre-post effects within a group.

### *Training effects*

*Glucose*

In the training group, no significant differences were found regarding glucose levels fasting, after 1h and 2h, however there is a decreasing trend after 12 weeks. Fasting glucose levels decrease with 1,5%, glucose levels after 1h decrease with 9,1% and glucose levels after 2h decrease with 12%.

*Insulin*

Fasting insulin levels were significantly different between groups after 12 weeks ($p<0,05$). The fasting insulin in the control group increased after 12 weeks ($p<0,05$).

*HOMA-index*

In the training group, no significant differences were seen regarding fasting HOMA-index, after 1h and 2h. The change of fasting HOMA was significant between groups ($p<0,05$). Fasting HOMA-index remained equal in the training group and increased strong in the control group ($p<0,05$).

*Muscle strength*

In the exercise group the muscle endurance variables, total work and average power, increased significant compared to the control group ($p<0,05$). In the exercise group, total work and average power increased post training ($p<0,05$).

*Body composition*

Body composition changes were not significant between groups, neither at baseline nor after 12 weeks of training. However, fat free mass increased in the exercise group and as well in the control group. Percentage of fat decreased minimally in the exercise group.

*Exercise tolerance*

At baseline, there were no differences in $VO_2$ peak, $1^{st}$ ventilator threshold and $2^{nd}$ ventilator threshold $VO_2$. However, after 12 weeks of training the exercise group demonstrated an increase in peak $VO_2$ in comparison to the control group ($p<0,05$). The second ventilatory threshold $VO_2$ was significant between groups after intervention ($p<0,05$).

## Discussion

This study showed that glucose tolerance is severely disturbed in a general CHF population. Furthermore, patients with normal glucose tolerance could be distinguished from (pre)diabetic patients by the oral glucose tolerance test. Exercise training was able to improve glucose tolerance (insulin release) as well as isokinetic knee extension endurance. Exercise tolerance increased in the training group compared to the control group. Fasting insulin remained unchanged after training, while in the control group this significantly increased. There were no changes in body composition between the groups, but fat free mass increased and fat percentage tended to decrease after training.

### *Glucose tolerance*

In the present observational cohort study, the oral glucose tolerance test (OGTT) detected 12 patients (21%) with a normal glucose regulation, 22 patients (39%) were pre – diabetic and 23 patients (40%) were diabetic. This means that 79% of the study population had an impaired glucose tolerance. Egstrup et al. found a much lower prevalence of newly diagnosed pre – diabetes (23%) and diabetes (18%) in patients with heart failure. This could be due to the criteria for glucometabolic classification of the World Health Organization, which are more severe than those of the American Diabetes association (ADA) [9].

Other possible explanations for an impaired glucose tolerance are body mass index, smoking and physical activity in daily life that contribute to insulin sensitivity according the study of Sabelis et al [14]. Further research is needed to determine prevalence and explanatory factors for impaired glucose tolerance in patients with chronic heart failure.

The training study showed that, after a combined aerobic endurance and resistance training program, fasting insulin and fasting HOMA – IR remained stable while fasting insulin and fasting HOMA in the control group significantly increased. However, there were no significant changes in glucose after 12 weeks of training. Previous studies presented conflicting results on glucose tolerance after combined exercise training. One study reported a similar result as a decrease of fasting insulin and HOMA – IR after 3 weeks of endurance training. However, no randomization was performed and results were not compared to a control group [17]. Prescott et al. showed no significant changes in serological markers of glycemic control after 8 weeks of combined exercise training [19]. But, after 14 months of combined exercise training fasting glucose increased less in the exercise group [18]. Only Kemppainen et al. demonstrated a positive effect of 23% and 25% in whole body insulin-mediated glucose uptake after combined exercise training for 5 months. However in comparison with the control group there was no significant change [15, 16]. Further research is needed to determine the effect of combined exercise training on impaired glucose tolerance in patients with chronic heart failure.

*Muscle strength*

The total work and average power during isokinetic knee extension was significantly increased after training. Feiereisen et al. presented a similar result of 16% increase of total work in isokinetic knee extension endurance after 40 sessions of combined exercise training [23]. Another study showed that a combined training program of 6 months, at a frequency of 4 times/week, improved isokinetic leg muscle variables. Overall upper leg muscle function improved with 13%, but in comparison with the present study results in knee flexion were more significant than results in knee extension [24]. According to these results we can conclude that isokinetic muscle endurance improves after a combined training program for patients with chronic heart failure.

*Exercise tolerance*

Peak $VO_2$ increased in the training group compared to the control group after training intervention. The training group showed also an increase of $VO_2$ at 2nd ventilatory threshold compared to the control group. In comparison with Piepoli et al., who described a mean improvement in $VO_2$ peak of 20% after exercise training, the training response in this study was not very high [25]. In one study, patients with chronic heart failure even reached an increase of 27% in $VO_2$ peak. This could be due to a difference in study duration. The training period consisted of 5 months, 2 months more than ours [16]. Another possible explanation could be a different study population. The fact that our patients differ in age, severity of heart failure or that they are clinically stable for already 3 months can make a difference in results.

*Clinical implications*

It can be stated that a lot of people have undiagnosed impaired glucose tolerance. The task of health care professionals is to show they are pre – diabetic or diabetic with the oral glucose tolerance test in order to optimize therapy. The present study shows that a combined exercise training program is important in the rehabilitation of CHF patients. An increase in muscular strength endurance and exercise tolerance may lead to improvements in activities of daily life. Further research about an effective training program that improves glucose tolerance in patients with chronic heart failure is important.

*Limitations*

The exclusion rate in the study was high. This resulted in a small sample size and unbalanced groups. Furthermore, the golden standard to estimate insulin resistance is the euglycemic clamp test [26]. However, this test is more expensive and maybe too dangerous in a population of chronic heart failure because of the intravenous catheterization. Due to this reasons, the OGTT was chosen as the appropriate alternative [27]. Although, the training period of 12 weeks might not be very long, there is no consensus about the duration of the exercise program.

## Conclusion

The prevalence of impaired glucose tolerance in people with chronic heart failure is alarming. The most logical treatment is an increase in physical activity. Our data have shown that a combined aerobic endurance and resistance training program increased exercise tolerance and isokinetic muscle endurance in patients with chronic heart failure who were stable for three months. It stabilized fasting insulin and fasting HOMA – IR. However the effect of training on glucose tolerance remains unclear. Further research is necessary to conclude whether a combined aerobic endurance and resistance training program inhibits impaired glucose tolerance in patients with CHF.

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## Appendix

The guidelines for authors for publication of the European journal of cardiovascular Prevention & rehabilitation

The text should be double-spaced throughout and with a minimum of 3cm for left and right hand margins and 5cm at head and foot. Text should be standard 10 or 12 point. Number pages consecutively, beginning with the title page. All original papers must be arranged in sections under the headings and in the order indicated below (begin each on a separate page):

- Title page
    - The title page should carry the full title of the paper, consisting of no more than 20 words (only common abbreviations should be used if absolutely necessary); titles should be clear and brief, conveying the message of the paper.
    - All author's names: the full first name, middle name/initial (optional) and last name of each author should appear; if the work is to be attributed to a department or institution, its full name and location should be included. Persons listed as authors should be those who substantially contributed to the study's conception, design, and performance.
    - The affiliations of all the authors; when authors are affiliated to more than one institution, their names should be connected usinga,b,c. These letters should follow the surname but precede the address; they should be used only for the second and subsequent addresses.
    - Information about previous presentations of the whole or part of the work presented in the article.
    - The sources of any support, for all authors, for the work in the form of grants, equipment, drugs, or any combination of these.
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    - The name and address of the author responsible for correspondence concerning the manuscript, and the name and address of the author to whom requests for reprints should be made. If reprints are not to be made available, a statement to this effect should be included.
    - The peer-review process as well as publication will be delayed if you do not provide up to date e-mail address, telephone and fax numbers.
    - Wordcount: please list full wordcount (including references).

- **Structured abstract**

  The second page should carry an abstract not exceeding 250 words and should include sections on Background, Design, Methods, Results and Conclusions. Please list abstract wordcount at the end of the abstract.

- **Keywords**

  The abstract should be followed by a list of 3-10 keywords which will assist the cross- indexing of the article and will be published. The terms used should be from the Medical Subject Headings list of the Index Medicus.

- **Suggest Reviewers**

  It is desirable to indicate about 3 reviewers which would have a sufficient area of expertise to review your submission. Whilst this is not mandatory, it will help Editors and shorten period of your manuscript review.

- **Text**

  Full papers of an experimental or observational nature should be divided into sections headed Introduction, Methods, Results and Discussion.

  Use of abbreviations should be kept to an absolute minimum; abbreviations and abbreviated phrases should be written out at first mention followed by the abbreviation in parentheses. Avoid those not accepted by international bodies. Systéme International (SI) units should be used where appropriate.

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