Exercise capacity with special reference to type 2 diabetes

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To my beloved family Jonas, Elsa and Edvin

Abstract

Physical inactivity and obesity is a growing health problem world wide.

Three different samples with a wide range of glucose tolerance were included in the thesis to represent a wider population. The exercise capacity was studied in one group of healthy sedentary middle aged men with normal glucose tolerance in study I and II. In a group of elderly men with normal glucose tolerance (NGT), impaired glucose tolerance (IGT) and with type 2 diabetes (T2D) was the influence of insulin sensitivity on exercise capacity studied (Study III). Exercise testing and exercise training in individuals with T2D was examined in a group of middle aged women with T2D in study IV and V.

The performance of a maximal incremental cycle test in sedentary healthy male subjects was highly affected by lower extremity muscular strength and muscular endurance (Study I). Also upper body muscular strength correlated to exercise capacity as measured by cycle ergometry. When exercise capacity and muscular strength of the upper body increased in response to combined supervised group training, the correlation between muscular strength of the upper body and exercise capacity improved (Study II). Exercise capacity assessed during cycling was affect by whole body insulin sensitivity and the waist-hip ratio (Study III). Also, fibre type composition (Study I and III) and capillary density (Study III) contributed to peak exercise capacity. Estimation of VO_{2peak} according to Åstrand sub-maximal exercise testing significantly overestimates directly measured VO_{2peak} in women with T2D (Study IV). Improved insulin sensitivity appeared to be related to exercise intensity rather than duration, whereas improved HbA1c appeared to be related to exercise volume in T2D women (Study V).

Though closely related, there may be different indices explaining VO_{2peak} and WR_{peak}. Muscular strength and muscular endurance of not only the legs but also the arms and trunk may be important aspects of peak exercise capacity during a cycle test in healthy sedentary men. Exercise capacity is independently related to insulin sensitivity, muscle fibre composition and waist/hip ratio in subjects with NGT, IGT and T2D whom are matched for age and BMI. This suggests that metabolic abnormalities in skeletal muscle are of prime importance for the reduction in exercise capacity in over a wide range of insulin sensitivity. Sub-maximal tests should be used with caution in patients with T2D. Improvement in insulin sensitivity after six months combined supervised group training in female diabetic subjects is related to exercise intensity, whereas the reduction in HbA1c is related mainly to training volume. Metabolic effects of training may be seen in the absence of improved exercise capacity.

Svensk sammanfattning

(SUMMARY IN SWEDISH)

Fysisk inaktivitet och fetma är ett växande hälsoproblem i hela världen.

Tre olika grupper av individer med ett brett spektrum av glukostolerans ingick i avhandlingen. Arbetskapacitet har studerats i en grupp friska fysiskt inaktiva medelålders män med normal glukostolerans i studie I och II. Hos en grupp äldre män med normal glukostolerans (NGT), nedsatt glukostolerans (IGT) och med typ 2 diabetes (T2D) studerades påverkan av insulinkänsligheten på arbetskapaciteten (studie III). Arbetskapacitet och effekten av kombinerad grupp träning studerades i en grupp medelålders kvinnor med T2D i studie IV och V.

Arbetskapaciteten vid cykelarbete hos inaktiva friska män påverkades av nedre extremitetens muskelstyrka och muskulära uthållighet (Studie I), även överkroppens muskelstyrka relaterade till arbetskapacitet mätt på en ergometercykel. När överkroppens muskelstyrka ökade som svar på kombinerad gruppträning, ökade sambandet mellan muskelstyrka i överkroppen och arbetskapacitet (Studie II). Arbetskapacitet vid cykling påverkas av hel kropps insulinkänslighet och midja-höft kvoten (Studie III). Även muskelfibersammansättning (Studie I och III) och kapillär densitet (Studie III) bidrog till den maximala arbetskapaciteten. Uppskattning av VO_{2peak} enligt Åstrand submaximal cykel test överskattar direkt mätt VO_{2peak} hos kvinnor med T2D (studie IV). Ökad insulinkänslighet föreföll vara relaterad till träningens intensitet snarare än varaktighet, medan sänkning av HbA1c föreföll vara relaterad till träningsvolym hos kvinnor med T2D (Studie V).

Även om VO_{2peak} och WR_{peak} är nära relaterade, kan det finnas olika förklaringsmekanismer. Muskelstyrka och muskulär uthållighet, inte bara benen utan även i armar och bål, kan vara viktiga aspekter vid ett maximalt cykeltest hos friska inaktiva män. Arbetskapaciteten var beroende av insulinkänslighet, muskelfibersammansättning och midja-höft kvoten hos individer med NGT, IGT och T2D som är matchade för ålder och BMI. Detta tyder på att metabolastörningar i skelettmuskel är av avgörande betydelse för arbetskapaciteten i en grupp med ett brett spektrum av insulinkänslighet. Submaximala tester för att skatta VO_{2peak} bör användas med försiktighet hos patienter med T2D. Förbättrad insulinkänslighet efter sex månaders kombinerad gruppträning hos kvinnliga diabetiker var kopplat till träningsintensitet, medan minskningen av HbA1c är främst relaterad till träningsvolym. Metabola effekter av träning kan ses i avsaknad av en ökad arbetskapacitet.

Contents

List of publications

I. Segerström ÅB, Holmbäck AM, Hansson O, Elzyri T, Eriksson KF, Ringsberg K, Groop L, Wollmer P, Thorsson O. *Relation between cycling exercise capacity, fibre type composition and lower extremity muscle strength and muscle endurance.* (Submitted for publication 2010)

II. Segerström ÅB, Holmbäck AM, Hansson O, Elzyri T, Eriksson KF, Ringsberg K, Groop L, Thorsson O, Wollmer P. *Upper body muscle strength and endurance in relation to peak exercise capacity during cycling in healthy sedentary male subjects*. (Accepted for publication 2010, Journal of Strength and Conditioning Research)

III. Segerström ÅB, Elgzyri T, Eriksson KF, Groop L, Thorsson O, Wollmer P. *Exercise capacity in relation to body fat distribution and muscle morphology in elderly male subjects with impaired glucose tolerance, type 2 diabetes and matched controls*. (Manuscript)

IV. Segerström ÅB, Glans F, Eriksson KF, Groop L, Thorsson O, Wollmer P. *Assessment of exercise capacity in women with type 2 diabetes*. Clin Physiol Funct Imaging 2008:294-8.

V. Segerström ÅB, Glans F, Eriksson KF, Holmbäck AM, Groop L, Thorsson O, Wollmer P. *Impact of exercise intensity and duration on insulin sensitivity in women with type 2 diabetes.* (Submitted for publication 2010)

Abbreviations

$\Delta VO_2\ \Delta WR^{-1}$	Movement economy (1, 2)
ACSM	American Collage of Sport Medicine
ATP	Adenosine triphosphate
BMI	Body mass index (3)
C_AO_2-C_VO_2	Extraction of oxygen by exercising muscles from the capillaries
CO_2	Carbon dioxide
CP	Creatine phosphate
CV	Coefficient of variance
EVO_{2peak}	Estimated maximal oxygen consumption (4)
FBG	Fasting blood glucose
FFA	Free fatty acid
FITT	Frequency (F), intensity (I), time of duration (T), Type or mode (T) of exercise (5)
GLUT	Glucose transporter (6)
GLUT-1	Glucose transporter 1 (6)
GLUT-4	Glucose transporter 4 (6)
H_2O	Water
Hb	Haemoglobin
HbA1c	Glycated haemoglobin
HOMA	Homeostatic model assessment (7)
HR_{peak}	Peak heart rate (1, 2)
HRR	Heart rate ratio (8)
$HRR_{\%}$	Heart rate ratio in percent (8)
$HR_{exercise}$	Heart rate during exercise training (8)
IFG	Impaired fasting blood glucose (9)

IGT	Impaired glucose tolerance (9)
KE	Knee extension
KF	Knee flexion
MVC	Maximal voluntary contraction
O_2	Oxygen
$O_2\ HR^{-1}$	Oxygen pulse
OGTT	Oral glucose tolerance test
RER	Respiratory exchange ratio (2)
RM	Repetition maximum
RPE	Rate of perceived exertion (10)
sEMG	Surface electromyography
SV	Stroke volume (1, 2)
T2D	Type 2 diabetes (9)
VE	Ventilation (1, 2)
VO_{2max}	Maximal oxygen consumption (1, 2)
VO_{2peak}	Peak oxygen consumption (1, 2)
WHO	World health organisation
WHR	Waist hip ratio
WR_{peak}	Peak work rate (1, 2)

Definitions

Aerobic Capacity	Is in this thesis, VO_{2peak}, which is the highest value of VO_2 in an exercising subject during the last minute of an incremental exercise test before abortion due to exhaustion.
Capillary density	Number of capillaries per muscle fibre.
Exercise	A subset of physical activity that is planned, structured, repetitive and purposeful in the sense to improve or maintain physical fitness (11, 12).
Exercise Capacity	Exercise at maximal intensity.
Exercise Duration	Time during which exercise training is performed (5).
Exercise Frequency	Number of days per week (5) on which exercise training is performed.
Exercise Intensity	Level on which exercise training is performed relative to peak values of HR and/or VO_2 (5).
Exercise Volume	Is the quantity of exercise, measured as exercise duration and intensity (5).
HR_{peak}	Is the highest heart rate in an exercising subject during the last minute of an incremental exercise test before abortion due to exhaustion.
Insulin Resistance	Impaired insulin effect compared to matched controls (7).
Insulin Sensitivity	Biological effect from a specified amount of insulin (7).
Muscular Endurance	Is the ability of a muscle group to exert external force for series of consecutive muscle contractions (5, 13).
Muscular Strength	Is the maximal torque a muscle or muscle group can generate at a determined velocity (11).

M-value	Insulin sensitivity measured by hyperinsulinemic-euglycemic clamps (14).
Peak Torque	Is the single highest torque produced by the muscular contraction during a fixed range of a motion (15).
Physical Activity	Any bodily movement produced by skeletal muscles that result in energy expenditure (11, 12).
Physical Fitness	Includes aerobic capacity, muscular strength, body composition and flexibility, composing a set of attributes that people have or achieve that relates to the ability to perform physical activity (5, 12).
RER	Produced amount of carbon dioxide (CO_2) divided by consumed amount of oxygen (O_2)(2).
RER_{peak}	Is the highest RER in an exercising subject during the last minute of an incremental exercise test before abortion due to exhaustion.
Sedentary	Not participating in at least 30 minutes of moderate intensity physical activity on at least three days of the week for at least three month (5).
Total Work	Is the amount of work accomplished for the entire set of contractions (15).
VO_{2kg}	Is the highest value of VO_2 (ml min^{-1}) measured in an exercising subject during the last minute of an incremental exercise test before abortion due to exhaustion divided by body weight in kg (1, 2).
VO_{2max}	Is the highest theoretical physiological value of VO_2 in an exercising subject (1, 2).
VO_{2peak}	Is the highest value of VO_2 (l min^{-1}) measured in an exercising subject during the last minute of an incremental exercise test before abortion due to exhaustion (2, 16).
Work Rate (WR)	Is mechanical work reflected as external power which is measured in watt, W (17).
WR_{peak}	Is the highest value of WR performed by an exercising subject during an incremental exercise test before abortion due to exhaustion (1, 2).

Thesis at a glance

	Aim	Methods	Result	Conclusion
I	To determine the relation between peak oxygen uptake (VO_{2peak}), peak work rate (WR_{peak}), fibre type composition and lower extremity strength and endurance during a maximal incremental cycle test.	An incremental cycle test, isokinetic tests of the knee at 60° s^{-1} and 180 s^{-1} and muscle biopsy from m vastus lateralis was performed.	Backward and forward regression analyses showed that KE strength, KF endurance and the percentage of type 1 fibres could explain up to 40% of the variation in VO_{2peak} and WR_{peak}.	The performance of sedentary subjects in a maximal incremental cycle test is highly affected by knee muscle strength and endurance. Fibre type composition also contributes, but to a smaller extent.
II	To investigate the relation of upper body strength and endurance to VO_{2peak} and WR_{peak} during an incremental cycle exercise test in sedentary healthy male subjects before and after six months of combined supervised group training.	An incremental cycle test, muscle strength and muscle endurance of the upper body was assessed by bench press and by isometric measurements of trunk extensors and flexors..	Bench press and trunk extensor MVC correlated to exercise capacity at baseline as well as after training. Training increased VO_{2peak} and WR_{peak}. The correlation between trunk extensor MVC and exercise capacity improved after training.	Upper body strength may affect exercise capacity by increasing the rider's ability to generate force on the handlebar that can be transmitted to the pedals.
III	To examine the impact of insulin sensitivity and muscle morphology on exercise capacity.	An incremental, maximal exercise test on a cycle ergometer, hyperinsulinemic-euglycemic clamp and muscle biopsy.	Backward and forward regression analyses showed that insulin sensitivity, Type 1 muscle fibres and WHR could explain up to 40% of the variation in VO_{2peak} and WR_{peak}.	Exercise capacity is independently related to insulin sensitivity, muscle fibre composition and WHR in subjects with NGT, IGT and T2D who are matched for age and BMI.
IV	To compare VO_{2peak} evaluated from a sub-maximal exercise test to direct measurements of VO_{2peak} in women with T2D.	Twelve-week training program was evaluated with a sub-maximal exercise test according to Åstrand and Rhyming and an incremental, maximal exercise test on a cycle ergometer at baseline, 6 and 12 weeks.	In a Bland-Altman analysis, poor agreement between EVO_{2peak} and VO_{2peak} was found. EVO_{2peak} systematically overestimated VO_{2peak} by 476±1310 ml min^{-1}.	Sub-maximal tests should be used with caution in patients with T2D.
V	To examine the effect of group exercise training on exercise capacity, insulin sensitivity and HbA1c in women with T2D.	Combined supervised group training during six months was evaluated with an incremental bicycle test, hyperinsulinemic-euglycemic clamps and HbA1c.	VO_{2peak} did not change significantly. Insulin sensitivity increased and HbA1c decreased significantly in the group exercising at a higher volume after 6 months.	Improvement in insulin sensitivity after six months combined training in women with T2D is related to exercise intensity, whereas the reduction in HbA1c is related mainly to training volume.

Introduction

Type 2 diabetes is a huge health problem all over the world and it is growing rapidly (18). Among risk factors for developing T2D a sedentary life style is known to be important (19). Individuals with type 2 diabetes are also known to have lower exercise capacity compared to controls (20, 21). One of the cornerstones in treatment of type 2 diabetes is exercise (19), even though not all type 2 diabetic individuals increase their exercise capacity after an exercise training period (22).

Physiotherapists in Sweden commonly use supervised group training as treatment of different diseases (23). Supervised group training consists mostly of combined exercise training with aerobic-training, resistance-training and stretching routines aimed to increase overall fitness. Little is known about the disease specific effects of combined supervised group training.

In Sweden, supervised group training has a long history as treatment of different diseases. Per Henrik Ling (1776-1839) started to prescribe physical exercise in the 19th century. Different movement routines were used for both treatment and prevention of disease. Ling was inspired by the German philanthropinists JB Basedow and CG Salzman who started to systemise body movements and analyze their physiological effects. Basedow and Salzman were in turn inspired by the ideas of Rousseau about national education (24). Ling's vision was to educate the nation physically and Ling-gymnastics became part of school education and was so until 1940ies. The ideas of Ling became gradually old-fashioned and were therefore not used systematically anymore (25). Supervised group training started again in lager scale in 1980s, and different kinds of group training were developed. The purpose of this exercise training was to maintain or improve physical fitness. In 2000ies the idea of prescribing exercise training as treatment of diseases arose again.

The overall aim of supervised group training regimes is to maintain and/or increase the physical fitness of the exercising individual. It is essential to have knowledge about exercise physiology, even disease specific exercise physiology, and how to assess different aspects of exercise capacity in disease when prescribing exercise training as treatment of disease.

Exercise Capacity

Exercise is all and any physical activity from skeletal muscle contraction resulting in generating force (11). Performance of exercise includes both mechanical and metabolic power. Mechanical power is defined as external power, reflecting the biomechanical situation. The metabolic power reflects the internal power, produced in the muscle cells via aerobic and anaerobic re-synthesis of adenosine triphosphate (ATP) (11).

Biological work can be expressed as mechanical work, chemical work and transport work (17). Mechanical work is reflected as external power which is measured in watt, W, expressing the distance, s, and a force, N, which has been overcome during a specific amount of time, t (17). In the literature this is referred to as power, power output or work rate (WR) (26). Chemical work is connected to the internal power which will be referred to as VO_2. At a sub-maximal level there will be a linear relationship between WR and VO_2. This relationship does not necessarily exist at peak exercise (1, 2). At peak exercise anaerobic metabolic mechanisms will also be involved to ensure re-synthesis of ATP (11, 17). Transport work is energy consumed by active transport of different substrates through the cell membrane (17). Metabolic power exceeds mechanical power. The exceeding power energy appears as heat. The efficiency is the mechanical power divided by metabolic power and will be about 20-25% (11).

Aerobic capacity

Aerobic capacity was described by Fick already in the 1870s. He showed that oxygen consumption is dependent on the heart's ability to deliver blood to the exercising muscles, by means of heart rate (HR) and stroke volume (SV) (27). The ability to transport oxygen, via haemoglobin (Hb), and the extraction of oxygen by the exercising muscles, C_AO_2-C_VO_2, will also influence the aerobic capacity.

$$VO_2 = (HR \cdot SV) \cdot (1.39 \cdot Hb) \cdot (C_AO_2 - C_VO_2) \quad \text{Fick, 1870}$$

Maximal aerobic capacity, VO_{2max}, has been defined as VO_2 at a constant work load exercise that fails to increase by 150 ml min^{-1} by Taylor in 1955 (2). This definition has been argued to have weaknesses (28). Increase of oxygen consumption by 150 ml min^{-1} is a large fraction at peak exercise. In normal individuals during incremental exercise only one-third performing maximal exercise reach this levelling-off effect (2).

When aerobic capacity values are reported they are often expressed relative to body weight (5). Subjects with large body size have larger heart and lungs compared to those with smaller body size. This is an advantage in oxygen delivery and in C_AO_2-C_VO_2 due to lager muscle mass. Larger body size however gives more body mass to support with oxygen, which can be a disadvantage (1).

Peak heart rate (HR_{peak}) is genetically predetermined and decreases with aging (1). Estimation of HR_{peak} can be made as 220-age. This estimation predicts HR_{peak} in 95% of a population within a standard deviation of ± 10 beats min^{-1} (29). The ability to increase aerobic capacity has been shown to be dependent on the SV rather than HR_{peak} (1).

Haemoglobin in the red blood cells, erythrocytes, transports up to 98% of the oxygen (30). The content of Hb has been shown to highly determine the aerobic capacity (31, 32). A content of Hb within a range of 140 to 180 g l^{-1} for men and 115 to 160 g l^{-1} for women is considered to be normal (1).

Oxygen consumption occurs mainly in the mitochondria (31). Transport of oxygen from the blood to the mitochondria is by diffusion. High capillary density around the muscle cells facilitates diffusion of oxygen (O_2) into the muscle cells, which has been shown to increase aerobic capacity. Extraction of oxygen from the arterial blood to the exercising muscles cells is maintained as long as there is a peripheral diffusion gradient (31).

Respiration

Oxygen diffuses from the alveolus of the lung into the red blood cells in the capillaries surrounding the alveolus (17). Ventilation of the lung increases during exercise as the need of oxygen increases in the exercising muscles (2).

Muscular strength and muscular endurance

Skeletal muscles produce force and movement. The exercising muscle is organized in motor units. Each unit is controlled by a motor neuron, with its cell body in the spinal cord and the axon extending to specific muscle fibres (11, 17). The muscle fibres are classified into subgroups, type I (slow twitch, oxidative), type IIa (fast twitch, oxidative/glycolytic), and type IIx (fast twitch, glycolytic) (1, 11, 17). The axon attached to the type I fibres is thinner than that to the type II fibres. This makes the type I fibres more excitable than the type II fibres. The difference in the threshold of excitation determines the recruitment order of the muscle fibres (11).

The ability of the skeletal muscles to produce force is dependent on neuronal factors as motor unit recruitment and discharge rate. Mechanical properties such as moment arm of the limb, architecture, length and speed of contraction of the muscle influences the force produced. Cross-sectional area and fibre composition of the muscle also affects the force development (11). The skeletal muscles are able to produce force with movement (dynamic/kinetic) and without (static/isometric) any movement of the body. Kinetic movements are concentric (shortening of the muscle) and eccentric (prolonging the muscle) (17). Isokinetics refers to the muscle working with accommodating resistance providing constant angular or linearly velocity (33).

Metabolic capacity

Energy to produce metabolic power comes from food, via the gastrointestinal tract, as fat, carbohydrates and proteins. Carbohydrates and fat are mainly used for energy production by synthesis of ATP. Carbohydrates are stored as glucogen especially in the muscles and the liver while fat is stored mostly as adipose tissue and intramuscular triglycerides. Glycose is transported in the blood to the exercising muscles. Fat is transported as free fatty acids (FFA) (17).

All cells have glucose transport proteins, glucose transporters (GLUT). The muscle fibres contain insulin-independent GLUT-1 and insulin-dependent GLUT-4. Glucose uptake at rest is meditated by GLUT-1. During exercise or after a meal glucose enters into the muscle cells via GLUT-4 (6). Insulin induces translocation of GLUT-4 from its intracellular compartment to the surface of the cell via the insulin-signalling cascade (34). Translocation of GLUT-4 has been shown to be induced by muscle contraction without insulin (35).

Resynthesis of ATP via creatine phosphate (CP) and anaerobic glycolysis takes place in the cytoplasma of the cell. Oxidation occurs in the mitochondria (17). The oxidative capacity in the muscles is dependent of the amount of mitochondria and the oxidative capacity in the mitochondria (36). High capillary density ensures delivery both of oxygen and glucose and fat to the exercising muscles which promotes oxidation (36). Type I fibres have a high content of mitochondria and small amounts of oxygen are stored bind to myoglobin (17). Capillary density is high around type I muscle fibres (37), providing type I fibres with a high oxidative capacity (17). Type II fibres have less mitochondria but store more glycogen than type I fibres, to provide the type II fibres a large glycolytic capacity (17).

Exercise Testing

Maximal aerobic capacity

There are a number of methods to assess aerobic capacity as a measure of physical fitness. Maximal aerobic capacity can be assessed with both maximal and sub-maximal exercise testing. The decision of what test to be used is dependent on which sort of equipment available and the population to be tested (5, 38).

Measurement of maximal oxygen uptake (VO_{2peak}) during a progressive exercise test on a cycle or a treadmill is considered the gold-standard. This examination requires access to quite expensive equipment for analysis of gas exchange, and a maximal exercise tests should be supervised by qualified personnel. A cheaper possibility is to measure the maximal work rate on a cycle ergometer or treadmill. There are also methods for assessment of maximal work rate based on sub-maximal exercise. These methods are cheap and easy to perform. One of the more common methods is described by Åstrand and Rhyming (4). This entails exercise on a cycle ergometer at steady state with a

constant, sub-maximal load. The VO_{2max} is estimated from a nomogram on the basis of work rate and heart frequency. This method has been widely applied in studies of healthy subjects and patients with various diseases (39), and is, owing to its simplicity, appealing as a means of following patients during an exercise intervention.

Maximal exercise tests

Direct assessment of aerobic capacity requires maximal exertion. One criterion of maximal exertion is that the exercise is prolonged to have a stable or plateau effect on the circulation. Not all individuals reach this plateau (2). Different criteria are used to ensure peak exercise (28) when a plateau is not reached; heart rate (HR) should be in the range of 15 beats minute^{-1} from HR_{peak}, calculated by 220-age (29, 38). Respiratory exchange ratio (RER) is to exceed 1.10 (38, 40). Rating of perceived exertion according to Borg on the original scale (RPE), 6-20, should exceed 17 and on the revised scale (Cr 10), 0-10, should be perceived above 9 (40). The end point is the functional maximum, WR_{peak}. The measured VO_2 is not necessarily the individual's VO_{2max} (1). Few individuals are able to reach their true VO_{2max} (1). When the criteria for maximum are not reached, VO_2 is recommended to be reported as peak values (38).

Maximal exercise testing adds the opportunity to estimate several indices not possible with sub-maximal testing. Assessment of VO_{2peak}, WR_{peak}, HR_{peak} and peak ventilation (VE_{peak}) is possible (1, 2). The use of open circuit spirometry during maximal exercise testing gives the possibility to estimate the anaerobic threshold (2, 40). Analysis of RER, movement economy ($\Delta VO_2\ \Delta WR^{-1}$) and oxygen pulse ($O_2\ HR^{-1}$) adds further understanding of the subject's exercise capacity (1, 2).

Sub-maximal exercise tests

The purpose of a sub-maximal exercise test is to estimate $VO_{2\ max}$ (1, 38, 40). The purpose of a sub-maximal test can also be to evaluate the functional performance (38).This will not be discussed further in this thesis.

Sub-maximal exercise testing is dependent on knowing the WR (1, 38, 40). Estimating $VO_{2\ max}$ from a sub-maximal test is based on determining the heart rate (HR) response to one or more sub-maximal WR (40). During a sub-maximal exercise test where $VO_{2\ max}$ is estimated from HR response several assumptions are made (1, 40).

- A steady-state HR is reached for each WR
- HR response is consistent every day
- There is a linear relationship between HR and WR
- WR_{max} reflects $VO_{2\ max}$
- HR_{max} is uniform for a given age
- Mechanical efficiency ($\Delta VO_2\ \Delta WR^{-1}$) is the same for every individual

All these assumptions need to be met to get as accurate estimation as possible (40).

Cycling as an application of exercise during exercise capacity measurement

Cycling involves the use of large muscles groups and is therefore one of the most common test modality in Sweden to assess aerobic exercise capacity (1). Cycle ergometers provide good conditions to assess and adjust work rate and in subjects familiar with cycling the motion is highly repeatable (1). Cycling is a non-weight-bearing test modality in comparison with treadmill which is a weight-bearing test modality. Treadmills provide the possibility of performing common activity as walking and running. Assessment and adjustment of work rate is harder than during cycling and the motion is not as repeatable as during cycling (1). Therefore cycling was used as test modality in this thesis.

Muscular strength and muscular endurance

Assessment of muscular strength and muscular endurance can be executed in different ways depending on the purpose of the measurement. Functional performance testing challenges the muscular strength, muscular endurance, postural control and dynamic joint stabilization, by evaluating number of repetitions, seconds or measuring length (13). Isokinetic muscular strength and muscular endurance testing is performed using a computerized dynamometer. Isolated testing of single muscle groups during standardized angular velocity is intended. Evaluation of the isokinetic testing is performed by measuring of the moment (27) during the motion. Different kinds of calculations can be made from these measurements (33).

Metabolic capacity

Indirect calorimetry

Substrate utilization can be analysed during exercise from measurements of the composition of the breathing gases (17). When glucose ($C_6H_{12}O_6$) and fat ($C_{16}H_{32}O_2$) are oxidized carbon dioxide (CO_2) is produced along with ATP and water (H_2O). To oxidize glucose, six O_2 are required and six CO_2 are produced, 1:1 ratio.

$$C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O + 36ATP$$

When fat is oxidized 16 CO_2 are produced and 23 O_2 are required, 7:10 ratio.

$$C_{16}H_{32}O_2 + 23O_2 \rightarrow 16CO_2 + 16H_2O + 130ATP$$

The RER is VCO_2 produced divided by VO_2 consumed. An RER of 0.7 shows that mainly fatty acids are being oxidized and an RER of 1.0 that glucose only is oxidized. When RER is exceeding 1.0 CO_2 from the carbon acid buffer is contributing to the ratio (2).

Insulin sensitivity

Assessment of insulin sensitivity is done by analysing the effect of insulin on glucose uptake (7), e.g. during a hyperinsulinemic clamp, considered gold-standard, where both insulin and glucose is infused to the patient. The amount of glucose infused to keep blood glucose at a level of 6 mmol l^{-1} determines the insulin sensitivity (7, 14). A HOMA index is a mathematical model to determine insulin sensitivity. It is performed by repeated measurements of blood glucose and plasma insulin (7).

Glucose homeostasis

Fasting blood glucose (FBG) is used as a measure of momentary blood glucose control (41) whereas glycated haemoglobin (HbA1c) is used as a measure of blood glucose control over time (2-3 month) (7). An oral glucose tolerance test (OGTT) is performed in the morning after a nights fasting. A total of 75 g glucose is taken orally and venues plasma glucose is analysed after 2 hours. Levels below 6.0 mmol l^{-1} of fasting plasma glucose are considered as normal (9).

Exercise Training

Exercise has beneficial effects both to maintain and to increase physical fitness and health (12, 42). To maintain physical fitness, healthy adult individuals are recommended to exercise 30 minutes per day at moderate to vigorous intensity, equivalent to an energy expenditure of 150 kcal per day or 1000 kcal per week (42).

To increase physical fitness the exercise training effects are greater if exercise is prescribed and supervised (43). Since the exercise interventions may be very different and adapted to the individual, it appears to be important to verify that the prescribed exercise increases the subject's exercise capacity.

Prescribing exercise is based on the dose-response relationship between physical activity and health (5), i.e. higher dose of physical activity gives a greater response. Using the FITT concept provide a tool to adjust the exercise prescription to the individual taking frequency (F), intensity (I), time (T) or duration and type (T) or mode of exercise in to account (5).

Cardiovascular capacity

To increase aerobic capacity, healthy individuals are recommended to exercise at an intensity of above 60 %, vigorous intensity, of the heart rate ratio (HRR) (5). RPE is recommended to be in the range of 12 to 16 (10, 40). The Swedish exercise recommendations for healthy subjects are exercise intensity between 55-90% of HR_{max} to increase the aerobic capacity (23). To maintain fitness an intensity of 40-60%, moderate intensity, HRR is recommended (5). Exercise intensity at a moderate level, a minimum of 30 minutes, more than 5 times per week adding up to a total of at least 150

minutes per week is recommended for most adult individuals. Vigorous exercise is recommended to be performed 20-25 minutes more than 3 days per week to a total of 75 minutes. Aerobic exercise should be performed using large muscle groups (5, 44).

Muscular strength and muscular endurance

To increase muscular strength and muscular endurance in healthy adult individuals, resistance training is recommended to exercise major multijoint muscle groups targeting both agonist and antagonist muscle groups. Eight to twelve repetitions at 60-80% of 1 RM of each exercise for a total of two to four sets with two to three minutes rest in between are recommended to improve muscular fitness (5). The exercise program should be performed two to three days per week to increase the muscular strength (5, 42, 45).

Metabolic capacity

Exercise enhances insulin sensitivity after a single bout in humans (46-48). The effect the exercise maintains about 48 hours (49). Aerobic endurance exercise has traditionally been seen as the most suitable exercise mode to maintain and increase glycemic control (19, 50-52). Strength exercise has lately been shown to be beneficial to glucose metabolism, by improving insulin sensitivity (19, 52-54). Exercise combining aerobic endurance training and strength training has been shown to contribute to both improved glycemic control and fitness (52, 55-57).

Type 2 diabetes

Diabetes is a disease characterised by high blood glucose. In diabetes type 1, insulin production is destroyed due to autoimmune mechanisms, while sensitivity for insulin in the cells of the body remains (58). Characteristics of type 2 diabetes (T2D) are insulin resistance in the muscle and liver cells in combination with insufficient ability of the β-cells in the pancreas to produce insulin. This will lead to enhanced blood glucose levels (59).

Epidemiology

About 220 million people have T2D in the world today (60). Within 15 years the number of people with T2D is thought to be about 300 million (18). The disease is no longer a phenomenon of the western world but is spreading all over the world (18, 60).

Definition of type 2 diabetes and type 2 diabetes pathology

According to the World Health Organization (WHO) an individual suffers from T2D if the fasting plasma glucose levels is above 7.0 mmol l^{-1} or above 11.1 mmol l^{-1} 2 hours after an OGTT (table 1)(9).

Table 1. Definition of T2D, impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) according to WHO (9).

	T2D	IGT	IFG
Fasting plasma glucose (mmol l^{-1})	≥ 7.0	< 7.0	6.1-6.9
2-h plasma glucose (mmol l^{-1})	≥ 11.1	< 11.0	<7.8

Risk factors and pathogenesis

There is strong genetic predisposition for T2D. If one of the parents has T2D the risk of developing T2D increases with 40% but heritage in itself can not explain the steep increase of T2D (59). Also acquired conditions as obesity (58) and a sedentary life style (19, 61) seem to be important factors in the aetiology of T2D. Obesity increases the risk of developing insulin resistance (62). Not only obesity itself but also body fat distribution around the waist increases the risk further to develop insulin resistance and T2D (63, 64). The combination of obesity and insulin resistance are greater risk factor to develop T2D than just one of the two (65, 66). IGT and IFG are risk factors to develop T2D, thus high levels of blood glucose give high risk to develop T2D. The combination of IGT and IFG increases the risk to develop T2D (67).

Adipose tissue has impact on the pathogenesis of T2D. Hormones that are released from the adipose tissue and influence insulin activity in other tissues have been identified (59). Insulin resistance in adipose cells leads to an increase of lipolysis and increased levels of blood lipoproteins, so-called lipotoxity, which decreases insulin sensitivity further (68, 69).

Influence of type 2 diabetes on exercise capacity

It is well known that maximal aerobic capacity is reduced in people with T2D compared to matched controls. The aerobic capacity is reduced with 18-33% when measured relatively to the bodyweight (20, 21, 70-73) and with 13-17% not adjusted for body weight (21, 73). Aerobic capacity seems to be impaired to a higher degree in women than in men with T2D (20, 22). Sub-maximal work rate is also reduced in individuals with T2D. VO_2 consumption during an incremental exercise test will be lower (20) and lactate production (74) higher at every single level of WR compared to matched controls. The cause of the reduced exercise capacity can be found at several levels of the cardio-respiratory and musculoskeletal systems.

Slower HR response and consequently slower VO_2 response to exercise has be seen in individuals with T2D compared to normal and obese controls (21). In a comparison of exercise capacity at different levels of FBG and HbA1c in individuals with T2D has shown that individuals with FBG above 6.5 mmol l^{-1} had a slower HR response to exercise than those with FBG below 6.5 mmol l^{-1} (41). The ventilatory response was lower in the individuals with HbA1c above 6.1% than individuals with HbA1c below 6.1%. This alteration was seen both at maximal and sub-maximal exercise (41).

Autonomic neuropathy is common in individuals with T2D which reduces the heart work capacity and reduces the parasympatic adjustment of the heart rate. High levels of blood glucose are seen as the major reason for neuropathy (75). Individuals with T2D have a myocardial dysfunction, with impaired left ventricle function (76, 77). Altered metabolism in the myocardium (78) and endothelial dysfunction of the coronary arteries (79) may influence the myocardial function.

Insulin has not only metabolic effects but also affects the endothelia. Insulin stimulates the production of new capillaries and has vasodilatory effects in normal individuals. It has been suggested that 25% of insulin glucose uptake effects are related to its hemodynamic effects (78).

There is proof that the peripheral oxygen extraction is reduced in patients with T2D. This can be explained by an altered function of the endothelia in the capillaries (78). T2D patients are also known to have a lager proportion of type II muscle fibres than healthy matched controls (36, 80, 81) which leads to a lower oxidative activity in the muscles of T2D patients.

Exercise recommendations in type 2 diabetes

Current exercise recommendations for individuals with T2D do not differ much from healthy individuals (5, 23). American Collage of Sport Medicine (ACSM) exercise recommendation for patients with T2D to increase aerobic capacity is to exercise at intensities of 50 to 80% of HRR or VO_{2max} (5). The Swedish recommendation for these patients is 40 to 70% of VO_{2max} to increase the aerobic capacity (23). The duration of each session is recommended to be 20 to 60 minutes per day in bouts of at least 10 minutes (5). The exercise should be repeated about 3 to 7 times per week (5).
The individual should aim for a total of 150 minutes per week or 1 000 kcal with further benefits of increasing to 300 minutes per week (5). Additionally, resistance exercise training should be included in an exercise training program for individuals with T2D. Resistance training should be performed 2-3 days per week, at an intensity of 60-80 % of 1 RM. Two to three sets of eight to twelve repetitions. Exercise training should be performed using large muscle groups (5).

Aim of the thesis

To study different aspects of exercise capacity, such as aerobic capacity, work rate, muscular strength, muscular endurance, muscle fibre distribution and metabolic capacity in healthy sedentary subjects and in subjects with impaired glucose tolerance and type 2 diabetes.

Research questions

Will muscular strength and muscular endurance of the upper body and knee contribute to exercise capacity during an incremental exercise test?

Will body composition, muscle fibre type composition, insulin sensitivity and blood glucose homeostasis contribute to exercise capacity during an incremental exercise test?

Is sub-maximal exercise testing valid for women with type 2 diabetes?

Can combined supervised group training influence glucose homeostasis in women with type 2 diabetes?

Subjects

All subjects were recruited as part of larger studies on T2D in the Malmö region, Sweden. All individuals lived a sedentary life and none of the subjects were participating in any organized physical activity before the studies.

Study I and II

In study I 39 male sedentary healthy subjects (38.4 ± 4.5 years, BMI 28.3 ± 3.3 kg m^{-2}) and in study II 31 male sedentary healthy subjects (38.0 ± 4.2 years, BMI 28.4 ± 2.9 kg m^{-2}) participated as a part of a lager study on heritage of T2D. All subjects had a normal glucose tolerance test. There were no significant differences in subject and study characteristics between the subjects with heritage for T2D and subjects without. The subjects were therefore analysed as one group. In study II the subjects performed six month of combined supervised group training.

Study III

Thirty-nine male subjects with T2D (65.5 ± 1.5 years, BMI 27.1 ± 3.9 kg m^{-2}), 49 male subjects with IGT (65.1 ± 1.7 years, BMI 27.0 ± 3.0 kg m^{-2}) and 53 matched NGT (65.6 ± 1.8 years, BMI 25.8 ± 3.3 kg m^{-2}) participated in the study.

Study IV and V

Twenty-seven female subjects (50 ± 7 years, BMI 32.9 ± 3.1 kg m^{-2}) participated in study IV and 22 female subjects in study V. In study V eleven subjects exercised at low volume (51.8 ± 6.5 years, BMI 32.1 ± 3.5 kg m^{-2}) and eleven at high volume (49.8 ± 7.3 years, BMI 33.5 ± 2.2 kg m^{-2}). All women included in study IV and V hade T2D and the subjects were collected for a study on ethnicities. Approximately half of the subjects were first generation immigrants from countries in the Middle East.

Ethics

All subjects gave written informed consent prior to their inclusion. The studies were approved by the regional ethical review board at Lund, Sweden.

Methods

Design

Study I, II and IV were observational studies in single groups focusing on the relation between physiological variables influencing exercise capacity. We employed a pre-post design in study II and IV to analyse changes in the correlations after a combined supervised group training period. Considering the high reproducibility of the dependent variables, VO_2 and WR, we also thought it possible to estimate the effect of combined supervised group training. Assessment methods of the independent variables were chosen based on previous reported reproducibility data (study I and II). Study III was also observational but with three groups with different glucose tolerance for comparison of the influence of glucose homeostasis on exercise capacity. To study the effect of exercise intensity, duration and frequency on glucose homeostasis a pre-post design with two groups dichotomised into high and low volume of combined supervised group training was used (study V).

Incremental cycle test (Study I, II, III, IV and V)

Study I and II

An incremental exercise test was performed on an ergometer cycle (Marquette Hellige Medical Systems 900 ERG, Milwaukee, WI, USA). In study I and II the test was performed at baseline and in study II also after 6 months of training.

Work load began at 50 W and increased with 15 $Wmin^{-1}$. To enable the cardiovascular adjustment to constant load exercise to be studied, the workload was held constant at 40% of VO_{2peak} (4)) for 4 min (82). This was performed to allow analysis of VO_2 kinetics. The VO_2 kinetic analysis is not included in this thesis. Pedalling rate was maintained at 60 rpm using both visual feedback and verbal encouragement. VO_2 and VCO_2 were measured breath-by-breath (Oxycon Mobile, Jeager, Hoechberg, Germany). Heart rate was monitored continuously during the test (Polar T 61, POLAR, Oulu, Finland). The subjects were verbally encouraged to exercise to exhaustion and $VO_{2\ peak}$ was not considered to be reached until RER exceeded 1.10. Calibration of the gas sensors was performed before each test with a certified gas mixture. Air flow was calibrated before each test using a calibration syringe.

Study III

An incremental, maximal exercise test was performed on an electrically braked bicycle ergometer (Bosch EAG 551 Berlin, Germany). The subjects started to exercise at 80 W and continued to exhaustion with the workload increasing continuously by 15 W every minute (83). Pedalling rate was maintained at 60 rpm using both visual feedback and verbal encouragement. Expired gas was sampled continuously via a mixing chamber and analysed for the concentration of O_2 and CO_2 (Sensor medics 2900, Bilthoven, Netherlands). Measurements were obtained every 20 s during 1 minute at rest, during exercise and for 1 minute during recovery. Heart frequency was measured by means of electrocardiography. All patients were required to exercise until RER exceeded 1.0 which was aided by verbal encouragement. Work rate was determined as the end value in Watt.

Study IV and V

An incremental exercise test was performed on an electrically braked bicycle ergometer (Bosch EAG 551, Berlin, Germany) in study IV at baseline, after six weeks and after 12 weeks of training and in study V at baseline and after 6 months of training.

The subjects started to exercise at 30 W and continued to exhaustion with the workload increasing continuously by 15 W every minute (83). Pedalling rate was maintained 60 rpm using both visual feedback and verbal encouragement. Expired gas was sampled continuously via a mixing chamber and analysed for the concentration of O_2 and CO_2 (Sensor medics 2900, Bilthoven, Netherlands). Measurements were obtained every 20 s during one minute at rest, continuously during exercise and for one minute during recovery. Heart rate was measured by means of electrocardiography. All patients were required to exercise until exhaustion, which was aided by verbal encouragement and RER exceeded 1.0. Work rate was determined as the peak value in Watt.

Measurements of muscular strength and muscular endurance (Study I and II)

Muscular strength and muscular endurance were assessed using isokinetic and isometric tests and a functional performance test. Each subject performed the muscular strength and muscular endurance capacity tests in the same order, starting with a five minutes warm-up on an ergometer cycle with a work load of 1 W (kg body weight)$^{-1}$. The test series started with the isokinetic tests, followed by a dynamic endurance test and finally isometric tests.

Study I

The isokinetic tests were performed on a computerised dynamometer (Biodex Multi-Joint System III, Biodex Medical Systems, Inc., Shirley, NY, USA), and the dynamometer calibration was verified before testing each test day. Subjects were seated in a comfortable position with the backrest angled at 100° to the seat. Velcro straps were

placed across the thigh, pelvis and chest to minimize body movements and to isolate the movement of the knee joint. The arms were crossed over the chest during the test. The mechanical axis of the dynamometer was aligned with the transverse axis of the knee joint, with the lateral femoral epicondyle used as the bony landmark. The weight of the leg was recorded and gravity adjustment was made using the computer software. The range of movement was from 10° to 100° of knee flexor. Isokinetic concentric knee extensor and flexor strength of the right knee were assessed, using two test protocols. Five maximal concentric knee extensor-flexor cycles at 60° s^{-1}, with no rest between the repetitions, were performed. After a 60 s rest the subjects performed 30 consecutive maximal extensor-flexor cycles at 180° s^{-1}. Before each test protocol the subjects performed two sub-maximal extensor-flexor cycles at the pre-selected angular velocity. Each subject was instructed to exert maximal voluntary effort by contracting as hard and as fast as possible.

Study II

The dynamic endurance test was a bench press performed in the supine position. The subjects lifted a 19 kg barbell by arm extension at a rate of 25 repetitions per minute. The number of lifts to straight arm was counted as one trial (84). Four to five single lifts with a wooden stick were performed prior to the test in order to familiarise the subjects with the test procedure. Bench press will further on be referred to as upper body work.

The isometric tests, maximal voluntary contraction (MVC), of the extensors and flexors of the trunk, were measured in a special frame with a strain gauge dynamometer (Universal Frame, Roby Elektronik, AB, Södertälje, Sweden). The subjects were tested in an upright standing position and strapped to the dynamometer frame around the trunk at the level of the inferior angle of scapulae and around the pelvis. All subjects were asked to increase their effort gradually to achieve MVC in both extension and flexion of the trunk. Verbal encouragement was used. Three efforts to reach MVC were performed, with 30 s rest in between repetitions, and the results were expressed as the mean of the three efforts. Trunk muscle extensor and flexor endurance was performed in the same position as trunk extensor and flexor MVC. The subjects were asked to increase the force against the strap gradually until they reached 60% MVC and then to maintain this position as long as possible. One effort was recorded (85).

Muscle biopsy (Study I and III)

Fibre typing

Muscle biopsies were taken from the right vastus lateralis muscle in the fasting state under local anaesthesia (Lidocaine 10%), using 6 mm Bergström needle (66) (Stille AB, Sweden). The muscle samples were frozen in liquid nitrogen, and serial sections (10μm) were cut using cryostat at -20 °C. Myofibrillar ATPase histochemistry was performed after preincubation at PH 4.37, 4.6, and 10.3 to identify muscle fibre types (type 1, 2a and 2x) (86). Computer image analysis was performed using BioPix IQ 2.0.16 software (BioPix AB, Sweden).

Analysis of blood samples (Study III, IV and V)

HbA1c

HbA1c was assessed by HPLC (mono S, Pharmica LKB No 17-0547-01) and plasma glucose was analyzed with hexokinase method (Beckman Syncron CX System chemistry).

Oral glucose tolerance test

An OGTT was performed in the morning after a night's fasting. A total of 75 g glucose was taken orally and venous plasma glucose was analysed before glucose intake after 40 minutes and 120 minutes. Plasma glucose was analyzed with hexokinase method (Beckman Syncron CX System chemistry).

Hyperinsulinemic-euglycemic clamps

Hyperinsulinemic-euglycemic clamps were carried out at baseline, after 3 months and after 6 months intervention. The subjects underwent clamp at 24-72 hours after the last supervised group exercise. The clamp was performed after 10 hours of overnight fast. The subjects were requested not to smoke during the fast. An infusion (infusion rate 45 mU m^{-2}) of short acting human insulin (Actrapid, Novo Nordisk, Denmark) was started and continued for 120 minutes. Blood samples for the measurement of plasma glucose were obtained at 5 minutes intervals throughout the clamp. A variable glucose infusion of 20% glucose was started to maintain plasma glucose concentration unchanged at 5.5 $mmoll^{-1}$, with a coefficient of variance (CV) of 6%. Insulin sensitivity was calculated from the glucose infusion rates during the last 60 minutes of the euglycemic clamp (M-value) and expressed as glucose uptake per body weight (14).

Exercise training sessions (Study II, IV and V)

Heart rate was monitored continuously during each exercise session by a Polar belt to assess exercise intensity (Polar Fitness F1, POLAR, Oulu, Finland).

Study II

The subjects participated in combined supervised group training three times per week for six months. Each week one session of one hour spinning class and two sessions of one hour aerobics class were performed.

During the spinning class a specially designed ergometer cycle (Pulse, Pulse Fitness, Congleton, England) was used and the sessions were led by a certified instructor. The work load is individually adjusted by breaking the wheel during cycling. No additional strength training exercises were included in the session.

Aerobics combines rhythmic aerobic-training, resistance-training and stretching routines aimed to improve all fitness elements. The aerobics classes were performed to music and led by certified instructors. The classes included a warm-up period, rhythmic aerobic-training mixed with strength exercises for arm, leg, abdominal and back muscles, cool-down and stretching exercises. Resistance-training was performed with the subject's own body weight as resistance, such as push ups, crunches, sit ups and belly backs.

Study IV and V

All patients were invited to take part in six months exercise training program. This consisted of one hour supervised combined group exercise training twice a week and the patients were also instructed to walk for one hour once per week at a level of 12-13 on Borg's 20 graded scale for rating of RPE (10).

The supervised combined group exercise training consisted of aerobics. Aerobics combines rhythmic aerobic-training, resistance-training and stretching routines aimed at improving all fitness elements. The aerobics classes were performed to music and led by certified instructors. The classes included a warm-up period, rhythmic aerobic-training mixed with resistance exercises for arms, leg, abdominal and back muscles, cool-down and stretching exercises. Resistance-training was performed with the individuals own body weight as resistance, such as push ups, crunches, sit ups and belly backs.

Table 2. Summary of methods in the studies included in the thesis.

	Study I	**Study II**	**Study III**	**Study IV**	**Study V**
Study design	Observational	Pre-post	Observational	Pre-post	Pre-post
Study groups	Single group	Single group	Three groups	Single group	Two groups
Population	Heredity study	Heredity study	Elderly men study	Ethnicity study	Ethnicity study
Follow-up time		6 month		6 weeks and 12 weeks	6 month
Subjects (n)	39	31	141	27	22
Age (years)	38 ± 5	38 ± 4	65 ± 2	50 ± 7	49 ± 7
BMI (kg m^{-2})	28.3 ± 3.3	28.4 ± 2.9	26.6 ± 3.4	32.9 ± 3.1	32.9 ± 2.9
Assessment methods					
Cycling exercise test	X	X	X	X	X
Muscular strength and muscular endurance	X	X			
Muscle biopsy	X		X		
Insulin sensitivity			X	X	X
Glucose tolerance			X	X	X
Exercise training					
Combined supervised group training		X		X	X

Calculations

Study I

Knee muscular strength and muscular endurance

Peak torque (27) was defined as the single highest torque produced during the five consecutive muscular contractions performed at the angular velocity of 60º s^{-1} (15). Total work (Nm s^{-1}) was the amount of work accomplished for the entire set of 30 contractions performed at the angular velocity of 180º s^{-1}. Peak torque can be interpreted as strength of the muscles during a certain angle speed. Total work can be used as a measure of endurance of the muscles working during a specific angle speed (15). Peak torque 60º s^{-1} will further on be referred to as strength and total work 180º s^{-1} as endurance.

Study III

Group classification

When data were analysed in this study the participants were divided into three groups according to WHO classification of diabetes (9). After OGTT venous blood test of blood glucose NGT was defined as blood glucose <7.8 mmol l^{-1} after 120 minutes, IGT 7.8-11.0 mmol l^{-1} and T2D ≥ 11.1 mmol l^{-1}.

Study V

Exercise intensity

The exercise intensity was expressed as a percentage of the heart rate ratio (HRR%) calculated as

$$HRR\% = \frac{HR_{exercise} - HR_{rest}}{HR_{peak} - HR_{rest}} \text{ x } 100$$

where $HR_{exercise}$ is the mean heart rate during each exercise session and HR_{rest} is the heart rate recorded before each exercise session, whereas HR_{peak} was obtained during the exercise test at baseline (8).

Exercise duration

The exercise duration was defined has the mean duration (min $week^{-1}$) of supervised group session attended during the six months. One hour of walking per week was included for all subjects.

Exercise volume

Exercise volume (HRR% min $week^{-1}$) was calculated as the exercise intensity multiplied by the exercise duration.

Group dividing process

When data were analysed in this study the participants were retrospectively divided into two groups. One group had exercised above the 50^{th} percentile of the exercise volume (high volume group) and one group had exercised below the 50^{th} percentile of the exercise volume (low volume group).

Statistics

Values throughout are given as means and standard deviations (±SD). Paired Students t-tests were used when comparing means within groups and un-paired between groups. Pearson's correlation was used to analyse relationships between variables. SPSS (version 13.0, SPSS Inc, Chicago, Illinos, USA) was used for the statistical analyses and the $p<0.05$ criterion was used for establishing statistical significance in all studies in the thesis.

Study I

Stepwise multiple linear regression analyses, both backward and forward, were performed. In the backward regression, independent variables were excluded due to collinearity during the multiple regression analysis. When no collinearity was found between independent variables, a forward regression analysis was performed. Dependent variables were VO_{2peak} and WR_{peak}. Independent variables were KE and KF muscular strength, KE and KF muscular endurance and fibre type composition (type 1, 2a and 2x fibres). Models are reported together with the adjusted R^2 values as assessments of the best fit.

Study II

Dependent variables were VO_{2peak} and WR_{peak}. Independent variables were bench-press, trunk extensor MVC, trunk extensor endurance, trunk flexor MVC and trunk flexor endurance.

Study III

Variance analysis was obtained with one way ANOVA. The Scheffe test was used for post hoc analysis. Multiple linear regression analyses, both backward and forward, were performed as described above. Dependent variables were $VO_{2peak}\ kg^{-1}$ and $WR_{peak}\ kg^{-1}$. Independent variables were BMI, WHR, HbA1c, M-value, muscle fibre distribution and capillary proportion. Models are reported together with the adjusted R^2 values as assessments of the best fit.

Study IV

The relations between HR and WR, VO_2 and HR and VO_2 and work rate were investigated with linear regression. EVO_{2peak} and VO_{2peak} were compared in a Bland-Altman analysis (87).

Study V

HbA1c and M-value before and after training as well as the changes in HbA1c and M-value after training showed skewed distributions. They were therefore log-transformed before statistical analysis.

Results

Study I

The multiple regression analyses showed that KE strength, KF endurance and the percentage of type 1 fibres could explain up to 40% of the variation in VO_{2peak} and WR_{peak} of which the percentage of type 1 fibres contributed to ~ 10%. KF endurance was the most dominant factor for VO_{2peak} (20%) and KE strength for the WR_{peak} model (18%). KE strength and KE endurance were collinear (r_p =0.73, p<0.001). The best fit of the stepwise multiple regression analyses included KE strength as an independent variable (Table 3 and 4).

Comments

Both KE strength and KF endurance related significantly to VO_{2peak} and WR_{peak} at about the same degree, reflecting the well known close relation between VO_{2peak} and WR_{peak}. Stepwise multiple regression analysis revealed that KF endurance was the most dominant factor to explain the variance of VO_{2peak} while KE strength was the most dominant factor explaining the variance of WR_{peak}. Since WR_{peak} is known to increase after VO_{2peak} has been reached in performing an incremental cycle test, a certain degree of anaerobic, strength related capacity must be involved in this variable. The tendency for KE strength to be more closely related to WR_{peak} than to VO_{2peak} is therefore to be expected. Conversely, since VO_{2peak} is considered to be a measure of aerobic capacity, the finding that VO_{2peak} was dominated primarily by knee muscular endurance rather than strength is also expected.

Table 3. Adjusted R^2 values and p-values between VO_{2peak} measurements and the significant independent variables: KF endurance, type 1 muscle fibres and KE strength.

Independent variables	Dependent variable: $VO_{2\ peak}$	
	R^2	P-value
KF Endurance	0.20	0.010
Type 1 muscle fibres	0.26	0.014
KE strength	0.36	0.017

Table 4. Adjusted R^2 values and p-values between WR_{peak} measurements and the significant independent variables: KE strength, type 1 muscle fibres and KF endurance.

Independent variables	Dependent variable: WR_{peak}	
	R^2	P-value
KE strength	0.18	0.008
Type 1 muscle fibres	0.30	0.002
KF endurance	0.40	0.010

KE : Knee extension
KF : Knee flexion
Strength : Peak torque 60° s^{-1}
Endurance : Total work 180° s^{-1}

In previous sEMG studies, muscle activity in different leg muscle groups during the propulsive phase in cycling has been analysed. It has been demonstrated that knee extensors contribute to WR_{peak} with 39-49% and knee flexors with 9-10% (88, 89). This is in accordance with our study, where KE strength was the most important contributor to the variation in WR_{peak} with up to 18%. However, considering the alleged importance of quadriceps muscles compared to hamstring muscles in cycling performance (88, 89), the dominance of KF instead of KE endurance is somewhat surprising. Differences in methods to assess muscle load may to some extent explain the differences in our findings compared to earlier sEMG studies. sEMG measures only the total amount of muscle activity whereas in isokinetic dynamometry it is possible to get separate indices of muscular strength and muscular endurance (88, 89). KF endurance may, however be of greater importance at peak exercise than earlier accounted for (88, 89).

Study II

VO_{2peak} and WR_{peak} increased by 11 and 15 % with training, respectively. Improvement was also seen in bench-press, which increased by 30 % and in trunk extensor MVC (+11 %) as well as trunk extensor endurance (+23 %). Trunk flexor MVC and trunk flexor endurance, on the other hand, did not change significantly.

VO_{2peak} and WR_{peak} correlated closely (r_p=0.81 at baseline and r_p=0.82 at six months, $p<0.001$ respectively), as could be expected. Bench-press and trunk extensor MVC showed significant correlations to VO_{2peak} and WR_{peak} at baseline, but no such correlations were observed for trunk extensor endurance or flexor measurements. After combined supervised group training, the correlation between bench-press and exercise capacity remained similar, whereas the correlation between trunk extensor MVC and exercise capacity increased. Also, trunk flexor MVC approached significant correlation with VO_{2peak} (p=0.09) and WR_{peak} (p=0.06) after training. There were still no correlation between trunk extensor or flexor endurance and exercise capacity (Table 5).

Table 5. Pearson's correlation coefficient (r_p) between measurements of muscular strength and endurance of the upper body and VO_{2peak} and WR_{leg}.

	Baseline		6 months	
	VO_{2peak}	WR_{peak}	VO_{2peak}	WR_{peak}
Bench-press	0.36*	0.57**	0.46**	0.46**
Trunk extensor MVC	0.43*	0.39*	0.54**	0.60**
Trunk extensor endurance	-0.24	-0.09	-0.21	-0.24
Trunk flexor MVC	-0.11	0.05	0.29	0.33 †
Trunk flexor endurance	-0.26	-0.19	0.13	0.15

Significant correlation *: $p < 0.05$ **: $p< 0.005$
†: p=0.07

Comments

The hypothesis was that upper body muscular strength and muscular endurance could affect the subject's ability to apply force effectively to the pedals and thereby affect exercise capacity on the cycle ergometer. A significant correlation between exercise capacity and muscular strength and muscular endurance of the upper body was seen. This is analogue with previous studies showing that bicycle riders may apply high forces at the handlebar that can be transmitted to the pedals (90-93). High forces at the handlebar have been recorded especially during starting (91) and seated climbing (90). These situations may be equal to cycling at high work load at the end of an incremental exercise test. The biker's ability to apply force at the handlebar may thus contribute to exercise capacity as measured by cycle ergometry. We also found significant correlations between trunk extensor MVC and exercise capacity. The trunk may be involved in the transfer of force from the arms to the legs, and the muscular strength and muscular endurance of the trunk may thereby influence exercise capacity.

In line with expectations, the subjects increased their VO_{2peak} and WR_{peak} after six months of training. Muscular strength and muscular endurance of the upper body also improved after training. This may be caused by spinning, during which the arms and upper body are used to support part of the body mass, but also related to the resistance training during the mixed exercise. The correlation between trunk extensor MVC to VO_{2peak} as well as WR_{peak} increased after training. Furthermore, the correlation between trunk flexor MVC and WR_{peak} approached statistical significance after training, but not before. The improved correlation after training may result from an increased ability to use the upper body to generate force during cycling and/or better cycling technique and co-ordination. Increased upper body muscular strength and muscular endurance may allow the subject to assume a better working position for the legs to create force onto the pedals. An influence of body position on exercise capacity during cycling has previously been demonstrated. Ashe et al., (94) thus found that VO_{2peak} and WR_{peak} were higher in an upright position than in the aero position in untrained subjects. Gnehm et al., (95) reported similar findings in elite cyclists. Body position may also influence muscular strength and muscular endurance of the lower extremity (96).

Study III

Even if the groups were matched for body weight, there were small differences between the groups in WHR with significance attained between NGT and T2D.

All subjects exercised to exhaustion. There was a progressive reduction in exercise capacity, both expressed as VO_{2peak} and WR_{peak} from subjects with NGT to IGT to T2D, although the difference between subjects with IGT and T2D did not reach statistical significance.

Subjects with T2D had a smaller proportion of Type I fibres than subjects with NGT. There was no significant difference in muscle morphology between subjects with IGT and NGT. The differences between subjects with IGT and T2D were borderline significant. Subjects with IGT as well as subjects with T2D had higher capillary density

than subjects with NGT. There was no significant difference between subjects with IGT and T2D in muscle morphology.

Multiple regression analysis (Table 6) in the whole material with VO_{2peak} as dependent variable showed insulin sensitivity to be the most important factor, followed by Type I fibres (as expected, there was high collinearity between Type I and Type IIx fibres; Type I yielded the best fit). WHR and capillary density also influenced VO_{2peak} in the multiple regression analysis. A total of 42 % of the variance in VO_{2peak} was explained by the four independent variables. Similar results were obtained if WR_{peak} was used as dependent variable, with the exception that capillary density did not contribute significantly to the model (Table 7).

Table 6. Adjusted R^2 values and P values between $VO_{2\ peak}\ kg^{-1}$ and the significant independent variables: M-value, Type 1 fibre, WHR and capillary density

Independent variables	Dependent variable $VO_{2\ peak} k\ g^{-1}$	
	Adjusted R^2	P values
M-value	0.25	P<0.001
Type 1 fibre	0.34	P<0.001
WHR	0.40	P=0.010
Capillary density	0.42	P=0.032

Table 7. Adjusted R^2 values and P values between $WR_{peak}\ kg^{-1}$ and the significant independent variables: M-value, Type 1 fibre and WHR.

Independent variables	Dependent variable $WR_{peak}\ kg^{-1}$	
	Adjusted R^2	P values
M-value	0.33	P<0.001
Type 1 fibre	0.40	P<0.001
WHR	0.44	P=0.013

$VO_{2\ peak}\ kg^{-1}$:Peak oxygen consumption relative to body weight
$WR_{peak}\ kg^{-1}$: Peak work rate relative to body weight
M-value: insulin sensitivity measured with hyperinsulinemic-euglycemic clamps per body weight
WHR: waist hip ratio

Comments

The multiple regression analyses showed exercise capacity to be primarily related to insulin sensitivity, muscle fibre composition and WHR. This suggests that metabolic abnormalities in skeletal muscle are of prime importance for the reduction in exercise capacity. This observation is in agreement with the widely held opinion that insulin resistance is a primary defect in T2D (97) and that reduced exercise capacity occurs at a very early stage of the progression to T2D (98). WHR was also included in the multiple regression model, indicating that abdominal obesity is an independent factor affecting exercise capacity. Similarly, Nyholm et al (71), in a study of first degree relatives of patients with T2D found insulin stimulated glucose uptake to be related to exercise capacity, visceral obesity (measured by computed tomography) and a family history of T2D, in a multiple regression analysis. In a study of lean and obese men with NGT or IGT, Riou et al (99) found that exercise capacity correlated with waist circumference when adjusted for fat mass. Taken together, these results indicate that abdominal obesity is associated with reduced exercise capacity. Possible mechanisms may be related to low-grade inflammation of adipose tissue (100).

Study IV

Mean EVO_{2peak} was 27 % higher than mean VO_{2peak}, at baseline but the difference was not statistically significant. During the exercise program, EVO_{2peak} increased significantly ($p<0.01$ at twelve weeks) compared to baseline, while no significant improvement was noted in VO_{2peak}. Thus, the differences between tests was significant after six and twelve weeks ($p<0.01$). Poor agreement was found, when the results of all measurements of EVO_{2peak} and VO_{2peak} were compared in a Bland-Altman analysis. EVO_{2peak} systematically overestimated VO_{2peak} by 476±1310 ml min^{-1}. Pearson's correlation coefficient between VO_{2peak} and EVO_{2peak} was 0.029.

(Figure 1 A-B). Filled symbols in the Bland-Altman plot show subjects with autonomic neuropathy and/or treatment with beta blockers.

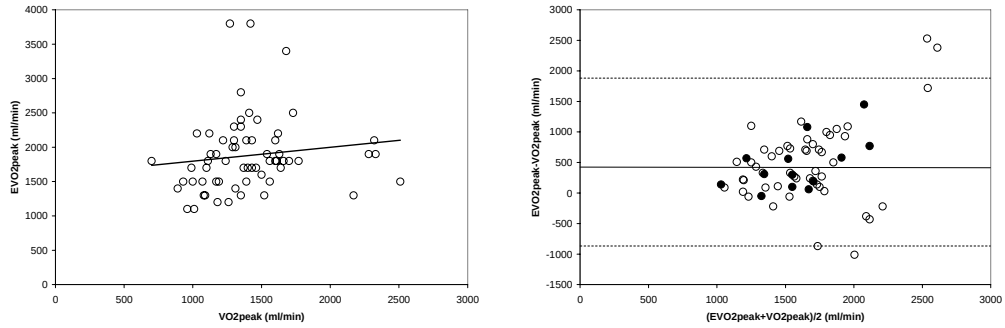

Figure 1 A-B Correlation between VO_{2peak} and EVO_{2peak} at baseline, 6 weeks and 12 weeks (**A**). Bland-Altman plot of the mean of both VO_{2peak} and EVO_{2peak} and the difference between EVO_{2peak} and VO_{2peak} at baseline, 6 weeks and 12 weeks. Filled symbols in the Bland-Altman plot show subjects with autonomic neuropathy and/or treatment with beta blockers (•) (**B**).

Comments

VO_{2peak} was systematically overestimated by the sub-maximal test in our patients. There are several possible explanations for this. The estimation of VO_{2peak} from a sub-maximal test relies on a linear relation between heart rate and VO_2 (4). Patients with T2D have a blunted heart rate response to constant-load exercise (20). A number of studies have also shown patients with T2D to have lower heart rate than normal subjects at moderate workloads during a progressive exercise test (41, 101, 102). Maximum heart rate may also be lower in diabetics, especially if they have autonomic neuropathy (103). Autonomic neuropathy and treatment with beta blockers may contribute to the findings in some of our patients, even if these patients do not differ substantially from the rest of the material (Figure 1 A-B). Abnormal heart rate response to exercise therefore seems a likely explanation for the overestimation of VO_{2peak} in the sub-maximal test.

The sub-maximal exercise test showed increased EVO_{2peak} after the training period. The design of the Åstrand test however, requires aspects of physical capacity other than VO_{2peak} of the test person to be unchanged between tests for EVO_{2peak} to reflect true changes in aerobic capacity only. Thus, in our subjects, increased EVO_{2peak} could be explained by increased mechanical efficiency and/or an increase in muscular strength; at a given heart frequency, the power output would be greater with improved efficiency and strength.

Study V

When the material was dichotomized according to exercise volume, there was approximately 50 % difference between the two groups in exercise volume. There was a spectrum of subjects training at low intensity and with long duration and vice versa as supported by a lack of correlation between exercise intensity and duration (r_p=0.39, p=0.07).

There were no significant changes in VO_{2peak}, VO_2 (kg body weight)$^{-1}$, or WR_{peak} in either group after the training period. HbA1c decreased and insulin sensitivity increased significantly after six months of training in the high volume group.

Correlation analysis was performed between exercise intensity, duration and volume with insulin sensitivity and HbA1c measured at six months and also with changes in insulin sensitivity and HbA1c during the training period (Table 8). The change in insulin sensitivity during training showed a significant correlation to training intensity and volume but not to duration. HbA1c at the end of the training period as well as change in HbA1c showed significant negative correlations to duration and volume of training, even if there was no correlation to intensity.

Table 8. Pearson's correlation coefficients between exercise variables and insulin sensitivity and HbA1c measured after the training period as well as the changes during the training period (ΔM-value and ΔHbA1c). M-value and HbA1c were log-transformed before analysis due to non-normal distribution.

Exercise	M-value (mg kg^{-1} min^{-1})	HbA1c (%)	ΔM-value (mg kg^{-1} min^{-1})	ΔHbA1c (%)
Intensity	0.15	-0.33	0.54*	-0.37
Duration	0.16	-0.60**	0.19	-0.46*
Volume	0.16	-0.56**	0.53*	-0.50*

Significant correlation coefficients between variables * $p<0.05$, ** $p<0.005$

Comments

Insulin sensitivity

The finding that insulin sensitivity increased only in subjects in the high volume group supports the concept that certain energy expenditure is required for this effect to occur. The correlation analyses indicate that, for a given training volume, intensity rather than duration is related to improved insulin sensitivity. It has been suggested that certain total energy expenditure is required to enhance insulin sensitivity (49, 104). Most previous studies of exercise effects on insulin sensitivity in T2D have used primarily endurance exercise (54, 104-112). Fewer studies have been performed on resistance exercise (54, 113, 114) and combined exercise (56, 57). While most studies using endurance exercise show increased insulin sensitivity, there are exceptions (54, 105, 107). The studies on resistance and combined exercise show consistently an increase in insulin sensitivity (54, 56, 57, 113, 114). Sigal et al., (56) suggested that combined exercise results in greater increase in insulin sensitivity than endurance or resistance exercise alone. The impact of training intensity and duration has, however, not previously been addressed in diabetic subjects. The limited information available in non-diabetic subjects is conflicting (115, 116).

HbA1c

It is well known that training can reduce HbA1c in subjects with T2D (117). We found a reduction in the high volume group only and that the reduction in HbA1c was best correlated with training volume. Significant reduction in HbA1c was also found in some previous studies with similar training volume (11600-18200 HRR% min $week^{-1}$) as in our high volume group (57, 106, 110, 111). Other studies with lower training volume (4800-8775 HRR% min $week^{-1}$) showed no effect on HbA1c (54, 108, 118). Our results are thus in agreement with previous studies.

The reason why reduction in HbA1c is related to training volume is probably that moderate as well as intense exercise has a short-lasting reduction in plasma glucose (119, 120). Regular exercise, even of moderate intensity, may have additive exercise effect and may therefore reduce HbA1c over time.

General discussion

Main findings

The performance of a maximal incremental cycle test in sedentary male subjects was highly affected by lower extremity muscular strength and muscular endurance (Study I). Also upper body muscular strength correlated to exercise capacity as measured by cycle ergometry. When exercise capacity and muscular strength of the upper body increased in response to combined supervised group training, the correlation between muscular strength of the upper body and exercise capacity improved (Study II). Exercise capacity assessed during cycling was strongly related to whole body insulin sensitivity and the WHR, to a lesser extent (Study III). Also, fibre type composition (Study I and III) and capillary density (Study III) contributed to peak exercise capacity.

Estimation of VO_{2peak} according to Åstrand sub-maximal exercise testing (4) significantly overestimates directly measured VO_{2peak} in women with T2D (Study IV).

Insulin sensitivity increased and HbA1c decreased significantly after combined supervised group training in subjects achieving relatively higher exercise volume, whereas no significant changes were seen in subjects achieving a lower exercise volume. Improved insulin sensitivity appeared to be related to exercise intensity rather than duration, whereas improved HbA1c appeared to be related to exercise volume in T2D women (Study V).

Knee and upper body muscular strength and muscular endurance

Exercise training of strength and endurance of the knee and upper body muscles may influence exercise capacity at least in untrained subjects during cycling. In light of the findings in study I and II exercise recommendations for healthy sedentary subjects to increase the exercise capacity during cycling may also include strength training.

Muscle fibre composition

The proportion of type 1 muscle fibres has earlier been shown to contribute to VO_{2peak} (121), which were also found in study I and III (Tables 3 and 6). The explanation of the variance in WR_{peak} from type 1 muscle fibres (Tables 4 and 7) was twice as high as the explanation of $VO_{2\ peak}$ from type 1 muscle fibres in both study I and III. Previous studies of non-athletic individuals with a high proportion of type 1 fibres in the thigh muscles have also demonstrated high muscular endurance (total work) during isokinetic testing whereas individuals with a low proportion of type 1 fibres have high strength

(peak torque) values (122). The significant correlation between knee muscular endurance and VO_{2peak} that was found in our study was therefore anticipated.

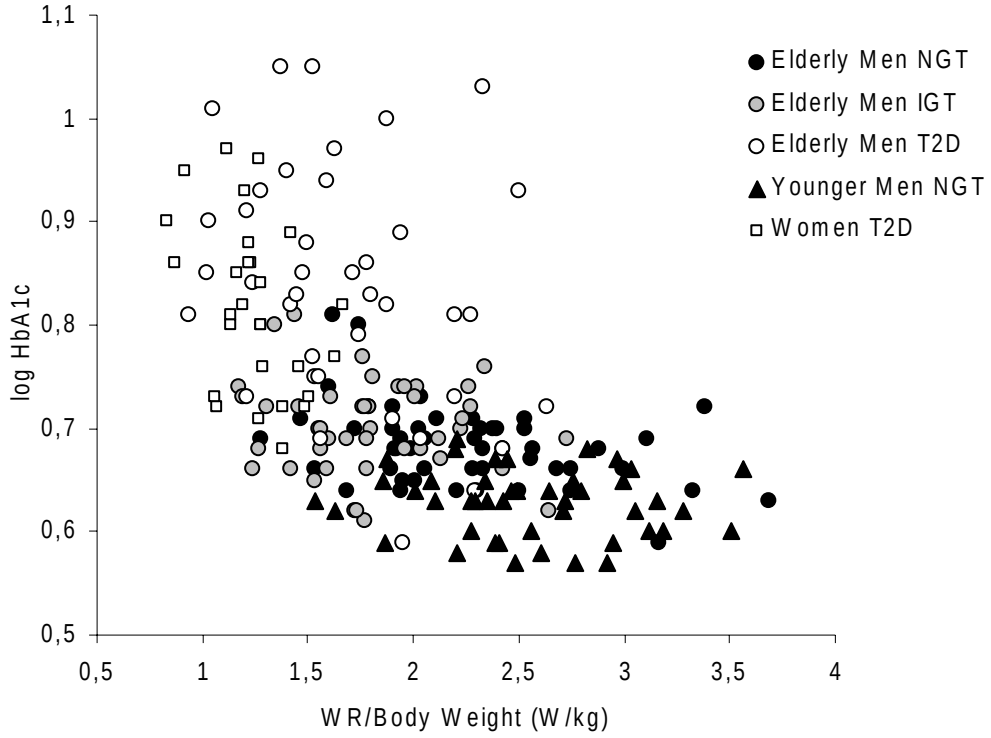

Figure 4. Subjects from study I-V (n=214).

Glucose homeostasis

We found a close relation ship between insulin sensitivity and VO_{2peak} kg^{-1} when analysing data from study III, IV and V (Figure 4). Highly significant correlation between HbA1c and WR kg^{-1} during analysis of data from all studies in this thesis was found (Figure 5). Both insulin sensitivity and HbA1c will affect exercise capacity (Figure 4 and 5).

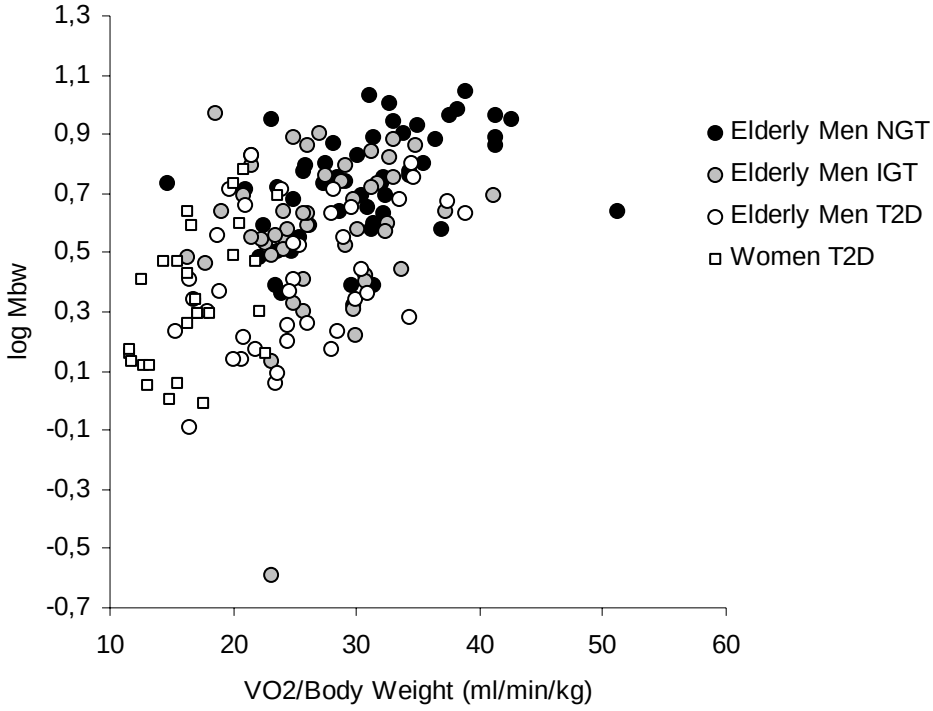

Figure 5. Subjects from study III-V (n=169).

Gender differences

When analysing data from study III and study IV, highly significant gender differences in exercise capacity in T2D individuals with equally impaired glucose tolerance were found (Figure 6). Even when adjusting for both body size and age, the differences in exercise capacity remained highly significant (Table 11). Compared with a healthy population (29) the gender difference was greater than could be expected. Regensteiner (22, 73, 123) has earlier described gender differences in aerobic capacity in individuals with T2D. The men's (study III) exercise capacity was 20 % higher compared with the women in study IV. The decrease in exercise capacity compared to a healthy population was greater in the women (study IV) than the men (study III). This has recently been reported by Huebschmann et al (123), where a difference in exercise capacity of 35 % was found. In light of this, the findings by Boulé et al. (124), that women have less effect from exercise training on the cardiovascular system then men is noteworthy.

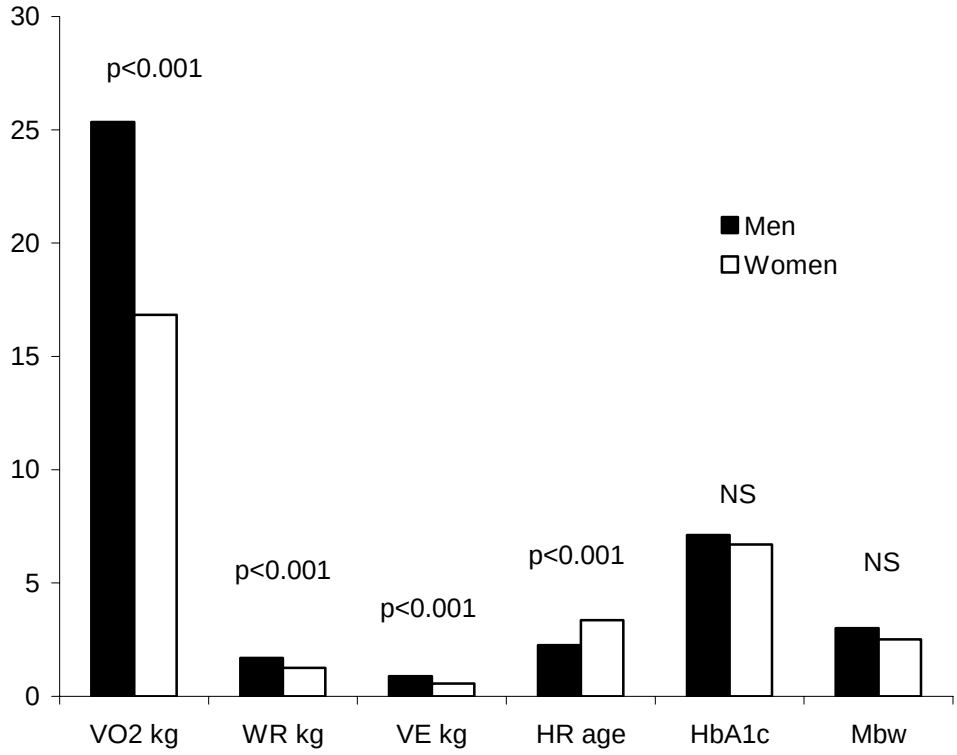

Figure 6. Gender differences in subjects with T2D (Study III-V). Men (n=39) and women (n=28).

The fact that individuals in study V all were women may be an explanation for the poor effect on exercise capacity. It is most vital to get more information about how women with T2D should exercise to benefit cardiovascular from exercise training.

Table 11. Gender differences in subjects with T2D (Study III-V).

	Men (n=39)	Women (n=28)	p-value
VO_{2peak} Body Weight $^{-1}$ (ml min^{-1} kg^{-1})	25.3 ± 6.1	16.8 ± 3.6	p<0.001
WR_{peak} Body Weight $^{-1}$ (W kg^{-1})	1.7 ± 0.4	1.2 ± 0.2	p<0.001
VE Body Weight $^{-1}$ (l min^{-1} kg^{-1})	0.9 ± 0.2	0.6 ± 0.1	p<0.001
HR age^{-1} (Beat min^{-1} year^{-1})	2.2 ± 0.2	3.4 ± 0.6	p<0.001
HbA1c (%)	7.1 ± 1.9	6.7 ± 1.3	NS
Mbw	3.0 ± 1.6	2.5 ± 1.4	NS

HRage = HRpeak adjusted for age
Values are mean ± SD
Significantly different data (p<0.05)

Exercise recommendations

The current exercise recommendations for T2D individuals are very wide in range. The Swedish recommendations for aerobic exercise training are 40-70% of VO_{2max} exercise intensity (23). The duration of the exercise is 20 to 60 minutes per session and the exercise should be repeated three to five times per week (23). Resistance training and daily activity are also recommended (23). A 20 minute session three times per week will give a volume of 60 minutes per week and a 60 minute session five times per week a volume of 300 minutes per week. Including the intensity the recommendation will vary from 2400-21000 % min $week^{-1}$.

Effects of aerobic exercise on aerobic capacity in individuals with T2D have been evaluated in a meta-analysis. The exercise was performed on various forms of fitness machines, such as bicycles, treadmills or rowing machines. The intensity of the exercise in the meta-analysis studies ranged from 50% to 75% of $VO_{2\ peak}$. Frequency of training was three to five times per week and the duration of each session was 40-60 minutes. In the meta-analysis VO_{2peak} increased with about 11% in these studies (124). Studies of fitness training in T2D has primarily been performed with endurance exercise (54, 73, 104-106, 108, 110-112, 118) but also with combined exercise (57). In studies where an increase in VO_{2peak} has been demonstrated, exercise has amounted to 120-280 minutes per week (57, 73, 104, 106, 108, 110-112). In studies where no increase in VO_{2peak} was achieved, exercise amounted to 80, 90 or 240 minutes weekly. All studies were conducted at training intensity above 60% of VO_{2peak}. (54, 57, 73, 104-106, 108, 110-112, 118). Burns et al., (105) suggested that subjects with T2D respond less to training than healthy subjects, but this has not been a consistent finding (73, 125, 126).

There are no specific exercise recommendations concerning how to influence glucose homeostasis. Aerobic exercise was previously thought to be the most suitable exercise mode for T2D (19, 50, 51). Exercise volume has also been shown by others to be needed to enhance glucose homeostasis (57, 106, 110, 111). In two recent reviews on the therapeutic benefits of exercise in T2D, the authors stated that a combined bout of aerobic and strength exercise training was preferred to enhance glucose control (49, 126). No differences were shown in a meta-analysis on effects of aerobic, resistance or combined exercise on HbA1c (127). Exercise studies using combined exercise have shown inconsistent results (55-57). One reason may be that the intensity, frequency and duration of exercise have varied. Exercise volume and exercise intensity had been analysed in obese non-diabetic individuals (116, 128). Both studies concluded that a certain weekly amount of exercise was needed to enhance insulin sensitivity. Houmard et al., (116) suggested an exercise volume of 170 minutes per week. Regarding intensity the studies were inconsistent (116, 128). It has been shown in a meta-analysis that exercises improve glycaemic control in individuals with T2D (124, 129). The greatest effect was achieved when exercise was performed at an intensity of 75% of VO_{2peak} (124). The effect on HbA1c was more dependent on intensity than volume. It was also shown that insulin sensitivity was increased 24 hour after exercise. This effect had disappeared after 72 hour. Therefore it is important to conduct exercise on a regular basis to maintain the positive effects on insulin sensitivity. Women with T2D were reported to have less effect of exercise on the cardiovascular system than men.

Increased physical activity is considered an important life-style modification in subjects with T2D. Supervised group training is often advocated as a means of maintaining adherence (130). A meta-analysis has shown that the effect of exercise on fitness is greater if exercise is prescribed, supervised and performed in groups (43).

Current exercise recommendation regarding exercise intensity may be to low to achieve an increase in glucose homeostasis in terms of HbA1c and insulin sensitivity. Further research is required to confirm this.

Conclusions

The performance of a maximal incremental cycle test in sedentary male subjects was highly affected by knee muscular strength and muscular endurance (Study I). Also upper body muscular strength correlated to exercise capacity as measured by cycle ergometry (Study II).

Exercise capacity assessed during cycling was strongly related to whole body insulin sensitivity and the waist-hip ratio, to a lesser extent (Study III). Also, muscle fibre type composition (Study I and III) and capillary density (Study III) contributed to peak exercise capacity.

Estimation of VO_{2peak} according to Åstrand sub-maximal exercise testing significantly overestimates directly measured VO_{2peak} in women with T2D (Study IV).

Insulin sensitivity increased and HbA1c decreased significantly after combined supervised group training in subjects achieving relatively higher exercise volume, whereas no significant changes were seen in subjects achieving a lower exercise volume (Study V).

Perspective

Generally, clinical guidelines do not provide in depth information about the most suitable type and intensity of exercise to optimise the gain of exercise in different subgroups of T2D individuals (131). More research is needed about exercise intensity, frequency, duration, volume and mode to enable more thorough exercise prescriptions.

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