# ABSTRACT

**Background:** The prevalence of type 2 diabetes (T2D) is positively associated with aging and its severity increases over time. Exercise training is a cornerstone in T2D management, considered the best non-pharmacological treatment to prevent and postpone T2D development. However, few studies have examined the long-term effect of aerobic exercise at different intensities in order to improve glucose metabolism in elderly.

**Objectives:** To investigate the most effective training intervention for glucose metabolism in a general older population. Furthermore, to examine the effect of aerobic exercise at different intensities in a sub-group of older adults with impaired fasting glucose (IFG, ≥5.6mmol/L or >100mg/dL).

**Methods:** In total, 179 men and 200 women (70-74 years) were recruited and randomly located into a control group or one of the two training groups: moderate-intensity (MIT) or high-intensity (HIT). Both training groups exercised twice a week but at different intensities (70% and 90% of peak heart rate for MIT and HIT, respectively). Changes after 3 years in fasting glucose (FG), long-term glucose ($HbA_{1C}$) and health-related variables were measured.

**Results:** Three years of intervention did not change FG in the general population. It was however reduced in IFG control and HIT subgroups (-3.9% and -5.3% respectively, $P \leq 0.05$). $HbA_{1C}$ was ameliorated in both the general population (3.0%, 3.4% and 3.1% respectively) and IFG participants (2.8%, 2.7% and 1.9% respectively). Peak oxygen uptake ($VO_{2peak}$) was increased within-HIT group in both the general population (4.8%) and IFG participants (10.6%)

**Conclusion:** In the general population, three years of exercise did not have an effect in FG, but a significant reduction in $HbA_{1C}$ was found in all three intervention groups. Importantly, among IFG participants, both control and HIT decreased FG levels, while $HbA_{1C}$ was reduced in all intervention groups. Our data shows that HIT should be implemented as part of the treatment strategies in older adults with IFG.

# Table of contents


Abstract..... 3
Introduction..... 7
$HbA_{1C}$..... 7
Fasting glucose..... 9
Other health-related variables..... 10
HIT vs. MIT as a borderline for medicine..... 11
Methods..... 14
Design..... 14
Participants..... 14
Training intervention..... 15
Clinical assessment..... 16
Exercise test..... 16
Data analysis..... 18
Results..... 20
Participants..... 20
Descriptive characteristics on baseline data..... 21
Training adherence..... 21
Impaired fasting glucose participants..... 22
Effect of exercise on different variables..... 23
Health-related variables and blood markers..... 23
$HbA_{1C}$ and fasting glucose..... 24
Impaired fasting glucose participants..... 26
Health-related variables and blood markers..... 26
$HbA_{1C}$ and fasting glucose..... 26
Discussion..... 29
Exercise influence on glucose metabolism..... 29
$HbA_{1C}$..... 29
Fasting glucose..... 31
Anthropometry..... 33
Exercise capacity..... 34
Limitations..... 38
Conclusion..... 40
Acknowledgements..... 42
Attachments..... 44
References..... 48

## INTRODUCTION

Type 2 diabetes (T2D) is a condition characterized by progressive insulin secretory defect due to insulin resistance [1]. It substantially increases the risk of micro- and macro- vascular diseases, with cardiovascular disease (CVD) being the major cause of morbidity and mortality among these patients [2-4]. The International Diabetes Federation (IDF) has estimated that around 415 million people worldwide live with diabetes [5]. The T2D prevalence was estimated in ca. 12% for males and females over 70 years old in 2000, and it is predicted to increase over 120-140 million between 2000 and 2030 [6].

Patients with diabetes are much more likely to develop coronary heart disease (CHD) than their healthy counterparts (incidence rate 30.9 vs. 12.4, 95% of confidence interval, CI) [7]. Especially elderly have a uniquely elevated risk of mortality [8]. The prevalence of risk factors for macro-vascular disease such as hypertension is 2 to 4 times more common in elderly with T2D [9].

Exercise training is found to improve glycaemic control [8-10]. It also seems to have the potential to reduce blood pressure and cholesterol in T2D individuals [10, 11]. As secondary measures related to T2D, training itself has demonstrated to lower additional clinical risk factors such as body mass index (BMI) or waist circumference (WC) [12, 13].

Regular physical activity is associated with higher levels of physical fitness and a reduced risk of CHD [14, 15]. Peak exercise oxygen consumption ($VO_{2peak}$) is an accurate and reliable method for determining exercise capacity [13], and T2D is associated with impaired exercise capacity [16]. Of particular importance is the consistent observation that people with diabetes have decreased physical fitness as measured by $VO_{2peak}$ [17, 18]. Physical activity (PA) is thus a key element in the prevention and management of T2D, along with diet and medication [19].

### $HbA_{1C}$

The Standards of Medical Care in Diabetes (2015) established the criteria for diabetes diagnose in $HbA_{1C} \geq 6.5\%$ for hyperglycaemic patients [20]. The mechanism behind T2D is based on a dysregulation in glycaemic control [21]. It is considered as one of the biggest risk factors as it accounts for worsening on CHD, CVD and total mortality when increased levels are observed [22]. $HbA_{1C}$ is closely linked to prognosis in

stroke survivors or determining levels of physical fitness as well as other traditional cardiovascular risk factors [15, 16].

There is growing evidence about the effects of exercise on glycaemic control on glucose metabolism. Several types of exercises, including different types of intensity, are indeed being considered [23-25]. Literature on T2D patients have shown that high-intensity training (HIT) or short interval training have yielded greater benefits than moderate exercise (MIT), especially focusing on glucose control and other risk factors such as blood lipids, blood pressure and fat mass, among others [23-26].

The meta-analysis by Snowling et al. about the effect of exercise training on glucose control and T2D risk factors matched the improvements seen in $HbA_{1C}$ with those which can be provoked by diet, drugs or insulin [23]. Indeed, the 0.6% reduction in $HbA_{1C}$ after aerobic exercise is similar to that experienced by drug monotherapy (0.5-1.5% decrease), following the meta-analysis by Chudyk et al. [24].

Regarding the duration of the training, a review by Thomas et al. reported that those studies lasting less than 3 months involved a decrease in $HbA_{1C}$ of -0.8% (95% CI, $P \leq 0.05$), whereas those who were carried out for less than 6 months showed a decrease of -0.7% in the same glucose parameter (95% CI, $P \leq 0.05$) [26]. In the critical analysis developed by Aguilera-Equía et al., however, $HbA_{1C}$ did experience no change after 12 weeks of HIT in 15 T2D adults (55-75 years) [27].

A study in 18 T2D male (50-70 years) by Eriksen et al. confirmed 3 sessions of 10min daily to be preferable than only one session in order to improve fasting glucose (FG, 3.3% vs. -9.6% respectively, $P \leq 0.05$) [28]. Clearly, the results in the literature are inconsistent when it comes to the best intensity and duration of exercise training on glucose metabolism, and long-term interventions in older adults are lacking.

Additionally, high-intensity progressive resistance training has shown to be effective in reducing $HbA_{1C}$ in elderly (60-80 years) with T2D [29]. They performed either a high-intensity intervention combined with weight loss program or only a weight loss program. $HbA_{1C}$ was significantly more reduced in the first group. Despite of these investigations, recent research affirms to exist no significant differences between HIT and MIT when measured in reference to $HbA_{1C}$ [27]. Furthermore, self-monitoring of fasting glucose along with a healthy diet was positively associated with changes on

glycaemic control, according to a prospective observational study by Houle et al. [30]. All considered, a reduction on $HbA_{1C}$ accounts for a decreased risk of diabetic complications, and hence its importance of being lowered [30].

**Fasting glucose**

Impaired fasting glucose (IFG) is referred as high fasting glucose in diabetes patients, also known as impaired glucose tolerance (IGT) [5]. Diabetes disease with regard to fasting glucose is diagnosed at ≥ 126mg/dl (7.0mmol/L) [25]. Impaired fasting glucose has been identified as > 100mg/dl (5.6mmol/L) [20].

Beneficial adaptations as a result of three different exercise modes (aerobic, resistance and combined training) have been reported as concomitants to enhanced fasting glucose, according to the study by Snowling & Hopkins [23]. These have also been associated to improvements seen on $HbA_{1C}$, and combined training seemed to have been the most favourable training modality in both variables ($HbA_{1C}$ and FG) [23].

Other studies, as the one carried out by Dunstan et al., reported no changes on FG in 36 T2D overweight adults (60-76 years), after having followed either a high-intensity progressive resistance training plus moderate weight loss or a weight loss program plus a control program; yet a modest decrease of 1.4mmol/L after three months was observed [29].

Fasting glucose has been shown to be influenced by exercise [31, 32]. Oppositely, detraining has been responsible for reversing the benefits obtained by a 9-month program based on strength and aerobic training (AT), according to the study by Tokmakidis et al. [33]. It was also found to decrease thanks to exercise training from pre- to post-test in 13 T2D women (-12.0%, 95% CI). Furthermore, following the same study, the resumption of training resulted in a moderate decrease as well for fasting glucose (-9.5%, 95% CI), which supports the beneficial adaptations as a product of retraining [33].

Generally, aerobic exercise has resulted in remarkable reductions in fasting glucose regardless of its intensity [32]; however, in both metabolic syndrome and T2D patients, HIT has induced major improvements [34]. In this same line are the findings of Healy et al., who concluded that increased breaks in sedentary time were positively associated with fasting glucose, among others [35].

Fasting glucose has plus been seeing as strongly associated with both risks of CVD and death from any cause [36]. Indeed, an exponential relationship between fasting glucose and the incidence of CVD events has been observed in the past scientific literature, and therefore the potential importance of stabilizing glucose metabolism [31].

**Other health-related variables**

There is consistent evidence that high cardiorespiratory capacity is directly correlated with improvements on glycaemic control and other parameters associated with diabetes development, such as lipid profile [22, 37, 38]. Cardiorespiratory fitness (CRF) indeed has been shown to be the single best predictor for premature death [39]. At the same time, low cardiorespiratory fitness is associated with impaired insulin sensitivity and hence prone to worsen both insulin resistance syndrome (IRS) and T2D, according to a study by Leite et al. [40]. A low $VO_{2peak}$ is found to be associated with high $HbA_{1C}$ ($r = -0.33$) as well as high FG ($r = -0.34$) [41].

$VO_{2peak}$ has been found to be lower in T2D individuals when compared to overweight counterparts ($15.4 \pm 2.5$ml/kg/min vs. $17.8 \pm 3$ml/kg/min respectively, $P \leq 0.05$) [18]. Although regular exercise most often increases $VO_{2peak}$, the optimal volume and intensity in older adults is still motive of debate. In a study designed by Grelier et al. twelve T2D patients performed a three-month exercise program combining both aerobic and resistance training two times per week [42]. Results showed $VO_{2peak}$ to remain unchanged after the training intervention. These results are in line with those of Middlebrooke et al., who found no significant improvement of $VO_{2peak}$ after a 6-month aerobic exercise program on T2D patients with good glycaemic control [43].

Regarding body composition, an investigation by Eeg-Olofsson et al. detected progressively higher risks for both fatal and nonfatal CHD and CVD on T2D patients at higher BMI levels were presented ($\geq 18.5$ kg/m$^2$) [44]. Though most patients with T2D present a BMI > 25, more than the half are obese (> 30) [45], and thus have an increased amount of intra-abdominal fat. In these terms, waist circumference (WC) seems to be considered a stronger predictor than both BMI and hip-to-waist ratio (WHR), taking into account that intra-abdominal fat constitutes a greater risk factor for T2D than overall adiposity [46, 47].

There is a strong association between measures reflecting abdominal obesity and the development of T2D, and hence reducing WC may reduce its progression [48]. Furthermore, individuals with higher WC are more likely to have diabetes and CVD compared with those with normal WC [47].

For the important role of exercise and PA in weight loss and maintenance, the literature is clear that caloric restriction accompanied by a certain amount of AT would induce an increased weight loss rather than AT alone [49]. However, programs of PA generally may only experience modest weight loss (< 2kg), according to Swift et al. [50].

A significant direct association was linked to a substantial decrease in the visceral fat content of 42 T2D patients [49]. Also, MIT has resulted in pronounced changes on visceral fat content, known to be linked to CVD risk [51]. This, however, did not alter cardiac function, as seen in this clinical intervention by Jonker et al. [51].

**HIT vs. MIT as borderline for medicine**

It has always aroused a great interest to the scientific world whether one specific training or intensity is the most adequate in order to develop the greatest benefits on health. Specifically, in T2D, the findings tend to be diverse.

However, regarding HIT, effectively improved cardiac function in T2D patients reporting diastolic dysfunction, according to a randomized controlled trial (RCT) by Hollekim-Strand et al. [52]. 4x4 interval training induced major benefits than did MIT after 12 weeks of supervised exercise on different measures such as improved diastolic and systolic function, decreased $HbA_{1C}$ and enhanced $VO_{2peak}$ in this study, among others [52].

Despite of these findings, a study carried out by Taylor et al. discovered that similar improvements matched for physical fitness and physical function in people with T2D [53]. It is worth mentioning though that HIT performed resistance training at an intensity of 100% of the 8 maximum repetitions (RM) along with endurance at 50-65% of their resting heart rate [53]. This hence should be looked into in order to disassociate endurance training from resistance training responses on T2D patients.

Regarding pre-diabetic individuals, a study by Rynders & Weltman concluded that it should be more looked into the duration of the exercise programme, since it has been

mentioned the “lack of time” to exercise in this population [54]. HIT has, in this study, been considered a time-efficient alternative when limited time is presented, as well as a tool for improving CVD risk factors [54].

As for $HbA_{1C}$, Terada et al. compared the feasibility of 12-week structured HIT vs. moderate-intensity continuous exercise on 15 individuals with T2D, resulting both to have little impact on $HbA_{1C}$ [55]. However, the small sample size must be considered here. Also, in a study carried out by Villa-Caballero et al., 33 subjects were screened to show decreased levels of $HbA_{1C}$ following HIT ($\geq$ 85% $VO_{2peak}$) on a treadmill, in comparison with non-diabetic individuals and sedentary T2D patients (7.3% vs. 5.1% and 8.7%, respectively) [56].

Furthermore, in a study by Marcus et al., it was found out that aerobic exercise training combined with eccentric resistance exercise on a stepper reported major benefits than aerobic exercise isolated on $HbA_{1C}$ levels in 15 T2D patients (-0.6% vs. -0.3%) [57]. This might be explained by mitochondrial adaptations and a higher basal metabolic rate following resistance training, which all together result in potentially greater absolute glucose uptake. Also glucose metabolism was shown to improve given the force-producing characteristics of eccentric training.

In a study by Hansen et al. HIT was found to produce greater changes than MIT on all BMI, body weight, $HbA_{1C}$ and $VO_{2peak}$ as expressed in ml/kg/min/, among many others, in 50 male T2D patients (BMI 32 ± 4kg/$m^2$) [58]. Interval training, indeed, supports major benefits over general lipid profile (low- and high-density lipoproteins as well as triglycerides), as observed in a RCT by Earnest et al. [59].

The primary aim of the present study was to evaluate the effect of three years of aerobic exercise, with different intensities, in fasting glucose and long-term glucose ($HbA_{1C}$) in older adults. Further, to examine the effect of aerobic exercise at different intensities in a sub-group of older adults with impaired fasting glucose. Our hypothesis is that participants performing HIT will have a larger reduction in both fasting glucose and $HbA_{1C}$ when compared to MIT and control, in both the general population and in people with impaired fasting glucose.

## Methods

### *Design*

This project is a study of a larger randomized controlled trial looking at the effect of five-years of training on both morbidity and mortality in older adults [60]. It is known as 'Generasjon100' and it is conducted by the scientific group Cardiac Exercise Research Group at the Faculty of Medicine, Norwegian University of Science and Technology. All tests are performed at St. Olav's Hospital in Trondheim, Norway.

Participants involved in 'Generasjon100' were randomized 'a priori' into two training groups (moderate- or high-intensity) or a control group.

The aim of this study is to look at the effect of different intensities of exercise on fasting glucose and $HbA_{1C}$ in older adults. Secondary, it is to be examined the effect on other health-related variables such as peak oxygen uptake or blood markers variables. It was originally approved by the Regional Ethical Committee (REK) on February 2016 (**Attachment 1**).

### *Participants*

The general inclusion and exclusion criteria for 'Generasjon100' (and this study) are presented in **Table 1**. In total, 405 participants (200 women) came in for three years testing between August 2015 till and through February 2016, and were thus included in the present study. However, 5 participants started taking medication for diabetes during the study, hence being excluded from the analysis of the present study. Additionally, 21 participants were excluded in the analysis as they did not remain in fasting state for equal to or longer than 8 hours.

**Table 1.** Inclusion and exclusion criteria.

| | |
|---|---|
| **INCLUSION CRITERIA** | - Born in 1936 – 1942<br>- Capable of walking 1km at least<br>- Good health status in order to partake in this study (as measured by researchers and medical staff) |
| **EXCLUSION CRITERIA** | - Medication administered from the 3rd year<br>- Fasting time less than 8 hours |

| | |
|---|---|
| | - Illness or disabilities that preclude exercise or hinder completion of the study<br>- Uncontrolled hypertension<br>- Symptomatic valvular, hypertrophic cardiomyopathy, unstable angina, primary pulmonary hypertension, heart failure or severe arrhythmia<br>- Diagnosed dementia<br>- Cancer that makes participation impossible or exercise contraindicated. Considered individually, in consultation with physician<br>- Chronic communicable infectious diseases<br>- Test results indicating that study participation is unsafe<br>- Participation in other studies conflicting with participation in Generation 100. |

***Training intervention***

Participants were previously randomized into three different intervention groups:

1. *Control group* was encouraged to follow current recommendations for physical activity in Norway ('Helsedirektoratet. Folkehelse: Fysisk aktivitet: Anbefalinger', 2011), which was 30 min of moderate-level physical activity every day. No further supervision was determined.

2. *Moderate-intensity (MIT) group* followed an exercise routine of ca. 50 minutes of moderate intensity 2 times per week. The intensity was set to 70% of their peak heart rate ($HR_{peak}$) or the equivalent to 13 (capable of talking frame) on the Borg scale of perceived exertion (**Attachment 2**) throughout the whole training.

3. *High-intensity (HIT) group* started with a 10 minutes warm-up period, followed by 4 intervals lasting 4 minutes each and 3 active breaks of 3 minutes each between intervals. A cool-down for 5 minutes completed the session. They also exercised two times per week. The training intensity was 85-95% of the relative $HR_{peak}$ or its equivalent on the Borg scale of 16 for the intervals. The active breaks were performed under 60-70% of each participant's $HR_{peak}$ or 12 on the Borg scale.

***Clinical assessment***

Clinical testing was performed at baseline (2012/2013) and after three years intervention (2015).

Previous to the first screening, participants were advised to remain in fasting state and avoid exercise training along with any substance which includes nicotine, caffeine or alcohol twelve hours before testing.

Height and waist circumference (WC) were measured, along with body weight (kg) and body composition (BMI, muscle and visceral mass and fat percentage). For the latest, bioelectrical impedance was used (Inbody 720, BIOSPACE©, South Korea). Participants using pacemakers were excluded from the test. Demographic characteristics such as height, age and gender were plotted on the scale.

Blood samples were obtained using current procedures from St. Olav's Hospital in Trondheim. Serum triglycerides, HDL (high-density lipoproteins), hs-CRP (high-sensitivity C-reactive protein), $HbA_{1C}$ (glycosylated haemoglobin), glucose and total cholesterol were included as part of the analysis. A fasting glucose ≥5.6mmol/L was used in order to categorize people with IFG [20].

For taking blood pressure and resting heart rate, a Phillips IntelliVue MP50 monitor data was used (Boeblingen©, Germany). Two measurements were performed in the right arm, with one minute break between each measurement. If systolic blood pressure differed ≥10mmHg or diastolic blood pressure differed ≥6 mmHg, an additional third measurement was taken. The average of the two last measurements was used as mean blood pressure.

***Exercise test***

All participants were asked to refrain from alcohol, caffeine or nicotine at the test day.

A cardiopulmonary exercise testing (CPET) was implemented. Data collection has involved the manipulation of different laboratory instruments such as treadmills Woodway as well as ergometers Monarch. The software used has been in most occasions MetaSoft 1 and MetaSoft 3 (Cortex Biophysik GmbH©, Germany), as well as Custo Diagnostic (Custo med GmbH©, Germany) in order to test participants suffering from heart disease.

All participants with history of heart disease were evaluated under ECG (electrocardiogram) monitor, and the ACCF/AHA guidelines (American College of Cardiology Foundation/American Heart Association) were followed in order to assess the scope of the disease [61]. Participants were tested on the same gas analyzer at baseline and after three years. Volume was calibrated right after every single test, and gas analyzer was performed after every 4th participant. Heart rate monitors were fastened to the participant right before starting the 10min warm-up (Polar Electro©, Finland). Most participants were assigned to perform the warm-up on a treadmill; however, due to several conditions, some of them preferred the bike in order to carry out the exercise (n = 6). The warm up period was performed under an individually submaximal level (corresponding to moderate intensity, 60-70% of their $VO_{2peak}$), and its workload was depending on a series of characteristics: 1) history of self-reported physical activity levels (PALs), 2) heart rate assessment, 3) feedback from the participant on the perceived effort, using a Borg scale. After the warm-up period, participants put on a facemask (Hans Rudolph©, Germany) that was connected to a mixing chambers gar-analyzer in order to capture the gases exchange parameters.

The following variables were recorded during the test: heart rate, oxygen uptake, ventilation, inclination of the treadmill, speed for the treadmill (or watts if tested on bicycle), respiratory exchange ratio (RER) and perceived exertion using the Borg scale. After four minutes of submaximal work, speed or inclination was gradually

increased (1km/h or 2% respectively, 10 watts/30 sec. on the bike) until exhaustion or when $VO_{2peak}$ was reached.

A maximal test was reached when $VO_2$ was not increased by 2mL/kg/min (between 30 second epochs) despite an increase in workload, in addition to achieving a RER value of ≤1.05. The gas analyzer reported the variables every 10 second. $VO_{2peak}$ was assessed by taking the average of the last three highest consecutive values. However, peak RER was the highest among the RER values, corresponding to the same three highest $VO_{2peak}$ values. Peak heart rate was the highest obtained in the test. In total, 211 participants reached a valid $VO_{2max}$ value, whereas 150 of them were reported to reach their $VO_{2peak}$ and 18 participants were not recorded; that is, 55.7% of the participants did not reach a true maximal value and hence they have been categorized under the $VO_{2peak}$ classification. Also, heart rate recovery (HRR) was taken after 1 minute passed since the participant completed the test.

A questionnaire including multiple health and lifestyle dimensions was distributed among the participants. The questionnaire included 21 health-related questions including information about history of heart disease (i.e., angina pectoris, heart failure, and myocardial infarction) or stroke haemorrhage, among others.

***Data analysis***

The software used for all the data analysis was IBM SPSS Statistics 20 (SPSS Inc., USA). Paired sample t-tests were used in order to compare the results within groups. Analysis of covariance (ANCOVA) was used to determine differences between groups. Also, non-parametric tests were chosen for not normally distributed variables (as it happened with high-sensitivity C-reactive protein or hs-CRP). Confidence interval was set at 95%. Normality distribution was hence assessed against a normal curve on a histogram. A P-value of ≤ 0.05 was defined as statistically significant. Data is presented on the tables as mean ± standard deviation (SD). Also, data presented on the figures refer to the standard error (SE) of the mean values.

## RESULTS

### Participants

**Figure 1** shows the flowchart of participants from the baseline. A total of 1567 participants have been randomized into three groups: control, moderate-intensity training (MIT) and high-intensity training (HIT). From these, a total of 405 have been followed up in a three year period. After screening, 5 participants were excluded from the analysis given that they started on medication for treatment of type 2 diabetes (T2D) during the study. Additionally, 21 participants were excluded due to have not remained in fasting state for less than 8h. In total, 159 of them had a fasting glucose higher or equal to 5.6mmol/L (>100mg/dL).

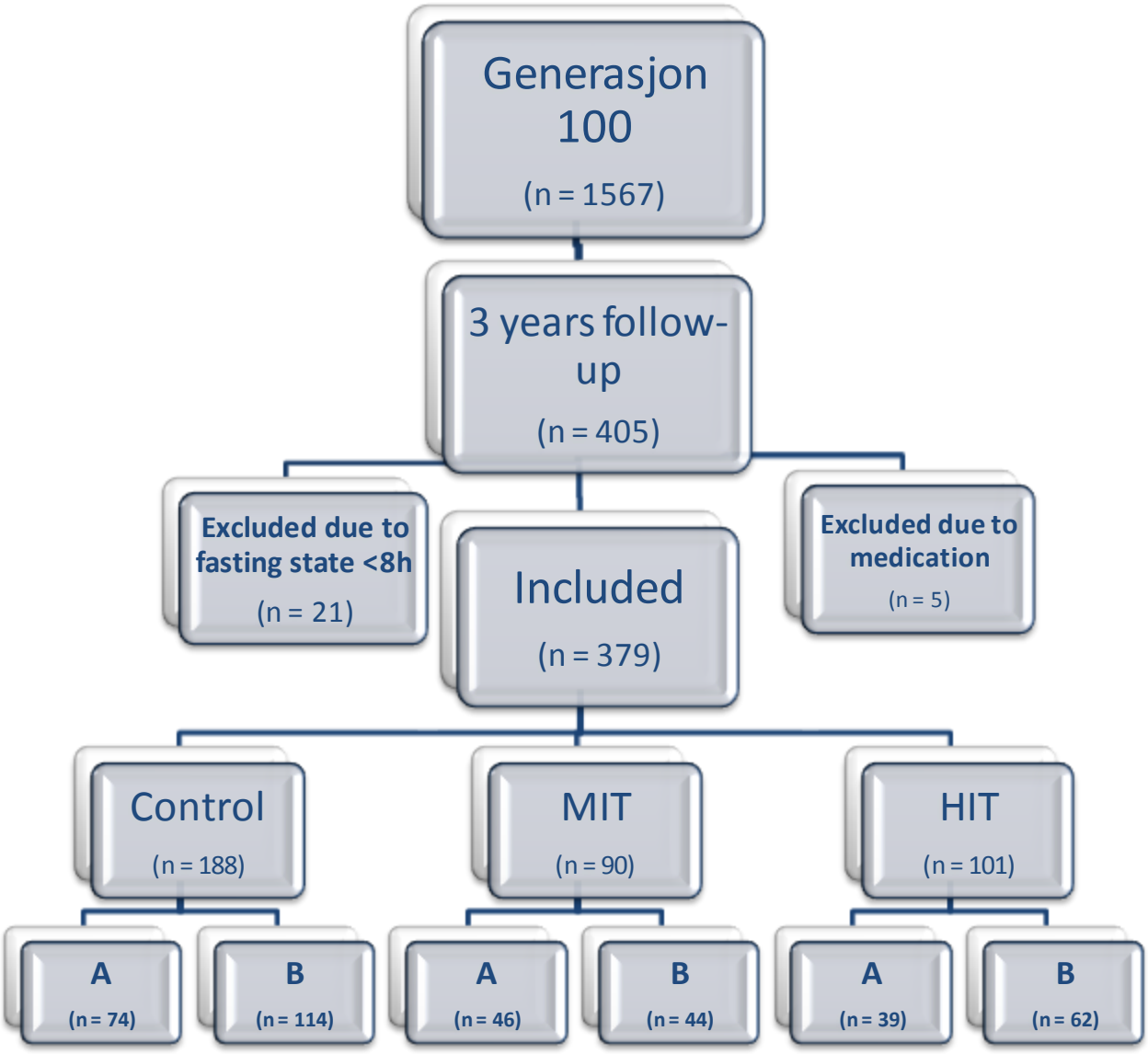


**Figure 1**. Flowchart of the participation. MIT = moderate-intensity training group, HIT = high-intensity training group, A = impaired fasting glucose individuals (≥5.6mmol/L or >100mg/dL), B = normal fasting glucose.

## Descriptive characteristics on baseline data

**Table 1** represents the baseline values for all the participants included in the analysis. There were no significant differences in any of the variables at baseline.

**Table 1**. Baseline data.

| | Control (n = 188) | MIT (n = 90) | HIT (n = 101) |
|---|---|---|---|
| | **Pre** | **Pre** | **Pre** |
| **Men/women** | 87/101 | 38/52 | 54/47 |
| **Age (years)** | 71.5 ± 1.3 | 71.4 ± 1.3 | 71.4 ± 1.4 |
| **Height (cm)** | 170.1 ± 8.7 | 169.1 ± 8.5 | 170.6 ± 7.6 |
| **Weight (kg)** | 73.5 ± 12.3 | 74.4 ± 11.7 | 73.9 ± 13.0 |
| **BMI (kg/m$^2$)** | 25.3 ± 3.2 | 26.0 ± 3.5 | 25.3 ± 3.2 |
| **Minerals (mg/L)** | 3.6 ± 0.7 | 3.6 ± 0.6 | 3.6 ± 0.6 |
| **SBT (mmHg)** | 134.4 ± 17.2 | 133.7 ± 17.8 | 133.1 ± 17.5 |
| **DBT (mmHg)** | 75.7 ± 9.2 | 75.5 ± 8.9 | 75.3 ± 8.8 |
| **History of diabetes (%)** | 8 ± 27.2 | 4 ± 20.7 | 6 ± 23.8 |
| **History of CVD (%)** | 5 ± 22.6 | 9 ± 28.8 | 4 ± 19.6 |

Data is presented as mean ± SD (standard deviation). MIT = moderate-intensity training group, HIT = high-intensity training group, n = number, BMI = body mass index, SBT = systolic blood pressure, DBT = diastolic blood pressure, CVD = cardiovascular diseases.

## Training adherence

**In total, 304 participants followed the prescribed intervention, 70 did not and 5 preferred not to answer:**

- **Control group:**
  - ✓ **167 did adhere to the established training program**
  - × **19 did not**
  - ? **2 did not answer**
- **Moderate-intensity training group:**
  - ✓ **76 did adhere to the established training program**
  - × **13 did not**
  - ? **1 did not answer**
- **High-intensity training group:**
  - ✓ **61 did adhere to the established training program**
  - × **38 did not**
  - ? **2 did not answer**

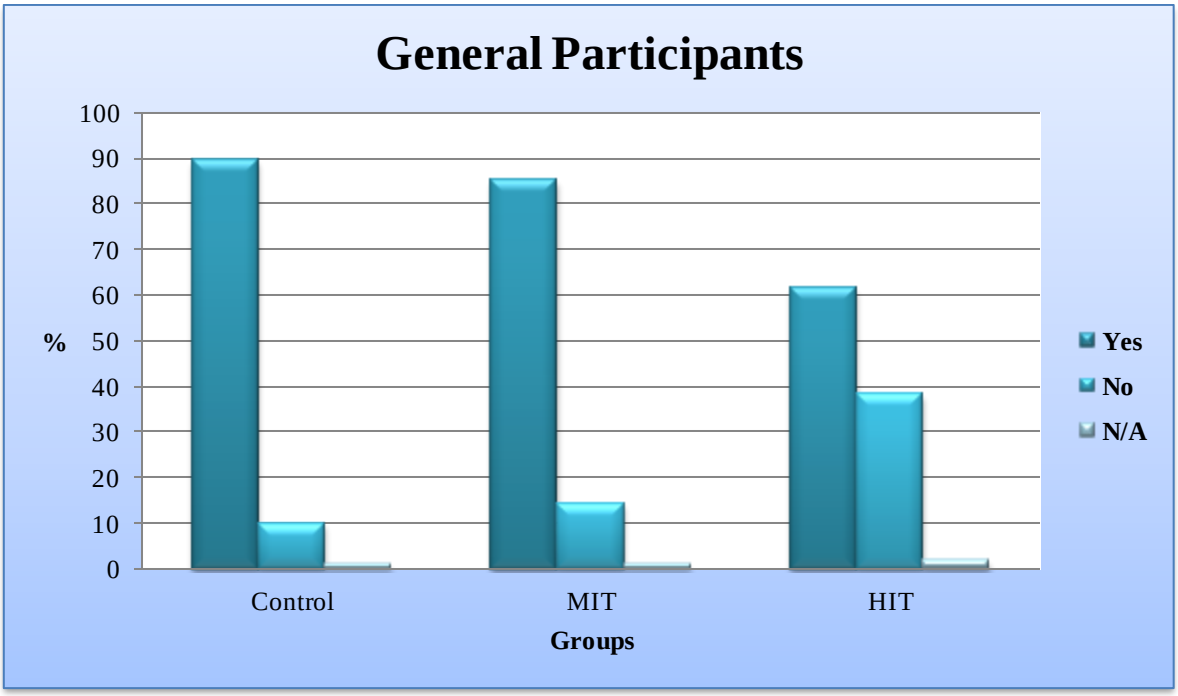


**Figure 2**. Participants' training adherence. % = percentage, MIT = moderate-intensity training group, HIT = high-intensity training group.

## Impaired fasting glucose participants

**With regards to the impaired fasting glucose participants, 133 did follow the prescribed intervention, 24 did not and 2 did not answer:**

- **Control group:**
  - ✓ **69 did adhere to the established training program**
  - × **5 did not**
- **Moderate-intensity training group:**
  - ✓ **40 did adhere to the established training program**
  - × **5 did not**
  - ? **1 did not answer**
- **High-intensity training group:**
  - ✓ **24 did adhere to the established training program**
  - × **14 did not**
  - ? **1 did not answer**

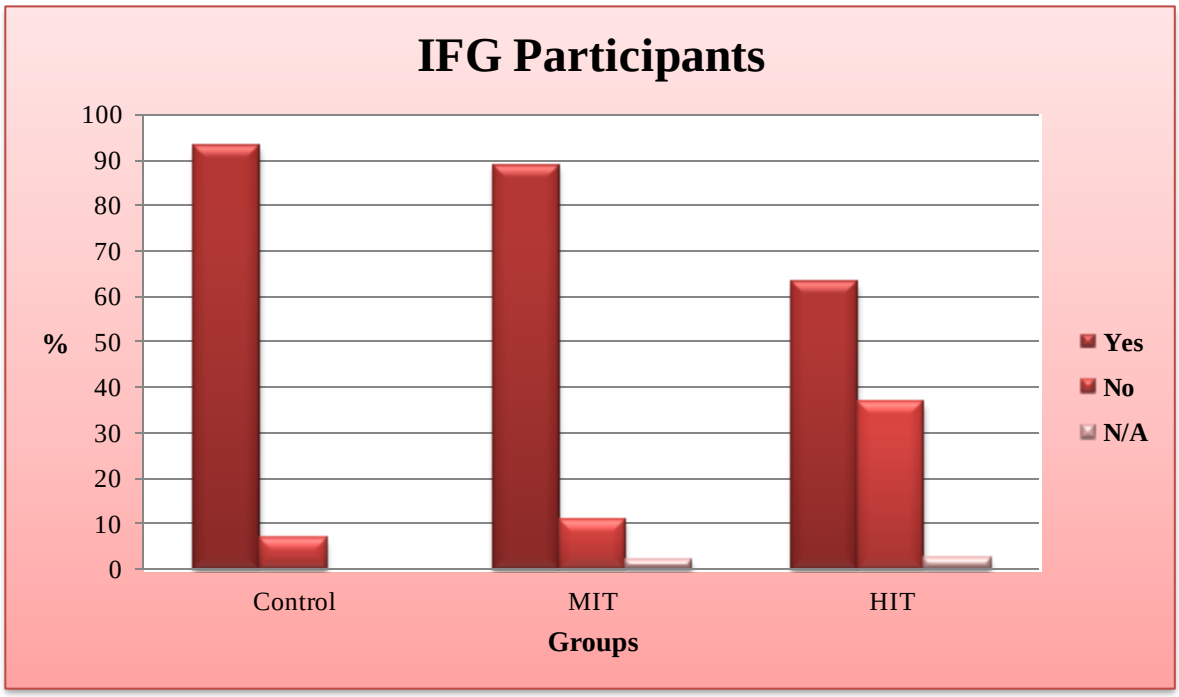


**Figure 3**. IFG participants' training adherence. IFG = impaired fasting glucose, % = percentage, MIT = moderate-intensity training group, HIT = high-intensity training group.

### Effect of exercise on different variables

#### *Health-related variables and blood markers*

**Table 2** below represents the effect of the different interventions on health-related variables and blood markers. The change perceived in weight was only significant within HIT (-1.1 ± 2.7kg, $P \leq 0.05$). $VO_{2peak}$ as measured in relative values was incremented by 2.1% for MIT and by 4.8% in HIT ($P \leq 0.05$). Muscle mass was most decreased in HIT (-0.7 ± 1.0kg, $P \leq 0.05$). Fat percentage was only incremented in control (3.4%, $P \leq 0.05$), whereas it got reduced in HIT (-3.6%, $P \leq 0.05$). However, visceral fat increased in both control and MIT (4.6% and 3.8% respectively, $P \leq 0.05$). With regard to blood markers, high-sensitivity C-reactive protein (hs-CRP) was only decreased in HIT (-0.93 ± 2.08mg/L, $P \leq 0.05$). High-density lipoproteins (HDL) increased in HIT (3.0%, $P \leq 0.05$). Triglycerides (TGs) were reduced in all three intervention groups (-11.4%, -10.3% and -13.3% respectively for control, MIT and HIT, $P \leq 0.05$). Haemoglobin (HB) did only decrease in control and HIT (-0.16 ± 0.54mmol/L and -0.31 ± 0.65mmol/L respectively, $P \leq 0.05$).

**Table 2**. Differences between the intervention groups in health-related variables and blood markers.

| | Control (n = 188) | | MIT (n = 90) | | HIT (n = 101) | |
|---|---|---|---|---|---|---|
| | **Pre** | **Post** | **Pre** | **Post** | **Pre** | **Post** |
| **Weight (kg)** | 73.5 ± 12.3 | 73.6 ± 12.0 | 74.4 ± 11.7 | 74.3 ± 11.5 | 73.9 ± 13.0 | 72.8 ± 12.2$^{*\dagger\S}$ |
| **$VO_{2peak}$ (L/min)** | 2.2 ± 0.6 | 2.2 ± 0.7 | 2.2 ± 0.6 | 2.3 ± 0.7 | 2.3 ± 0.6 | 2.4 ± 0.7$^{*\dagger}$ |
| **$VO_{2peak}$ (ml/kg/min)** | 30.5 ± 6.7 | 30.2 ± 7.5 | 29.8 ± 6.9 | 30.5 ± 7.7 | 30.9 ± 6.7 | 32.4 ± 8.0$^{*\dagger}$ |
| **Muscle mass (kg)** | 28.4 ± 6.0 | 27.9 ± 5.7$^{*}$ | 28.5 ± 5.7 | 27.9 ± 5.5$^{*}$ | 29.1 ± 6.1 | 28.3 ± 5.7$^{*}$ |
| **Fat (%)** | 29.4 ± 8.1 | 30.4 ± 8.2$^{*}$ | 30.0 ± 8.5 | 30.8 ± 8.8$^{*}$ | 28.2 ± 7.2 | 28.7 ± 7.3 |
| **Visceral fat ($cm^2$)** | 107.5 ± 30.3 | 112.5 ± 30.4$^{*}$ | 110.5 ± 32.5 | 114.4 ± 34.1$^{*}$ | 105.4 ± 28.5 | 106.5 ± 28.2$^{\dagger}$ |
| **Waist (cm)** | 93.3 ± 10.2 | 93.6 ± 11.3 | 93.3 ± 10.4 | 93.6 ± 10.7 | 92.1 ± 10.5 | 91.0 ± 10.0$^{*\dagger}$ |
| **hs-CRP (mg/L)** | 2.15 ± 3.46 | 2.27 ± 6.17$^{*}$ | 2.37 ± 3.17 | 2.51 ± 5.72$^{*}$ | 2.16 ± 3.23 | 1.23 ± 1.14$^{*}$ |
| **HDL (mg/L)** | 1.82 ± 0.52 | 1.82 ± 0.54 | 1.79 ± 0.50 | 1.79 ± 0.47 | 1.79 ± 0.57 | 1.84 ± 0.56$^{*}$ |
| **LDL (mg/L)** | 3.59 ± 1.00 | 3.57 ± 0.98 | 3.39 ± 0.90 | 3.36 ± 0.87 | 3.49 ± 0.87 | 3.50 ± 0.96 |
| **TGs (mg/dL)** | 1.14 ± 0.56 | 1.01 ± 0.46$^{*}$ | 1.15 ± 0.51 | 1.03 ± 0.49$^{*}$ | 1.13 ± 0.51 | 0.98 ± 0.41$^{*}$ |
| **HB (mmol/L)** | 14.42 ± 1.04 | 14.25 ± 1.08$^{*}$ | 14.30 ± 0.98 | 14.20 ± 0.91 | 14.51 ± 1.07 | 14.20 ± 1.03$^{*}$ |

Data is presented as mean ± SD (standard deviation). MIT = moderate-intensity training group and HIT = high-intensity training group; n = number, $VO_{2peak}$ = peak oxygen consumption, hs-CRP = high-sensitivity C-reactive protein, HDL = high-density lipoproteins, LDL = low-density lipoproteins, TGs = triglycerides, HB = haemoglobin. *Significant differences within-group: $P \leq 0.05$. †Significant differences between HIT & control: $P \leq 0.05$. §Significant differences between HIT and MIT: $P \leq 0.05$.

### *$HbA_{1C}$ and Fasting Glucose*

**Table 3** shows the differences from baseline and after three years of intervention for both fasting glucose (FG) and long-term glucose ($HbA_{1C}$). Control, MIT and HIT managed to reduce their $HbA_{1C}$ levels significantly (3.0, 3.4 and 3.1% respectively, $P \leq 0.05$). There were no significant differences between any of the groups for both variables (FG and $HbA_{1C}$).

**Table 3**. Effect of a three-year intervention on glucose and long-term glucose.

| | Control (n = 188) | | MIT (n = 90) | | HIT (n = 101) | |
|---|---|---|---|---|---|---|
| | **Δ** | **CI** | **Δ** | **CI** | **Δ** | **CI** |
| **FG (mmol/L)** | -0.03 ± 0.54 | (-0.04, 0.11) | -0.03 ± 0.64 | (-0.10, 0.16) | -0.07 ± 0.64 | (-0.06, 0.20) |
| **$HbA_{1C}$ (mmol/L)** | -0.17 ± 0.19 | (0.14, 0.20)* | -0.19 ± 0.21 | (0.15, 0.24)* | -0.17 ± 0.19 | (0.13, 0.21)* |

Data is presented as mean ± SD (standard deviation). MIT = moderate-intensity training group, HIT = high-intensity training group; n = number, FG = fasting glucose, $HbA_{1C}$ = glycosylated hemoglobin, **Δ** = mean difference, CI = confidence interval. *Significant differences within-group: $P \leq 0.05$.

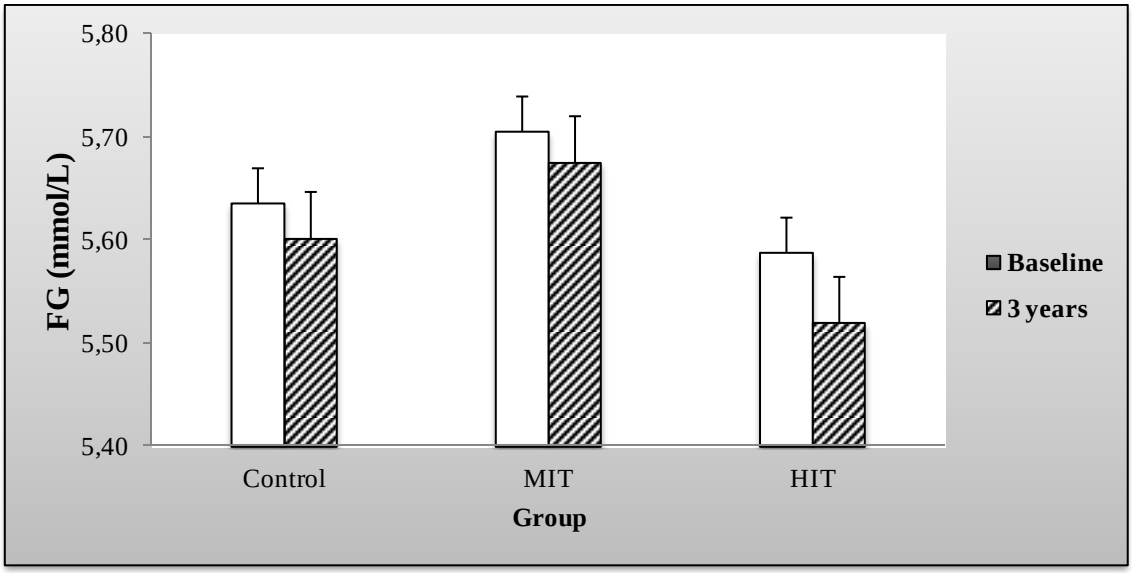


**Figure 4**. Differences in glucose from baseline and after three years of intervention. Error bars stand for the standard error of the mean value for both baseline and after three years. FG = fasting glucose, MIT = moderate-intensity training group, HIT = high-intensity training group.

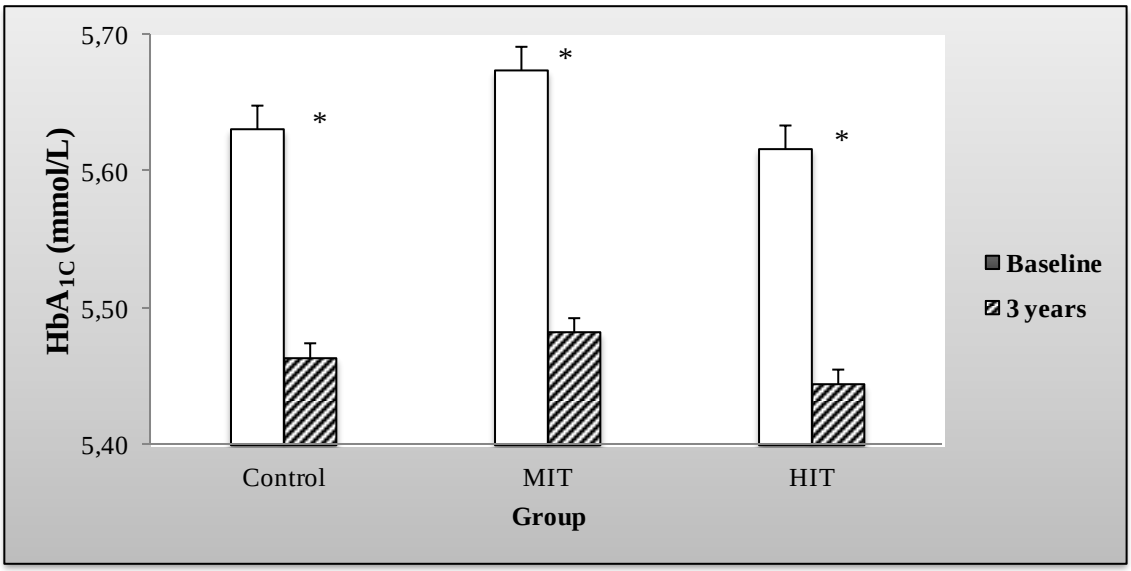


**Figure 5**. Differences in long-term glucose from baseline and after three years of intervention. Error bars stand for the standard error of the mean value for both baseline and after three years. $HbA_{1C}$ = glycosylated haemoglobin, MIT = moderate-intensity training group, HIT = high-intensity training group. *Significant differences within-group: $P \leq 0.05$.

***Impaired fasting glucose participants***

Health-related variables and blood markers

**Table 4** represents the effect of all interventions in health-related variables and blood markers for impaired fasting glucose (IFG) participants (≥5.6mmol/L or >100mg/dL). Weight only decreased significantly in HIT (-1.8%, $P \leq 0.05$). In addition, HIT increased $VO_{2peak}$ as expressed both per absolute values (L/min) and per relative values (ml/kg/min, 8.9 and 10.6% respectively, $P \leq 0.05$). The decrease in waist was found significant within-group in HIT (-1.7 ± 4.3kg, $P \leq 0.05$). Both fat percentage and visceral fat were significantly increased after 3 years in control (0.9 ± 3.3 and 4.7 ± 12.7$cm^2$ respectively, $P \leq 0.05$). Concerning blood markers, haemoglobin (HB) in HIT represented the major reduction as seen among IFG participants (-0.40 ± 0.66mmol/L, $P \leq 0.05$).

**Table 4**. Differences between the intervention groups in health-related variables and blood markers among IFG participants.

| | Control (n = 74) | | MIT (n = 46) | | HIT (n = 39) | |
|---|---|---|---|---|---|---|
| | **Pre** | **Post** | **Pre** | **Post** | **Pre** | **Post** |
| **Weight (kg)** | 77.6 ± 11.6 | 77.1 ± 11.3 | 76.3 ± 11.3 | 75.6 ± 11.0 | 80.1 ± 11.8 | 78.6 ± 11.0$^{*}$ |
| **$VO_{2peak}$ (L/min)** | 2.4 ± 0.6 | 2.4 ± 0.6 | 2.3 ± 0.6 | 2.4 ± 0.8 | 2.3 ± 0.6 | 2.5 ± 0.7$^{*\dagger}$ |
| **$VO_{2peak}$ (ml/kg/min)** | 31.2 ± 6.8 | 31.0 ± 7.2 | 30.5 ± 7.0 | 30.9 ± 9.0 | 28.7 ± 6.1 | 31.7 ± 8.1$^{*\dagger\S}$ |
| **Muscle mass (kg)** | 30.2 ± 5.9 | 29.4 ± 5.6$^{*}$ | 29.0 ± 5.6 | 28.3 ± 5.5$^{*}$ | 31.3 ± 5.5 | 30.4 ± 5.0$^{*}$ |
| **Fat (%)** | 29.5 ± 7.8 | 30.4 ± 8.1$^{*}$ | 30.7 ± 8.6 | 31.4 ± 8.8 | 29.2 ± 6.8 | 29.6 ± 7.2 |
| **Visceral fat ($cm^2$)** | 114.5 ± 28.5 | 119.2 ± 29.0$^{*}$ | 115.2 ± 31.5 | 118.5 ± 32.6 | 116.5 ± 27.9 | 116.8 ± 28.4 |
| **Waist (cm)** | 96.5 ± 10.0 | 97.2 ± 10.4 | 95.5 ± 9.0 | 94.8 ± 9.7 | 97.4 ± 8.7 | 95.8 ± 9.0$^{*\dagger}$ |
| **hs-CRP (mg/L)** | 2.77 ± 4.82 | 1.67 ± 1.86$^{*}$ | 2.27 ± 2.12 | 2.60 ± 5.28$^{*}$ | 2.49 ± 3.20 | 1.45 ± 1.47$^{*}$ |
| **HDL (mg/L)** | 1.74 ± 0.49 | 1.72 ± 0.53 | 1.72 ± 0.45 | 1.74 ± 0.44 | 1.63 ± 0.55 | 1.71 ± 0.54$^{*}$ |
| **LDL (mg/L)** | 3.51 ± 0.93 | 3.49 ± 0.95 | 3.44 ± 0.86 | 3.44 ± 0.91 | 3.29 ± 0.83 | 3.30 ± 0.98 |
| **TGs (mg/dL)** | 1.23 ± 0.64 | 1.11 ± 0.55$^{*}$ | 1.26 ± 0.52 | 1.11 ± 0.58 | 1.26 ± 0.58 | 1.01 ± 0.39$^{*}$ |
| **HB (mmol/L)** | 14.69 ± 0.91 | 14.54 ± 1.01 | 14.45 ± 0.96 | 14.25 ± 0.88 | 14.73 ± 0.82 | 14.33 ± 0.91$^{*}$ |

Data is presented as mean ± SD (standard deviation). MIT = moderate-intensity training group and HIT = high-intensity training group; n = number, $VO_{2peak}$ = peak oxygen consumption, hs-CRP = high-sensitivity C-reactive protein, HDL = high-density lipoproteins, LDL = low-density lipoproteins, TGs = triglycerides, HB = haemoglobin. *Significant differences within-group: $P \leq 0.05$. †Significant differences between HIT & control: $P \leq 0.05$. §Significant differences between HIT and MIT: $P \leq 0.05$.

$HbA_{1C}$ and Fasting Glucose

**Table 5** shows the differences from the baseline to the three years follow-up data for both fasting glucose and long-term glucose ($HbA_{1C}$) variables in the impaired fasting glucose (IFG) participants. Once again $HbA_{1C}$ was reduced in all groups (-2.8, -2.7 and -1.9% respectively, $P \leq 0.05$). Fasting glucose also decreased in both control and HIT (-3.9 and -5.3% respectively, $P \leq 0.05$).

**Table 5**. Effect of a three-year intervention on glucose and long-term glucose among IFG participants.

| | Control (n = 74) | | MIT (n = 46) | | HIT (n = 39) | |
|---|---|---|---|---|---|---|
| | **Δ** | **CI** | **Δ** | **CI** | **Δ** | **CI** |
| **FG (mmol/L)** | -0.24 ± 0.58 | (0.11, 0.38)* | -0.08 ± 0.86 | (-0.17, 0.34) | -0.33 ± 0.52 | (0.16, 0.50)* |
| **$HbA_{1C}$ (mmol/L)** | -0.11 ± 0.23 | (0.06, 0.17)* | -0.15 ± 0.23 | (0.09, 0.22)* | -0.16 ± 0.22 | (0.09, 0.24)* |

Data is presented as mean ± SD (standard deviation). MIT = moderate-intensity training group, HIT = high-intensity training group; n = number, FG = fasting glucose, $HbA_{1C}$ = glycosylated hemoglobin, **Δ** = mean difference, CI = confidence interval. *Significant differences within-group: $P \leq 0.05$.

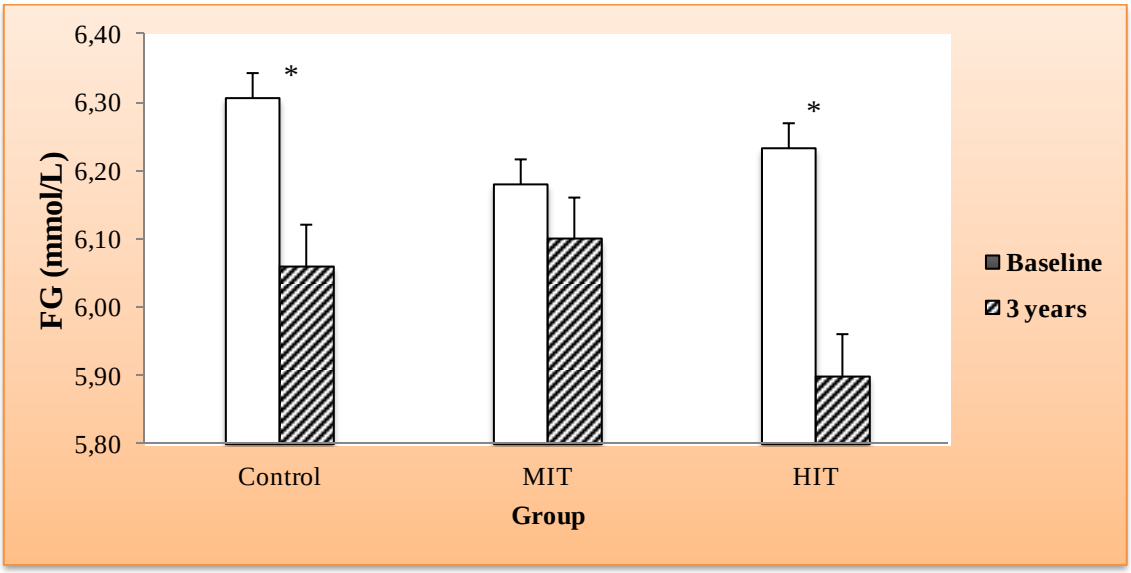


**Figure 6**. Differences in glucose from baseline and after three years of intervention. Error bars stand for the standard error of the mean value for both baseline and after three years. FG = fasting glucose, MIT = moderate-intensity training group, HIT = high-intensity training group. *Significant differences within-group: $P \leq 0.05$.

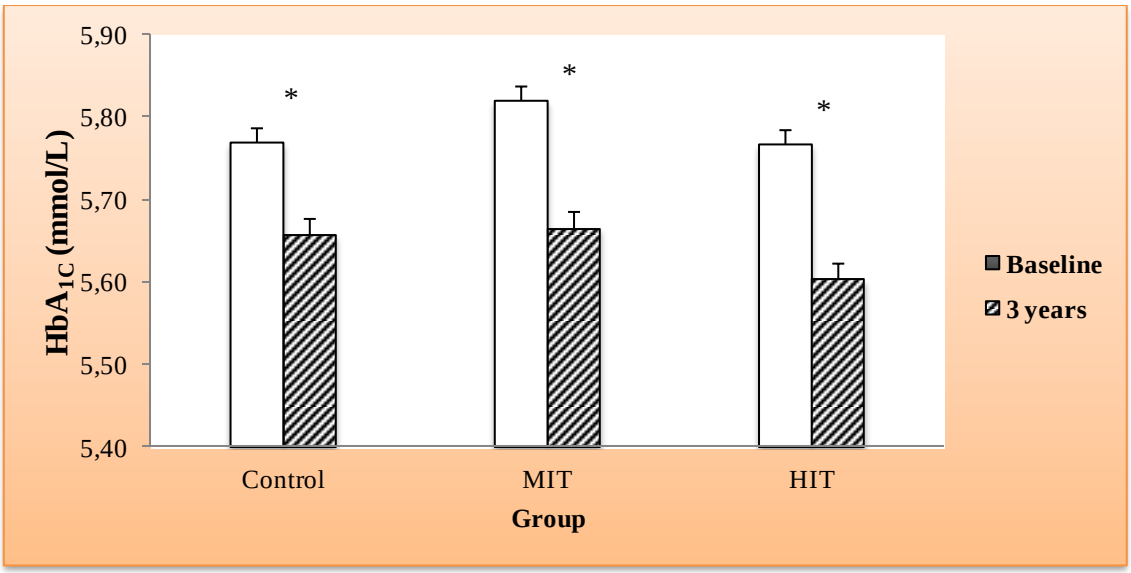


**Figure 7**. Differences in long-term glucose from baseline and after three years of intervention. Error bars stand for the standard error of the mean value for both baseline and after three years. $HbA_{1C}$ = glycosylated haemoglobin, MIT = moderate-intensity training group, HIT = high-intensity training group. *Significant differences within-group: $P \leq 0.05$.

## DISCUSSION

We have for the first time evaluated the effect of three years of aerobic exercise in the general older population. Further, our study provides important information on the long-term effect of aerobic exercise in older men and women with impaired fasting glucose (IFG).

The main findings of the present study are that $HbA_{1C}$ was reduced in all three intervention groups, in both the general older population and in IFG. However, fasting glucose (FG) was only changed among IFG individuals after having performed HIT for a total length of three years. It also accompanied reductions in the control group as for this subgroup.

All weight, peak oxygen uptake ($VO_{2peak}$) and muscle mass were changed within-HIT group as a response to the three-year intervention in the general population. Same results were obtained regarding waist and high-density lipoproteins (HDL). Oppositely, the lipid profile was only improved within-control and MIT groups in this same population. High-sensitivity C-reactive protein (hs-CRP) and triglycerides (TGs) were the only variables among blood markers which changed within all groups. Regarding the rest of the parameters in the general older population, weight was found significantly reduced between HIT and control as between HIT and MIT. Peak oxygen consumption was also significant between HIT and control as markers of exercise capacity. The same applied for both fat and visceral fat.

Among IFG participants, HIT induced the great majority of within-group changes seen in this group. This was the case for weight, $VO_{2peak}$, waist, HDL as well as TGs and haemoglobin. Once again, hs-CRP was modified within all the intervention groups among IFG individuals. Significant changes between HIT and control were observed for exercise capacity markers ($VO_{2peak}$) along with waist circumference (WC) in this subgroup. The former also presented differences between HIT and MIT.

### Exercise influence on glucose metabolism

#### *$HbA_{1C}$*

$HbA_{1C}$ reductions are within the expected outcomes of this study in both populations, except for the control group. However, no significant differences were found between groups. This goes in line with the study of Hansen et al., who did not find any interaction between groups regarding exercise intensity and the decrease in $HbA_{1C}$

content [58]. Aguilera-Equía et al. coincided with this finding in his critical analysis of the study by Terada et al. [55], when affirming to be no significant differences between groups with regard to the training intensity and $HbA_{1C}$ [27].

Interestingly, $HbA_{1C}$ did decrease over the three-year intervention for both the general older population and IFG participants in our study. This is of significant importance given that in previous literature it has been shown rather an increase in this parameter for all healthy (n = 198), pre-diabetic (n = 20) and T2D individuals (n = 17) following a 12-week resistance exercise program [62].

On the contrary, a randomized control trial (RCT) by Karstoft et al. showed that HIT, such as interval-walking, induced a more pronounced change in $HbA_{1C}$ and other glycaemic parameters than did continuous-moderate walking over a period of 5 weeks (6.9 ± 0.2mmol/L to 6.8 ± 0.3mmol/L vs. 6.6 ± 0.2mmol/L to 6.6 ± 0.3mmol/L, respectively) [63].

Among IFG participants, as well as in the general older population, all three intervention groups presented improved $HbA_{1C}$. Similar results were obtained in a previous study when exploring the comparison between an exercise intervention based on treadmill running together with one of equal nature plus a HIT programme on stationary bicycle (n=20) [64]. However, when comparing with a control group, other authors such as Yavari et al. found that $HbA_{1C}$ in 35 T2D individuals (40-65 years) did not experience changes over 16-week of aerobic exercise (50-80% $VO_{2peak}$) as for control participants (n = 30), whereas it was modified with the training intervention ($P \leq 0.05$) [65].

In the aforementioned study by Elsisi et al., the group including HIT to their routine managed to decrease $HbA_{1C}$ by 7.26% when compared to the only-treadmill group ($P \leq 0.05$) [64]. Simultaneously other authors, such as Solomon et al., asseverate that good glycaemic control is correlated with high cardiorespiratory fitness, as measured by the positive association of $VO_{2peak}$ and glucose tolerance [41].

Common risk factors for persons suffering from type 2 diabetes (T2D) included all of the above. It exists a link between the different types of diabetes-associated cardiovascular diseases, such as coronary heart disease (CHD) and obesity [2]. Indeed, a mean $HbA_{1C}$ of 6.5% when compared to that of 7.5% is associated with a risk

reduction of up to 20% for the former [22]; and in a study by Jekal et al., those with lower cardiorespiratory fitness have shown to report a higher level of obesity as measured by abnormalities in all blood pressure (BP), WC and for the latter [66]. Also, the change observed in $HbA_{1C}$ in 57 T2D adults was found significant, after being followed-up for weight loss over 6 months (-0.39 ± 1.51mmol/L, $P \leq 0.05$) [67].

As in reference to our study, this supports greatly the evidence that a small decrease in long-term glucose markers can indeed induce severe reductions seen on risk factors, such as those exposed in the study by Madsen et al. [37]. All participants in our study had lower $HbA_{1C}$ at the beginning of the intervention, and a reduction was remarkable in all three intervention groups in the general population. It could also have provoked concomitant reductions in other health-related markers. Same results could have been obtained among IFG participants.

Much of the scientific literature seems to approve that the reduction seen on $HbA_{1C}$ is rather related to training volume than intensity [68]. However, when referring to glycaemic control, some authors have speculated that it is required to prescribe a structured frequency, volume and intensity, as Llopis & García-Galbis state [69]. Also, following the systematic review from this same author, a training program combining both aerobic and resistance training provoked major benefits on glucose metabolism [69].

***Fasting glucose***

No significant changes were found as for fasting glucose in any of the intervention groups of the general population. Nevertheless, in IFG participants both control and HIT induced significant reductions. These results vouch for those seen previously on the literature [70, 71, 72]. Mainly, with regard to the control group, the changes perceived in our study might have been due to the already high levels of fasting glucose observed from the baseline cohort in this group. This evidence coincides with that collected in a previous study by Norton et al. [73].

There were no significant changes between any of the groups as for both the general older adults and the IFG participants with regard to FG. These results oppose those originally discovered by Devan et al., who found differences between trained (n = 9) and untrained (n = 14) IFG older adults (18-79 years, $P \leq 0.05$) [74].

Although as Taha et al. found statistically significant differences between groups when exercising 45 male subjects (40-55 years) while performing either HIT or continuous moderate aerobic training for 3 times in 10 weeks ($P \leq 0.05$) [75], others have found to exist the same non-statistically difference between groups as seen in our study [41], [76].

HIT per se provides a better outcome seen in FG among T2D patients [41, 43, 72, 77], also when related to other cardiovascular risk factors [23, 26, 64]. Simultaneously, it serves as an efficient tool in order to prevent the spread of T2D [38, 43, 78]. Obesity, which is found to be greatly mediated by aerobic exercise [70, 79, 80], when reduced, has been demonstrated to help individuals return to normal fasting glucose state [81].

In a randomized trial by Marquis-Gravel et al., it was assessed several glycaemic parameters on 72 obese subjects (53 ± 9 years, BMI: 35.3 ± 5.3 kg/m$^2$) [70]. After 9 months of exercise, including HIT and resistance training, FG was found to be reduced by -0.31 ± 0.64mmol/L ($P \leq 0.05$) [70]. A low-volume of HIT can also lead to comparable results as seen in a study by Little et al., where FG decreased in 8 T2D patients after 2 weeks of HIT (11.07 ± 1,70mmol/L to 9.57 ± 1.00mmol/L, $P \leq 0.05$) [72].

In a pilot study by Miller et al., 8 obese men (fat percentage > 26%), after having completed a four-week high-intensity circuit training, found FG to be reduced (4.90 ± 0.35mmol/L in baseline to 4.77 ± 0.35mmol/L after the intervention, $P \leq 0.05$). Such a short-term intervention seemed to be enough to improve several physiological markers tied to obesity development [68]. Still, in 39 obese patients, moderate-intensity circuit training has shown to achieve small but significant reductions in FG over only 2 weeks of training (5.9mmol/L to 5.6mmol/L, $P \leq 0.05$) [76].

In other studies, weight has however shown to be not a sufficient countermeasure in order to prevent the development of T2D in this kind of participants [82]. Indeed, a study by Malin et al. revealed that FG was not reduced to the same extent in IFG individuals than in normal fasting glucose ones [82], most likely being related to insulin sensitivity [83]. Hence other training alternatives, as the ones included in our study, must be put into practice in order to obtain improved FG for this kind of population.

***Anthropometry***

The reduction in body weight seen in the different training groups seems to be mediated by the within-group significant changes seen in muscle mass as well. Along with exercise capacity and fat variables, body weight (kg) was the only variable to be found statistically significant between HIT and control in the general population. The latter also accompanied significant changes between HIT and MIT in the general population.

This has not been the case for visceral fat, which increased in both control and MIT in the general population. This was also the case when measuring fat percentage, which also incremented in the same groups. Similar results have been observed previously in the scientific literature [84, 85]. Following 1-year diet along with moderately intense physical activity (≥175min/week), 28 female and 14 male T2D participants (57.8 ± 6.8 years) experienced a weight loss of 7-10%, which at the same time induced reductions on both subcutaneous and visceral adipose tissue (12.5% and 22.9%, 25.6% and 37.5% respectively, $P \leq 0.05$) [49].

Waist circumference was among those to present reduced values after three years of intervention in HIT as well in the general population. WC has been with anteriority proposed as positively associated with mortality and metabolic abnormalities [85]. This is explained by the presence of one or more of other metabolic risk factors, such as lipoproteins, blood pressure or glucose. It is also considered a valuable marker in order to predict diabetes [47]. Abdominal obesity has additionally been strongly associated with the development of T2D [48]. Reducing WC has indeed shown to improve the regulation of several adipose tissue secreted factors, which ultimately impair the enhancement of the disease [48].

Aerobic exercise (>85%$HR_{max}$) reduced WC more than resistance training in a RCT by Bacchi et al. (n = 19/group, -3.2cm vs. -2.4cm respectively, $P \leq 0.05$) [38]. WC is evidently mediated by the content of abdominal fat, and abdominal fat volume has also been affected by moderate-exercise training when combining a high energy expenditure task such as high-altitude trekking (-129ml, $P \leq 0.05$) [57]. Further, Tjønna et al. achieved to decrease WC significantly after 12 months of HIT in overweight adolescents, in two of his studies (-5cm and -7.2cm respectively, $P \leq 0.05$) [80, 86].

Aging itself contributes to sarcopenia or loss of muscle mass and strength [87] which simultaneously triggers fat infiltration into skeletal muscle [71]. Progressive resistance strength training has to date served as an effective intervention in order to prevent muscular dysfunction and the consequent dystrophy, especially if HIT predominates [88]. On a recent analysis by Porter, it was still determined that HIT helps on increasing protein synthesis along with muscle hypertrophy [89]. In our study, all three groups had a significant decrease in muscle mass. Thus, aerobic exercise over a three-year period is not a sufficient way to prevent the age-related loss of muscle mass.

Only HIT resulted in changed body weight (kg) in IFG participants. Further, we observed a significant change in both WC and muscle mass. The former variable was also presenting significant changes between HIT and control groups within IFG classification. In line with our study, body mass index (BMI) was decreased after 4 years of a weight control program in 562 T2D individuals (45-75 years) with severe obesity ($\geq$40 kg/m$^2$) from 44.7 $\pm$ 0.1kg/m$^2$ to 42.6 $\pm$ 0.2kg/m$^2$ ($P \leq 0.05$) [79].

Previously, it has been noted that, among IFG individuals, both body mass index (BMI) and WC decreased after increasing the subjects' physical activity levels (PAs) to $\geq$30 min and 5 times weekly [64]. According to Chae et al., in 285 females (FG > 100mg/dl) WC, among many other parameters, was found to be decreased by 80.6% when assessing their relative risks for metabolic syndrome in high fitness participants (as tested against a sit-up program for 30 seconds) [32]. Furthermore, both WC and BMI were found significantly changed after 265 individuals (FG at baseline: 6.1mmol/L) reported history of conditioning to strenuous exercise during 3 years [12].

***Exercise capacity***

Low fitness levels as measured by $VO_{2peak}$ has previously been associated with IFG as well as served as an independent predictor of all-cause mortality [41, 90]. In our study, $VO_{2peak}$ was increased after HIT in both the general population and IFG participants. This goes in line with other studies, in which exercise capacity was incremented among IFG and normal FG subjects after a HIT intervention (70-95% $VO_{2peak}$, $P \leq 0.05$) [80, 86].

The major evidence regarding training and its previously-researched benefits when targeting global adaptations (cardiac and pulmonary) has been witnessed by numerous authors to date [25, 58, 64, 80, 84, 86, 91]. With regard to T2D, it has been shown that

a low exercise capacity is intrinsically linked to developing an increasing tendency towards CVD events [13]. $VO_{2peak}$ has indeed been lowered by the presence of this disease, as shown in a study by Brandenburg et al. [18]. Following this author, exercise capacity has led to improvements in 8 T2D women's fitness capacity. These improvements have also corresponded to better results than those seen in the 9 overweight women from the control group, after 3 months of training (28% vs. 8% respectively, $P \leq 0.05$) [18].

As the main influence over physical capacity, HIT has evidently produced the major changes as seen in much of the scientific literature [72, 84, 86, 92]. Many of these adaptations on cardiac autonomy, physical function and aging in T2D participants have been a product of an amelioration of the subject's exercise capacity [26, 57, 58]. Endurance exercise has as well helped on preventing the decline seen in mitochondrial function on elderly individuals [72].

$VO_{2peak}$ significantly increased after HIT in participants with IFG. Likewise, AIT was found to increase $VO_{2peak}$ by 35% in 32 metabolic syndrome patients, and further comparison with continuous moderate exercise (CME) revealed that it existed a difference of 19% [86]. Furthermore, $VO_{2peak}$ increased by 27.2 ± 7.2ml/kg/min to 28.1 ± 6.8ml/kg/min in 39 T2D patients (62 ± 5 years) with CAD ($P \leq 0.05$), under a 6-month exercise prescription of home-based endurance training and strength training for 30min each [93]. However, results obtained in studies such as the one by Byrkjeland et al. for T2D + CAD patients (63.1 ± 7.9 years), showed that 52 participants exercising for 150min weekly during 12 months (MIT and HIT combined) did not experience any changes on $VO_{2peak}$ ($P = 0.077$) [94].

Ciolac et al. demonstrated in 44 healthy women (25 ± 4.4 years) that AIT was superior in enhancing cardiorespiratory fitness (15% vs. 8% when compared to CME, $P \leq 0.05$), despite of being equally effective in improving insulin sensitivity ($P \leq 0.05$) [95]. HIT indeed appears to be a better modifier of FG in participants at risk of T2D at the same time [96]. $VO_{2peak}$, which bears decreased levels from baseline in T2D participants [40], has been improved in metabolic syndrome participants (n = 12) as a result of short-term aerobic exercise training (70-75% $VO_{2peak}$) for 1h daily within 10 days (from 23.9 ± 1.9ml/kg/min to 25.3 ± 1.4ml/kg/min) [97].

Our study shows that in the general older population, aerobic exercise with both moderate-intensity and high-intensity is effective in reducing $HbA_{1C}$. However, HIT induced changes in several of the other measured health-related variables, and thus indicates that this type of exercise is more beneficial for improving risk factors associated with T2D. In people with IFG we found that although $HbA_{1C}$ was reduced for all groups, HIT induced changes on FG along with those health-related parameters being observed in our study. Moreover, with exception of fat markers and low-density lipoproteins, the rest of the variables been cited in our study were found to be decreased as for the HIT intervention.

## LIMITATIONS

Two important limitations were present throughout the analysis and representation of this study, which may have influenced its outcomes.

First of all, the training adherence gives evidence to the fact that a big amount of the participants in the HIT group (a total of 38 out of 99, which is equivalent to the 38.4%) decided not to engage in the prescribed intervention. Same result is obtained when focusing on the sub-group classification (IFG individuals), showing that only 24 out of 38 did follow the exercise prescriptions (63.2%).

It clearly declares that those participants who were first randomized and located into the HIT group decided to modify their training basis and hence this could have led into different results. This could be due to an existing confounding factor, when several types of exercise interventions can be prescribed under similar intensities to HIT (80-95% $VO_{2peak}$) but with differences with regard to total volume, duration or frequency of the training program. Therefore, we tend to think that there could have been even more pronounced changes seen in all parameters.

Second and last, medication could have affected the outcomes of our study. A majority of 104/159 IFG participants (65.4%) admitted having been taking some kind of medication, and it is unknown whether they changed their doses during the study. Thus, this could have influenced our results and hence have caused major differences between those who were under medication throughout the intervention from those who were not.

## CONCLUSION

After three years of aerobic exercise intervention, long-term glucose was reduced in the general older population and in impaired fasting glucose individuals. Thus, for long-term interventions, exercise intensity does not seem to be crucial for a reduction in $HbA_{1C}$ in older adults. Fasting glucose was only reduced after HIT in the impaired fasting glucose participants. In addition, HIT resulted in more favourable changes in other health parameters, indicating that this type of exercise is preferable and hence should be included in the strategy to mitigate the spread and development of type 2 diabetes in older men and women with impaired fasting glucose.

**ACKNOWLEDGEMENTS**

I would like to deeply show my appreciation to my supervisor, Dorthe Stensvold, who has always had so clear the patients' needs regarding their health enhancement through exercising, as seen to date in the scientific literature.

Another great consideration deserves every participant involved in the 'Generasjon100' group project, who has carried out a great effort during exercise testing in order to help us obtain all the possible data.

Also, but not last, to every engineer in our group, who has provided me with more than enough training to possibly continue my research pathways after the completion of my master degree.

To all of you, I wish you the best in your future endeavours and thank you for making the best out of my stay in Norway.

## ATTACHMENTS

**Attachment 1**. Approval of 'REK'

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

| Region: | Saksbehandler: | Telefon: | Vår dato: | Vår referanse: |
|---|---|---|---|---|
| REK sør-øst | Mariann Glenna Davidsen | 22845526 | 15.02.2016 | 2015/2351 REK sør-øst B |
| | | | Deres dato: | Deres referanse: |
| | | | 08.12.2015 | |

Vår referanse må oppgis ved alle henvendelser

Dorthe Stensvold
NTNU

**2015/2351 Effekten av tre års trening på glukoseregulering hos eldre**

**Forskningsansvarlig:** NTNU
**Prosjektleder:** Dorthe Stensvold

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK sør-øst) i møtet 20.01.2016. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10, jf. forskningsetikkloven § 4.

**Prosjektleders prosjektbeskrivelse**
*"Målet med studien er å se på hvilken type trening som er mest effektiv for glukoseregulering hos eldre. Dette er en substudie av Generasjon 100. Deltakerene er randomisert til kontroll, trening med høy intensitet eller trening med moderat intensitet. Målet er å se på hvilken type trening som er mest effektiv for en forbedring på faste glukose og HBA 1c."*

**Komiteens vurdering**
*Redegjørelse:* Denne studien baserer seg på data fra Generasjon 100, som er et tidligere godkjent REK-prosjekt. Studien skal sammenligne tidligere innhentede data i form av Vo2 max, vekt, høyde, blodtrykk, blodprøvesvar, midjemål og kroppssammensetning, med nye tilsvarende data etter tre års trening (høst 2015/vår 2016).

*Info- og samtykkeskriv:* Studien skal kun innhente data fra et allerede godkjent prosjekt hvor deltakerne allerede har gitt sitt samtykke. Samtykket i hovedprosjektet omfatter også at det kan hentes ut data til denne type underprosjekter.

Komiteen har ingen forskningsetiske innvendinger til at prosjektet gjennomføres.

**Vedtak**
Komiteen godkjenner prosjektet i henhold til helseforskningsloven § 9 og § 33.

Godkjenningen er gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknaden.

Tillatelsen gjelder til 01.06.2016. Av dokumentasjonshensyn skal opplysningene likevel bevares inntil 01.06.2021. Opplysningene skal lagres avidentifisert, dvs. atskilt i en nøkkel- og en opplysningsfil. Opplysningene skal deretter slettes eller anonymiseres, senest innen et halvt år fra denne dato.

Besøksadresse: Gullhaugveien 1-3, 0484 Oslo
Telefon: 22845511
E-post: post@helseforskning.etikkom.no
Web: http://helseforskning.etikkom.no/

Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder *"Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse- og omsorgssektoren"*

*Sluttmelding og søknad om prosjektendring*
Prosjektleder skal sende sluttmelding til REK sør-øst på eget skjema, jf. hfl. § 12. Prosjektleder skal sende søknad om prosjektendring til REK sør-øst dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.

*Klageadgang*
Du kan klage på komiteens vedtak, jf. forvaltningslovens § 28 flg. Klagen sendes til REK sør-øst B. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK sør-øst B, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Komiteens avgjørelse var enstemmig.

Med vennlig hilsen

Grete Dyb
førsteamanuensis dr. med.
leder REK sør-øst B

Mariann Glenna Davidsen
rådgiver

**Kopi til:**
- *NTNU, Institutt for sirkulasjon og bildediagnostikk*
- *Instituttleder Toril Nagelhus Hernes, Institutt for sirkulasjon og bildediagnostikk, NTNU*

**Attachment 2**. 'Borg scale'

Exercise is Medicine

NTNU

# HVOR TUNG ER BELASTNINGEN?

| | |
|---|---|
| 6 | |
| 7 | Meget, meget lett |
| 8 | |
| 9 | Meget lett |
| 10 | |
| 11 | Ganske lett |
| 12 | |
| 13 | Litt anstrengende |
| 14 | |
| 15 | Anstrengende |
| 16 | |
| 17 | Meget anstrengende |
| 18 | |
| 19 | Svært anstrengende |
| 20 | |

Norsk versjon av Borgs skala:

Borg GA. **Perceived Exertion.** *Exerc Sport Sci Rev.* 1974;2:131-53.

**REFERENCES**


1. American Diabetes, A., *(2) Classification and diagnosis of diabetes.* Diabetes Care, 2015. **38 Suppl**: p. S8-S16.
2. Cade, W.T., *Diabetes-related microvascular and macrovascular diseases in the physical therapy setting.* Phys Ther, 2008. **88**(11): p. 1322-35.
3. Laakso, M., *Cardiovascular disease in type 2 diabetes from population to man to mechanisms: the Kelly West Award Lecture 2008.* Diabetes Care, 2010. **33**(2): p. 442-9.
4. McMurray, J., Gerstein, HC, Holman, RR & Pfeffer, MA, *Heart failure: a cardiovascular outcome in diabetes that can no longer be ignored.* Lancet Diabetes Endocrinol, 2014. **2**(10): p. 843-51.
5. Federation, I.D., *IDF Diabetes Atlas, 7th edn.* International Diabetes Federation, 2015.
6. Wild, S., et al., *Global prevalence of diabetes: estimates for the year 2000 and projections for 2030.* Diabetes Care, 2004. **27**(5): p. 1047-53.
7. Nichols, G.A., et al., *The incidence of congestive heart failure in type 2 diabetes: an update.* Diabetes Care, 2004. **27**(8): p. 1879-84.
8. Carnethon, M.R., et al., *Diabetes and coronary heart disease as risk factors for mortality in older adults.* Am J Med, 2010. **123**(6): p. 556 e1-9.
9. Nathan, D.M., J. Meigs, and D.E. Singer, *The epidemiology of cardiovascular disease in type 2 diabetes mellitus: how sweet it is ... or is it?* Lancet, 1997. **350 Suppl 1**: p. SI4-9.
10. Vijan, S., et al., *Screening, prevention, counseling, and treatment for the complications of type II diabetes mellitus. Putting evidence into practice.* J Gen Intern Med, 1997. **12**(9): p. 567-80.
11. *Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group.* BMJ, 1998. **317**(7160): p. 703-13.
12. Morris, J.N., et al., *Vigorous exercise in leisure-time: protection against coronary heart disease.* Lancet, 1980. **2**(8206): p. 1207-10.
13. Seyoum, B., et al., *Exercise capacity is a predictor of cardiovascular events in patients with type 2 diabetes mellitus.* Diab Vasc Dis Res, 2006. **3**(3): p. 197-201.
14. Rosengren, A. and L. Wilhelmsen, *Physical activity protects against coronary death and deaths from all causes in middle-aged men. Evidence from a 20-year*

*follow-up of the primary prevention study in Goteborg.* Ann Epidemiol, 1997. **7**(1): p. 69-75.

15. Siscovick, D.S., et al., *Physical activity and primary cardiac arrest.* JAMA, 1982. **248**(23): p. 3113-7.

16. Poirier, P., et al., *Impact of left ventricular diastolic dysfunction on maximal treadmill performance in normotensive subjects with well-controlled type 2 diabetes mellitus.* Am J Cardiol, 2000. **85**(4): p. 473-7.

17. Bauer, T.A., et al., *Skeletal muscle deoxygenation after the onset of moderate exercise suggests slowed microvascular blood flow kinetics in type 2 diabetes.* Diabetes Care, 2007. **30**(11): p. 2880-5.

18. Brandenburg, S.L., et al., *Effects of exercise training on oxygen uptake kinetic responses in women with type 2 diabetes.* Diabetes Care, 1999. **22**(10): p. 1640-6.

19. Colberg, S.R., et al., *Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association: joint position statement executive summary.* Diabetes Care, 2010. **33**(12): p. 2692-6.

20. American Diabetes, A., *Standards of medical care in diabetes.* Diabetes Care, 2004. **27 Suppl 1**: p. S15-35.

21. Menni, C., et al., *Biomarkers for type 2 diabetes and impaired fasting glucose using a nontargeted metabolomics approach.* Diabetes, 2013. **62**(12): p. 4270-6.

22. Eeg-Olofsson, K., et al., *New aspects of HbA1c as a risk factor for cardiovascular diseases in type 2 diabetes: an observational study from the Swedish National Diabetes Register (NDR).* J Intern Med, 2010. **268**(5): p. 471-82.

23. Snowling, N.J. and W.G. Hopkins, *Effects of different modes of exercise training on glucose control and risk factors for complications in type 2 diabetic patients: a meta-analysis.* Diabetes Care, 2006. **29**(11): p. 2518-27.

24. Chudyk, A. and R.J. Petrella, *Effects of exercise on cardiovascular risk factors in type 2 diabetes: a meta-analysis.* Diabetes Care, 2011. **34**(5): p. 1228-37.

25. American Diabetes, A., *Diagnosing diabetes and learning about prediabetes.*

26. Thomas, D.E., E.J. Elliott, and G.A. Naughton, *Exercise for type 2 diabetes mellitus.* Cochrane Database Syst Rev, 2006(3): p. CD002968.

27. Aguilera Eguia, R.A., et al., *[Effect of high-intensity interval training on the reduction of glycosylated hemoglobin in type-2 diabetic adult patients].* Medwave, 2015. **15**(2): p. e6079.

28. Eriksen, L., et al., *Comparison of the effect of multiple short-duration with single long-duration exercise sessions on glucose homeostasis in type 2 diabetes mellitus.* Diabetologia, 2007. **50**(11): p. 2245-53.

29. Dunstan, D.W., et al., *High-intensity resistance training improves glycemic control in older patients with type 2 diabetes.* Diabetes Care, 2002. **25**(10): p. 1729-36.

30. Houle, J., et al., *Glycaemic control and self-management behaviours in Type 2 diabetes: results from a 1-year longitudinal cohort study.* Diabet Med, 2015. **32**(9): p. 1247-54.

31. Boule, N.G., et al., *Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: a meta-analysis of controlled clinical trials.* JAMA, 2001. **286**(10): p. 1218-27.

32. Chae, J.S., et al., *Supervised exercise program, BMI, and risk of type 2 diabetes in subjects with normal or impaired fasting glucose.* Diabetes Care, 2012. **35**(8): p. 1680-5.

33. Tokmakidis, S.P., et al., *Training, detraining, and retraining effects on glycemic control and physical fitness in women with type 2 diabetes.* Horm Metab Res, 2014. **46**(13): p. 974-9.

34. da Silva, C.A., et al., *High-intensity aerobic training improves endothelium-dependent vasodilation in patients with metabolic syndrome and type 2 diabetes mellitus.* Diabetes Res Clin Pract, 2012. **95**(2): p. 237-45.

35. Healy, G.N., et al., *Breaks in sedentary time: beneficial associations with metabolic risk*. Diabetes Care, 2008. **31**(4): p. 661-6.

36. Selvin, E., et al., *Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults.* N Engl J Med, 2010. **362**(9): p. 800-11.

37. Madsen, S.M., et al., *High Intensity Interval Training Improves Glycaemic Control and Pancreatic beta Cell Function of Type 2 Diabetes Patients.* PLoS One, 2015. **10**(8): p. e0133286.

38. Bacchi, E., et al., *Relationships between cardiorespiratory fitness, metabolic control, and fat distribution in type 2 diabetes subjects.* Acta Diabetol, 2014. **51**(3): p. 369-75.

39. Meyer, K., Niemann, S., Abel, T., *Gender differences in physical activity and fitness - association with self-reported health and health-relevant attitudes in a middle-aged Swiss urban population.* J Public Health, 2004. **12**(4): p. 283-90.

40. Leite, S.A., et al., *Low cardiorespiratory fitness in people at risk for type 2 diabetes: early marker for insulin resistance.* Diabetol Metab Syndr, 2009. **1**(1): p. 8.

41. Solomon, T.P., et al., *Association between cardiorespiratory fitness and the determinants of glycemic control across the entire glucose tolerance continuum.* Diabetes Care, 2015. **38**(5): p. 921-9.

42. Grelier, S., et al., *Effects of a three-month combined training program on the cardiopulmonary and muscle strength capacities of type 2 diabetic subjects.* J Sports Med Phys Fitness, 2013. **53**(1): p. 56-64.

43. Middlebrooke, A.R., et al., *Six months of aerobic exercise does not improve microvascular function in type 2 diabetes mellitus.* Diabetologia, 2006. **49**(10): p. 2263-71.

44. Eeg-Olofsson, K., et al., *The triglycerides-to-HDL-cholesterol ratio and cardiovascular disease risk in obese patients with type 2 diabetes: an observational study from the Swedish National Diabetes Register (NDR).* Diabetes Res Clin Pract, 2014. **106**(1): p. 136-44.

45. Daousi, C., et al., *Prevalence of obesity in type 2 diabetes in secondary care: association with cardiovascular risk factors.* Postgrad Med J, 2006. **82**(966): p. 280-4.

46. Wang, Y., et al., *Comparison of abdominal adiposity and overall obesity in predicting risk of type 2 diabetes among men.* Am J Clin Nutr, 2005. **81**(3): p. 555-63.

47. Janiszewski, P.M., I. Janssen, and R. Ross, *Does waist circumference predict diabetes and cardiovascular disease beyond commonly evaluated cardiometabolic risk factors?* Diabetes Care, 2007. **30**(12): p. 3105-9.

48. Freemantle, N., et al., *How strong is the association between abdominal obesity and the incidence of type 2 diabetes?* Int J Clin Pract, 2008. **62**(9): p. 1391-6.

49. Gallagher, D., et al., *Changes in adipose tissue depots and metabolic markers following a 1-year diet and exercise intervention in overweight and obese patients with type 2 diabetes.* Diabetes Care, 2014. **37**(12): p. 3325-32.

50. Swift, D.L., et al., *Effect of exercise training modality on C-reactive protein in type 2 diabetes.* Med Sci Sports Exerc, 2012. **44**(6): p. 1028-34.

51. Jonker, J.T., et al., *Exercise and type 2 diabetes mellitus: changes in tissue-specific fat distribution and cardiac function.* Radiology, 2013. **269**(2): p. 434-42.

52. Hollekim-Strand, S.M., et al., *High-intensity interval exercise effectively improves cardiac function in patients with type 2 diabetes mellitus and diastolic*

*dysfunction: a randomized controlled trial.* J Am Coll Cardiol, 2014. **64**(16): p. 1758-60.

53. Taylor, J.D., et al., *Effects of moderate- versus high-intensity exercise training on physical fitness and physical function in people with type 2 diabetes: a randomized clinical trial.* Phys Ther, 2014. **94**(12): p. 1720-30.

54. Rynders, C.A. and A. Weltman, *High-intensity exercise training for the prevention of type 2 diabetes mellitus.* Phys Sportsmed, 2014. **42**(1): p. 7-14.

55. Terada, T., et al., *Feasibility and preliminary efficacy of high intensity interval training in type 2 diabetes.* Diabetes Res Clin Pract, 2013. **99**(2): p. 120-9.

56. Villa-Caballero, L., et al., *Hemodynamic and oxidative stress profile after exercise in type 2 diabetes.* Diabetes Res Clin Pract, 2007. **75**(3): p. 285-91.

57. Marcus, R.L., et al., *Comparison of combined aerobic and high-force eccentric resistance exercise with aerobic exercise only for people with type 2 diabetes mellitus.* Phys Ther, 2008. **88**(11): p. 1345-54.

58. Hansen, D., et al., *Continuous low- to moderate-intensity exercise training is as effective as moderate- to high-intensity exercise training at lowering blood HbA(1c) in obese type 2 diabetes patients.* Diabetologia, 2009. **52**(9): p. 1789-97.

59. Earnest, C.P., et al., *Interval training in men at risk for insulin resistance.* Int J Sports Med, 2013. **34**(4): p. 355-63.

60. Stensvold, D., et al., *A randomised controlled study of the long-term effects of exercise training on mortality in elderly people: study protocol for the Generation 100 study.* BMJ Open, 2015. **5**(2): p. e007519.

61. Writing Committee, M., et al., *2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines.* Circulation, 2013. **128**(16): p. e240-327.

62. Geirsdottir, O.G., et al., *Effect of 12-week resistance exercise program on body composition, muscle strength, physical function, and glucose metabolism in healthy, insulin-resistant, and diabetic elderly Icelanders.* J Gerontol A Biol Sci Med Sci, 2012. **67**(11): p. 1259-65.

63. Karstoft, K., et al., *The effects of free-living interval-walking training on glycemic control, body composition, and physical fitness in type 2 diabetic patients: a randomized, controlled trial.* Diabetes Care, 2013. **36**(2): p. 228-36.

64. Elsisi, H., Aneis, YM & Mounir, KM, *Impact of high-intensity interval training on HbA1C in patients with type 2 diabetes mellitus.* Bull Fac Phys Ther, 2015. **20**(2): p. 168-75.

65. Yavari, A., A.M. Hajiyev, and F. Naghizadeh, *The effect of aerobic exercise on glycosylated hemoglobin values in type 2 diabetes patients.* J Sports Med Phys Fitness, 2010. **50**(4): p. 501-5.

66. Jekal, Y., et al., *Association between Obesity and Physical Fitness, and Hemoglobin A1c Level and Metabolic Syndrome in Korean Adults.* Korean Diabetes J, 2010. **34**(3): p. 182-90.

67. Delahanty, L.M., et al., *Improving diabetes outcomes through lifestyle change--A randomized controlled trial.* Obesity (Silver Spring), 2015. **23**(9): p. 1792-9.

68. Miller, M.B., et al., *The effect of a short-term high-intensity circuit training program on work capacity, body composition, and blood profiles in sedentary obese men: a pilot study.* Biomed Res Int, 2014. **2014**: p. 191797.

69. Llopis, P.G.-G., MR, *Control glucémico a través del ejercicio físico en pacientes con diabetes mellitus tipo 2. Una revisión sistemática.* Nutr Hosp, 2015. **31**(4): p. 1465-72.

70. Marquis-Gravel, G., et al., *Intensive lifestyle intervention including high-intensity interval training program improves insulin resistance and fasting plasma glucose in obese patients.* Prev Med Rep, 2015. **2**: p. 314-8.

71. Huffman, D.M. and N. Barzilai, *Role of visceral adipose tissue in aging.* Biochim Biophys Acta, 2009. **1790**(10): p. 1117-23.

72. Little, J.P., et al., *Low-volume high-intensity interval training reduces hyperglycemia and increases muscle mitochondrial capacity in patients with type 2 diabetes.* J Appl Physiol (1985), 2011. **111**(6): p. 1554-60.

73. Norton, L., K. Norton, and N. Lewis, *Exercise training improves fasting glucose control.* Open Access J Sports Med, 2012. **3**: p. 209-14.

74. DeVan, A.E., et al., *Regular aerobic exercise protects against impaired fasting plasma glucose-associated vascular endothelial dysfunction with aging.* Clin Sci (Lond), 2013. **124**(5): p. 325-31.

75. Taha, M., Abdeen, HA & Abdelsamaia, RA, *High-intensity interval versus continuous moderate aerobic training as a prophylaxis of diabetic nephropathy.* Intern J Diab Res, 2016. **5**(1): p. 14-9.

76. Robinson, E., et al., *Short-term high-intensity interval and moderate-intensity continuous training reduce leukocyte TLR4 in inactive adults at elevated risk of type 2 diabetes.* J Appl Physiol (1985), 2015. **119**(5): p. 508-16.

77. Carey, V.J., et al., *Body fat distribution and risk of non-insulin-dependent diabetes mellitus in women. The Nurses' Health Study.* Am J Epidemiol, 1997. **145**(7): p. 614-9.

78. Segerstrom, A.B., et al., *Impact of exercise intensity and duration on insulin sensitivity in women with T2D.* Eur J Intern Med, 2010. **21**(5): p. 404-8.

79. Unick, J.L., et al., *The long-term effectiveness of a lifestyle intervention in severely obese individuals.* Am J Med, 2013. **126**(3): p. 236-42, 242 e1-2.

80. Tjonna, A.E., et al., *Aerobic interval training reduces cardiovascular risk factors more than a multitreatment approach in overweight adolescents.* Clin Sci (Lond), 2009. **116**(4): p. 317-26.

81. Shimizu, S., et al., *Effects of changes in obesity and exercise on the development of diabetes and return to normal fasting plasma glucose levels at one-year follow-up in middle-aged subjects with impaired fasting glucose.* Environ Health Prev Med, 2001. **6**(2): p. 127-31.

82. Malin, S.K. and J.P. Kirwan, *Fasting hyperglycaemia blunts the reversal of impaired glucose tolerance after exercise training in obese older adults.* Diabetes Obes Metab, 2012. **14**(9): p. 835-41.

83. Yoshida, Y., et al., *Effects of weight loss in obese subjects with normal fasting plasma glucose or impaired glucose tolerance on insulin release and insulin resistance according to a minimal model analysis.* Metabolism, 2004. **53**(9): p. 1095-100.

84. Lindstrom, J., et al., *The Finnish Diabetes Prevention Study (DPS): Lifestyle intervention and 3-year results on diet and physical activity.* Diabetes Care, 2003. **26**(12): p. 3230-6.

85. Dagan, S.S., et al., *Waist circumference vs body mass index in association with cardiorespiratory fitness in healthy men and women: a cross sectional analysis of 403 subjects.* Nutr J, 2013. **12**: p. 12.

86. Tjonna, A.E., et al., *Aerobic interval training versus continuous moderate exercise as a treatment for the metabolic syndrome: a pilot study.* Circulation, 2008. **118**(4): p. 346-54.

87. Lauretani, F., et al., *Age-associated changes in skeletal muscles and their effect on mobility: an operational diagnosis of sarcopenia.* J Appl Physiol (1985), 2003. **95**(5): p. 1851-60.

88. Liu, C.J. and N.K. Latham, *Progressive resistance strength training for improving physical function in older adults.* Cochrane Database Syst Rev, 2009(3): p. CD002759.

89. Porter, M.M., *The effects of strength training on sarcopenia.* Can J Appl Physiol, 2001. **26**(1): p. 123-41.

90. Van de Veire, N.R., et al., *Fasting blood glucose levels are related to exercise capacity in patients with coronary artery disease.* Am Heart J, 2006. **152**(3): p. 486-92.

91. Ryan, A.S., *Insulin resistance with aging: effects of diet and exercise.* Sports Med, 2000. **30**(5): p. 327-46.

92. Mensink, M., et al., *Study on Lifestyle Intervention and Impaired Glucose Tolerance Maastricht (SLIM): preliminary results after one year.* Int J Obes Relat Metab Disord, 2003. **27**(3): p. 377-84.

93. Karjalainen, J.J., et al., *Effects of exercise prescription on daily physical activity and maximal exercise capacity in coronary artery disease patients with and without type 2 diabetes.* Clin Physiol Funct Imaging, 2012. **32**(6): p. 445-54.

94. Byrkjeland, R., et al., *Effects of exercise training on HbA1c and VO2peak in patients with type 2 diabetes and coronary artery disease: A randomised clinical trial.* Diab Vasc Dis Res, 2015. **12**(5): p. 325-33.

95. Ciolac, E.G., et al., *Effects of high-intensity aerobic interval training vs. moderate exercise on hemodynamic, metabolic and neuro-humoral abnormalities of young normotensive women at high familial risk for hypertension.* Hypertens Res, 2010. **33**(8): p. 836-43.

96. Jelleyman, C., et al., *The effects of high-intensity interval training on glucose regulation and insulin resistance: a meta-analysis.* Obes Rev, 2015. **16**(11): p. 942-61.

97. Baynard, T., et al., *Short-term exercise training improves aerobic capacity with no change in arterial function in obesity.* Eur J Appl Physiol, 2009. **107**(3): p. 299-308.