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# The effect of exercise rehabilitation on insulin resistance in patients diagnosed with MASLD.

## A protocol for a randomized controlled trial

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# Acknowledgment

A master's dissertation typically represents the culmination of the academic program that has been undertaken over the past five years. By writing the acknowledgement the realization dawns that this final project is coming to an end.

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## List of abbreviations

MASLD = metabolic dysfunction associated liver disease

CMFR = cardiometabolic risk factor

HCC = hepato cellular carcinoma

IHTG = intra hepatic fat content

IR = insulin resistance

VLDL = very low-density lipoprotein

DNL = de novo lipogenesis

T2DM = type 2 diabetes mellitus

FFA = free fatty acids

ROS = reactive oxygen species

IL = interleukin

TNF = tumor necrosis factor

PPAR-$\gamma$ = peroxisome proliferation activated receptor-$\gamma$

GLUT4 = glucose transport 4

AMPK = AMP-activated protein kinase

SOCS = suppressor of cytokine

Wmax = Maximal power output

PGC-1$\alpha$ = peroxisome proliferator-activated receptor gamma co-activator – 1 alpha

IRS = insulin receptor substrate

VAT = visceral adipose tissue

AT = aerobic training

RT = resistance training

HIIT = high intensity interval training

SIT = sprint interval training

AIT = aerobic interval training

LGIMD = low glycemic index Mediterranean diet

CPET = cardiopulmonary exercise test

1RM = one repetition max

VT = ventilatory threshold

WU = warming up

CD = cooling down

CAP = controlled attenuation parameter

HDL = High density lipoprotein

LDL = low density lipoprotein

SF36 = 36-item short form health survey

BMI = body mass index

FM = fat mass

FFM = fat free mass

ALT = alanine transamirase

AST = aspartate transamirase

# Abstract (English)

Background

MASLD is a very common liver disease, set to become the number one cause of hepato cellular carcinoma (HCC). Lifestyle factors are known to be the driving force in the development of MASLD and pharmaceutical management of early stage MASLD is limited. Therefore, evidence-based exercise prescription is a necessity towards delaying the progression of the disease. A vast amount of literature is available about the effect of exercise interventions on the pathogenesis and pathophysiology of MASLD. However, there is scarce evidence about the effect of a concurrent training program.

Therefore, we aimed to develop an isocaloric concurrent training program with the intent to investigate the effect on clinical parameters related to MASLD, particularly insulin resistance (IR).

Methods and analysis

All participants undergo a 14-week exercise regimen. They are randomly assigned to two groups: Group A receives aerobic and resistance training, while Group B undergoes high-intensity interval training and resistance training. Pre- and post-intervention assessments include cardiopulmonary exercise testing (CPET), one-repetition maximum (1RM) testing, functional assessments, and blood analysis. The primary outcome variable is insulin resistance (IR), measured using the homeostatic assessment model for insulin resistance (HOMA-IR). Secondary outcome variables encompass liver steatosis and fibrosis (assessed via Fibroscan), cardiorespiratory fitness, blood biochemistry markers (ALT, AST, IL-6, IL-8, TNF-α, HDL, LDL, triglycerides), and body composition. Data will be analyzed using repeated measures ANCOVA.

Results

Three subjects are discussed, and individual feedback is given regarding the assessment and exercise protocol. Patient one performed a hypotensive event during baseline assessment resulting into the allocation to group A. Patient two showed a hypertensive crisis (184/123 mmHg) and a cardiologist has been consulted conform the safety measures prior to the advancement to the exercise protocol. Patient three, allocated to group B, performed the CPET revealing a very poor physical fitness, to ensure safety and as results of unspecific data, the HIIT - protocol has been changed to an aerobic interval training (AIT) – protocol.

Conclusion:

If the provided protocol implements successfully, it provides evidence for a combined exercise intervention in insulin resistance in patients diagnoses with MASLD.

Keywords: Metabolic dysfunction associated liver disease (MASLD), insulin resistance (IR), aerobic exercise, high intensity interval training (HIIT), resistance training.

# Abstract (Dutch)

Achtergrond

MASLD is een veelvoorkomende leveraandoening en staat op het punt om nummer één oorzaak te worden van hepatocellulair carcinoom. Levensstijl factoren zijn de drijvende kracht voor de ontwikkeling van MASLD, waarbij medicamenteuze behandeling in de vroege stadia van de ziekte niet bestaan. Daaruit volgt dat evidence-based inspanningsrevalidatie een noodzaak is met oog op het vertragen van de aandoening. De literatuur voorhanden omtrent inspanningsrevalidatie en het effect op de pathogenese en de pathofysiologie van MASLD is zeer uitgebreid. Echter, er is weinig evidentie beschikbaar over het effect van een trainingsprogramma bestaande uit een combinatie van verschillende oefenvormen. Wij hebben een isocalorisch gecombineerd oefenprotocol ontwikkeld met als doel het effect er van te toetsen aan de klinische manifestatie van MASLD, specfiek insuline resistentie.

Methode en analyse

Alle deelnemers volgen een trainingsprotocol van 14 weken. De deelnemers worden willekeurig verdeeld in twee groepen: Groep A ontvangt aerobe en weerstandstraining, terwijl Groep B hoge-intensiteit intervaltraining en weerstandstraining ondergaat. Voor- en na-interventie beoordelingen omvatten cardiopulmonale inspanningstests (CPET), één-repetitie maximum (1RM) tests, functionele beoordelingen en bloedanalyse. De primaire uitkomstvariabele is insulineresistentie (IR), gemeten met behulp van het homeostatische beoordelingsmodel voor insulineresistentie (HOMA-IR). Secundaire uitkomstvariabelen omvatten leversteatose en fibrose (beoordeeld via Fibroscan), cardiorrespiratoire fitheid, bloedbiochemische markers (ALT, AST, IL-6, IL-8, TNF-α, HDL, LDL, triglyceriden) en lichaamssamenstelling. De gegevens worden geanalyseerd met behulp van een herhaalde metingen ANCOVA.

Resultaten

Drie deelnemers zijn beschreven en individuele feedback over de metingen en het protocol wordt voorzien. Deelnemer 1 deed een hypotensief event tijdens de basismeting wat resulteerde in de toewijzing tot groep A. Deelnemer twee deed een hypertensieve crisis (184/123 mmHg), waardoor een cardioloog geraadpleegd werd, conform de veiligheidsvoorschriften, alvorens er (eventueel) een verderzetting is van de deelname aan de studie. Deelnemer 3, toegewezen aan groep B, vervolledigde de CPET met als resultaat een zeer zwakke fysieke fitheid. Om de veiligheid te garanderen is voor deze persoon het HIIT- protocol gewijzigd naar een aeroob interval training (AIT) – protocol.

Conclusie:

Indien het protocol succesvol toegepast kan worden, dient het als een evidence-based gecombineerd oefenprogramma in een MASLD-populatie.

Trefwoorden: Metabolic dysfunction associated liver disease (MASLD), insuline resistentie, aerobe training, interval training, krachttraining.

# Introduction

Metabolic dysfunction associated steatotic liver disease (MASLD) is a very common liver disease, set to become number one cause of Hepato cellular carcinoma (HCC) worldwide (1). MASLD is a disease characterized by excessive fat accumulation, associated with insulin resistance, and defined by the presence of steatosis in >5% of hepatocytes. If hepatic steatosis is diagnosed, the presence of any cardiometabolic risk factor (CMFR) (see table 1) would suggest MASLD. In case of excessive alcohol consumption, the term MetALD or ALD is indicated, dependent on the extent of alcohol (2).

MASLD and intrahepatic fat content

The most crucial feature of MASLD is the increased intrahepatic triglyceride (IHTG) content (3). IHTG rises when the TG production is greater than the combined rates of TG disposal in very low-density lipoprotein (VLDL) and intrahepatic oxidation of TG-derived fatty acids. Fatty acids used for the rise of IHTG content come from: a) fatty acids released into the systemic and portal circulation by lipolysis of TGs in subcutaneous and intra-abdominal adipose tissues. b) fatty acids released into the systemic circulation by postprandial lipolysis of TGs in chylomicrons; c) hepatic lipolysis of TGs in plasma lipoproteins delivered to the liver; and d) fatty acids synthesized de novo from nonlipid precursors in the liver (4,5). The de novo synthesis of fatty acids encompasses a complex process where acetyl-coA is converted into malonyl-coA. Malonyl-coA goes through multiple cycles of condensation, decarboxylation and reductions to form 1 palmitate molecule. Even when the mechanisms for the increase in de novo lipogenesis (DNL), in patients diagnosed with MASLD is not well known, it is assumed that circulating glucose and plasma insulin, linked with IR, stimulates hepatic DNL. Ballestri et al showed that DNL is upregulated by activation of the sterol regulatory element binding protein 1c and carbohydrate response element binding protein, in response of increased circulating glucose and plasma insulin (6).

MASLD and hepatic insulin resistance

The interaction between MASLD and IR is very complex. Patients with MASLD have a two-time greater risk of developing diabetes mellitus type 2 (T2DM) (7). The consensus used to be that IR was a risk factor for MASLD. Over the last years there was more evidence for a bi-directional link revolving around the interaction between IR, oxidative stress, and inflammation. In a healthy population insulin act as an anabolic hormone in adipose tissue, increasing lipogenesis and decreasing lipolysis, particularly post-prandial. However, in insulin resistance, regulatory pathways are modified, resulting in increased lipolysis, causing a

surge of free fatty acids (FFA) and eventual fat overload of hepatocytes (8). Mitochondrial dysfunction follows, leading to incomplete oxidation of FFA and exacerbating hepatic insulin resistance (9). Additionally, gluconeogenesis increases while insulin-dependent glycogen synthesis decreases. The intricate relationship among insulin resistance, oxidative stress, and inflammation stems from mitochondrial dysfunction, reactive oxygen species (ROS), and harmful lipids, culminating in localized inflammation that dampens insulin signaling. Within the liver, insulin receptor substrate 1 (IRS) and IRS2 play pivotal roles in regulating insulin sensitivity. Inflammatory cytokines such as IL-8 activate insulin resistance by promoting the expression of suppressor of cytokine signaling (SOCS) 1 and 3, which, in turn, hinder hepatic insulin signaling by facilitating IRS degradation (10).

MASLD and systemic insulin resistance

The role of skeletal muscle, particularly glucose transporter 4 (GLUT4), is essential when discussing insulin resistance. There are multiple fiber types in human muscle: type I fibers are slow twitch fibers, have the most mitochondria and depend mostly on oxidative pathways, type IIa fibers are fast twitch fibers, have less mitochondria and depend on oxidative/glycolytic pathways and type IIx fibers are fast twitch that depend mostly on glycolytic pathways (11). This review states that particularly glucose transporter 4(GLUT4) is expressed the most in slow, oxidative fiber types. Furthermore, insulin stimulated glucose uptake is greater is type IIa muscle fibers compared to type IIx muscle fibers (12). These finding indicate the importance of the oxidative capacity of the fibers regarding insulin sensitivity. Patients with IR and abdominal obesity show the same abnormalities considering muscle fiber type: low percentage muscle fiber type I, increased type II fibers and low capillary density (13). This causes a decrease in GLUT4 receptors, less glucose uptake, and more IR. Holmäng et al showed, in rats, that exposure to increased insulin levels for seven days provokes a reduction of the muscle fiber type I while the proportion of muscle fiber type II increased (14). Providing evidence that IR further decreases the oxidative muscle fibers, resulting in a vicious cycle. Insulin-independent glucose uptake as response to acute exercise is not fully understood, however, it has been established that insulin independent glucose uptake is greater is type II (a and x) muscle fibers, 3.5hours post exercise then type I muscle fibers (15). Indicating the substantial benefit exercise interventions could provide regarding IR and glucose levels.

MASLD and mitochondrial dysfunction

*Hepatic mitochondrial dysfunction*

Hepatic mitochondrial dysfunctions reported in MASLD are alteration and depletion of mitochondrial DNA, decreased activity of respiratory chain complexes and flawed mitochondrial ß-oxidation (16).

These mitochondrial changes can be linked with increasing ROS production (17), DNA damage and membrane lipid peroxidation. These changes are considered important factors concerning hepatocyte injury associated with MASLD (18). Over the last years mitochondrial dysfunction has been gaining attention in the literature. A recent review posits that, on top of the earlier described alterations in the mitochondria, the overload of FFA in the liver results in an increase of mitochondrial fission led to a disintegrated network of mitochondria in the hepatocytes. This process aggravates the mitochondrial dysfunctions such as reduced performance of the electron transport chain resulting in increased proton leaking and ultimately increased ROS production (19). The previously mentioned findings could suggest that mitochondrial dysfunction is the foundation of MASLD and IR. Furthermore, Rector et al states that mitochondrial dysfunction precedes IR and liver steatosis. They showed that reduced hepatic fatty oxidation and mitochondrial enzyme activity precedes MASLD development and IR. Simultaneously, glycemic control worsened, anti-oxidative capacity decreases, oxidative stress increases and hepatic mitochondrial content and function are reduced (20). Fletcher et al showed that different exercise modalities induce changes on different indices of hepatic mitochondrial dysfunction, these changes are not dependent on the mitochondrial content. Furthermore, they state that exercising in a fasted state upregulate genes related to gluconeogenesis probably leading to an enhanced mitochondrial function and content (21).

*Skeletal muscle mitochondrial dysfunction*

Next to hepatic mitochondrial dysfunction, skeletal muscle mitochondria display dysfunctions as well. An RCT performed by Axelrod et al, showed that lipid infusion in healthy, sedentary people causes mitochondrial fission and fragmentation. The same study noticed an accompanied decrease peripheral and hepatic insulin sensitivity (22). Structured exercise is known to have large beneficial effects when it comes to mitochondrial dysfunction. A recent review states that the volume of the training is an important determinant of mitochondrial content. Training volume has a strong correlation (r=0.71) with citrate synthase activity, an acknowledged indicator of mitochondrial content (23,24). On the other hand, training intensity is an important regulator for mitochondrial respiration. Exercise performed at an intensity >90% Wmax is shown to have beneficial effects regarding absolute mass specific mitochondrial respiration, intensity at >100% Wmax returns the most benefit over time (21). When increasing intensity, the dominant

bioenergetic pathway becomes the oxidation of glucose into pyruvate and ultimately lactate. Lactate acts as an upstream signal of peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α), the master regulator of mitochondrial biogenesis (25).

MASLD and inflammation

Hepatic inflammation is an important regulator concerning the progression of MASLD. An association has been shown between the upregulation and release of pro-inflammatory mediators such as tumor necrosis factor-α(TNF-α), interleukin 6(IL-6) and -8(IL-8) and MASLD (26). Exercise is shown to be effective in reducing ROS production, TNF-α, IL-6 and IL-8. Moreover, peroxisome proliferation activated receptor-γ(PPAR-γ) is known to have anti-inflammatory and anti-fibrotic effects in patients with MASLD (27) and is upregulated by exercise (28).

MASLD and aerobic exercise

Aerobic exercise positively influences insulin resistance (IR) (29,30,31), even in patients without significant weight loss (32), suggesting its standalone efficacy. However, combining exercise with dietary adjustments yields the greatest IR benefits (33), particularly in individuals with poor glycemic control (34). Cuthbertson et al. demonstrated a notable enhancement in peripheral insulin sensitivity following a sixteen-week aerobic regimen in a MASLD population, highlighting the importance of exercise intensity in rehabilitation (35). Yet, hepatic IR remained unaffected, emphasizing the nuanced impact of exercise. Consideration of exercise volume is crucial; one study prescribing 120 minutes of weekly aerobic activity for 23 weeks yielded no changes in insulin sensitivity or controlled attenuated parameter (CAP) (36). Notably, aerobic exercise induces reductions in intrahepatic triglycerides (IHTG) (37,38), through mechanisms such as mitochondrial biogenesis and enhanced FFA oxidation (39). Additionally, exercise decreases hepatic FFA accumulation via PPAR-γ activation (40). Studies suggest that a 15% reduction in BMI effectively enhances liver function, with improvements observed independent of weight loss, underscoring the broader benefits of exercise beyond mere weight management (41,42).

MASLD and resistance training

Regarding resistance training, there seems to be a significant decrease in IR (43,44) and liver fat content (45,46,47,48). Next to the changes in IR and liver fat content, body composition shows a significant improvement. For patients with low cardiorespiratory fitness/strength, resistance training could be a good starting point of the rehabilitation. It should be noted that some studies do not have positive results

regarding resistance training. Zelber-Sagi et al showed there was no difference in HOMA-IR and HbA1C between resistance training and stretching (49). This is confirmed by Keating et al and Lee et al showing no significant decrease in visceral adipose tissue (VAT), liver steatosis, or IR (50,51).

MASLD and high intensity interval training

High intensity interval training improves insulin sensitivity (52,53). The increase in insulin sensitivity can be explained by the improved insulin signaling in the skeletal muscle. The time spent at high intensity or interval frequency did not significantly influence intervention effectiveness when speaking of fasting glucose, fasting insulin, HbA1c or IR (54). However, a recent study in adolescents showed that a short term supervised HIIT exercise program did not alter IR, yet there was a significant improvement in IHTG (55). This suggest that there is minimal amount of workload necessary to induce changes regarding insulin resistance. This is confirmed by Maclean et al, where a six-week sprint interval training (SIT) of two sessions each week did not alter the parameters regarding IR or IHTG (56).

Muscle fibers respond well to training, but different types of training cause different adaptations. Endurance training elicits an increase in mitochondrial content (57). However, in an overweight population, HIIT causes a greater increase in mitochondrial content compared to moderate continuous aerobic training, as shown by an RCT of De Strijcker et al (58). A possible explanation could be that patients with obesity have a higher percentage of type II muscle fibers, which results in being more responsive to exercise with a higher glycolytic demand (59). To our knowledge, no human trials have been carried out looking for the effect of exercise on hepatic mitochondrial dysfunction. A rodent study compared various exercise interventions (aerobic, HIIT and sedentary behavior combined or not with a high fat diet) and its effect of hepatic mitochondrial dysfunction, concluding not one single type is superior to the other in increasing mitochondrial content or hepatic mitochondrial metabolism (60). Combining the evidence above, high intensity training, next to endurance training, could produce significant improvements for insulin sensitivity in a MASLD population. One single blinded RCT compared resistance training, moderate-intensity continuous aerobic training and HITT. They reported similar reductions concerning IHTG, between the three groups. However, HIIT was the only intervention with significant reductions regarding hepatic stiffness (61). Thus, volume, intensity and/or calory restriction play a crucial role to elicit change in hepatic IR and MASLD.

Research on combined exercise interventions such as HIIT and aerobic exercise, aerobic exercise and resistance training, or HIIT and resistance training is limited. Voudouris et al. conducted a seven-day intervention combining aerobic exercise and resistance training, resulting in decreased intrahepatic

triglycerides (IHTG) but no change in IR (62). A 20-week program combining aerobic exercise and resistance training showed improved body composition and liver lipid profiles, consistent with findings from three similar studies (63,64,65,66). Shah et al. (2009) additionally observed enhanced endothelial function due to reduced ROS and increased nitric oxide (NO) availability. Franco et al. compared six interventions, with a combination of aerobic exercise and low glycemic index Mediterranean diet (LGIMD) producing the most significant reductions in CAP after 90 days. Despite longer weekly exercise duration, PA1 showed greater CAP reduction than PA2 (67). While some studies suggest combined aerobic exercise and resistance training yields optimal benefits for triglyceride content (68), others indicate that HIIT and resistance training improve hepatic triglyceride content but not insulin sensitivity or glucose control, possibly due to insufficient HIIT duration (69).

To date no pharmaceutical management is available in the early stages of MASLD. The advice that the patients receive is incoherent and not tailored to the patient's needs. It has been proven time and again that structured exercise elicits positive effects on the pathogenesis and the pathophysiological pathways of MASLD. Duration and intensity have a crucial role in exercise treatment of MASLD and hepatic IR, too little volume or intensity do not induce significant impact on hepatic changes. In addition, the effect of exercise on mitochondrial biogenesis and mitochondrial respiration should be taken into consideration. However, the optimal distribution regarding the type of exercise is not well studied, on top of that it is not known how the modalities should be incorporated in a training cycle. One study showed that lifelong sporty individuals showed no improvement regarding insulin sensitivity after a 6 weeks HIIT intervention, in comparison to sedentary individuals who had a significant improvement. It must be stated that the sedentary individuals had a precondition phase of 6 weeks with 150min of exercise each week. A possible theory could be that the lifelong athletes were to well-conditioned to gain a significant impact regarding insulin sensitivity (70). These findings could indicate that the exercise program should be individually tailored, depending on starting exercise capacity of the patient. The MASLD population is usually poorly conditioned (71), suggesting the possible benefit they could get from HIIT.

It is remarkable that little studies have looked at the effect of a combined exercise intervention in a population diagnosed with MASLD, especially studies including HIIT.

Earlier studies incorporating HIIT into the combined exercise intervention did not produce any significant impact concerning IR, arguably due to insufficient total time spent at high intensity. Therefore, we tried to maximize the time spent at high intensity, in combination with resistance training. The comparison with the combination of aerobic exercise and resistance training will be made to indicate whether one combination

is superior to the other or vice versa. It could be possible that a combination of varies types of exercise leaves a different physiological signature than a single type of exercise. This study will be an attempt to look at the difference between a combination of HIIT with resistance training and aerobic training and resistance training.

# Methods and analysis

## Study setting and organization

### Recruitment and screening

All patients will be recruited at the liver MASLD outpatient clinic of Ghent University Hospital, by physicians. During consultation eligible participants will be given sufficient information of the study and ICF.

*Inclusion criteria:*

- The diagnosis of MASLD, confirmed by medical imaging (Fibroscan) or liver biopsy.
- The absence of significant liver fibrosis, confirmed by Fibroscan (<7,5kPa or >7,5 and <10 kPa and no liver fibrosis on biopsy).
- Age between 18 – 75 years

*Exclusion criteria:*

- The presence of other severe liver conditions, which have an impact on the clinical presentation of the patient.
- Severe cardiovascular (NYHA class 2), respiratory (GOLD 3), renal (stage 4 chronic kidney disease) orthopedic or other disabilities that could impair the safety of the patient, or what could lead to non-compliance of the exercise protocol.
- Pregnancy
- Treatment with direct effect on MASLD for example: GLP-1 analogues

### Patient and public involvement

Patients will be asked to give feedback about the designed protocol. Topics discussed are:

- Feasibility: are there elements which lead to incompletion of the training sessions?
- The intensity: how is the intensity perceived?
- Home exercise: is it possible to perform the training sessions at home?
- Duration of the protocol: is a 14-week period realistic?
- Frequency: is a frequency of 3x/week realistic and is it possible to combine the sessions with personal and professional life?
- Diet: is it possible to not compensate for the increase in physical activity?

## Intervention

### Study protocol

The participants will be randomly assigned to one of two intervention groups in a 1:1 allocation ratio. Group A will receive a combination of aerobic and resistance training, while Group B will receive a combination of HIIT and resistance training.

For safety and exercise physiology reasons (increase basic fitness first) groups will start with a combination of aerobic and resistance training during the first six weeks of the study. Thereafter, group A will continue the combination of aerobic and resistance training and group B will start their combination of HIIT and resistance training. Both groups will receive the exercise intervention three times a week for a total period of 14 weeks in total (see appendix; figure 2).

### Baseline assessment

The subjects that meet the in- and exclusion criteria are invited to Ghent university hospital department rehabilitation sciences. The assessment consists of 4 major categories: anthropometrics (body mass, fat free mass and fat mass), fitness/functional testing (CPET, 1RM, handgrip strength, six-minute walking distance and timed chair-stand-test), cardiovascular risk (blood pressure, AGE, HOMA-IR, lipid profile, inflammation) and quality of life (SF36 quality of life questionnaire). The blood markers (ALT, AST (liver enzymes), IL-6, IL-8, TNF- α (inflammation), cholesterol, triglycerides, high-density lipoprotein and low-density lipoprotein (lipid profile) needed for this study are gathered from the routine blood analysis performed at the liver outpatient clinic of Ghent University hospital. The baseline assessment will be performed before and after the 14-week intervention protocol. The 1RM-test will be performed after every change in intensity according to the protocol (see below). This ensures the subjects will perform at their true percentage of their 1RM.

## Exercise protocol

The protocols are designed to be isocaloric, ensuring that the energy expenditure of both groups is identical.

Group A: Aerobic training + resistance training protocol.

The one-hour training sessions will be divided into a warming up (WU), three blocks of aerobic training (AT), interspersed by two blocks of resistance training (RT) and a cooling down (CD). During the first six weeks, patients will perform warm-up exercises (WU) on a cycling ergometer at 90% of the first ventilatory threshold (VT1) for five minutes. Aerobic training (AT) will also be done on a cycling ergometer, treadmill or cross-trainer at 100% of VT1 for ten minutes. The first resistance training (RT) block will consist of three sets. Each set will be performed at 20 RM. The first two sets consist of 15 repetitions, the third set will be performed until exhaustion, with two minutes of rest in between each set. The exercises in first RT block are: the squat exercise and vertical traction. The second RT block will be the chest press and adductor press. Finally, cool-down exercises (CD) will be done on the cycling ergometer less than 90%VT1. For Group A, the intensity will progress starting from week seven. The AT will be performed at 110% VT1, and the RT will consist of two sets of twelve repetitions at 15 RM, the third set will be performed until failure. Starting from week 11, the AT will be performed at 120% VT1, and the RT will consist of three sets of eight repetitions at 10 RM, the third set will be performed until failure. Patients will also be given exercises to perform at home, consisting of brisk walking. During the first six weeks, the walking will be performed at 60% HRmax, while from week seven, it will be performed at 70% HRmax. Finally, from week 11, patients will perform brisk walking at 80% HRmax.

Group B: HIIT + resistance training protocol.

Group B will follow the same program as Group A for the first six weeks. Starting from week seven, Group B will have their own program, which will include a warm- up (WU), three blocks of high-intensity interval training (HIIT) on a cycling ergometer, two blocks of resistance training (RT), and a cool-down (CD), following the same structure as Group A. The WU will be five minutes long. The HIIT-blocks will be performed based the Gibala protocol (72). From week 7 until week 11 the HIIT blocks consists of 1 minute at 100% VT2 followed by 1 minute light pedaling at 80%VT1, this will be repeated five times. From week 11 until week 14 the same structure is used, for this period the light pedaling will be performed at 90%VT1. This change

in intensity during the rest periods ensures group A and group B are isocaloric. The RT will progress similarly to Group A, and the CD will be five minutes of light pedaling on the cyclo-ergometer. If VT2 is not achieved, 90% of VO2max will be used for the calculation of the intensity for the intervals.

The home program for Group B will include a ten-minute WU of brisk walking at 50% HRmax, followed by the HIIT program. The HIIT program consist of 3 rounds of eight minutes. Each round will be one minute on, one minute off. The minute in which the subjects are performing, there will be two exercises (see appendix: table 3). Each exercise is performed 30 seconds. The program will end with a ten-minute CD of easy walking.

### Guidelines for Participants

The participants are asked to report if there is any change in diet or habit of daily physical activity that is different from their usual habits before the study. We guide the participants in maintaining the same lifestyle as before the study as much as possible. They are asked to be cautious not to eat remarkably more/unhealthier or less/healthier than before the start of the study. The participants will complete a Food Frequency Questionnaire so that significant dietary interventions or changes can be registered. This helps identify any potential confounding bias during the data processing stage.

### Blinding and randomization

The participants will either be randomly allocated to group A or group B.. Within these subgroups the subject will be randomly assigned to group A or B. The randomization will be performed using ResearchRandomizer.

## Outcome measures

### Primary outcome measures

Insulin resistance

Venous blood samples will be taken after a 12-hour fast. Three blood samples of 15 milliliter (ml) each will be drawn. One extra tube will be drawn for potential further analysis. The biochemical analysis will be carried out by laboratory staff, at Ghent University, blinded to group A or B. Insulin resistance will be measured with homeostasis model assessment for insulin resistance (HOMA-IR). HOMA-IR is calculated by multiplying fasting glucose (in mmol/L) and insulin (in mU/mL) and dividing the product by 22.5 (73).

## Secondary outcome measures

Liver steatosis

Transient elastography, commonly known as FibroScan, employs a non-invasive ultrasound technique to measure liver fat content. The fibroscan probe, functioning as both a receiver and emitter, emits a 50 Hz shear wave. Subjects are positioned supine with their right arm in 180° abduction during the test. Placed between the ribs opposite the right liver lobe and away from its border, the probe determines fat accumulation using the CAP score. The CAP score ranges from 100 dB/m to 400 dB/m, with a normal range accepted as below 238 dB/m (74). The assessment of liver steatosis using CAP-values show a high accuracy with an area under the curve of 0.87 (75).

Fibrosis

Fibrosis will be measured with transient elastography (FibroScan), as described above (liver steatosis). Liver stiffness is measured in kilopascals (kPa). Values between two and seven kPa are considered normal. Values between 7.5 kPa and 14kPa is moderate to severe scarring, anything above 14kPa is considered cirrhosis (75).

Body composition

Anthropometric measurements will be collected on testing day. Weight is measured to the nearest of 0.1 kilograms(kg) with a bioelectrical impedance scale. Bioelectrical impedance analysis (BIA) will be performed providing fat free mass and fat percentage. The subjects will be asked to wear light clothes and no shoes. Height is measured to the nearest of 0.1meters (m). BMI is calculated by dividing weight (in kg) by height (in m) squared. Waist circumference will be measured, with measuring tape, in standing position, just above the iliac crest, to the nearest of 0.1 centimeters (cm) (76). Males or females with a waist circumference greater than 94 centimeter(cm) or 80 cm, respectively, are at greater risk for developing metabolic syndrome or T2DM (77).

AGE-reader

Advanced glycation end products will be measured by means of the age-reader (Diagnoptics technologies BV, Groningen, The Netherlands). The subjects will place their forearm with the volar side on the pad. The age reader emits UV-light with a peak wavelength of 360-370nm. Light reflected and emitted from the skin

is measured by photodiodes (78,79). If the patient deviates more than one standard deviation(sd) from the mean, the result is interpretated as an increased risk for the development of metabolic diseases (80).

Blood biochemistry

Liver enzymes of alanine transamirase (ALT) and aspartate transamirase (AST) will be measured as well as IL-6, IL-8 and TNF-α, cholesterol, tryglicerides, HDL and LDL. These measurements are standard of care at the liver MASLD outpatient clinic. A reduction in ALT of ≥ 17U/L is known to be a significant decrease, with an aera under the curve of 0.83 (81).

Cardiorespiratory fitness

A cardiopulmonary exercise test (CPET) will be used to evaluate cardiorespiratory fitness. The subjects will perform an incremental test (ramp protocol) on a cyclo-ergometer starting at 25W with gradual increase of 25W every minute. Electrocardiogram and heart rate will be recorded continuously, and every two minutes blood pressure will be measured. The subjects will be encouraged to perform until their self-determined capacities or until a physician stops the test out of safety reasons.

Strength

An indirect 1 repetition max test will be used to assess the level of strength. A physiotherapist will define a test weight so that subjects would be able to achieve six to 12 repetitions at the most. From this number of repetitions, the 1 RM was calculated using the Holten diagram. The Holten diagram relates the number of repetitions to the percentage of maximum strength.

Functional testing

Grip strength and muscle fatigue

Grip strength is evaluated in a stance position with the arm of the subjects flexed in 90°, alongside the body. Starting with the dominant hand, the subject is asked to squeeze with as much force as possible. This is repeated three times with 30sec rest in-between. The procedure is repeated for the non-dominant hand. Muscle fatigue is tested in the same position. The subject will be asked to squeeze with as much force as possible for as long as possible. The test is finished when the grip strength drops 50% of the maximum grip

strength, both for the dominant and non-dominant side. It has been reported that grip strength has a high ICC of 0.98 for both the dominant and non-dominant hand (82).

Six-minute walking distance (6MWT)

The six-minute walking distance is performed in a 20m long corridor. The subjects are asked to cover as much distance as possible in six minutes without running. The subjects able to stop at any given moment but are encouraged to continue as soon as possible. The 6MWT has a significant correlation (r=0.66) with exercise capacity (83). An ICC of 0.99 has been reported in older adults with T2DM (82,84).

Timed-chair-stand test

The timed-chair-stand test measures the maximum number of repetitions a subject can rise to a full stance from a seated position, without pushing off with their arms, in 30 seconds. The number of completed stances is considered the score of the subject. This test is correlated with the strength of the lower limbs (85). An ICC of 0.92 has been reported in older adults with T2DM (82).

Quality of life

Quality of life (QoL) will be measured with the 36-item short form survey instrument (SF 36) (86). The scoring system contains two steps. First the numeric values are translated according to the scoring table (see appendix). Secondly, the items in the same scale are taken together to create the eight scale scores (87).

## Statistical analysis

### Datamanagement plan

Data collection will be done through clinical assessment and medical records. Demographic data (sex, age), clinical data (body composition, transient elastography (steatosis and fibrosis), blood biochemistry, HOMA-IR), exercise capacity (CPET, 1RM-test, 6MWT, Timed chair stand test, grip strength, muscle fatigue) will be collected and stored. An independent researcher will enter the data manually (pseudonymized) in REDCap software, that will be stored on to the secured network of Ghent university hospital. The data processing

will be executed by final years physiotherapy students. The metadata will be made public to enhance transparency. After the termination of the study the collected data will be stored in a prospective research biobank for potential new research. Both personal data and medical data will be preserved for at least 25 years.

### Statistical analysis plan

All data will be analyzed using a repeated measures ANCOVA. Baseline distribution will be analyzed using the Shapiro-Wilik test. Between group analysis will be performed using the student's t-test. Repeated measures ANCOVA will be used to assess differences between groups over time. Since the participants are randomly allocated there should not be any difference in liver steatosis and IR. Age, BMI, medication intake, risk for hypo- and hyperglycemia, cardiorespiratory fitness and sex will be included as covariates. Per protocol analysis will be performed and the subjects will be included if the attendance rate is more than 90%. Intention to treat analysis will too be performed. The mean +- standard deviation will be calculated and compared to the 95%- confidence interval. The level of significance will be fixed at $p < 0.05$. The data will be analyzed using IBM SPSS statistics version 27.

## Results

The results of three participants will be reported in this section. Concise feedback will be given on the individualized protocol and potential events during testing. A detailed discussion of a training session and the exercise protocol in total can be found in the discussion.

### Patient 1

#### Clinical and physical data

Baseline characteristics are summarized in table 2 (see appendix; table 2). Physical examination revealed the next findings: height, 169 cm; weight, 106.9 kg; BMI, 37.4; fat mass (FM), 41.6 kg; fat free mass (FFM), 65.3 kg; waist circumference, 120 cm, and blood pressure of 144/103 mmHg. AGE value is 1.6.

Blood analysis resulted in an insulin value of 68 and a fasting glucose value of 106, subsequently HOMA-IR value was calculated resulting in 17,8, putting the participant above the reference value of 2. ALT and AST respectively are 41 and 28. Triglycerides have a value of 123 mg/dl, cholesterol of 170 mg/dl, LDL of 106 mg/dl and HDL of 41mg/dl.
Transient elastography showed a fatty liver of 5,7 kPA and a CAP value of 391 kPA. Echography indicated severe steatosis, grade 3.

The CPET revealed a maximal oxygen uptake (VO2peak) of 2,41 ml/min/kg, VT1(bpm) of 159 and VT2 (BPM) of 193, maximal heart rate (HRmax) is 194 bpm. 1 RM-test showed a one repetition maximum for the squat, low row, chest press, adductor exercise as follows: 37.6kg, 68.5 kg, 53 kg and 66.3 kg, respectively.
When it comes to functional testing the participant performed 555 m for the 6MWT with a resting heart rate of 100bpm and a maximal heart rate of 168 bpm, 1 minute recovery resulted in a decrease of 28 bpm. The handgrip strength test resulted in 54 N on the right side (dominant) and 48 N on the left side, the muscle fatigue test was 15.18s. The subjects performed 14 rises in the chairs stand test and scored 52.13 on the SF36 scale.

### Individualized protocol

After the 1RM-test the patient had an unexpected hypotensive event as a result of performing a possible Valsalva-maneuvers during the execution of the exercises. Subsequently, it was decided that this subject would be assigned to group A. The exercise program for this patient goes as follows (the global structure of the training can be found in methods):

Week one to six, the training at Ghent university hospital consists of a 5-minute WU at 143BPM/95W. The aerobic training block is performed at 159BPM/106W for ten minutes. The strength training, consisting of the squat, chest press, adductors and low row will be performed at 22kg, 30kg, 40 kg and 40 kg, respectively. The session is terminated by a 5-minute CD at 143 BPM/ 95w. The home exercise is performed at 116 BPM.

Week seven to 11, the training at Ghent university hospital consists of a 5-minute WU at 143BPM/95W. The aerobic training block is performed at 175BPM/116W for ten minutes. The strength training, consisting of the squat, chest press, adductors and low row will be performed at 26,5 kg, 37 kg, 46 kg and 48 kg,

respectively. The session is terminated by a 5-minute CD at 143 BPM/ 95w. The home exercise is performed at 136 BPM.

Week 11 to 14, the training at Ghent university hospital consists of a 5-minute WU at 143BPM/95W. The aerobic training block is performed at 191BPM/127W for ten minutes. The strength training, consisting of the squat, chest press, adductors and low row will be performed at 32 kg, 45kg, 56 kg and 58 kg, respectively. The session is terminated by a 5-minute CD at 143 BPM/ 95w. The home exercise is performed at 155 BPM.

### Feedback on training session

Because of the autonomous response of the subject during strength testing, it was decided to allocate the subject into group A. Next to the syncope, the high resting pulse (100BPM) has been taking into consideration. The high pulse leads to a smaller buffer of the patient to a decrease in blood pressure and/or puts a ceiling on the cardiac autonomic response of the patient. The impaired cardiac autonomic response could be the result of the higher resting heart rate (and thus low heart rate variability), indicating the absence of the parasympathetic nervous system and an overactive ortho sympathetic nervous system during rest, resulting in an impaired response to acute stress to the body during exercise.

## Patient 2

### Clinical and physical data

Baseline characteristics are summarized in table2 (see appendix; table 2). During physical examination, the patient reported a very high blood pressure (184/123 mmHg). A cardiologist will be consulted in advance of the CPET and the start of the exercise program.

Physical examination revealed the next findings: height, 166 cm; weight, 79,4 kg; BMI, 28.8; fat mass (FM), 31.8 kg; fat free mass (FFM), 47.6 kg; waist circumference, 103. AGE value is 1.9.
Blood analysis resulted in an insulin value of 50 and a fasting glucose value of 157, subsequently HOMA-IR value was calculated resulting in 19.4, putting the participant above the reference value of 2. ALT and AST respectively are 105 and 51.
Triglycerides have a value of 222 mg/dl, cholesterol of 244 mg/dl, LDL of 134 mg/dl and HDL of 74/dl.

Transient elastography showed a fatty liver of 6,8 kPa and a CAP value of 319 kPA. Echography indicated moderate steatosis, grade 2.

When it comes to functional testing the participant performed 535 m for the 6MWT with a resting heart rate of 92bpm and a maximal heart rate of 132 bpm, 1 minute recovery resulted in a decrease of 45 bpm. The handgrip strength test resulted in 32 N on the right side (dominant) and 28 N on the left side, the muscle fatigue test was 50,60s. The subjects performed 19 rises in the chairs stand test.

## Feedback on training session

The training sessions will not be started in advance of the approval from a cardiologist. Awaiting the result, an alternative exercise schedule will be made based on the 6MWT. The baseline 6MWT will be used. The duration of the schedule will be three weeks after which a retest will take place. Based on previous research, the training frequency will three times per week, with every training session having a total duration of 20 minutes (excluding WU and CD) (88). The first week the patient will walk at 80% of the 6MWT speed, the second week 90% and the third week at 100%. The warming up and cooling down will be performed at 60% of the 6MWT speed each lasting 2.5 minutes.

In this case the schedule looks like:

Test:

Actual distance 6MWT = 535m

Actual 6MWT speed = 535*10 = 5350 m/h = 5.3 km/h

Training schedule:

Week one: treadmill walking speed: 0.8* 5,3 = 4,2 km/h

Week two: treadmill walking speed: 0;9*5,3 = 4,7 km/h

Week three: treadmill walking speed: 5,3 km/h

Each training will have a warming up and cooling down performed at a walking speed if 3.1 km/h each lasting 2,5 minutes.

Retest.

## Patient 3

### Clinical and physical data

Baseline characteristics can be found in table2 (see appendix; table 2). Physical examination revealed the next findings: height, 159 cm; weight, 109.3 kg; BMI, 43,2; fat mass (FM), 48,6 kg; fat free mass (FFM), 60,7 kg; waist circumference, 117 cm and blood pressure, 135/72 mmHg. AGE value is 1,4.
Blood analysis resulted in a insulin value of 50 and a fasting glucose value of 87, subsequently HOMA-IR value was calculated resulting in 10.7, putting the participant above the reference value of 2. ALT and AST respectively are 90 and 91. Triglycerides have a value of 100 mg/dl, cholesterol of 238 mg/dl, LDL of 176 mg/dl and HDL of 40 mg/dl.
Transient elastography showed a fatty liver of 6,3 kPA and a CAP value of 325 kPA.

The CPET revealed a maximal oxygen uptake (VO2max) of 1,85 ml/min/kg, maximal heart rate (HRmax) of 188 BPM, VT1(bpm) of 164 and VT2 (BPM) of 188. 1 RM-test showed a one repetition maximum for the squat, low row, chest press, adductor exercise as follows: 27.6 kg, 37.6 kg, 52.8 kg and 54.3 kg, respectively. When it comes to functional testing the participant performed 500 m for the 6MWT with a resting heart rate of 132 bpm and a maximal heart rate of 180 bpm, 1 minute recovery resulted in a decrease of 40 bpm. The handgrip strength test resulted in 35 N on the right side (dominant) and 30 N on the left side, the muscle fatigue test was 42,26s. The subjects performed 13 rises in the chairs stand test.

### Individualized training protocol

Patient 3 has been allocated to group B. The modalities are (the global structure of the training sessions can be found in methods):
Week one to six, the training at Ghent university hospital consists of a 5-minute WU at 148BPM/22,5W. The aerobic training block is performed at 164BPM/25W for ten minutes. The strength training, consisting of the squat, chest press, adductors and low row will be performed at 16.5kg, 31.6kg, 32.5 kg and 22.5 kg, respectively. The session is terminated by a 5-minute CD at 148 BPM/ 22.5w. The home exercise is performed at 113 BPM.

From week 7 to 11, the patient starts with the HIIT-training. The training at Ghent university hospital consists of a 5-minute WU at 148BPM/22,5W. The interval training block is performed at 148bpm/22,5w and 170bpm/157w. The strength training, consisting of the squat, chest press, adductors and low row will be performed at 19kg, 37 kg, 38 kg and 26 kg, respectively. The session is terminated by a 5-minute CD at 148 BPM/ 22.5w. The home exercise is performed at 94bpm, and the exercises prescribed are completed.

From week 11 to 14, The training at Ghent university hospital consists of a 5-minute WU at 148BPM/22,5W. The interval training block is performed at 130bpm/20w and 170bpm/157w. The strength training, consisting of the squat, chest press, adductors and low row will be performed at 23,5, 44,5 kg, 46 kg and 32 kg, respectively. The session is terminated by a 5-minute CD at 148 BPM/ 22.5w. The home exercise is performed at 94bpm, and the exercises prescribed are completed.

### Feedback on training session

According to the American Heart Association classification this patient is very poorly conditioned. As a result, the ventilatory thresholds were not clear. VT1 could not be established due to unspecific data, presumably due to an already increased ventilation at low intensity. For this reason, VT1 has been placed at 25W. Taking these results into consideration, is has been decided to change the HIIT-protocol for this patient to aerobic interval training (AIT) to ensure the safety of the patient. From week 7 to 11, the aerobic intervals will consist of 3 minutes at an intensity that equals to 50% of the difference of VT1 and VT2 (176bpm and 100w) and 5 minutes at an intensity that equals to 100% of VT1 (164bpm/25w). From week 11 to 14, the intensity remains equal for the work and rest intervals, the duration goes up to 4 minutes. The strength training will remain as planned.

## Discussion

Complex interactions between IR, mitochondrial dysfunction and inflammation are key features in the development of MASLD. Exercise has been proven to be a very effective method to reduce earlier mentioned disabilities. We provided an exercise protocol based on current available research on exercise rehabilitation on IR in patients diagnoses with MASLD. In summary we attempted to compile a concurrent exercise protocol emphasizing different physiological pathways from a bioenergetic point of view. Aerobic exercise affecting the oxidative pathways and muscle fiber type I and HIIT emphasizing the glycolytic

pathways and muscle fiber type II, as thoroughly discussed in the introduction. Yet, the resistance training part of the protocol is identical. The reasoning is twofold. Firstly, as already mentioned; there is little evidence available on the impact of a concurrent exercise program, independent which kind of exercise. Subsequently it has been decided that the resistance training part will be identical to truly know if a combination of aerobic exercise and resistance training is superior to a combination of HIIT and resistance training or vice versa. Secondly, the World Health Organization guidelines states that an adult (18-65 years) should aim to be physically active for 150 minutes to 300 minutes each week, accompanied with at least 2 times resistance training of the major muscle groups (89). Therefore, both combinations incorporate resistance training.

*Feasibility*

For patient three we opted to change the protocol with regards to safety measures. The very poorly conditioned patient did a substandard CPET. As a result of risk management, we opted to change the HIIT protocol to an AIT protocol, keeping the intensity of the patient below the second ventilatory threshold. However, a recent study looked at the safety and feasibility of HIIT in patients diagnosed with MASLD. The participants performed a 12-week HIIT intervention of 3 training session per week. Each session consisted of a 5-minute WU at 60% HRmax, followed by 4 x 4 minutes at 85%-90% HRmax interspersed by 3 minutes recovery at 60% HRmax, finishing with a 5-minute CD, concluding that HIIT is safe and efficacious for patients diagnosed with MASLD(90). Furthermore, a recent meta-analysis suggests that HIIT interval training is feasible and safe in cardiac rehabilitation. The study states that a 1-minute low-volume HIIT exercise program (5 x 1 minute on-1minute off) is more tolerable then a 4x4 exercise HIIT program. The low-volume HIIT program even results in a greater impact compared to the 4x4 program, since the patients cannot hold the high intensity for 4 minutes (91). These studies suggest the original protocol should be safe and the subjects should aim to the prescribed intensity, despite the poor cardiorespiratory fitness of the population.

*AGE-reader*

Advanced glycation end products are associated with micro- and macrovascular complications and is believed to be an added value with the determination of cardiovascular risk (92). It has been proven that accumulation of AGE is related to the progression of MASLD to MASH and responds to increased oxidative stress and inflammation (93). Thus, the measurement of AGE's should be an added, non-invasive, clinical marker. However, our findings are inconsistent with these statements. The obtained AGE-values differ from reality, the values are within the normal range for healthy persons. For one of the subjects the AGE could diverge because of the skin phototype. Mulder and colleagues showed that in subjects with skin phototype

(V an VI) no reliable measurement can be performed (94). However, the other subjects are Caucasian therefore other variables should be considered.

*confounders*

The absence of a diet intervention will have an impact on the results of the study. We hypothesize that this will be two-sided. Firstly, in response to being more physically activate, the subjects could increase their calorie intake through dietary adjustments. This increase could possibly blur the effect of an exercise intervention on the clinical and physiological representation of MASLD and IR. Secondly, according to the Hawthorn effect individuals alter their behavior in response to being aware of their research participation and the fact that they are being studied (95). In this case the participants could, conscious of subconscious, alter their diet or physical activity outside the prescribed exercise protocol causing bias towards the results and their interpretation (96). For this reason, a food questionnaire has been added, to plot potential compensations of the participants. However, it should be noted that despite this added insight gained from the questionnaires into the dietary behavior of the subject, they are solely dependent of the recall of the patient. The same reasoning could be used for the change in behavior regarding physical activity. Physical activity is increased due to exercise protocol, however next to the training sessions the patients could increase their daily step count leading to a potential greater impact on, for example, IR then we could acquire had they only been doing the prescribed exercise protocol. These potential biases could be countered with an increased input from technological tools (e.g. pedometer) or subscribing a more detailed protocol considering the amount of calorie consumption and daily step count (e.g. between 8000 and 10 000 steps/day).

*financial restrictions/ Blinding patients and therapist*

This study is part of a master's dissertation of physiotherapy students, hence the total budget for the study is relatively modest. The modest budget results in no golden standard measurement manners with regards to the outcome variables. For example, the diagnosis of MASLD is performed via echography and not liver biopsy, the current golden standard or magnetic resonance imaging (MRI). Furthermore, the IR diagnosis is not performed using the hyper insulinemic euglycemic clamp, instead a less expensive, yet reliable (as mentioned in methods), method (HOMA-IR) has been used.

Blinding of the patients was not possible. Due to the difference in exercise protocol, it is clear to the patients to which group they are randomized. This should not have an impact on the outcome of the study. The same argument can be made for the attending physiotherapy students. The students support the participants during the training sessions, compromising the blinded randomization. However, because of

the well described exercise intensities that should be executed, the knowledge to which group each participant is randomized should not impact the results of the study. On top of that, two of the lead authors are solely involved with the recruitment of the subjects and not the execution of the randomization and training sessions, diminishing the bias towards blinding.

*Timeline*

Due to unanticipated circumstances (the approval of the ethics committee was delayed due to technological errors leading to an insurmountable time loss) the start of the recruitment of the participants had to be postponed. Besides, our protocol has a total duration of 14 weeks, adding one week before and after the training period for the assessments of the subjects coming together at 16 weeks in total. The timeframe was too narrow to be able to fully assess the recruited subjects. Therefore, the intention of the master's dissertation shifted towards a thorough protocol study. The baseline results of the recruited patients and their feedback has been taken into consideration when discussing this protocol. The continuation of the study is secured, and the total duration is currently estimated at another 20 months. Provided that the current rate of recruitment, 3 to 4 subjects each month, can be hold.

## Conclusion

If the provided protocol implements successfully, it not only provides evidence for a combined exercise intervention in insulin resistance in patients diagnoses with MASLD but also provides a well-balanced exercise regime conform the WHO guidelines to improve metabolic health.

# Appendix

## cardiometabolic risk factors:

1. BMI≥ 25kg/$m^2$ OR WC > 94cm (M), 80cm(F)
2. Fasting serum glucose≥ 5,6 mmol/L OR 2-hour post-load glucose levels ≥ 7,8mmoml/L OR HbA1c ≥ 5,7% OR T2DM OR treatment for T2DM
3. Blood pressure ≥ 130/85 mmHg OR specific anithypertensive drug treatment
4. Plasma triglycerides ≥ 1,70mmoml/L OR lipid lowering treatment
5. Plasma HDL-cholesterol ≤ 1;0mmol/L (M), ≤ 1,3 mmol/L (F) OR lipid lowering treatment

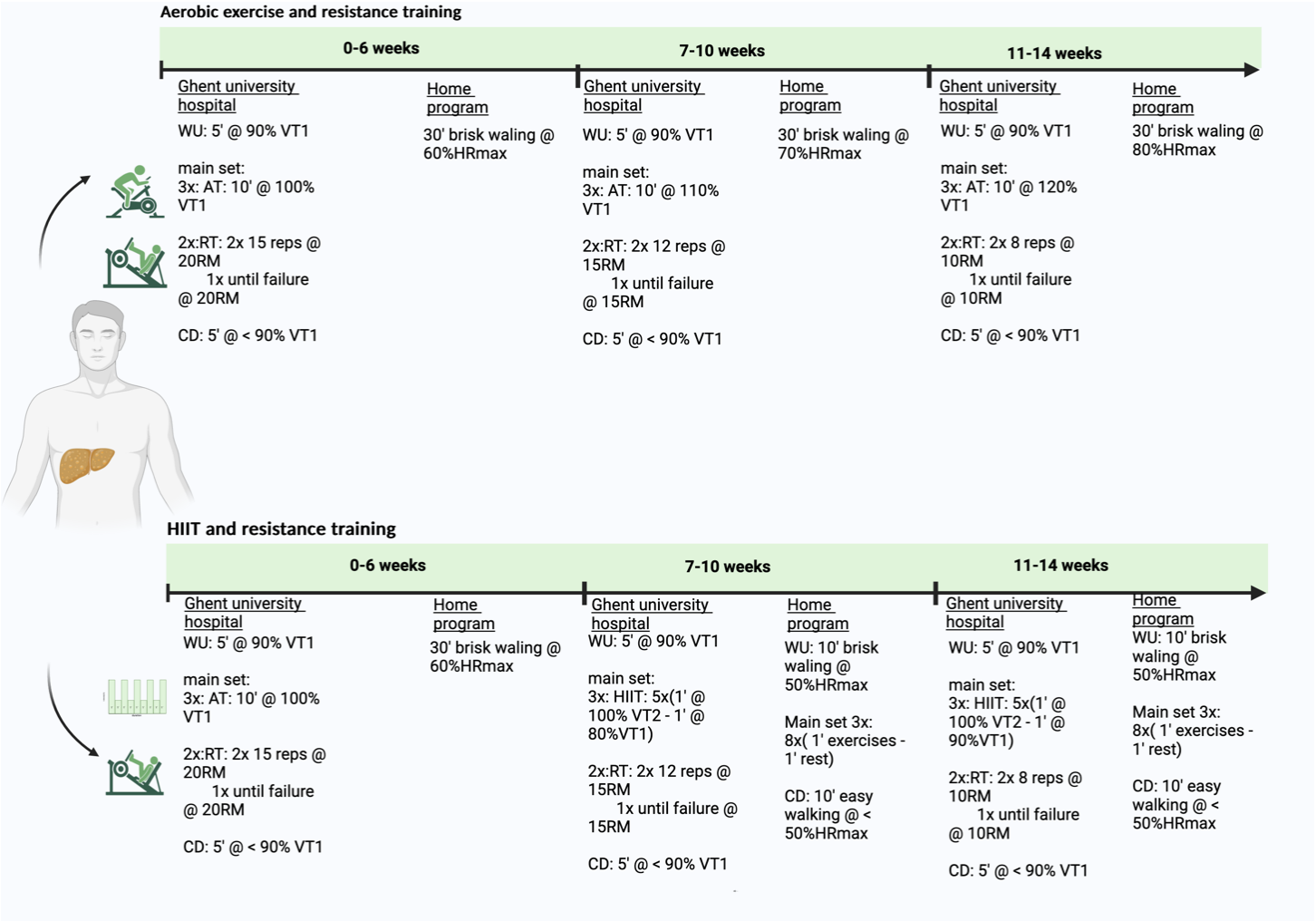


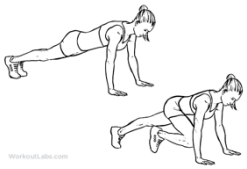
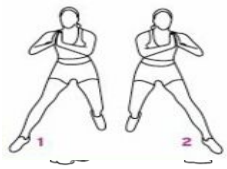
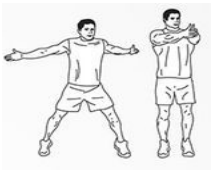
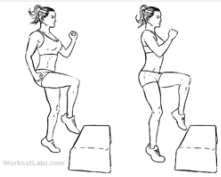

*Figure 2: Exercise protocol group A&B*

| *Participant* | *1* | *2* | *3* |
|---|---|---|---|
| | *Body composition* | | |
| *Sex* | M | F | F |
| *Age* | 26 | 53 | 26 |
| *Height (cm)* | 169 | 166 | 159 |
| *Weight (kg)* | 106,9 | 79,4 | 109,3 |
| *BMI* | 37,4 | 28,8 | 43,2 |
| *Waist circumference (cm)* | 120 | 103 | 117 |
| *Fat%* | 38,9 | 40,1 | 44,5 |
| *FM (kg)* | 41,6 | 31,8 | 48,6 |
| *FFM (kg)* | 65,3 | 47,6 | 60,7 |
| *AGE* | 1,6 | 1,9 | 1,4 |
| *Triglycerides* | 123 | 222 | 100 |
| *Cholesterol* | 170 | 244 | 238 |
| *LDL* | 106 | 134 | 176 |
| *HDL* | 41 | 74 | 40 |
| *Blood pressure (mmHg)* | 144/103 | 184/123 | 135/72 |
| *6MWD (m)* | 555 | 535 | 500 |
| *Handgrip strength L/R (N)* | 54/48 | 32/28 | 35/30 |
| *Muscle fatigue (s)* | 15,18 | 50,6 | 42,26 |
| *30CST* | 14 | 19 | 13 |
| | *CPET* | | |
| *VO2 peak (ml/kg/min)* | 2,41 | / | 1,85 |
| *HR max (bpm)* | 194 | / | 188 |
| *W max (Watt)* | 200 | / | 175 |
| *RER* | 1,17 | / | 1,25 |
| *VT1 (Watt)* | 106 | / | 25 |
| *VT1 (bpm)* | 159 | / | 164 |

| | | | |
|---|---|---|---|
| *VT2 (Watt)* | 181 | / | 175 |
| *VT2 (bpm)* | 193 | | 188 |
| | *1RM test (kg)* | | |
| *Chest press* | 53 | 18,8 | 52,8 |
| *Low Row* | 68,5 | 27,8 | 37,6 |
| *Adductors* | 66,3 | 37,5 | 54,3 |
| *Squat* | 37,6 | | 27,6 |
| *Leg extension* | | 17,9 | |
| *Leg Curl* | | 20,8 | |
| | Blood biochemistry | | |
| *Fasting glucose* | 106 | 157 | 87 |
| *Insulin* | 68 | | 50 |
| *HOMA-IR* | 17,8 | | 10,7 |
| *ALT* | 41 | 105 | 90 |
| *AST* | 28 | 51 | 91 |
| *IL-6* | | | |
| *IL-8* | | | |
| *TNF-α* | | | |
| | *Transient elastography* | | |
| *Fibroscan* | 5,7 | 6,8 | 6,3 |
| *CAP* | 391 | 319 | 325 |
| *Echography* | Severe steatosis (grade 3) | Moderate steatosis (grade 2) | / |
| *SF36* | 52,13 | / | / |

Table 2: baseline characteristics participants.

Abbreviations: BMI; body mass index, FM; fat mass, FFM; fat free mass, AGE; advanced glycated end products, LDL; low density lipoprotein, HDL; High density lipoprotein, 6MWD; 6 minute walking distance, 30 CST; timed chairs stand test, CPET; cardiopulmonary exercise test, HR; heart rate, RER: respiratory exchange ratio, VT; ventilatory threshold, 1RM; 1 repetition max, HOMA-IR; homeostatic model assessment for insulin resistance, ALT; alenine transamirase, AST; aspartate transamirase IL-6; interleukin – 6, IL8; interleukin – 8 , TNF-α; tumor necrosis factor - α, CAP; controlled attenuation parameter

| *Exercise:* | *Name:* | *Duration:* | *Rest:* |
|---|---|---|---|
| *1* | Jumping jacks | 30 sec | |
| |  | | 1min |
| *2* | Burpees | 30 sec | |
| |  | | |
| *3* | Mountain climbers | 30 sec | |
| |  | | |
| *4* | Lateral jumps | 30 sec | 1min |
| |  | | |
| *5* | Seal jacks | 30 sec | |
| |  | | |
| *6* | High knee steps | 30 sec | 1min |
| |  | | |
| *7* | Toe taps | 30 sec | |
| |  | | 1min |
| *8* | Jumping squats | 30 sec | |

| | | |
|---|---|---|
| |  | |

*Table 3: Home exercises- HIIT program*

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## Populariserende samenvatting

Niet-overdraagbare aandoeningen, zoals hart- en vaatziekten en diabetes, zijn tegenwoordig de belangrijkste oorzaak van overlijden. Veel van deze aandoeningen ontstaan door een ongezonde levensstijl, met te weinig lichaamsbeweging en te veel bewerkte voedingsmiddelen. Een gevolg hiervan kan een vette lever en insulineresistentie zijn, waarbij het lichaam moeite heeft om suiker effectief te verwerken.

Veel onderzoek heeft al aangetoond dat gestructureerde lichaamsbeweging een positieve invloed kan hebben op het metabolisme van patiënten. Echter, er zijn nog steeds hiaten in ons begrip van welk type oefeningen het meest effectief zijn. Het huidige advies voor patiënten is vaak te algemeen en onnauwkeurig.

Dit onderzoek probeert hier verandering in te brengen door te kijken naar hoe verschillende vormen van lichaamsbeweging het fysiologisch profiel van patiënten beïnvloeden. Patiënten worden verdeeld in twee groepen: groep A volgt een trainingsprogramma met aerobe en krachtoefeningen, terwijl groep B een programma met high intensity intervaltraining (HIIT) en krachtoefeningen volgt.

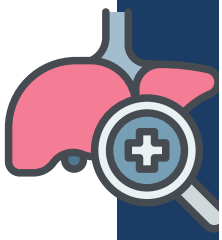
Het doel is om te zien welke benadering het meest effectief is. De resultaten van deze studie kunnen bijdragen aan het ontwikkelen van gerichte trainingsprogramma's voor patiënten, waardoor ze beter kunnen omgaan met hun aandoening en hun algehele gezondheid kunnen verbeteren.

FACULTY OF MEDICINE AND HEALTH SCIENCES

# HET EFFECT VAN INSPANNINGSREVALIDATIE OP INSULINE RESISTENTIE BIJ MENSEN MET MASLD

## Niet-overdraagbare aandoeningen

Belangrijkste oorzaak van overlijden
Ontstaan door ongezonde levensstijl, met te weinig lichaamsbeweging en te veel bewerkte voedingsmiddelen
**Mogelijk gevolg: insulineresistentie en/of vette lever**

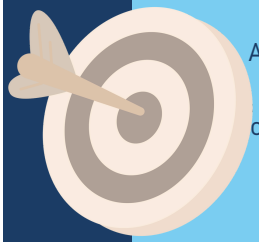


## Lichaamsbeweging

Onderzoek toont ontegensprekelijk aan dat gestructureerde lichaamsbeweging een positieve invloed heeft op het metabolisme van een individu. Echter,
**het huidig advies is vaak onnauwkeurig en te algemeen.**

## Huidig onderzoek

Zoektocht naar effect van verschillende vormen van lichaamsbeweging op het fysiologisch profiel van een patiënt. Twee trainingsgroepen (groep A en B) krijgen een ander programma voorgeschoteld en worden met elkaar vergeleken
Groep A: combinatie van aerobe- en krachttraining
Groep B: combinatie van HIIT en krachttraining



## Doel van het onderzoek

Achterhalen welke benadering is het meest effectief. Deze onderzoeksresultaten kunnen bijdragen tot het ontwikkelen van een gericht trainingsprogramma om zo de
**ziekte beter onder controle te houden.**

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## Maatschappelijke meerwaarde

Metabole en endocriene aandoeningen zijn alom tegenwoordig in de maatschappij. Dit heeft een detrimente impact op zowel op het sociaaleconomisch luik van de maatschappij als op de medische sector. De medicatie en begeleiding van MASLD-patiënten worden tegemoetgekomen door het RIZIV. Het spreekt voor zich dat dit een enorme kost is voor de maatschappij. Cijfers vrijgegeven door het RIZIV tonen dat in 2021 meer dan 250 miljoen euro werd uitgegeven in apotheken aan medicatie voor diabetespatiënten, dit zowel aan insuline (en analogen) en bloedglucose reducerende medicatie (exclusief insuline) (98). Indien een concreet trainingsprogramma een positief effect kan hebben op de insulinesensitiviteit bij patiënten met insulineresistentie, zal dit uiteindelijk leiden tot een daling van de afhankelijkheid van insulinemedicatie. Naast deze rechtstreekse economische impact zorgt een trainingsprogramma voor een toename van de fysieke fitheid van een persoon. Deze toename heeft een positieve invloed op het fysiek en mentaal welzijn van het individu. Dit, samen met een toename in het zelfvertrouwen, zal ertoe leiden dat deze persoon beter kan deelnemen aan de maatschappij. Wetenschappelijk onderzoek toont aan dat Een gestructureerd trainingsprogramma kan bijdragen aan het minder prematuur staken van de activiteiten op de werkvloer (99). In een populatie met overgewicht die laag op de socio-econmische ladder staat is het ook aangetoond dat een intensieve sportbegeleiding leidt tot een verbetering van levenskwaliteit en deelname aan de maatschappij (100).

Het kan echter niet de bedoeling zijn dat elk individu een intensieve begeleiding, en de kost die daar aan gekoppeld is, nodig heeft om van de voordelen van het sporten te genieten. Dit onderzoek kan een stap in de juiste richting zijn om een globaal, doch gestructureerd advies te kunnen geven naar de patiënten toe. Verder onderzoek zal moeten uitwijzen hoe men deze informatie best overbrengt naar de MASLD-populatie, en hoe men deze mensen warm moet maken tot het volgend van gestructureerd trainingsprogramma.

FACULTY OF MEDICINE AND HEALTH SCIENCES

# Approvement of ethics committee

Afzender : Commissie voor medische ethiek

Prof. Dr. Anja Geerts
Maag-, darm- en leverziekten
UZ Gent

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| **Aanvrager** | **datum** | **pagina** |
| Patrick Calders | 05/01/2024 | 1/6 |
| **Onze referentie:** | **EudraCT-nr:** | **Belg. Regnr:** |
| ONZ-2023-0453 | | B6702023000625 |

**Betreft:**

**Effect van high intensity inspanningsrevalidatie op leververvetting, insulinegevoeligheid en cardiovasculair risico bij patienten met MASLD.**

**Effect of high intensity exercise rehabilitation on liver steatosis, insulin sensitivity and cardiovascular risk in patients with MASLD**

**Positief advies conform de wet van 7 mei 2004 betreffende experimenten op de menselijke persoon**

Beste collega

De Commissie Medische Ethiek (CME) verbonden aan de Universiteit Gent (Ugent) en het Universitair Ziekenhuis Gent (UZ Gent) heeft het bovenvermelde dossier onderzocht en besproken op haar vergadering van 14/11/2023.

Na raadpleging van de bijkomende informatie en/of aangepaste documenten met betrekking tot dit dossier, is de CME van oordeel dat de voorgestelde studie, zoals beschreven in het protocol, wetenschappelijk relevant en ethisch verantwoord is.

EC geeft daarom op 02/01/2024 een gunstig advies over deze studie.

Ingediende documenten: zie bijlage 1
Ledenlijst: zie Bijlage 2
Aandachtspunten: zie Bijlage 3a

**ALGEMENE DIRECTIE**
Commissie voor Medische Ethiek

**VOORZITTER:**
Prof. dr. R. Peleman

**SECRETARIS:**
Dr. L. Goossens

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Met vriendelijke groeten,
Prof. dr. Renaat Peleman
Voorzitter
Commissie voor Medische Ethiek U(Z) Gent

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CC: FAGG
Cc: HIRUZ_CTU (Clinical Trial Center UZ Gent)

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Unofficial translation in English:

**Positive advice in accordance with the law of 7 May 2004 on experiments on the human person**

The Ethics committee (EC) of University Ghent (Ugent) and Ghent University Hospital (UZ Gent) has examined and discussed the above mentioned dossier at its meeting of 14/11/2023.

After consulting the additional information and/or modified documents related to this dossier, the CME is of the opinion that the proposed study, as described in the protocol, is scientifically relevant and ethically justified.

EC therefore gives on 02/01/2024 a favourable opinion on this study

Submitted documents: see Annex 1
List of members: see appendix 2
Points of concern: see appendix 3b

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