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**FACULTY OF GRADUATE AND
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The Effect of Exercise Training on Physical Fitness in Type 2 Diabetes Mellitus

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The Effect of Exercise Training on Physical Fitness in Type 2 Diabetes Mellitus

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Thesis submitted to the
Faculty of Graduate and Postdoctoral Studies
In Partial fulfillment of the requirements
For the M.Sc. degree in Human Kinetics

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Joanie Larose, Ottawa, Canada, 2009



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Your file *Votre référence*
ISBN: 978-0-494-61183-8
Our file *Notre référence*
ISBN: 978-0-494-61183-8

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ACKNOWLEDGEMENT

I would like to thank my thesis supervisor Glen Kenny for his support and guidance over the past two years and for taking me on as a student. I have learnt a lot from you and you were always there when I needed help. I would also like to give special recognition to the entire DARE team for all the work they put into this study. Although I did not get the chance to work with you directly, I am grateful for all your time and efforts directed towards this study. Special thanks to Penny Phillips for providing me information regarding the DARE trial whenever I needed it and for taking the time to find documents when they were not readily available. Thank you to Ron Sigal for his support and guidance during this entire process. I did not get the chance to interact with him often but I am grateful for his input and aid in the development of this thesis. Many thanks to Farah Khandwala for her statistical expertise and for providing me with amazing outputs. In addition, I would like to thank Farah for taking the time to review my interpretations of the results and for talking with me when I had difficulties making sense of some of the results. Thank you to my colleagues; Rachel, Candice, Angela, Dan, Lucie, Jill, Jane and Bruno, for encouraging me and for offering me guidance whenever I needed it. I would like to thank my family and friends for all their support and for putting up with me over the last two years. It is amazing to me how much you can accomplish when you have the love and support of those surrounding you. Thank you mom and dad for encouraging me and for reminding me to take things one step at a time. Simon and Tania, thanks for your support even though I did not get a chance to see you guys very often. Sylvia, special thanks for supporting my ambitions and for being there every step of the way. Thank you to my friends and co-workers as well for your support and well wishes. Finally yet importantly, I would like to thank my committee members, Denis

Prud'Homme and Pascal Imbeault for their time and constructive criticism during this process.

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ABSTRACT

We compared the effects of different exercise modes on cardiorespiratory fitness and muscular strength as well as the rate of strength development in individuals with T2DM. 251 participants in the DARE trial were randomly allocated to aerobic training (A), resistance training (R), combined training (A+R) or controls. $\dot{V}O_{2peak}$, workload and treadmill time were determined following maximal exercise testing at 0 and 6 months. Muscular strength was measured as the 8 RM on the leg press, bench press and seated row. The rate of strength development was measured as monthly workload increments (month 1-6) on 11 strength exercises. $\dot{V}O_{2peak}$ improved by 1.73 and 1.93 mL O_2 /kg/min with A and A+R respectively compared to C ($p < 0.05$). Strength improvements were significant following A+R and R on the leg press (A+R:48%, R:65%) bench press (A+R:38%, R:57%) and seated row (A+R:33%, R:41%) ($p < 0.05$). There was a clear trend towards slowing in strength development in R and A+R over time. In brief, A+R leads to similar fitness improvements compared to A and R alone. Although strength development had a tendency to level off over time, it is important to consider that reductions in hemoglobin A1C occurred up to 6 months with R and were even greater with A+R.

INTRODUCTION

Important life style changes over the years, notably excessive food consumption and a decrease in physical activity (Kahn, Prigeon et al. 2001), are contributing factors to the deteriorating health of the adult population in North America. A major consequence of overeating and physical inactivity is the increasing rate of obesity and the associated co-morbidities which include Type 2 Diabetes Mellitus (T2DM) (Erhman, Gordon et al. 2003). Obesity and insulin resistance, along with a genetic predisposition significantly increase the risk of developing T2DM. In fact, 80 to 90 % of individuals suffering from T2DM are obese (Canadian Diabetes Association, 2005-2007).

Type 2 Diabetes Mellitus is a progressive disease characterized by defects in both insulin secretion and insulin action (DeFronzo 1999). This disease is a growing international health concern. It is estimated that close to two million Canadians and 177 million individuals worldwide are suffering from T2DM (Canadian Diabetes Association,2005-2007). This number is expected to reach 3 million in Canada and 300 million worldwide by 2025 (Canadian Diabetes Association,2005-2007), World Health Organization, (WHO, 2003). In addition, the complications requiring medical interventions associated with this disease, including heart disease, strokes, kidney disease, neuropathy, nerve damage, depression as well as foot, skin and eye complications, are taking a toll on the Canadian Health Care System (Gregg, Beckles et al. 2000; Gæde, Vedel et al. 2003). A striking \$13.2 billion dollars are spent each year for treatments related to T2DM. This amount is expected to reach \$15.6 billion by 2010 and \$19.2 billion by 2020 (2005-2007).

Aging of the population is contributing to the prevalence of T2DM (Cowie, Rust et al. 2006). In Canada, for example, approximately 87% of diagnosed cases of diabetes are in

individuals between the ages of 45 and 75 (Statistics Canada, 2007). Moreover, the 2002 U.S National Health and Nutrition Examination Survey reported more diagnosed cases of diabetes amongst individuals between the ages of 60 and 64 (15.1%) as well as those 65 years or older (15.8%) compared to any other age group (Cowie, Rust et al. 2006). Aging is associated with reduced cardiorespiratory fitness and muscle strength which can lead to functional disability (Dunstan, Daly et al. 2002). Functional disability is defined by the inability to perform tasks of mobility including walking, climbing stairs and tasks of daily living such as housework, cooking meals and shopping (Stewart 2002). Studies amongst older adults with diabetes found that individuals suffering from T2DM experience difficulty accomplishing simple daily physical tasks (Gregg, Beckles et al. 2000; Gregg, Mangione et al. 2002). For example, Gregg et al. (Gregg, Beckles et al. 2000) reported that older women with diabetes are twice as likely to experience difficulty performing physical and household work when compared to healthy counterparts. As a consequence of the aging North American population, the incidence of T2DM will continue to rise unless lifestyle changes occur.

1.1 Exercise in Type 2 Diabetes Mellitus

The importance of exercise training in the treatment of diabetes has been demonstrated previously. Notably, in a meta-analysis of the effects of exercise on glycemic control and body mass in Type 2 diabetes mellitus, Boulé et al. (Boulé, Haddad et al. 2001) reported that hemoglobin A_{1c} (A1C) value was significantly reduced by 0.66% in the exercise groups compared to the control groups. A follow-up meta-analysis by the same researchers found a mean increase of 9.5% in maximal oxygen consumption (VO_{2max}) following moderate-intensity aerobic training compared to 1% decrease in sedentary controls (Boulé, Kenny et al. 2003).

Larger increases in aerobic capacity were found in individuals who engaged in higher intensity endurance training. One study, for example, reported a mean 41% increase in peak oxygen consumption (VO_{2peak}) following continuous training at 75% VO_{2peak} with one session of intermittent training at 85% VO_{2peak} (Mourier, Gautier et al. 1997). Maximal oxygen consumption and A1C levels have both been identified as modifiable risk factors for the development of diabetes complications, morbidity and mortality (Boulé, Kenny et al. 2003).

Recent evidence as well supports that resistance exercise training (RT) can produce significant health benefits in individuals with diabetes. A recent meta-analysis, for example, provides evidence that resistance training can be safe for patients with chronic heart failure and may be a beneficial form of rehabilitation (Braith and Beck 2008). Thus, this type of training can be enjoyable all the while producing significant health benefits. Research amongst individuals with diabetes has reported significant improvements in body composition (Eriksson, Taimela et al. 1997; Castaneda, Layne et al. 2002; Dunstan, Daly et al. 2002; Baldi and Snowling 2003; Fenicchia, Kanaley et al. 2004; Cauza, Hanusch-Enserer et al. 2005; Ibanez, Izquierdo et al. 2005), lipid profile (Honkola, Forsén et al. 1997; Castaneda, Layne et al. 2002; Cauza, Hanusch-Enserer et al. 2005) blood pressure (Castaneda, Layne et al. 2002; Dunstan, Daly et al. 2002; Cauza, Hanusch-Enserer et al. 2005), glycemic control (Castaneda, Layne et al. 2002; Dunstan, Daly et al. 2002; Baldi and Snowling 2003; Cauza, Hanusch-Enserer et al. 2005; Ibanez, Izquierdo et al. 2005), and strength (Honkola, Forsén et al. 1997; Dunstan, Puddey et al. 1998; Castaneda, Layne et al. 2002; Dunstan, Daly et al. 2002; Baldi and Snowling 2003; Cauza, Hanusch-Enserer et al. 2005; Ibanez, Izquierdo et al. 2005) following moderate intensity resistance training. High intensity training was also found to be suitable for older individuals with T2DM. Castenada et al. (Castaneda, Layne et al. 2002)

showed for the first time that high intensity resistance training improved strength and significantly reduced A1C in a high risk population of Latino older adults with poor glycemic control. Furthermore, Dunstan et al. (Dunstan, Daly et al. 2002) reported that supervised high intensity training was safe and well tolerated by older individuals with T2DM. While these studies show promising effects of exercise in the management of T2DM, the small sample sizes used limit the generalizability of the results.

There is growing evidence that the effect of combined aerobic and resistance training generate greater results in terms of glycemic control than either aerobic or resistance exercise training alone. In the Diabetes Aerobic and Resistance Exercise (DARE) trial (Sigal, Kenny et al. 2007), for example, 251 previously sedentary type 2 diabetic individuals were examined after random allocation to one of four study groups; aerobic exercise training, resistance exercise training, combined aerobic and resistance exercise training or a non-exercise control group. Improvements in glycemic control were found in all exercise groups, and the improvements in the combined aerobic and resistance exercise group were significantly greater than with either aerobic training or resistance training alone. Specifically, it was shown that A1C value was reduced by 0.9% in the combined group which was higher than both the aerobic (0.43%) and resistance training groups (0.3%) respectively. In the Italian Diabetes and Exercise Study (Balducci, Zanuso et al. 2008), it was found that combined aerobic and resistance training delivered better results in terms glycemic control, lipids, body composition, blood pressure and estimated cardiovascular risk than the study group receiving exercise counseling only. These studies provide compelling evidence for incremental benefits of using both training modalities for people with type 2 diabetes.

The DARE study reinforced the importance of both aerobic and resistance training, in particular when resistance training is combined with aerobic training, to improve A1C. It remains unclear however, if the improvements in A1C are associated with improvements in physical fitness as defined by improvements in cardiorespiratory fitness and/or strength. There is evidence to suggest that a relationship exists between improvements in A1C and changes in body composition or physical fitness. Boulé et al. (Boulé, Haddad et al. 2001) suggested in their meta-analysis that the differences in post-intervention A1C were not affected by weight loss or exercise intensity (METS) and volume (METS/hour). In a follow up meta-analysis of the effects of structured exercise training on cardiorespiratory fitness in T2DM, a significant correlation was reported between post-intervention standardized mean difference in VO_{2max} and post-intervention weighted mean difference in A1C ($r = -0.72$, $P = 0.04$) (Boulé, Kenny et al. 2003). Studies involving resistance exercise training have also hinted to an association between changes in A1C and body composition. For instance, Eriksson et al. (Eriksson, Taimela et al. 1997) indicated a strong inverse correlation ($r = -0.73$) between A1C and muscle cross-sectional areas after 3 months of circuit weight training. Castaneda et al. (Castaneda, Layne et al. 2002) reported strong inverse relationships between changes in A1C and lean body mass ($r = -0.35$, $p=0.03$) after high intensity weight training in older adults with diabetes. Aerobic and resistance training improve glucose control by decreasing hepatic and muscle insulin resistance thus increasing glucose disposal and storage in skeletal muscles through several mechanisms which have been reviewed elsewhere (Ivy, Zderic et al. 1999; Boulé, Kenny et al. 2003; Eves and Plotnikoff 2006). The extent of the relationship between improvements in long term glucose control and how it relates to physical fitness achieved through exercise training, however, remains unclear. In the present study, we investigate the effects of aerobic exercise

training, resistance exercise training and their combination on pre-specified secondary outcomes related to physical fitness (i.e., cardiorespiratory fitness and muscle strength) in the DARE trial and how changes in A1C relate to physical fitness.

1.2 Purpose

The primary aim of this study is to investigate the effects of aerobic exercise training, resistance exercise training and their combination on cardiorespiratory fitness and strength in the participants from the DARE study prior to and following 6 months of exercise training.

1.3 Objective

The main objective of the DARE study was to determine changes in A1C following three exercise training modalities in patients with T2DM. In the present study we examine the effects of aerobic exercise training (AT), resistance exercise training (RT) and combined exercise training (AR) versus a sedentary controls (C) on cardiorespiratory fitness and strength. We will also assess whether the response to training differs between older and younger participants. As a secondary objective, we are interested in determining if the changes in physical fitness are associated with changes in A1C and if this association (if any) differs in participants with lower or higher baseline A1C.

1.4 Hypotheses

1. Changes in cardiorespiratory fitness will be greater in AT and AR compared to the resistance and control groups. Improvements in cardiorespiratory fitness will be similar between aerobic exercise training and combined exercise training. Changes in strength will be greater following

resistance exercise training and combined exercise training. Improvements in strength will also be similar between RT and AR.

2. Changes in strength and cardiorespiratory fitness will be similar in younger and older individuals.

3. Changes in A1C will be associated to some extent with physical fitness this relationship will be stronger in participants with higher baseline A1C compared to those with lower baseline A1C.

1.5 Relevance

Low physical fitness in T2DM has been associated with a higher risk of functional disability, cardiovascular disease as well as cardiac and all-cause mortality compared to individuals with higher levels of fitness. In addition, elevated A1C has been associated with a higher risk of cardiovascular and microvascular disease. The DARE clinical trial demonstrated that aerobic exercise training, resistance exercise training and combined aerobic and resistance exercise training are as effective as oral hypoglycemic agents in reducing A1C (Sigal, Kenny et al. 2007). From a practical perspective, some individuals may find the commitment and the work associated with exercise training a deterrent, and may be more likely to opt for a simpler and equally effective option to lower blood glucose levels with the use of oral hypoglycemic agents. However, increasing the level of regular physical activity and/or exercise training is the only proven way to increase cardiorespiratory fitness and strength. Boulé et al. (Boulé, Kenny et al. 2003) suggested that a relationship exists between changes in cardiorespiratory fitness and A1C and Castaneda et al. (Castaneda, Layne et al. 2002) indicated that changes in lean body mass were linked to changes in A1C. Determining a relationship between fitness and A1C may offer a

better indication as to the effectiveness of current exercise guidelines in the management of T2DM. Additionally, to date it is unclear how different exercise modalities influence the association between A1C and physical fitness. The association between changes in A1C and fitness, and whether this association differs with aerobic and resistance exercise training alone or in combination warrants further investigation. This information could be used to develop more precise exercise guidelines which would elicit optimal gains in glycemic control and fitness since both are independently associated with a lower risk of morbidity and mortality from diabetes complications.

1.6 Limitations and Delimitations

Since patients receiving insulin or with advanced diabetes complications were excluded from this study, our results cannot be generalized to such individuals. Also, this study was not performed on an intention to treat basis and our results are representative of individuals who are willing to engage in regular exercise training thus cannot be generalized to individuals who do not wish to take on an active lifestyle. Finally, since our study is limited to individuals between the ages of 39 and 70, we do not know the exercise response of elderly individuals with T2DM.

1.7 Definitions

Hemoglobin A1C (A1C): The proportion of hemoglobin that is glycosylated which normally accounts for approximately 5% of total hemoglobin in non-diabetic individuals. A1C reflects the average concentration of glucose in the blood during the previous 2-3 months and is directly proportional to the concentration of glucose in the blood over the full life span of the red blood cells. Diabetes is considered to be well controlled when A1C is <7%.

Physical activity: The expenditure of energy above that of resting by contraction of skeletal muscle to produce bodily movement.

Exercise: A type of physical activity that involves planned, structured and repetitive bodily movement performed for the purpose of improving or maintaining physical fitness. The terms “physical activity” and “exercise” will be used interchangeably in this chapter.

Cardiorespiratory fitness/cardiorespiratory endurance/aerobic fitness: Refers to the circulatory and respiratory systems’ ability to supply oxygen during sustained physical activity.

Maximal Aerobic Capacity: Maximal amount of physiologic work that an individual can do as measured by oxygen consumption.

Aerobic exercise: Exercise that uses primarily aerobic energy-producing systems and involves the repeated and continuous movement of the same large muscle groups for extended periods of time (at least 10 minutes at a time). If performed with sufficient intensity and frequency this type of exercise increases cardiorespiratory fitness. Aerobic activities include walking, cycling, jogging, swimming etc.

Intensity of aerobic exercise: Generally described in relation to an individual’s maximal aerobic capacity ($\dot{V}O_{2max}$), as measured using indirect calorimetry during a graded maximal exercise test. An activity level corresponding to 40 to 60% of $\dot{V}O_{2max}$ is generally considered to be “moderate” in intensity, while “vigorous” aerobic activities consist of those performed at greater than 60% of $\dot{V}O_{2max}$.

Muscular fitness: Includes the force a muscle can exert (strength) and the ability of the muscle to perform continuously without fatigue (endurance).

Resistance exercise: Also known as strength training or weight training. Resistance exercise involves the use of muscular strength to work against a resistive load or move a weight.

Examples include lifting free weights, or using weight machines. Regular resistance exercise at sufficient (moderate to high) intensity increases muscular fitness.

Intensity of resistance exercise: The intensity of resistance exercise is often considered “moderate” if the resistance provided is between 50 and 74% of the maximum that can be lifted a single time (1 repetition maximum (RM)). High intensity resistance exercise involves resistance $\geq 75\%$ of 1RM.

Repetition: The number of times a resistance exercise is repeated during each set.

Set: A grouping of repetitions of a specific resistance exercise.

Strength: maximal force that can be applied by muscles during a single maximal contraction.

8 RM: Maximum amount of weight that can be lifted 8 times.

Ventilatory threshold: Oxygen uptake immediately below the exercise intensity at which pulmonary ventilation increases disproportionately relative to VO_2 .

2. LITERATURE REVIEW

2.1 Pathogenesis of Type 2 Diabetes Mellitus

2.1.1 Glucose Homeostasis

Glucose homeostasis occurs when glucose appearance in the bloodstream is counterbalanced by glucose uptake or utilization and is regulated by three main processes; insulin secretion, glucose uptake by tissues and hepatic glucose production (HGP) (Porte 2001). Normal glucose regulation is defined by the American Diabetes Association as a fasting plasma glucose level below 5.6 mmol/L and a 2 hour post-load plasma glucose level below 7.8 mmol/L (Rydéng, Standlc et al. 2007). Glucose homeostasis is tightly regulated in the fasting state and in the postprandial state. During fasting, glucose production and appearance in the circulation is assured by the liver. The liver will take up glucose when there is a sufficient amount in the blood and synthesize glucose when blood glucose levels fall (Gribble 2005). Glucose uptake at rest or in the fasting state is primarily done through insulin-independent mechanisms in tissues that require glucose as their main or only source of energy. The central nervous system and the brain are important glucose consumers and therefore play a key role in blood glucose clearance at rest (Porte 2001). Postprandial pathways responsible for glucose disposal rely on the action of insulin.

2.1.2 Insulin Action

Insulin is a hormone produced by the beta cells of the pancreas which responds to increased plasma glucose. Insulin secretion initiates glucose uptake by insulin sensitive tissues such as skeletal muscles, the liver and adipose tissue. Normal insulin secretion occurs in a biphasic pattern. The first phase secretion occurs early in the absorption process and is characterized as being sharp and rapid, reaching a peak within 3-5 minutes and lasting

approximately ten minutes (Porte 2001). The main effect of this first phase insulin secretion is to inhibit hepatic glucose production (HPG) and promote glucose uptake as well as glycogen synthesis within the liver. The second phase insulin secretion occurs in the absorptive state. It is more gradual and will last as long as blood glucose levels are elevated (Porte 2001). The most important site of insulin-mediated glucose disposal is in skeletal muscles through the main action of insulin sensitive glucose transport protein, GLUT-4 (Porte 2001). Glucose is then utilized by skeletal muscles as an energy source or is stored in the form of glycogen. Skeletal muscle glucose uptake is key to preventing hyperglycemia after a meal. Insulin also has a profound effect on adipose tissue. The presence of insulin in the circulation inhibits free fatty acid metabolism and release from adipocytes (lypolysis), which facilitates glucose uptake by the muscles (Porte 2001). These mechanisms are essential in the regulation of blood glucose and impairments of both insulin secretion as well as insulin sensitivity are key components in the pathogenesis of T2DM.

2.1.3 Type 2 Diabetes Mellitus

Type 2 Diabetes Mellitus is a progressive metabolic disorder that develops from impairments of both insulin secretion and insulin action (Leahy 2005). These defects compromise glucose homeostasis, often resulting in chronic hyperglycemia. Hyperglycemia can lead to more severe disorders if not well managed. The pathogenesis behind T2DM involves insulin resistance, excess hepatic glucose production and beta cell dysfunction (Cowie, Rust et al. 2006).

2.14 Insulin resistance

Insulin resistance is characterized by dysfunctions in the mechanisms of glucose transport and glycogen synthesis pathways (Leahy 2005). Consequently, glucose uptake in insulin sensitive tissues is impaired as well as its utilization for energy purposes, even when a sufficient amount of insulin is produced (Cowie, Rust et al. 2006). Insulin resistance is predominant in the liver and in peripheral tissues. As noted previously, the liver is an important organ in the maintenance of glucose homeostasis. In healthy individuals, insulin suppresses HGP and stimulates hepatic glucose uptake. In individuals with diabetes, HGP is not inhibited since insulin resistance disables the binding of this hormone to its receptors on the plasma membrane. As a result, unrestrained glucose production from the liver and the arrival of exogenous glucose in the circulation cause a pronounced elevation of glycemia.

Skeletal muscles are an important site of glucose disposal when glucose and insulin levels are elevated. Glucose transport into skeletal muscles occurs through facilitated diffusion. This process begins with the delivery of glucose from the blood to the interstitial space, transmembrane transport from the interstitial space to the inside of the muscle cell through transport proteins, and intracellular storage or use of glucose for energy production (Richter, Derave et al. 2001). The main insulin-dependant glucose transport protein isoform found in human skeletal muscles is GLUT-4. GLUT-4 is found mostly within small tubulo-vascular organelles in the cytoplasm of muscle cells (Richter, Derave et al. 2001). In healthy individuals, insulin binds to the receptor alpha-subunit located on the cell surface which initiates a cascade of events leading to the translocation of GLUT-4 to the cell membrane (Goodyear 1998; Brooks, Fahey et al. 2000). A defect in the intracellular signaling pathway leading to the translocation of GLUT-4 is thought to be responsible for the decline in insulin-mediated glucose uptake within

skeletal muscles of individuals with diabetes (Goodyear 1998). Peripheral insulin resistance reduces glucose disposal in skeletal muscles by approximately 55 % (Porte 2001)

Adipose tissues also use GLUT-4 transport proteins and are therefore sensible to the effect of insulin. In healthy individuals, the presence of insulin stimulates glucose uptake in adipose tissues where it is stored as triglycerides (Davis, Frank et al. 1979). Insulin also acts to inhibit free fatty acid release from adipose tissue in order to facilitate glucose disposal (Porte 2001). In T2DM, this mechanism is altered and lipolysis is not inhibited in the presence of insulin causing a decrease in glucose uptake and glycogen synthesis in skeletal muscles (Porte 2001). Insulin resistance in these three organs considerably increase blood glucose levels and is believed to be affected by genetics and environmental factors (Leahy 2005). In insulin resistant individuals who do not develop T2DM, an enhanced insulin secretion (hyperinsulinemia) from pancreatic beta cells alleviates the increase in plasma glucose. It is only when beta cells are no longer able to sustain a sufficient insulin secretion to counteract the exaggerated presence of glucose in the bloodstream do individuals progress to full blown T2DM (Leahy 2005).

2.1.5 Beta cell dysfunction

Beta cell dysfunction occurs in a biphasic pattern (Leahy 2005). In the earliest stages of the disease, beta cell dysfunction is observed through a reduced first phase insulin secretion resulting in elevated 2-hour plasma glucose and plasma insulin concentrations (Porte 2001; Leahy 2005). This hyper secretion of insulin serves to bring glucose levels back within near normal values (Leahy 2005; Prentki and Nolan 2006). As hyperglycemia worsens, progressive beta cell deterioration occurs, leading to a lowered beta cell mass (Leahy 2005). Butler et al.

(Butler, Janson et al. 2003) demonstrated that beta cell mass can be lowered as much as 40 to 60 % in individuals with diabetes when compared to weight-matched controls.

The pathogenic factors that lead to T2DM, such as obesity and physical inactivity, increase the risk of developing cardiovascular disease and other complications. An integral part of the treatment for this disease should involve well-structured exercise programs consisting of aerobic and resistance exercises, which improve both insulin sensitivity and glucose tolerance.

2.3 Physiological adaptations to exercise training

2.3.1 Insulin sensitivity and glucose uptake during exercise

Exercise training increases whole-body glucose utilization through a variety of factors. The mechanisms of enhanced insulin sensitivity in athletes versus sedentary individuals have been credited to greater muscle blood flow and capillarization as well as a greater amount of GLUT-4 protein which together increase glucose delivery and uptake in muscle cells. Athletes also exhibit enhanced activity of metabolic enzyme, notably muscle glycogen synthase activity, which improve glycogen synthesis and storage in skeletal muscles compared to sedentary counterparts (Ebeling, Bourey et al. 1993; Ivy, Zderic et al. 1999). Moreover, Ivy et al. (Ivy, Zderic et al. 1999) have attributed changes in body composition, muscle morphology and enhanced control over hepatic glucose production as the mechanisms responsible for increased insulin sensitivity and glucose uptake following exercise training. Specifically, a reduction in visceral adipose tissue, an increase in muscle mass, a greater conversion of fast twitch glycolytic IIb fibers to fast twitch oxidative IIa fibers as well as improved activity of enzymes responsible for phosphorylation, storage and oxidation of glucose are important adaptations to exercise training that are beneficial in the treatment of T2DM (Ivy, Zderic et al. 1999).

Individuals who suffer from T2DM display insulin resistance and a reduction in insulin-mediated glucose translocation in skeletal muscles although muscle GLUT-4 protein and mRNA concentrations remain unaffected (Dela, Ploug et al. 1994). Exercise training stimulates GLUT-4 translocation through contraction-dependent mechanisms which increase whole body glucose utilization even in insulin resistant individuals (Goodyear 1998; Brooks, Fahey et al. 2000). Additionally, Dela et al. (Dela, Ploug et al. 1994) found similar improvements in GLUT-4 protein content in 7 men with T2DM compared to healthy older men following 30 minutes per day of one-legged ergometer bicycle training, six days a week for nine weeks. This researcher also reported in a different study that the increase in muscle GLUT-4 concentration, which increased by $26 \pm 11\%$ in 7 healthy young men following aerobic training, is an important adaptation for training induced increases in insulin action (Dela, Handberg et al. 1993).

2.2.2 Physiological adaptations to aerobic exercise training

Cardiorespiratory fitness refers to the ability of the body to sustain prolonged exercise. The most recognized measure of cardiorespiratory fitness is maximal oxygen consumption (VO_{2max}). Maximal oxygen consumption is defined as the maximum rate of oxygen transport and utilization as verified by the leveling off of oxygen consumption with increasing work rate (Franklin 2007). However, most sedentary adults reach a level of volitional fatigue which is often below the attainment of their true VO_{2max} . As a result, the preferred terminology for the highest oxygen consumption attained is VO_{2peak} (Franklin 2007). Systemic adaptations of the cardiovascular, pulmonary and metabolic systems to aerobic training, resulting in more efficient oxygen delivery and consumption throughout the body, are often reflected in an increase of VO_{2peak} .

Cardiovascular system

The cardiovascular system is composed of blood, the heart as well as blood vessels through which blood is pumped to the body. With aerobic training, structural and functional improvements occur allowing the cardiovascular system to more efficiently deliver oxygen to working muscles. The adaptations to training benefit both maximal and submaximal exercise performance.

Blood is composed largely of red blood cells (45%) and plasma (~ 55%) (Robergs and Keteyian 2003). Red blood cells are mainly responsible for the transport of oxygen and carbon dioxide within the circulation while plasma functions include the circulation of cellular components (such as red blood cells), metabolites, nutrients, waste products and hormones as well as the maintenance of blood pressure, water exchange and water transport to name a few. Blood volume is thought to increase with endurance training which may lead to a higher maximal exercise capacity. For example, Warburton et al. (Warburton, Haykowsky et al. 2004) showed that blood volume increased by 10% and 12% following 12 weeks of interval and continuous aerobic training respectively in adult men. This group also indicated that the increase in blood volume following endurance training accounts for approximately 56% of the increase in VO_{2max} across a wide range of fitness levels. The increase in blood volume is partially attributed to a rise in plasma volume. Increased hormone and plasma protein levels including antidiuretic hormone (ADH), aldosterone and albumin, are prominent in the first couple of weeks of exercise and are responsible for the increase in plasma volume (Wilmore, Costill et al. 2004). In addition, the increase in red blood cells also increases blood volume and facilitates oxygen delivery to working muscles. Another important adaptation to aerobic training is the increase in the number and size of the capillaries surrounding muscle fibers (Wilmore, Costill et al. 2004). This change

usually occurs within a few weeks of training. Training also increases systolic blood pressure during exercise at maximal intensity which helps drive the blood more rapidly through blood vessels (Wilmore, Costill et al. 2004), which accompanied with a more efficient blood distribution during exercise, results in more oxygen rich blood being directed towards active muscles.

End-diastolic volume refers to the volume of blood contained in the left ventricle following diastole (Stewart 2002). With training, the increase in blood volume renders more blood for the filling of the left ventricle during diastole allowing more blood to be pumped out during systole. This is known as the Frank-Starling mechanism (Waburton, Haykowsky et al. 2004). Monitoring heart rate during an exercise program provides a good indication of the amount of work accomplished by the heart in order to meet the demands of working muscles (Wilmore, Costill et al. 2004). Maximal heart rate (HR_{max}) usually remains stable following training but for previously untrained individuals, HR_{max} may decrease. A slower heart rate allows greater filling of the left ventricle and consequently more blood is ejected at a lower energy cost with each contraction (Wilmore, Costill et al. 2004). This efficiency permits an optimal cardiac output to meet oxygen requirements in order to sustain longer bouts of exercise.

Pulmonary adaptations

Endurance training also leads to an increase in pulmonary ventilation during exertive exercise in order to bring in sufficient amounts of oxygen. This change is due to an increase in tidal volume (the amount of air inspired and expired during a breathing cycle) as well as an increase in respiratory rate (Wilmore, Costill et al. 2004). Because of the increase in pulmonary ventilation and the increase in pulmonary blood flow, the diffusion of oxygen and carbon dioxide

between the lungs and the blood (pulmonary diffusion) is also increased during maximal exercise. This allows for a greater amount of oxygen to enter the blood circulation and essentially be delivered to active muscles (Wilmore, Costill et al. 2004). With a greater proportion of blood being delivered to working muscle, active tissues become adept at extracting oxygen molecules from the circulation and use them in oxidative metabolism.

Metabolic adaptations

Metabolic adaptations to endurance training within muscle tissues include changes in muscle fibers, mitochondria density as well as oxidative enzymes. The predominant muscle fibers involved in aerobic type exercises are the slow twitch fibers. These fibers increase in cross sectional area and in number after aerobic training (Clausen 1976; Davis, Frank et al. 1979). Slow twitch fibers are enriched with myoglobin that shuttle oxygen molecules from the cell membrane to mitochondria. The increase in myoglobin content during endurance training can be as substantial as 75 to 80% of initial levels (Wilmore, Costill et al. 2004). Coinciding with the increase in slow twitch fibers and myoglobin content is the increase in size, number and efficiency of mitochondria (Kiessling, Piehl et al. 1971; Davis, Frank et al. 1979). Toledo et al. (Toledo, Menshikova et al. 2007) assessed whether daily moderate-intensity exercise combined with moderate weight loss would increase skeletal muscle mitochondrial content in individuals with T2DM. They found that skeletal muscle mitochondrial density increased significantly ($67 \pm 17\%$) following 20 weeks of aerobic training and dieting. The increase in mitochondrial efficiency ameliorates the activity of oxidative enzymes that accelerate the breakdown of substrates to produce ATP (Hollozy 1973; Davis, Frank et al. 1979).

Physiological adaptations of the cardiovascular, pulmonary and metabolic systems to aerobic training allow an increase in work performance and the ability to sustain longer bouts of exercise over time.

2.2.3 Physiological adaptations to resistance training

Muscle strength is defined as the force generation capacity of an individual. Resistance training increases muscular strength through a cascade of physiological alterations. The mechanisms that underlie training-induced increases in muscle strength are thought to occur through two main pathways; neural adaptations and muscle hypertrophy. In addition, muscle hyperplasia and endocrinal adaptations also lead to increases in muscular strength, albeit to a lesser extent than the aforementioned pathways (Frontera, Meredith et al. 1988; Charette, McEvoy et al. 1991; Staron, Karapondo et al. 1994; Robergs and Keteyian 2003).

Neural adaptations

Early improvements in strength during resistance training are attributed to neuromuscular adaptations rather than to muscle hypertrophy. It has been suggested that unconditioned individuals are unable to recruit a large number of motor units and their recruitment is asynchronous (Cerny and Burton 2001). Within the first few weeks of resistance training, adjustments in the nervous system allow the individual to learn to recruit all motor units. Increases in neural activation and muscle excitability also occur during strength training (Staron, Karapondo et al. 1994). These neural alterations not only provide greater motor unit recruitment, but it allows motor units to be stimulated in a more synchronous manner (Robergs and Keteyian 2003). Neuromuscular adaptations to training peak after three to four weeks of training at which

time the increase in muscle fiber size becomes the major contributor to strength gain (Cerny and Burton 2001).

Muscle Hypertrophy

Concomitant to changes in the neuromuscular system during the early stages of resistance training, there is also an increase in the expression of contractile proteins (Staron, Karapondo et al. 1994). The increase in contractile proteins contributes to muscle hypertrophy, which refers to the increase in muscle cross-sectional area of the major muscle fibers types: Type I (slow twitch), Type IIa (fast twitch oxidative/glycolic) and Type IIb (fast twitch glycolic) (Staron, Karapondo et al. 1994; Robergs and Keteyian 2003). Staron et al. (Staron and Johnson 1993) observed significant hypertrophy of all three muscle fibers types (Type I; 15%, Type IIa; 45%, Type IIb; 57%) in the vastus lateralis muscle of females after 20 weeks of heavy resistance training. In a previous study conducted by this team, increases in muscle fiber sizes (Type I; 15.6%, Type IIa; 17.3%) were reported after six weeks of resistance training (Staron, Leonardi et al. 1991). Staron et al. (Staron, Karapondo et al. 1994) later conducted a progressive resistance training program for lower extremities to evaluate the time course of skeletal muscle adaptation in males and females. A gradual increase in muscle cross-sectional area of all three fiber types was observed in both sexes after six to eight weeks of training. Moreover, Frontera et al. (Frontera, Meredith et al. 1988) trained 12 sedentary older males aged 60-72 and reported significant hypertrophy of both Type I and Type II fibers. Similarly, Charette et al. (Charette, McEvoy et al. 1991) investigated muscle fiber hypertrophy in 27 healthy older females aged 64-86 during 12 weeks of resistance training. Their results demonstrated a 20% increase in muscle cross-sectional area of Type II muscles fibers. These two studies provide strong evidence that

progressive weight-training programs can lead to muscle fiber hypertrophy and significant strength gains in older persons. In fact, the increase in muscle strength reported in the group of older females following training ranged between 28-115% of baseline values. In addition to increases in cross-sectional areas of both slow and fast twitch fibers, fast twitch fiber-type conversions have been observed following resistance training. In the studies by Staron et al. (Staron, Leonardi et al. 1991; Staron and Johnson 1993; Staron, Karapondo et al. 1994) significant decreases in the percentage of Type IIb fibers with a concomitant trend towards an increase in the percentage of Type IIa fibers were reported. In one study, they reported a significant decrease in the percentage of Type IIb fibers in males and females after as little as two weeks of training (Staron, Karapondo et al. 1994).

Hyperplasia and endocrinal adjustments

Animal studies have shown that overloading skeletal muscles leads to fiber splitting and/or the generation of new fibers (hyperplasia) (Sola, Christensen et al. 1973; Alway 1994). Subsequent to these results, the focus turned to whether hyperplasia occurred in human muscles following strength training. MacDougall et al. (MacDougall, Sale et al. 1984) investigated possible muscle fiber hyperplasia in the biceps of 12 male body builders in comparison with 13 age-matched control subjects with no previous history of resistance training. They found that despite large differences in muscle size between the two groups, the group of body builders had the same number of muscle fibers as the untrained group and concluded that muscle enlargement is mainly the result of muscle fiber hypertrophy and not hyperplasia.

Hormonal expression may also play a role in strength adaptations by stimulating muscle growth especially in males. Despite the fact that females have less lean body mass, a

smaller cross sectional area for all major muscle fibers, and a greater percentage of body fat than males, the only reported difference in the adaptive response to resistance training is in specific hormone levels involved in muscle protein synthesis. Staron et al. (Staron, Karapondo et al. 1994) reported greater resting levels of serum testosterone concentrations and lower serum cortisol levels in males after 7-9 weeks of resistance training whereas no such observations were made in the group of females. The increases in strength and muscle endurance following neuromuscular adaptations to resistance training improve functional capacity and prevent the development of sarcopenia and osteoporosis common with aging.

2.3 Exercise capacity and tolerance in Type 2 Diabetes Mellitus

2.3.1 Age related decline in cardiorespiratory fitness.

Maximal Oxygen uptake

The prevalence of T2DM increases with age and aging is associated with progressive decrements in various components of physical work capacity, notably declines in cardiorespiratory fitness and muscle strength (Castaneda, Layne et al. 2002). The cardiovascular system is an important component limiting physical work in older individuals. Deterioration in cardiovascular functioning is observed by a decline in maximal oxygen consumption. Maximal oxygen consumption declines roughly 30-35% between the ages of 20 and 65 (McArdle, Katch et al. 1994; Brooks, Fahey et al. 2000). The decline in cardiorespiratory fitness is influenced by age-related decrements in central and peripheral functions related to oxygen transport and utilization (McArdle, Katch et al. 1994). These include reductions in HR_{max} , stroke volume, arteriovenous oxygen difference, power output capacity, muscle mass as well as an increase in fat free mass (McArdle, Katch et al. 1994; Brooks, Fahey et al. 2000; Robergs and Keteyian 2003).

Cardiac output

The decline maximal oxygen uptake with aging is strongly associated with a decrease in maximal cardiac output. Maximal cardiac output is reported to be reduced 20-30% by the age of 65 (Fagard, Thijs et al. 1993). This reduction in cardiac output is mediated by declines in maximal heart rate and stroke volume. Shepherd et al. (Shepherd 1997) noted that age-related decrements in HR_{max} are mediated by a reduction in both ventricular compliance and catecholamine secretion along with a decrease in the number or sensitivity of myocardial adrenergic receptors. In addition, deconditioning, loss of muscle mass and the presence of chronic diseases are said to be partially responsible for the decline in maximal heart rate with aging (Brooks, Fahey et al. 2000; Astrand 2003). Stroke volume is mainly affected by a slower relaxation of ventricular walls, poor peripheral venous tone, varicose veins, and a decrease in plasma volume, red blood cells and total blood volume (Brooks, Fahey et al. 2000). As a result, blood flow to working muscles during exercise is reduced. Moreover, the narrowing and the loss of elasticity of major blood vessels supplying blood to skeletal muscles, heart and other organs affect blood flow (McArdle, Katch et al. 1994).

A decrease in arteriovenous oxygen difference with aging also contributes to the progressive decline in cardiorespiratory fitness. This decline is mainly due to decreases in fiber to capillary ratio, total hemoglobin, muscle mitochondrial density, oxidative enzymes and a reduction in respiratory capacity of skeletal muscles (Brooks, Fahey et al. 2000). The redistribution of a portion of cardiac output to tissues with a limited oxygen extraction capacity (i.e. skin) also affects arteriovenous oxygen difference with aging (Brooks, Fahey et al. 2000; Robergs and Keteyian 2003) .

Structural changes with increasing age occur within the pulmonary system. These changes include reductions in pulmonary blood volume, surface area, static elastic recoil of the lungs, compliance of chest walls and respiratory muscle strength whereas the size of the alveoli increases with age (Brooks, Fahey et al. 2000; Robergs and Keteyian 2003). The ability of the lungs to meet ventilatory requirements during maximal exercise progressively deteriorates between 30 and 60 years of age (Brooks, Fahey et al. 2000). These structural changes lead to declines in maximal ventilation, expiratory flow rate, forced expiratory volume in 1 second, tidal volume and vital capacity as well as a progressive increase in breathing frequency and residual volume (Erhman, Gordon et al. 2003; Robergs and Keteyian 2003). Maximal breathing capacity is reported to decrease 30% by age 60 and approximately 40% by 80 years of age (Robergs and Keteyian 2003). Vital capacity decreases 14% and residual lung volume is said to increase by 33% on average between the ages of 20 and 60 in males whereas total lung capacity remains relatively unchanged with aging (Brooks, Fahey et al. 2000).

2.3.2 Decline in cardiorespiratory fitness associated with Type 2 Diabetes Mellitus

Exercise capacity has been shown to be reduced in people with T2DM compared to age, body mass and activity matched controls even in the absence of diabetic complications (Regensteiner, Bauer et al. 1995; Kunitomi, Takahashib et al. 2000; Boulé, Haddad et al. 2001). A meta-analysis of the effects of structured exercise training on changes in cardiorespiratory fitness in people with T2DM reported a mean baseline VO_{2max} of 22.4 ml/kg/min in 212 individuals with a mean age of 55.7 years (Boulé, Kenny et al. 2003). The American Heart Association indicates that healthy males and females between the ages of 50 to 59 should have a VO_{2max} of approximately 36 ml/kg/min and 29 ml/kg/min respectively. Aside from advancing

age, previous studies have reported that several other factors are responsible for the deterioration of aerobic capacity in individuals with T2DM (McMillan 1979; Regensteiner, Bauer et al. 1995; Valberg and Macleay 1997). These include: underlying complications related to diabetes, a longer duration of diabetes, increased A1C, a prior history of cardiovascular disease, hypertension, the use of medications as well as ethnicity. Regensteiner et al. (Regensteiner, Bauer et al. 1995) observed that exercise time to exhaustion in people with T2DM is 24% lower than non-diabetic individuals. They also reported that VO_{2max} is reduced by 21% and that oxygen consumption at anaerobic threshold is lower in this group than non-diabetic counterparts. In addition, Kunitomi et al. (Kunitomi, Takahashib et al. 2000) undertook a controlled trial on exercise prescription by ventilatory threshold for Japanese individuals with T2DM. The primary finding of this study was that the individuals with diabetes reached ventilatory threshold at lower work rates than the healthy control group (T2DM; 62 \pm 14 watts (W), Control: 74 \pm 13 W). Impairments in left ventricular diastolic dysfunction, oxygen uptake kinetic response, endothelial vasodilator function and muscle oxidative enzyme capacity along with arterial stiffness and inflammation are believed to contribute to exercise intolerance in individuals with diabetes (Stewart 2002; 2003; Ribisl, Lang et al. 2007).

Oxygen uptake kinetic response refers to the rise in the consumption of oxygen (VO_2) to a steady-state during submaximal exercise (Regensteiner, Bauer et al. 1998). It is the rate at which the cardiovascular system is able to deliver oxygen to working muscles and the rate at which oxygen is consumed by the muscles during exercise. The VO_2 kinetic response occurs in three phases (Regensteiner, Bauer et al. 1998). At the start of exercise (phase 1), the increase in blood flow causes a sharp increase in the volume of oxygen. In Phase 2, VO_2 increases linearly with the increase in workload until a steady-state is attained. Phase 3 occurs when steady-state

oxygen consumption is achieved below the lactate threshold. A study amongst females with diabetes assessed oxygen uptake kinetic response and found that compared to obese and lean non-diabetic females, the group with diabetes had a lower submaximal VO_2 kinetic response (Regensteiner, Bauer et al. 1998). The amount of time required for the oxygen consumption to meet workload demands was prolonged in the group of females with diabetes but not in their obese counterparts.

The reduced cardiac output often seen in individuals with diabetes is partially attributed to age-related changes in cardiovascular functioning mentioned previously and to myocardial dysfunctions known as diabetic cardiomyopathy. This disease is thought to impair left ventricular function and affect oxygen diffusion and consumption by active muscles during exercise (Regensteiner, Groves et al. 2002). Left ventricular diastolic dysfunction may be responsible for the reduced left ventricular filling during diastole in T2DM (Stewart 2002). Although further research is required to fully understand the mechanisms behind left ventricular dysfunction in diabetes, feasible causes of these disturbances are related to potential myocardial ischemia (Stewart 2002). Myocardial ischemia is caused by the inability to maintain an adequate blood flow to the myocardium during exercise. This is commonly observed in patients with coronary heart disease (Fletcher, Balady et al. 2001).

Endothelial vasodilator function

The impairment of endothelial vasodilator function is associated to insulin resistance and contributes to a lower exercise capacity in T2DM (Reusch, Regensteiner et al. 2003; Regensteiner, Bauer et al. 2005). Sustained hyperinsulinemia is said to alter the activity of insulin-induced nitric oxide synthase (NOS) (Maiorana, O'Driscolla et al. 2002). Nitric oxide

synthase is responsible for synthesizing nitric oxide (NO) which is known as an endothelial derived relaxing factor (Erhman, Gordon et al. 2003)). Nitric oxide is responsible for smooth muscle relaxation (vasodilation) during exercise in order to increase blood flow (Porte 2001; Erhman, Gordon et al. 2003). Endothelial dysfunction in the coronary circulation could play a role in myocardial ischemia during exercise mentioned earlier (Stewart 2002).

Muscle fibers

Individuals with diabetes are reported to have a greater fast twitch (typeIIb) to slow twitch (type I) muscle fiber ratio (Fletcher, Balady et al. 2001). Slow twitch muscle fibers are suited for endurance training. They have a greater resistance to fatigue due to their high mitochondria density and therefore provide a better aerobic and oxidative capacity. Fast twitch (type IIb) fibers on the other hand have a high glycolytic and very low oxidative capacity (Fletcher, Balady et al. 2001). For this reason, a greater TypeIIb/TypeI ratio often observed in persons with diabetes could affect oxygen extraction and therefore reduce the capacity to sustain a prolonged period of exercise.

2.3.3 Age related decline in muscular strength

In addition to age related alterations in cardiorespiratory fitness, bone density and skeletal muscle strength are also reduced with aging. These two components are strong predictors of disability especially in individuals with low exercise capacity since strong bones. Aging is associated with a degenerative loss of skeletal muscle mass and strength, also known as sarcopenia. It has been suggested that after the age of 30, muscle cross sectional area and muscle density both decrease (Evans 1997). Evans (Evans 1997) reported that muscle strength decreases

by approximately 15 % per decade between the ages of 60 and 70 and by 30% subsequently in healthy individuals. Factors that influence the loss of muscle mass include physical inactivity as well as a decrease in the use the neuromuscular system (McArdle, Katch et al. 1994; Robergs and Keteyian 2003). Strength reduction with aging is associated with declines in muscle proteins, muscle respiratory capacity along with an increase in connective tissue and fat mass (McArdle, Katch et al. 1994; Evans 1997; Robergs and Keteyian 2003). Moreover, the loss or atrophy of muscle fibers, which is more marked in fast twitch (Type II) fibers, contributes to the decline in skeletal muscle strength (Brooks, Fahey et al. 2000). The mechanisms involved in muscle contraction are also affected by aging. Aging muscles become less excitable thus a greater stimulus is required for contraction and a longer period of time is needed for muscles to respond to that stimulus (Brooks, Fahey et al. 2000).

2.3.4 Decline in muscle strength associated with Type 2 Diabetes Mellitus

The loss in muscle strength is even more pronounced amongst aging persons with diabetes. Following a 10 year prospective cohort study of older females with diabetes, it was observed that females with diabetes are twice more likely than non diabetic females to be unable to perform physical or household tasks (Gregg, Mangione et al. 2002). The average yearly incidence of disability, defined as the inability to walk, climb 10 steps, do housework, shop or cook meals, was 9.8% for females with T2DM and only 4.7% for females without diabetes (Gregg, Mangione et al. 2002). Furthermore, in a study of 1391 males and females between the ages of 60 and 70 with and without diabetes, diabetes was associated with a lower gripping strength (41.8 kg) than individuals with impaired glucose tolerance (44.1 kg) (Sayer, Dennison et al. 2005). The numerous vascular and neural complications associated with this disease increase

the risk of physical disability by 2 to 3 times (Gregg, Mangione et al. 2002). In addition, a reduction in lean body mass has important repercussions on blood glucose disposal capacity, resting metabolic rate, bone density, insulin sensitivity as well as aerobic capacity (Evans 1997).

Even with a proven decrease in exercise tolerance amongst individuals with T2DM, there is no reason to suspect that cardiorespiratory fitness and muscular strength can not be improved with exercise training (Boulé, Kenny et al. 2003).

2.4 Hemoglobin A1C

2.4.1 Glycosylation of hemoglobin

Hemoglobin is a protein found in red blood cells which is responsible for oxygen transport. Hemoglobin is a tetramer of two pairs of polypeptide chains (α and β chains) attached to a heme group. Total hemoglobin in most adults is made up of hemoglobin A (~97%), hemoglobin A₂ (~ 1.5-3.5%) as well as fetal hemoglobin (<2%). The components of hemoglobin A (also referred to as minor hemoglobins) include A₁, A₀, A_{1a}, A_{1b} and A_{1c}. Hemoglobin A_{1c} (A1C) is formed by non-enzymatic glycation of the N-terminal valine of β chains. In essence, A1C is structurally identical to hemoglobin A except that a glucose molecule is linked to the N-terminal valine of β chains. The glycosylation of hemoglobin occurs in two steps. Initially, glucose reacts with the N-terminal valine to form an aldamine linkage also known as a Schiff base. Thereafter, the aldamine linkage undergoes an Amadori rearrangement to form a stable and nearly irreversible ketoamine linkage (McDonald and Davis 1979). The rate of formation of A1C depends on blood glucose concentration. During hyperglycemia for example, the highly permeable erythrocyte cell membrane exposes hemoglobin to the excess intracellular glucose (Gallagher, Le Roith et al. 2009). In the majority of healthy adults, A1C constitutes

approximately 5% of total hemoglobin while this percentage can reach up to 15% in individuals with diabetes (Bunn, Gabbay et al. 1978; Smith, Koenig et al. 1982).

2.4.2 A1C reflects long term glucose control

The association between elevated levels of A1C and diabetes was discovered in the 1960s, first by Huisman and Dozy (Huisman and Dozy 1962) and then by Rajhar (Rajbar 1968) who confirmed that an abnormal hemoglobin component was present in the blood of every diabetic patient he examined. Since the late 1970s, the concept that A1C reflects long term glucose control has been assessed by correlating various indicators of glucose control with A1C measurements (McDonald and Davis 1979). Koenig et al. (Koenig, Peterson et al. 1976), for example, hospitalized five patients with poor diabetic control as measured by urinary glucose excretion as well as fasting and postprandial blood glucose samples. Improvements in glucose control were noted after 1 to 2 months of diet, exercise and insulin administration while a reduction in A1C was observed ~4 weeks after better blood glucose control was achieved (84). In a study to track the changes in A1C over a period of 4 to 6 years, Meigs et al. (Meigs, Nathan et al. 1996) took two A1C measurements in 639 non-diabetic elderly individuals between 1986 and 1993. They concluded that A1C was a relatively stable index of glycemia in nondiabetic individuals over a number of years thus confirming its use as an informative epidemiological measure.

2.4.3 Microvascular and macrovascular complications

Type 2 Diabetes Mellitus increases the risk of developing microvascular and macrovascular complications. Microvascular diseases affect the small blood vessels in the retina

of the eyes (retinopathy) as well as the kidneys (nephropathy). Diabetic retinopathy is the leading cause of adult-onset blindness while nephropathy can lead to end-stage renal failure in affected individuals (DeFronzo 1999). Macrovascular disease targets larger blood vessels such as those going to the heart, brain and lower limbs. The risk of cardiovascular morbidity in patients with T2DM is increased by two to four times while the risk of death from a stroke or a myocardial infarction is two to six times higher when compared to their non-diabetic counterparts (Hu, Stampfer et al. 2001; Maiorana, O'Driscolla et al. 2002; Gæde, Vedel et al. 2003). The extent to which A1C could be used to predict long term diabetic complications has been of interest for many years. The glycosylation of proteins can severely alter their function. For example, the glycosylation of hemoglobin occurs at the N-terminal valine residue which is also the binding site of diphosphoglycerate (2,3-DPG) (Bunn, Gabbay et al. 1978; Kennedy and Baynes 1984). Diphosphoglycerate is a physiological regulator of hemoglobin function, notably hemoglobin's affinity for oxygen. A1C has a reduced reactivity with 2,3-diphosphoglycerate thus increasing oxygen affinity and decreasing its release to nearby tissues (Bunn, Gabbay et al. 1978; McDonald and Davis 1979). It is also thought that glucose can react with other proteins resulting in impaired protein and tissue function (McDonald and Davis 1979; Selvin, Marinopoulos et al. 2004). In a paper reporting on the relevance of hemoglobin glycosylation to diabetes mellitus, Bunn et al. (Bunn, Gabbay et al. 1978) highlighted the fact that the organs and tissues most affected by diabetic complications such as lens, nerves, kidney, retina, blood vessels, etc, are independent to the action of insulin and therefore are exposed to high levels of glucose concentrations during episodes of hyperglycemia. Nevertheless, earlier studies regarding the applicability of A1C as a predictor of long-term complications of diabetes were mostly negative. Trivelli et al. (Trivelli, Ranney et al. 1971) for example conducted the first large scale study

amongst 100 diabetic patients and reported no relationship between A1C levels and duration of diabetes, medication or diabetic therapy, renal disease, peripheral vascular disease, retinopathy, neuropathy as well cardiovascular disease. Furthermore, Koenig et al. (Koenig, Peterson et al. 1976), as well as Malone (Malone 1978), attempted to correlate A1C with microvascular disease but were unsuccessful. In the latter study, no correlation was found between A1C and indicators of diabetic microangiopathy and in the former study, there was no correlation between A1C and early markers of vascular damage. Long term complications of diabetes are gradual and may take many years to develop which may explain the lack of correlation with a single A1C measurement. On the other hand, A1C has been reported to correlate with established factors of atherosclerosis which can lead to macrovascular disease. These include plasma cholesterol and triglyceride levels (McDonald and Davis 1979). In a study amongst 558 non-diabetic adults between the ages of 40 and 79, it was reported that A1C was significantly correlated with total plasma cholesterol, low density lipoproteins, very low density lipoproteins, and total plasma triglycerides even after adjusting for age and obesity (Barret-Connor, Criqui et al. 1987). More recently, an association between A1C with micro and macrovascular disease was established in the participants from the UK prospective diabetes study (Stratton, Adler et al. 2000). Specifically, it was estimated that each 1% reduction in A1C was associated with a 37% reduction in the risk of developing microvascular complications and a 21% decrease in the risk of death related to diabetes.

2.5 Effects of exercise training on A1C and fitness in Type 2 Diabetes Mellitus

2.5.1 Aerobic exercise training

We mentioned earlier that T2DM increases the risk of CVD and that improvements in A1C following exercise training is associated with a substantial reduction of cardiovascular risk factors. Similarly, improvements in aerobic capacity reduce the risk of cardiovascular disease and overall mortality. For example, it has been reported that increasing the exercise time by one minute on a Balke protocol stress test (which is equivalent to an increase in oxygen consumption of 1.44 ml/kg/min), reduces the risk of overall mortality in people with diabetes by 7.9% (Blair, Kohl III et al. 1995; Brandenburg, Reusch et al. 1999). Previous studies have reported significant improvements in cardiorespiratory performance and A1C following aerobic exercise training in people with type 2 diabetes. For example, Schneider et al. (Schneider, Amorosa et al. 1984) reported on 20 individuals with T2DM and 11 control subjects during 6 weeks of supervised aerobic training. A1C was reduced from 12.2 to 10.7% and VO_{2max} increased by 8.4% (26.2 ± 1.1 to 28.4 ± 1.0 ml/kg/min). Walker et al. (Walker, Piers et al. 1999) tested the efficacy of a 12 week self reported walking program amongst normoglycemic and diabetic women. Following the study, A1C in the group of diabetic women decreased to a larger extent than their non diabetic counterparts (7.78 ± 1.37 to 7.19 ± 1.59 vs. 5.58 ± 0.31 to 5.38 ± 0.24). Also, women with T2DM demonstrated an improvement in cardiorespiratory fitness by lowering their walk time on a 1.6 km walking test from 9.29 to 8.24 minutes. A more recent study conducted by Toledo et al. (Toledo, Menshikova et al. 2007) used both weight loss and aerobic exercise to assess muscle mitochondrial capacity in subjects with T2DM over a period of four months. On most days of the week, 10 participants walked on a treadmill at 60-70% of HR_{max} for 30-40 minutes. One session per week was supervised throughout the 20 week intervention. This group reported a 17.7% improvement in A1C (7.9 ± 0.5 to 6.5 ± 0.3) along with 12% increase in VO_{2max} (43.5 ± 1.6 to

48.6±1.6 ml/kg/min). Mitochondrial density and size was also significantly increased following aerobic training.

Initial improvements of aerobic capacity appear to be more pronounced in individuals with low fitness regardless of obesity level. This was demonstrated in a study that compared women with T2DM to lean and overweight non-diabetic women in a three month exercise intervention (Brandenburg, Reusch et al. 1999). The three groups took part in exercise sessions thrice weekly using a treadmill, a cycle ergometer or a rowing machine. They exercised at 70-85% of HR_{max} for a period of 50 minutes. The women in the diabetic group had the lowest initial VO_{2max} of the three groups (17.7±4.0 vs. 21.8±2.9 in the overweight group and 25.1±4.7 ml/kg/min in the lean group). Following the three month intervention, the women with type 2 diabetes increased their VO_{2max} by 28% (17.7±4.0 to 22.4±5.5 ml/kg/min) compared to the overweight group (8%) and the lean group (no change). Changes in A1C from baseline were not reported.

Subsequent to the initial improvements of aerobic capacity, further changes may be dependent on the intensity of each exercise. For example, Mourier et al. (Mourier, Gautier et al. 1997) conducted a high intensity aerobic training program which resulted in substantial improvements of both aerobic fitness and glycemic control after 8 weeks. Following a short pre-training period of 2 weeks, the participants assigned to the training group engaged in two sessions per week of continuous aerobic training for 45 minutes at 75% of VO_{2peak}. On a separate day, the participants performed intermittent training consisting of five exercises at 85% of VO_{2peak} alternating with 3 minutes at 50% of VO_{2peak}. A1C value was reduced from 8.5 to 6.2% while VO_{2peak} and maximum workload increased by 41% (23.0±1.2 to 32.4±1.3 ml/kg/min) and 37% (161±6 to 220±13 W) respectively. Increasing training intensity for individuals with

diabetes who are already active may therefore provide additional benefits in cardiorespiratory fitness and glycemic control (Sigal, Kenny et al. 2004). The appropriate intensity level for individuals with diabetes who are at a greater risk of cardiovascular events has been subject of debate of the years. Nevertheless, high intensity exercise may have added benefits for individuals with T2DM, notably by promoting postexercise glucose uptake for the resynthesis of glycogen stores following greater muscle glycogen depletion (Fenicchia, Kanaley et al. 2004). For a more detailed description of aerobic exercise studies and outcomes for A1C and fitness refer to Table 1 in Appendix A.

2.5.2 Resistance exercise training

Increasing muscular strength and lean body mass are necessary to prevent and/or delay the development of sarcopenia, osteoporosis and to improve functional capacity amongst older individuals with diabetes (Eves and Plotnikoff 2006). Recent recommendations for the management of T2DM strongly suggest the integration of resistance training exercises in a well-rounded training program. Early studies have showed promising effects of resistance training on glycemic control and strength. For example, Eriksson et al. (Eriksson, Taimela et al. 1997) conducted the first study examining the effects of circuit resistance training on A1C in eight individuals with T2DM. After 3 months of progressive resistance training, A1C was reduced significantly (8.8% to 8.2%) and muscle endurance increased by 32%. The increase in lean body mass had a strong inverse correlation ($r = -0.73$) with the reduction in A1C. Honkola et al. (Honkola, Forsén et al. 1997), reported that 5 months of progressive circuit training twice a week significantly increased the number of repetitions that could be performed of various resistance exercises but was not sufficient to detect changes in A1C. Conversely, a 0.4% rise in A1C was

observed in the control group compared to the exercise group. Dunstan et al. (Dunstan, Puddey et al. 1998) studied 21 people with T2DM in the first randomized controlled trial looking at the effects of progressive moderate-intensity circuit resistance training on glycemic control for a length of 8 weeks. Data from eleven participants randomized to a circuit weight training group and ten subjects randomized to a control group were analyzed. In the training group, participants alternated between cycling and weight lifting stations for 60 minutes. There was no significant change in A1C (8.2 ± 0.5 to 8.0 ± 0.5) although significant improvements in strength (ranging from 15 to 43%) were reported. Since the completion of larger randomized controlled trial looking at the effects of high intensity resistance training in older individuals, notably the studies from Castaneda (Castaneda, Layne et al. 2002) and Dunstan (Dunstan, Daly et al. 2002), resistance training is now considered to be safe and effective for individuals with severe low exercise capacity who may not be able to adhere to habitual aerobic exercise training. Dunstan et al. (Dunstan, Daly et al. 2002) conducted a six month high intensity resistance training and weight loss program (RT + WL) amongst 36 older individuals with diabetes. The program involved 45 minutes of high intensity resistance training with a progression from 60% of 1-repetition maximum (1RM) to 75-85% 1RM. The workload increased when 3 sets of 10 repetitions could be performed while maintaining proper weight lifting technique. A1C was reduced by $1.2 \pm 0.9\%$ in the RT + WL group while no significant change was found in the weight loss only group ($0.4 \pm 0.8\%$). Significant increases in upper (41.7%) and lower body (28%) strength in the training group were also reported. Complementary to these findings, Castaneda et al. (Castaneda, Layne et al. 2002) also demonstrated significant improvements in A1C (8.7 ± 0.3 to 7.6 ± 0.2) and strength (33% whole body strength gain) following 16 weeks of high intensity resistance training in older individuals with T2DM (66 ± 2 years). The increase of

1.2 kg of lean tissue mass observed in the resistance group was significantly correlated with the improvement in A1C ($r = -0.35$). Baldi et al. (Baldi and Snowling 2003) more recently demonstrated that 10 weeks of more moderate-intensity resistance training could also evoke improvements in muscular strength (25 to 52%) and significant reductions in A1C (8.9 ± 0.8 to $8.4 \pm 0.6\%$). Consistent with the latter study, the reduction in A1C was inversely correlated with the 3.5% increase in fat free mass in the resistance training group ($r = -0.63$). Ibanez et al. (Ibanez, Izquierdo et al. 2005) also reported the beneficial effects of resistance training on maximal upper body strength and lower body strength (18.2% and 17.1% increase respectively). The small sample size ($n=9$), uncontrolled study design and relatively normal glycemic control at baseline may explain why no improvements in hemoglobin A_{1c} (6.2 ± 0.9 to 6.2 ± 0.9) were detected after 16 weeks of low repetition, heavy load resistance training amongst older individuals with diabetes.

Changes in A1C have previously been compared between aerobic exercise training and resistance exercise training. Cauza et al. (Cauza, Hanusch-Enserer et al. 2005), for example, compared the relative benefits of aerobic and resistance training on glycemic control after 4 months of training. Study participants performed either aerobic or resistance exercise training thrice weekly. The aerobic group exercised at 60% of VO_2 max while the strength training group increased their work intensity to keep the maximum number of repetitions performed between 10 and 15. Changes in physical performance were reported in both groups, notably an increase in VO_{2peak} in the aerobic group and strength gains in the resistance group. However, only the strength training group improved A1C (8.3 ± 1.7 to 7.1 ± 0.2) whereas no significant changes were observed in the aerobic training group (7.7 ± 0.3 to 7.4 ± 0.3). The higher initial A1C level in the resistance training group may explain why significant reductions were found in this group

but not in the aerobic training group. In fact, the DARE study demonstrated that exercise induced improvements in glycemic control were greater among participants with higher baseline A1C. It was also reported that in participants with lower baseline A1C, only combined aerobic and resistance training improved these values. Those with good glycemic control should therefore perform both types of training to further improve glycemic control through lifestyle measures (Sigal, Kenny et al. 2007). For a more detailed description of resistance exercise studies and outcomes for A1C and fitness refer to Table 2 in Appendix A.

2.5.3 Combined aerobic and resistance exercise training

While both aerobic and resistance training improve glycemic control and insulin sensitivity, aerobic training is aimed at improving cardiorespiratory fitness whereas resistance training targets muscle mass and strength. Combining aerobic and resistance training may therefore offer additional benefits in the management of T2DM through different mechanisms of action. Several studies prior to the DARE trial have examined the effects of combined aerobic and resistance exercises in individuals with T2DM (Tessier, Ménarda et al. 2000; Maiorana, O'Driscolla et al. 2002; Cuff, Meneilly et al. 2003; Loimaala, Huikuri et al. 2003; Balducci, Leonetti et al. 2004; McGavock, Mandic et al. 2004; Tokmakidis, Zois et al. 2004). Tessier et al. (Tessier, Ménarda et al. 2000) conducted a randomized controlled study including rapid walking and strength training thrice weekly in 39 (19=experimental group, 20=controls) individuals with T2DM over a 16-week period. No changes in A1C were observed (7.5 ± 1.2 to 7.6 ± 1.2) although treadmill time to exhaustion increased by 11% (423 ± 207 s to 471 ± 230 seconds). Similarly, McGavok et al. (McGavock, Mandic et al. 2004) randomized 17 individuals with diabetes to a combined cycle ergometry and resistance training program of moderate intensity

and 7 people to a control group for a period a 10 weeks. Maximal oxygen consumption improved by 15% though no changes in A1C (6.6 ± 0.9 to 6.4 ± 0.6) were observed following the exercise program. Cuff et al. (Cuff, Meneilly et al. 2003) carried out a 16 week study with 28 post menopausal females with diabetes randomized to one of three group; aerobic training only (AT only), aerobic and resistance training (AT+RT) and a control group. Aerobic exercises were performed on a treadmill, bicycle, stepper, elliptical or rowing machine at an intensity corresponding to 60-75% of heart rate reserve ($HR_{reserve}$) while the resistance phase included light weights with a progression to heavier loads. The study revealed no changes in A1C in any of the groups following the training period (AT+RT: $-0.1 \pm 0.22\%$, AT only: $-0.1 \pm 0.11\%$). Both exercise groups significantly improved VO_{2peak} (AT+RT; 10.2%, AT only; 13.1%) whereas muscular strength increased only in AT+RT (upper body load; 49%, lower body load; 42%). Tokmakidis et al. (Tokmakidis, Zois et al. 2004) trained 9 post menopausal women slightly younger (55 ± 6.7 vs. 60.9 ± 2.3) than the women in the study by Cuff for the same length of time (16 weeks). Unlike the previous study, Tokmakidis found a significant reduction in A1C (7.7 ± 1.7 to 6.9 ± 1) following training. Also reported were increases in exercise time to exhaustion (8.2 ± 1.2 min to 9.1 ± 0.9) as well was upper (150.5 ± 21.4 kg to 197.8 ± 15.8 kg) and lower body strength (48.3 ± 10.6 kg to 67.5 ± 11.1 kg). The exercise intensity for aerobic training ($70-80\% HR_{max}$) and resistance training ($60\% 1RM$) were greater in this study than the intensity used by Cuff. This enforces that a strong dose-response relationship may exist between exercise intensity and A1C. Other recent studies have found concomitant improvements of glycemic control and physical performance following combined training (Maioranaa, O'Driscolla et al. 2002; Loimaala, Huikuri et al. 2003). Loimaala et al. (Loimaala, Huikuri et al. 2003) conducted a year long study combining jogging/walking and resistance training twice a week and

reported a significant decrease in A1C in the exercise group (8.2 ± 2.1 to 7.6 ± 1.4). In addition, the participants in the training group improved their VO_{2max} by approximately 6% (31.9 ± 5.1 to 33.8 ± 5.5 ml/kg/min) and substantial gains in muscle strength were also observed. Maiorana et al. (Maiorana, O'Driscolla et al. 2002) used a randomized cross-over design to evaluate a circuit training program which alternated cycle ergometry, resistance training and treadmill walking at progressive workloads amongst 16 individuals with T2DM. After eight weeks, A1C was reduced significantly (8.5 ± 0.4 to 7.9 ± 0.3) and aerobic capacity, exercise time to exhaustion and muscular strength also improved by 13.2%. For a more detailed description of combined aerobic and resistance exercise studies and outcomes for A1C and fitness refer to Table 3 in Appendix A.

The DARE study trial most recently demonstrated that aerobic and resistance exercise training improved glycemic control, and that their combination was superior to either type of exercise training alone in previously inactive individuals with T2DM. It remains unclear however, if the improvements in A1C are linked to changes in physical fitness as defined by improvements in aerobic fitness or muscular strength. For this reason, the present study investigates the effects of aerobic exercise training, resistance exercise training and their combination on cardiorespiratory fitness and muscle strength and how improvements in A1C are associated with changes in physical fitness in the DARE trial.

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3. ARTICLES

ARTICLE #1

The Effect of Exercise Training on Physical Fitness in Type 2 Diabetes Mellitus

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Disclosure:

This study was supported by grants from the Canadian Institutes of Health Research (grant MCT-44155), the Canadian Diabetes Association (The Lillian Hollefriend Grant), and the Interfaculty Grant program of the University of Ottawa. The DARE trial investigators include Principal Investigators Ronald J. Sigal and Glen P. Kenny, co-investigators Robert D. Reid, Michelle Fortier, Denis Prud'homme, George A. Wells, Doug Coyle, Normand G. Boulé, Heather Tulloch, and Research Coordinator Penny Phillips. Dr. Sigal is a Senior Health Scholar of the Alberta Heritage Foundation for Medical Research; he was previously supported by a New Investigator Award from the Canadian Institutes of Health Research and the Ottawa Health Research Institute Lifestyle Research Chair. Dr. Kenny was supported by a Career Scientist Award from the Ontario Ministry of Health and Long Term Care and a University Research Chair. Dr. Boulé was supported by a Postgraduate Scholarship from the National Sciences and Engineering Research Council of Canada. Dr. Reid was supported by a New Investigator Award from the Heart and Stroke Foundation of Ontario. Dr. Tulloch was supported by a Doctoral Student Award from the Social Sciences and Humanities Research Council of Canada. Ms. Jennings was supported by an Ontario Graduate Scholarship. The provision of financial support does not in any way infer or imply endorsement of the research findings by either agency. The results of the present study do not constitute endorsement by ACSM.

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ABSTRACT

Few studies have compared changes in cardiorespiratory fitness between aerobic training only or in combination with resistance training. Additionally, no study to date has compared strength gains between resistance training and combined exercise training in type 2 diabetes mellitus (T2DM). **Purpose:** We evaluated the effects of aerobic exercise training (A), resistance exercise training (R), combined aerobic and resistance training (A+R) and a sedentary control group (C) on cardiorespiratory fitness and muscular strength in individuals with T2DM. **Methods:** 251 participants in the Diabetes Aerobic and Resistance Exercise (DARE) trial were randomly allocated to A, R, A+R or C. Peak oxygen consumption ($\dot{V}O_{2peak}$), workload and treadmill time were determined following maximal exercise testing at 0 and 6 months. Muscular strength was measured as the 8 RM on the leg press, bench press and seated row. Responses were compared between younger (39-54) and older (55-70) adults and between sexes. **Results:** $\dot{V}O_{2peak}$ improved by 1.73 and 1.93 mL O_2 /kg/min with A and A+R respectively compared to C ($p < 0.05$). Strength improvements were significant following A+R and R on the leg press (A+R:48%, R:65%) bench press (A+R:38%, R:57%) and seated row (A+R:33%, R:41%) ($p < 0.05$). There was no main effect of age or sex on training performance outcomes. There was however a tendency for older participants to increase $\dot{V}O_{2peak}$ more with A+R (+1.5 mL O_2 /kg/min) than with A only (+0.7 mL O_2 /kg/min). **Conclusion:** Combined training did not provide additional benefits nor did it mitigate improvements in fitness in younger subjects compared to aerobic and resistance training alone. In older subjects, there was a trend to greater aerobic fitness gains with A+R versus A alone.

Key words: Aerobic exercise, resistance exercise, cardiorespiratory fitness, strength, randomized controlled trial.

INTRODUCTION

Previous studies have found that exercise training induces improvements in physical fitness among individuals with type 2 diabetes mellitus (T2DM), as demonstrated by increments in maximal oxygen consumption ($\dot{V}O_{2max}$) and muscular strength. For example, Boulé et al. (4) reported in a meta-analysis a mean increase of 9.5% in $\dot{V}O_{2max}$ following moderate-intensity aerobic training ($\leq 70\% \dot{V}O_{2max}$) compared to 1% decrease in sedentary controls. Larger increases in aerobic capacity were found in individuals who engaged in higher intensity endurance training ($\geq 75\% \dot{V}O_{2max}$) (3). Recent evidence also suggests that resistance exercise training safely and effectively improves muscular strength and metabolic control in vulnerable populations (5, 6, 10). Castaneda et al. (6) and Dunstan et al. (10) studied the effects of high intensity resistance training in older adults (≥ 55 years) with T2DM. The former study reported a 33% increase in whole body strength (6) whereas the latter study found a 42% increase in upper body workload and 28% increase in lower body workload following 6 months of training (10). Although these studies show promising effects of exercise in improving physical fitness among individuals with T2DM, the small sample sizes used limit the generalizability of the results.

There is also growing evidence that the effect of combined aerobic and resistance training may be more beneficial in the management of T2DM. Recently, we reported that hemoglobin A1C (A1C) values decreased significantly with aerobic exercise training compared with a non exercising control group (- 0.51 %; $P=0.007$) and with resistance exercise training compared with the control group (- 0.38 % ; $P=0.038$). With combined exercise training, A1C values

decreased by an additional -0.46 % and -0.59% compared with the aerobic exercise training ($P=0.014$) and resistance exercise training ($P=0.001$) respectively (24). Interestingly, however, only one study has compared the effects of combined exercise training with those of aerobic exercise training alone (9) in terms of improvements in cardiorespiratory fitness in T2DM. Further, no study to date has compared increments in muscular strength with combined exercise training to those derived from resistance exercise training alone in individuals with T2DM. Among young healthy adults, combined exercise training proved as beneficial as aerobic exercise training alone to improve cardiorespiratory fitness but seemed to have a detrimental effect on strength development (8, 15). In one study, however, participants exercised 5 days per week and thus residual fatigue may have impacted the development of strength (15). Conversely, Wood et al. (29) reported that 3 days per week of concurrent aerobic and resistance exercise training in healthy older adults (≥ 60 years) led to similar improvements in strength as resistance exercise training alone.

The prevalence of T2DM typically increases with age and aging is usually associated with progressive decrements in various components of physical work capacity, notably declines in cardiorespiratory fitness and muscle strength (6). Moreover, exercise capacity has been shown to be reduced in people with T2DM compared to age, body mass and activity matched controls even in the absence of diabetic complications (4, 19, 21). Low cardiorespiratory fitness and decrements in bone density and skeletal muscle strength are strong predictors of disability among older individuals (12). As previously mentioned, a combined exercise program appears to generate greater reductions in A1C value than either aerobic or resistance training alone. It remains unclear, nonetheless, whether combined exercise training would provide similar gains in

both cardiorespiratory fitness and strength compared to either mode of training alone in individuals with T2DM. On the one hand, increased fatigue might have a negative impact on workout intensity compared to doing just one kind of exercise. Conversely, older individuals often have sarcopenia, and strength training might be helpful in permitting them to maximize their aerobic workouts.

In the present study we report the effects of aerobic exercise training, resistance exercise training and the combination of aerobic and resistance exercise training on cardiorespiratory fitness and muscular strength in the Diabetes Aerobic and Resistance Exercise (DARE) trial (24). An additional purpose of this investigation was to examine if fitness exercise responses in the training groups were affected by age and sex. We also examined the relationship between changes in hemoglobin A_{1c} (A1C) and changes in fitness outcomes. We hypothesized that changes in cardiorespiratory fitness and strength would be similar in the aerobic exercise training and resistance training exercise groups respectively compared to the combined aerobic and resistance training group. We also hypothesized that younger and older adults as well as men and women would respond similarly to exercise training and that a relationship would exist between changes in physical fitness and A1C.

METHODS

The DARE trial was a 26-week, single-center, randomized controlled trial with parallel group design that examined the effects of aerobic and resistance exercise training as well as their combination on glycemic control in type 2 diabetes mellitus (24). This study was approved by

the Ottawa Hospital Research Ethics Board and written informed consent from all participants was obtained.

Previously sedentary individuals between the ages of 39 and 70 years with type 2 diabetes mellitus were recruited through advertising, physicians and word of mouth. Inclusion criteria for the DARE trial included type 2 diabetes for at least 6 months and baseline hemoglobin A1C between 6.6% and 9.9% (normal = 4%-6%). Exclusion criteria are described elsewhere (24). The participants' baseline characteristics are presented in Table 1.

Run-in Phase. Participants exercised at community-based facilities, supervised by personal trainers. Prior to randomization, subjects entered a 4-week run-in period to assess compliance. Subjects performed 15-20 minutes of aerobic exercise at moderate intensity ($60\% \dot{V}O_{2peak}$) and 1-2 sets of 8 resistance exercises with supervision. Only subjects attending ≥ 10 of the scheduled 12 run-in sessions were eligible for randomization. Randomization was stratified by age (39 to 54 years and 55 to 70 years) and sex.

Exercise Intervention

Aerobic Exercise Training (A). A detailed description of the exercise training programs is available online (<http://www.annals.org/cgi/content/full/147/6/357>). The aerobic exercise training component consisted of participants exercising 3 times per week on treadmills and/or bicycle ergometers. Heart rate monitors (Polar Electro Oy, Kempele, Finland) were used to adjust workload to achieve target heart rates. Target heart rates were based on maximal heart rate

achieved during stress testing. Subjects progressed from 15-20 minutes per session at 60% of maximum heart rate, to 45 minutes per session at 75% of maximum heart rate.

Resistance Exercise Training (R). Subjects exercised three times per week, and training progressed gradually in length and intensity. The resistance exercise training group performed seven different exercises on weight machines each session, progressing to 2-3 sets of each exercise at the maximum weight that could be lifted 7-9 times. Participants alternated between two groups of 7 exercises targeting all major muscle groups. These were as follows: Group A: seated row, biceps curl, bench press, leg press, shoulder press and leg extension; and, Group B: lateral pulldown, triceps pushdown, chest press, leg press, upright row and leg curls.

Combined Exercise Training (A+R). The participants in the combined training group performed the full aerobic training program plus the full resistance training program to assure an adequate dose of each type of exercise.

Control Group (C). Subsequent to the run-in phase, participants assigned to the control group were asked to revert to their level of activity at baseline and to maintain this level for the remainder of the study.

Direct supervision by trainers occurred with equal frequency in all exercising groups. Individual exercise supervision was provided weekly for the first 4 weeks after randomization and biweekly thereafter. Attendance was verified through direct observation, exercise logs, and electronic scanning of membership cards.

Outcomes and measurements

Dependent variables included $\dot{V}O_{2peak}$, maximal workload, treadmill time, maximal heart rate (HR_{max}), as well as oxygen consumption ($\dot{V}O_2$), workload and heart rate (HR) at the ventilatory threshold and results from 8 repetition maximum (8-RM) testing on the seated row, bench press and leg press. Independent variables include effects for time, group, age and sex.

Maximal cardiorespiratory fitness ($\dot{V}O_{2peak}$) was determined during a maximal treadmill exercise stress test at the University of Ottawa Heart Institute. The test followed a ramp treadmill protocol with continuous time and 12-lead electrocardiogram monitoring (v.4.03, GE Marquette Medical Systems Inc.) as well as breath-by-breath analysis of oxygen consumption and carbon dioxide production (MedGraphics CPX-D Metabolic Cart, St. Paul, MN). Since older adults often do not reach a plateau in oxygen consumption, $\dot{V}O_{2peak}$ was measured as the highest minute rate of oxygen consumption achieved during the last 30 seconds of the test to volitional fatigue. Each participant performed the same ramp protocol during baseline and post intervention testing. We also obtained maximal workload (watts), HR_{max} (bpm; beats per minute) and exercise test duration (minute) from stress testing.

Ventilatory threshold was determined from maximal exercise stress tests using 2 criteria:

- 1) the point where ventilation (\dot{V}_E) increases disproportionately relative to $\dot{V}O_2$ (28) and; 2) the point of dislinear rise in carbon dioxide production ($\dot{V}CO_2$) relative to $\dot{V}O_2$ (V-slope method)
- (2). Both criteria were met for most subjects but in a few cases, the rise in \dot{V}_E relative to $\dot{V}O_2$

was easier to recognize and was used to determine the ventilatory threshold. These techniques have been shown to be sensitive and non-invasive measures for evaluating cardiorespiratory performance (21, 22, 28). Oxygen consumption, workload and heart rate were measured at the ventilatory threshold. One evaluator determined the ventilatory threshold for all participants at 0 and 6 months. The same evaluator repeated the assessment of all ventilatory thresholds no less than two weeks after the last ventilatory threshold had been determined to assure consistency in the results and because a second evaluator was not available for this study (20).

Muscular strength was determined for the leg press, bench press and seated row on a multi-station gym (Body Solid EXM-2000S). Strength was measured as the maximum weight that could be lifted eight times following an 8 repetition maximum (8-RM) protocol at baseline and 6 months. Proper lifting and breathing techniques were demonstrated by an exercise specialist prior to each exercise.

Hemoglobin A_{1C} value was measured between baseline and 6 months using turbidimetric immunoinhibition.

Statistical analysis. We used linear mixed effects models for repeated measures with an unstructured covariance matrix to model dependant variables by study groups over time. Dependant variables included measures for cardiorespiratory fitness ($\dot{V}O_{2peak}$ mL/O₂kg/min, $\dot{V}O_{2peak}$ mL O₂/kg LBM/min, HR_{max}, workload and treadmill time), submaximal aerobic fitness indices ($\dot{V}O_2$ mL O₂/kg/min, $\dot{V}O_2$ mL O₂/kg LBM/min, heart rate and workload at the ventilatory threshold) and strength (8-RM for leg press, bench press and seated row). To test whether

changes in fitness outcomes differed according to age, we reran the model with an additional term for age (dichotomized into younger (39-54 yrs) and older (55-70 yrs) participants). We also re-ran the model to test for significant differences between sexes. Within the mixed models, we estimated 95% confidence interval (CI) and P values for six inter-group comparisons (A+R vs. A, A+R vs. R, A+R vs. C, R vs. C, A vs. C and A vs. R). Unadjusted 95% CI are presented in the tables and figures. The level of significance was set at an overall alpha level of 0.05; however, we used Bonferroni adjustments to account for multiple comparisons. Thus, P values for inter-group comparisons were considered significant when P was <0.0083 (0.05 divided by six possible comparisons for each variable) and <0.0125 for within group comparisons (0.05 divided by four possible within group changes). Multiple regressions analyses were performed using linear mixed models. Measures of maximal and submaximal aerobic capacity as well as strength were entered as independent variables with A1C as the dependent variable and sex, age, ethnicity, duration of diabetes and oral hypoglycemic medication as covariates. We used SAS version 9.1 for all analyses.

RESULTS

Following the run-in phase, 60, 64, 64 and 63 participants were randomly allocated to aerobic exercise training, resistance exercise training, combined exercise training and a control group respectively. Following the run-in phase, 12 participants in aerobic training, 7 in resistance training, 8 in combined training and 3 in the control group dropped out of the study while several others did not have complete sets of data. As such, 48 participants from the aerobic exercise training group, 54 participants from resistance exercise training group, 54 participants from combined exercise training group and 60 participants from controls were included in the

analyses. Reasons for not completing the study included medical conditions, loss of interest and other personal or time commitments that interfered with the ability to participate or continue with the study.

General exercise outcomes

Cardiorespiratory fitness. $\dot{V}O_{2\text{peak}}$ relative to body mass (mL O_2 /kg/min) were significantly improved at 6 months with aerobic training and combined training ($P < 0.001$) and the changes were significant compared to the resistance training group (AT, $P = 0.007$; A+R, $P = 0.001$) and control group ($P < 0.001$) (Figure 1). No differences were observed between the aerobic training and combined training groups ($P = 0.638$) as well as between the resistance training and control groups ($P = 0.243$) for changes in $\dot{V}O_{2\text{peak}}$. The same results were observed when $\dot{V}O_{2\text{peak}}$ were adjusted for lean body mass (data not shown). Maximal workload and treadmill times were significantly increased at 6 months with aerobic training and combined exercise training ($P < 0.001$) (Table 2). Improvements in workload were also significant relative to the control group ($P < 0.001$) following aerobic training and combined training as well as compared to the resistance training group following aerobic training only ($P = 0.006$). Treadmill time improved significantly in the aerobic training and combined training groups compared to resistance exercise training ($P = 0.001$) and controls ($P < 0.001$). Maximal heart rate decreased significantly over time only in the aerobic exercise training group (161.42 ± 2.04 to 157.57 ± 2.26 beats/min, $P = 0.007$). No significant difference was observed for changes in maximal heart rate among the exercise training groups. The effect of training group did not vary according to age or sex for changes in $\dot{V}O_{2\text{peak}}$ (age, $P = 0.300$; sex, $P = 0.859$), workload (age, $P = 0.200$; sex, $P = 0.924$) and treadmill time (age, $P = 0.445$; sex, $P = 0.939$).

Submaximal Exercise Response. $\dot{V}O_2$ relative to body mass (mL O_2 /kg/min) at ventilatory threshold improved at 6 months with aerobic training and combined training ($P < 0.001$) as well as compared to the control group ($P < 0.001$) (Figure 2). After adjusting for multiples comparisons, improvements in $\dot{V}O_2$ at ventilatory threshold were not significantly greater with aerobic training and combined training than with resistance training (A, $P = 0.021$; A+R, $P = 0.013$). No differences were observed between the aerobic training and combined training groups ($P = 0.928$) as well as between the resistance training and control groups ($P = 0.138$) for changes in $\dot{V}O_2$ at ventilatory threshold. Workload at the ventilatory threshold significantly increased after 6 months for all training groups ($P < 0.001$). Relative to the control group, workload increased more in the aerobic and combined training groups (A, $P < 0.001$; A+R, $P = 0.002$) and also in the aerobic training group compared to the resistance training group ($P = 0.008$). The effect of training group on changes in submaximal aerobic responses did not differ according to age or sex.

Muscular strength. Leg press, bench press and seated row performance increased significantly in all exercise groups ($P < 0.001$) (Figure 3). A significant within group change over time was also found in the control group for the leg press ($P = 0.002$). In comparison to the control group, changes in leg press, bench press and seated row performances were greater in the resistance and combined exercise training groups ($P < 0.001$). Relative to the aerobic training group, greater strength development were found with resistance training on the bench press ($P = 0.005$) and with both resistance training and combined training on the seated row (R, $P = 0.001$; A+R, $P = 0.005$). Strength improvements in the resistance training group were not significantly different from

those obtained with combined training in any of the strength exercises. The effects of training group did not vary according to age or sex for changes.

Multiple regression analysis. Results from multiple regressions analysis show that after adjusting for exercise group, sex, ethnicity, age, duration of diabetes and oral hypoglycemic medication, improvements in physical fitness were not significantly associated with improvements in A1C; $\dot{V}O_{2peak}$ in mlO₂/kg/min (P = 0.064), maximal workload (P = 0.106), treadmill time (P = 0.125), $\dot{V}O_2$ in mlO₂/kg/min at ventilatory threshold (P = 0.523), workload at ventilatory threshold (P = 0.163), leg press (P = 0.254), bench press (P = 0.306) and seated row (P = 0.363).

DISCUSSION

We compared the effects of aerobic exercise training, resistance exercise training and the combination of aerobic and resistance exercise training to a non-exercising control group on cardiorespiratory fitness and muscular strength in previously sedentary individuals with T2DM. Following 6 months of exercise training, the aerobic and combined exercise training groups significantly increased $\dot{V}O_{2peak}$, maximal workload, treadmill time as well as $\dot{V}O_2$ and workload at the ventilatory threshold compared to the control group. Additionally, relative to the control group, muscular strength as measured on the seated row, bench press and leg press significantly increased in the resistance and combined exercise training groups. Strength performance was also significantly improved in the aerobic exercise training group, although the improvements were not significantly greater than the control group after adjusting for multiple comparisons. Our hypothesis that improvements in cardiorespiratory fitness and strength in the combined

group would be similar to those derived from aerobic exercise training alone and resistance exercise training alone respectively was supported.

Previous studies have reported improvement in cardiorespiratory fitness as measured by $\dot{V}O_{2peak}$, treadmill time and workload. Notably, Cauza et al. (7) showed that 4 months of endurance training 3 times per week at 60% of $\dot{V}O_{2peak}$ significantly improved $\dot{V}O_{2peak}$ by 1.49 mL O_2 /kg/min, which was paralleled by an increase in maximal workload (+12 watts) in 17 individuals with T2DM. Kadoglou et al. (18) reported that 4 days per week of aerobic training for 6 months between 50-75% of $\dot{V}O_{2peak}$ improved $\dot{V}O_{2peak}$ by 3.66 mL O_2 /kg/min and treadmill test duration by 0.79 minutes in 30 individuals with diabetes assigned to the exercise group. The responses were similar to those observed in the present study. We show that the aerobic exercise training group increased $\dot{V}O_{2peak}$ by 1.72 mL O_2 /kg/min which was paralleled by increments in workload (+23.6 watts) and treadmill time (+1.19 minute) in comparison to the control group. The results from our study also support that improvements in cardiorespiratory fitness following combined aerobic and resistance exercise training are similar to those derived from aerobic training alone. Specifically, $\dot{V}O_{2peak}$ increased by 1.93 mL O_2 /kg/min, maximal workload by 19.8 watts and treadmill time by 1.14 minute in the combined exercise group versus the control group. To our knowledge, Cuff et al. (9) published the only other study reporting similar improvements in $\dot{V}O_{2peak}$ between aerobic training alone (13.1%) and combined aerobic and resistance training (10.2%) in T2DM.

In parallel to the improvements in maximal aerobic performance, submaximal exercise performance was also significantly improved following exercise training. Oxygen consumption at the ventilatory threshold was increased by 1.33 mL O_2 /kg/min with aerobic training and 1.36 mL O_2 /kg/min following combined exercise training compared to controls. This is in contrast to a study by Vanninen et al. (27) where $\dot{V}\text{O}_2$ at the ventilatory threshold remained unchanged in men and women who were encouraged to increase their level of physical activity over 12 months. Ventilatory threshold as a percentage of $\dot{V}\text{O}_{2\text{peak}}$, however, remained unchanged between 0 and 6 months following aerobic training ($50.8 \pm 5.7\%$ vs. $51 \pm 5.1\%$) and combined training ($50.1 \pm 5.5\%$ vs. $51.2 \pm 5.1\%$). However, workload at the ventilatory threshold significantly increased by 14.8 watts with aerobic training and 9.9 watts with combined training relative to controls which to our knowledge, has also not been previously reported in individuals with T2DM.

A number of small studies previously found significant changes in strength following resistance exercise training in individuals with T2DM. Dunstan et al. (10) for example, reported a 42% and 28% increase in upper and lower body strength after 6 months of progressive resistance training whereas Castaneda et al. (6) reported a 33% improvement in whole body strength following 16 weeks of high intensity resistance training. In the present study, strength performance on the seated row, bench press and leg press increased by 41%, 57% and 65% respectively in the resistance exercise training group suggesting that the training stimulus provided in the exercise program was sufficient to elicit improvements in strength in older individuals with T2DM. Strength gains with combined training were comparable to those obtained from resistance training alone, notably seated row, bench press and leg press

performance improved by 33%, 38% and 48% respectively. This is in contrast to previous studies among younger healthy individuals where strength development was attenuated with a combined training program versus resistance training alone (15). To date, no other study has compared strength gains following combined exercise training to those obtained with resistance exercise training alone in individuals with diabetes. In concert with the results reported by Wood et al. (29) among older healthy individuals, the present study suggests that a combined exercise program does not alter strength development in adults with T2DM and that strength improvements are similar between resistance exercise training alone and combined aerobic and resistance training. Significant strength gains of 21%, 25% and 42% on the seated row, bench press and leg press respectively were also observed following aerobic exercise training and small strength improvements in the leg press were seen in the control group. The improvement in strength at 6 months in the control group could result from participants becoming familiar with lifting techniques and equipment and/or as a residual effect from the run-in phase where all participants performed both aerobic and resistance exercise training for a period of 4 weeks. In support of this, Staron et al. (25) previously trained 24 young women twice per week for a period of 20 weeks after which they underwent a detraining phase of 30-32 weeks. These women performed 1-RM tests on the leg press, leg extension and squat following the period of detraining. Although 1-RM values had decreased from the previous training period, all detraining values remained significantly greater than pretraining values suggesting that some adaptations to strength training may be retained for long periods after the cessation of training.

Cardiorespiratory fitness tends to decline with age which can lead to difficulties in performing daily physical or employment related tasks (13, 14). Regular physical activity is

important to delay or attenuate age-related decrements in cardiorespiratory fitness. In the present study, although no statistically significant effect of age on fitness change was found between the training groups, younger participants improved cardiorespiratory fitness to the same extent with aerobic exercise training alone (+1.91 mL_{O₂}/kg/min) and in combination with resistance training (+1.71 mL_{O₂}/kg/min), but older participants tended to increase cardiorespiratory fitness more with combined training (+1.5 mL_{O₂}/kg/min) than with only aerobic training (+0.7 mL_{O₂}/kg/min) (Figure 4). The older participants are likely to have had greater degree of sarcopenia, and the increased muscular fitness from resistance training may have helped them to maximize the benefits of aerobic training. Our results are consistent with the recommendations from the American College of Sports Medicine position stand on exercise and physical activity for older adults as well as the 2008 Physical Activity Guidelines Advisory Committee Report (23, 26) which suggest that older adults (≥65 years) could gain substantial health benefits from performing regular resistance training in addition to aerobic training.

Regular resistance exercise can prevent and/or delay the development of sarcopenia, osteoporosis and improve functional capacity in tasks of daily living amongst older individuals with diabetes. Several studies in recent years have demonstrated that resistance exercise training induces substantial gains in muscular strength among middle aged and older individuals (>55 years of age) with T2DM (1, 6, 11, 16, 17). Correspondingly, younger (39-54 yrs) and older (55-70 yrs) participants randomized to resistance training in our study displayed significant improvements in strength on the seated row, bench press and leg press. The results from our study also show that similar strength gains occurred in younger and older subjects

assigned to combined aerobic and resistance training on all strength exercises which has not been reported previously.

In summary, we showed significant improvements in cardiorespiratory fitness and strength following a 6-month exercise training program in individuals with T2DM. The combined exercise program did not seem to provide additional benefits nor did it mitigate changes in physical fitness in younger participants than aerobic or resistance training alone. In older subjects, there was a trend to greater aerobic fitness gains with combined training versus aerobic training alone. These findings provide additional evidence of the value of combined aerobic and resistance exercise training especially for older people with type 2 diabetes.

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Table 1. Participants' baseline characteristics.

	Combined (n = 64)	Aerobic (n = 60)	Resistance (n = 64)	Control (n = 63)
Men/women, <i>n/n</i>	40/24	39/21	40/24	41/22
Age, <i>y</i>	53.5 (7.3)	53.9 (6.6)	54.7 (7.5)	54.8 (7.2)
Non-Hispanic white race/other race, <i>n/n</i>	55/9	59/1	55/9	61/2
Duration of diabetes, <i>y</i>	5.2 (4.8)	5.1 (3.5)	6.1 (4.7)	5.0 (4.5)
Hemoglobin A _{1c} level %	7.67 (0.91)	7.68 (0.85)	7.71 (0.86)	7.66 (0.89)
Body weight	101.9 (30.4)	103.5 (31.0)	99.1 (30.4)	101.3 (28.6)
BMI	35.0 (9.6)	35.6 (10.1)	34.1 (9.6)	35.0 (9.5)

Values are mean ± SD.

Table 2. Mean (\pm SD) changes in maximal cardiorespiratory performance.

Variable	Mean		Difference in Change from Baseline to 6 Months (95% CI)	P Value
	Baseline	6 mo		
Workload (watts)				
Combined exercise group	156.1 (6.4)	175.2 (6.6)	–	<0.001
Aerobic training group	151.7 (6.5)	174.7 (6.8)	–	<0.001
Resistance training group	143.1 (6.3)	150.5 (6.5)	–	0.054
Control group	149.5 (6.4)	148.8 (6.4)	–	0.854
<i>Intergroup comparisons</i>				
Aerobic training vs. control	–	–	23.6 (12.8 to 34.3)	<0.001
Resistance training vs. control	–	–	8.1 (-2.3 to 18.5)	0.127
Combined exercise vs. control	–	–	19.8 (9.4 to 30.2)	<0.001
Combined exercise vs. aerobic training	–	–	-3.8 (-14.7 to 7.1)	0.496
Combined exercise vs. resistance training	–	–	11.6 (0.9 to 22.3)	0.033
Aerobic training vs. resistance training	–	–	15.4 (4.4 to 26.5)	0.006
HR_{max} (bpm)				
Combined exercise group	159.7 (1.9)	157.4 (2.1)	–	0.087
Aerobic training group	161.4 (2.0)	157.5 (2.2)	–	0.007
Resistance training group	156.3 (1.9)	155.9 (2.1)	–	0.811
Control group	157.3 (1.9)	156.0 (2.1)	–	0.304
<i>Intergroup comparisons</i>				
Aerobic training vs. control	–	–	-2.5 (-6.3 to 1.2)	0.187
Resistance training vs. control	–	–	0.9 (-2.6 to 4.6)	0.595
Combined exercise vs. control	–	–	-0.9 (-4.6 to 2.6)	0.593
Combined exercise vs. aerobic training	–	–	1.54 (-2.32 to 5.40)	0.432
Combined exercise vs. resistance training	–	–	-1.98 (-5.74 to 1.78)	0.300
Aerobic training vs. resistance training	–	–	-3.52 (-7.39 to 0.35)	0.074
Treadmill time (minute)				
Combined exercise group	9.8 (3.3)	11.0 (3.6)	–	<0.001
Aerobic training group	10.2 (3.4)	11.4 (3.8)	–	<0.001
Resistance training group	9.7 (3.3)	9.9 (3.6)	–	0.159
Control group	9.8 (3.3)	9.8 (3.6)	–	0.929
<i>Intergroup comparisons</i>				
Aerobic training vs. control	–	–	1.1 (0.6 to 1.7)	<0.001
Resistance training vs. control	–	–	0.2 (-0.2 to 0.7)	0.338
Combined exercise vs. control	–	–	1.1 (0.6 to 1.6)	<0.001
Combined exercise vs. aerobic training	–	–	-0.0 (-0.5 to 0.4)	0.860
Combined exercise vs. resistance training	–	–	0.8 (0.3 to 1.4)	0.001
Aerobic training vs. resistance training	–	–	0.9 (0.3 to 1.4)	0.001

CI = confidence interval; mo = month; HR_{max} = maximal heart rate; bpm = beats per minute
 Values are presented as means \pm SE.

FIGURE CAPTIONS

Figure 1. Mean (\pm SD) change in peak oxygen consumption (VO_{2peak} mL O_2 /kg/min), in the four study groups from baseline to 6 months. *, indicates significant change from 0 to 6 months. †, indicates significant difference from control group. §, indicates significant difference from resistance exercise training group.

Figure 2. Mean (\pm SD) change in oxygen consumption (VO_2 mL O_2 /kg/min) at the ventilatory threshold, in the four study groups from baseline to 6 months. Data are presented as means and 95% confidence intervals. *, indicates significant change from 0 to 6 months. †, indicates significant difference from control group. §, indicates significant difference from resistance exercise training group.

Figure 3. Changes in muscular strength (lbs) in the four study groups from baseline to 6 months. Data are presented as means and 95% confidence intervals. *, indicates significant change from 0 to 6 months. †, indicates significant difference from control group. §, indicates significant difference from aerobic exercise training group.

Figure 4. Mean (\pm SD) changes in peak oxygen consumption (VO_{2peak} , mL O_2 /kg/min) between younger participants (39-54 years) and older participants (55-70 years) in the four study groups from baseline to 6 months.

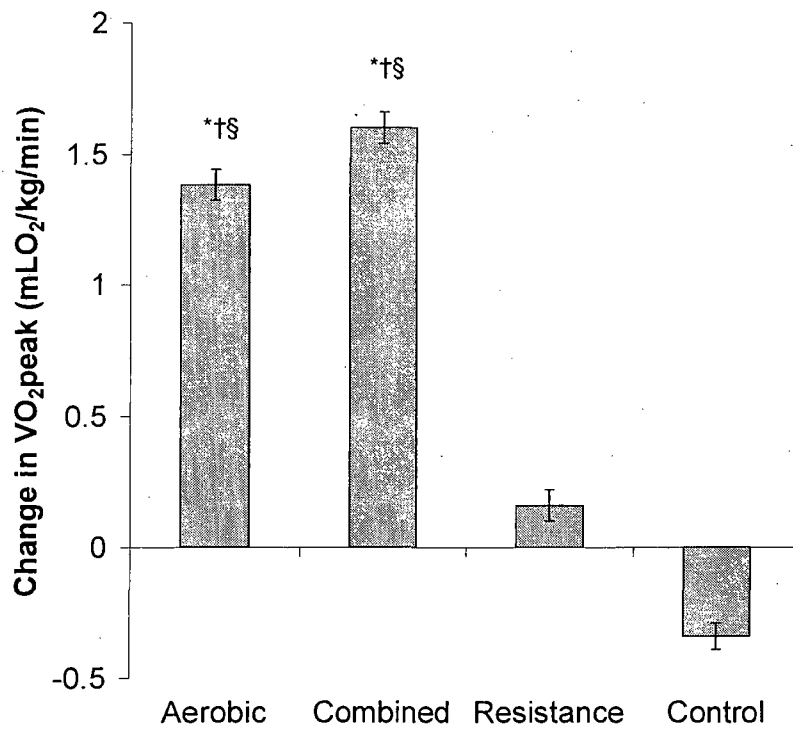


Figure 1. Mean (\pm SD) change in peak oxygen consumption (VO_{2peak} mL O_2 /kg/min), in the four study groups from baseline to 6 months. *, indicates significant change from 0 to 6 months. †, indicates significant difference from control group. §, indicates significant difference from resistance exercise training group.

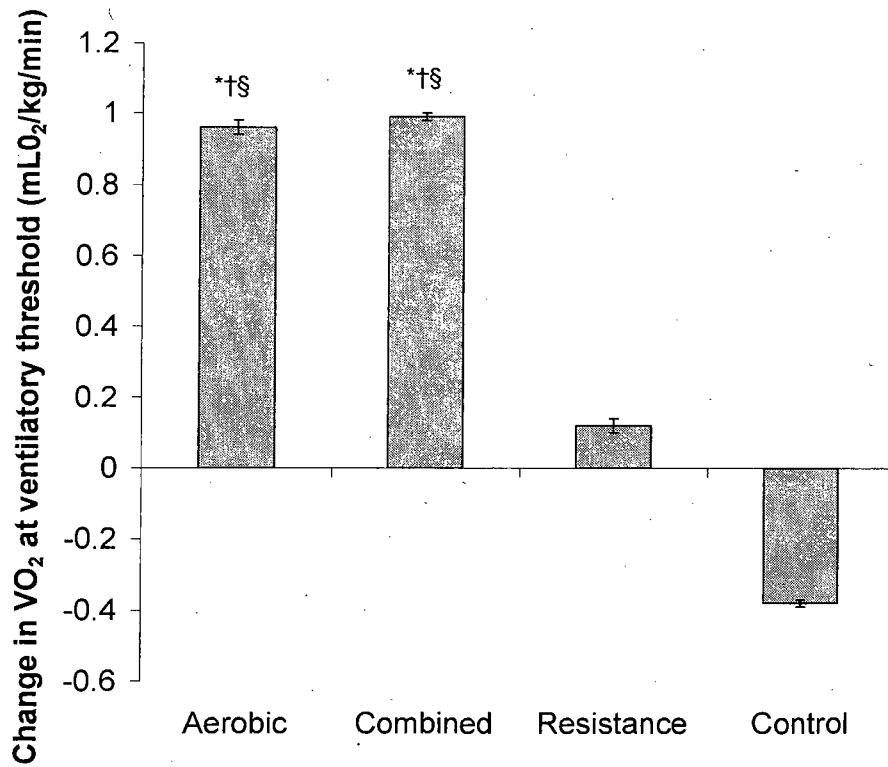


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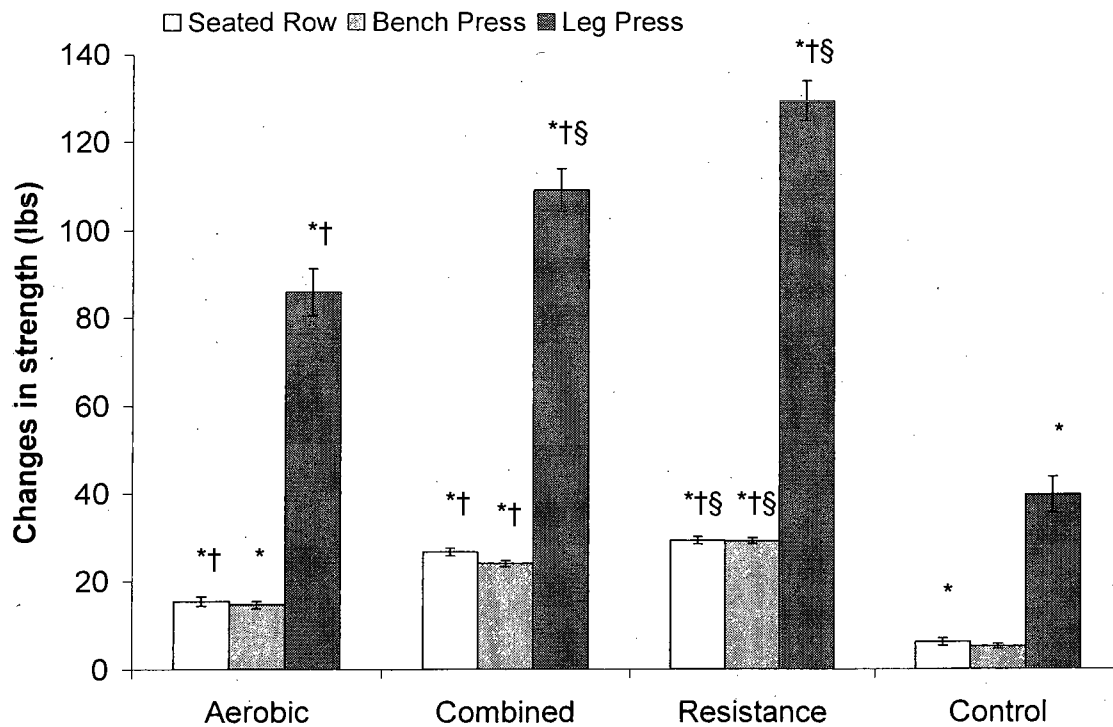


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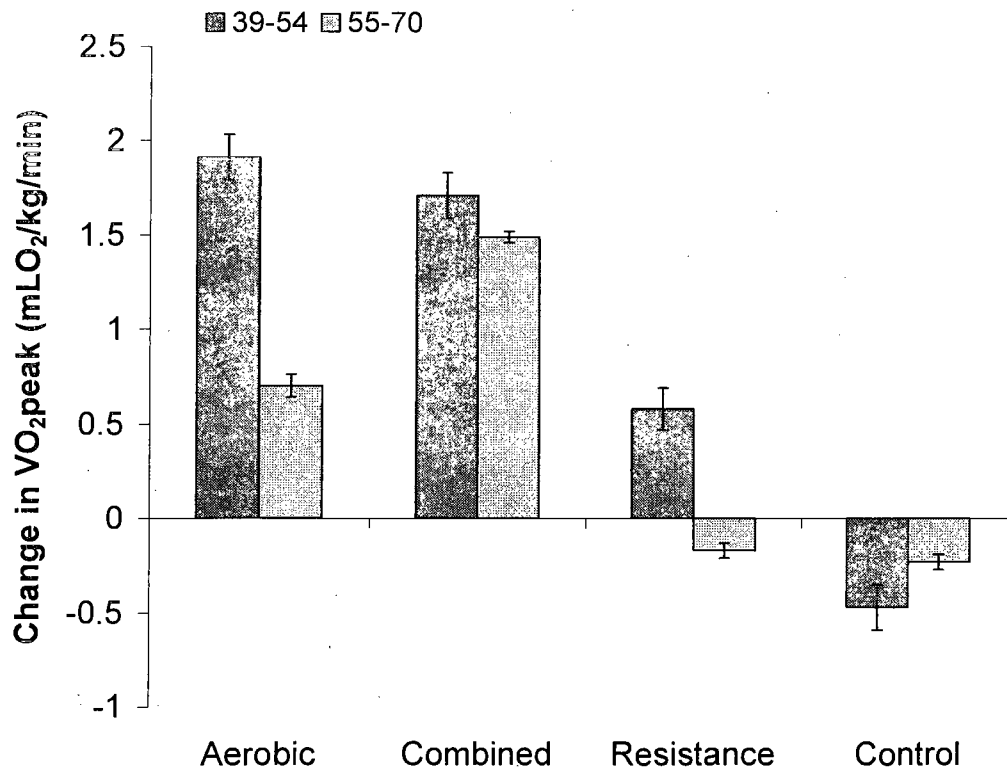


Figure 4. Mean (\pm SD) changes in peak oxygen consumption (VO_{2peak} mL O₂/kg/min) between younger participants (39-54 years) and older participants (55-70 years) in the four study groups from baseline to 6 months.

ARTICLE #2

Time Course of Strength Development in Type 2 Diabetes Mellitus

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Running title: Resistance training and type 2 diabetes

ABSTRACT

The rate of strength development has been reported in healthy individuals but little is known as to the time course of strength development in type 2 diabetes mellitus (T2DM). Also, it remains unclear how combined aerobic and resistance exercise training affects strength development. We examined the rate of strength development with resistance exercise training only (R) and in combination with aerobic exercise training in 119 participants aged 39-70 in the Diabetes Aerobic Resistance Exercise (DARE) trial (ClinicalTrials.gov NCT00195884). This was a single-center, randomized controlled trial with parallel groups design. Following a 4-week run-in phase, participants were randomized to 22-weeks of aerobic training only, resistance training only (R), combined training (A+R) or a control group. We analyzed only participants assigned to R and A+R for this sub-study. The outcomes were monthly workload increments (month 1-6) on 11 strength exercises. We compared workload progression for each strength exercise between R and A+R. Our results show that strength improved similarly in R and A+R. There was, however, a clear trend towards a slowing in strength development over time. A greater proportion of workload increments were measured between month 1-2 in both the upper body (51%) and lower body exercises (42%). Additional strength increments were consistently smaller in subsequent months. Workload increments had a tendency to decrease in A+R between 5-6 months on several exercises; seated row (-8.8 lbs), bench press (-28.6 lbs), biceps curl (-11.3 lbs), shoulder press (-9.7 lbs), lateral pulldown (-14.3 lbs) and leg extension (-15.6 lbs). Although strength development had a tendency to level off after 3 months, important reductions in hemoglobin A1C occurred up to 6 months with resistance training and were even greater with combined training.

Key Words: Resistance exercise, aerobic exercise, training periodization, exercise training, performance.

INTRODUCTION

The aging of the population is a major contributing factor to the prevalence of type 2 diabetes mellitus (T2DM) (Cowie et al. 2006). In Canada, approximately 88% of diagnosed cases of diabetes are in individuals between the ages of 45 and 75 (Statistics Canada 2009). Age-associated reductions in muscular strength and low exercise tolerance due to a lack of physical activity are common in persons with diabetes. A study amongst older adults (≥ 60 years of age) found that 32% of women and 15% of men with diabetes experience difficulty accomplishing simple daily physical tasks such as walking a quarter of a mile, climbing stairs or performing housework compared to 14% of women and 8% of men without diabetes (Gregg et al. 2000). Recent evidence that resistance training can be a safe and effective way of increasing muscular strength for elderly patients with diabetes (Castaneda et al. 2002; Dunstan et al. 2002) and patients with heart failure (Braith et al. 2008), has prompted current exercise guidelines to integrate resistance exercise training in a well-rounded training program for the management of T2DM.

The rate of strength development has been previously reported in young and healthy individuals (Hickson 1980; Hickson et al. 1994), as well as in middle-aged and elderly men and women (Frontera et al. 1988; Morganti et al. 1994; Hakkinen et al. 2000). These studies consistently show greater strength gains in the initial phases of a training program. There remains controversy, however, regarding the level and rate of improvement in muscular strength with resistance exercise training. For example, some report a plateau in strength development with short term (8-12 weeks) and/or long term (>12 weeks) resistance training, while others do not report slowing in gains over time (Frontera et al. 1988; Fiatarone et al. 1990; Morganti et al. 1994). Additionally, although several studies have reported improvements in strength from pre-

to post-intervention in individuals with T2DM, none have examined the time course of improvements in strength.

There is also compelling evidence for incremental benefits of combined aerobic and resistance training for individuals with diabetes. For example, previous studies have reported reductions in hemoglobin A1C (A1C) with aerobic exercise training and resistance exercise training alone, but these studies found that the combination of both training modalities reduced A1C to a greater extent (Snowling et al. 2006; Sigal et al. 2007). In the Italian Diabetes and Exercise Study (Balducci et al. 2008), combined aerobic and resistance training delivered better results in terms of glycemic control, lipids, body composition, blood pressure and estimated cardiovascular risk than the group receiving exercise counseling only. Although results from these studies imply that combined exercise training may be most beneficial to reduce A1C, it is unclear if combining aerobic and resistance exercises in a training program may have detrimental effects on strength development compared to resistance training alone. Some studies have reported that strength gains are attenuated and/or decreased when combined with aerobic exercise training (Hickson 1980; Chtara et al. 2008) while others suggest that strength improvements are similar between resistance training alone and in combination with aerobic training (McCarthy et al. 1995; Wood et al. 2001).

The present study examined the time course of strength development in previously inactive individuals with T2DM from the Diabetes Aerobic and Resistance clinical trial (DARE) (Sigal et al. 2007) (ClinicalTrials.gov NCT00195884). Further, we examined whether strength gains are attenuated with combined aerobic and resistance exercise training compared to resistance exercise training alone.

METHODS

This project is a sub-study of the Diabetes Aerobic and Resistance (DARE) clinical trial described elsewhere (Sigal et al. 2007). This trial was a single-center, randomized controlled trial with parallel group design that examined the effects of aerobic and resistance exercise training only as well as their combination on glycemic control in T2DM. For the purpose of this paper, only the participants allocated to the resistance exercise training and combined aerobic and resistance exercise training groups were analyzed. The Ottawa Hospital Research Ethics Board approved all methods and procedures and all participants provided written informed consent.

Participants

Previously sedentary individuals with T2DM were recruited through advertising, physicians and word of mouth. Inclusion criteria for the DARE trial included type 2 diabetes for at least 6 months and baseline A1C between 6.6% and 9.9% (normal= 4%-6%). Exclusion criteria are described elsewhere (Sigal et al. 2007). The participant characteristics are presented in Table 1.

Run-In Period

Participants exercised at community-based facilities, supervised by personal trainers. Prior to randomization, subjects entered a 4-week run-in period to assess compliance. Subjects performed 15-20 minutes of aerobic exercise and 1-2 sets of 8 resistance exercises, at moderate intensity and with supervision. Only subjects attending ≥ 10 of the scheduled 12 run-in sessions were eligible for randomization.

Exercise Intervention

Subjects exercised three times per week, and training progressed gradually in length and intensity. The resistance group performed seven different exercises on weight machines each session, progressing to 2-3 sets of each exercise at the maximum weight that could be lifted 7-9 times. Participants alternated between two groups of 7 exercises targeting all major muscle groups. These were as follows: Group A: seated row, biceps curl, bench press, leg press, shoulder press and leg extension; and, Group B: lateral pulldown, triceps pushdown, chest press, leg press, upright row and leg curls. The resistance exercise training program was designed to progressively increase the workload while maintaining the number of repetitions performed constant. When participants were able to perform more than 8 repetitions while maintaining proper form, the weight was increased. The combined exercise training group performed the full aerobic and resistance exercise training program. The aerobic exercise training component consisted of participants exercising on treadmills and/or bicycle ergometers. Heart rate monitors (Polar Electro Oy, Kempele, Finland) were used to adjust workload to achieve target heart rate. Subjects progressed from 15-20 minutes per session at 60% of maximum heart rate, to 45 minutes per session at 75% of maximum heart rate as determined through the maximal treadmill exercise test.

Direct supervision by trainers occurred with equal frequency in all exercising groups. Individual exercise supervision was provided weekly for the first 4 weeks after randomization and biweekly thereafter. Attendance was verified through direct observation, exercise logs, and electronic scanning of membership cards. Each participant was required to fill out an exercise log book following every training session. The amount of weight lifted (lbs), number of repetitions performed and the number of sets for each exercise were recorded.

Measurements

The total weight lifted for the 3 sets performed during the training session was calculated for each exercise (i.e., weight lifted x total number of repetitions x total number of sets). A weekly average was calculated from the total weight lifted from each session for weeks 5, 9, 13, 17, 21 and 26 which represent workloads at month 1, 2, 3, 4, 5 and 6 respectively. To find the absolute (lbs) change in workload between months, we subtracted the workload at a specific month with the workload from the previous month (i.e., workload at month 2 – workload at month 1). In order to find the relative (%) change from baseline, we divided the absolute change in workload between months by the workload from the previous month [i.e., (workload at month 2 – workload at month 1)/workload at month 1 x 100].

Statistical Analysis

We used independent T-tests to test for baseline differences between the two training groups. For the main analysis, a two-way repeated measures ANOVA was used to analyze the data using the repeated factor of time (levels: 1, 2, 3, 4, 5, and 6 months) and non-repeated factor of training group (levels: resistance training only, combined resistance and aerobic training). Dependent variables included measures for absolute and relative changes in strength for each exercise. We ran additional models in which age and sex were entered as covariates in addition to time, study group and time-by-group interaction. For ANOVA main effects, Greenhouse-Geiser corrected statistics are reported where the assumption of sphericity was not met. The level of significance was set at 0.05. All analyses were performed using the statistical software package SPSS 17.0 for Windows (SPSS Inc. Chicago, IL, USA).

RESULTS

Following the run-in phase, 64 subjects were randomly allocated to resistance training and 64 to combined aerobic and resistance training. Five participants in the resistance training group and 4 participants in the combined training group were excluded from the present analysis since they did not have data for any of the strength exercises subsequent to the run-in phase. Reasons for not completing the study included medical conditions, loss of interest and other personal or time commitments, which interfered with the ability to participate or continue with the study. Participants in both exercise groups were similar in age, sex and workload on all of the strength exercises at baseline (Table 1.)

Training Progression

Changes in strength between resistance training and combined training were not significantly different over time. There was a significant main effect for time with both groups showing improvements in absolute and relative workload, although workload increments tended to decrease over time for upper body (Figure 1) and lower body (Figure 2). The main effect for group was not significant for any of the strength exercises suggesting no difference in strength development between groups. There was however a tendency for workload increments to decrease between 5 and 6 months in several exercises with combined training (Table 2). Notably, workload increments decreased between 5 and 6 months in the combined group on the seated row (-8.8 lbs), bench press (-28.6 lbs), biceps curl (-11.3 lbs), shoulder press (-9.7 lbs), lateral pulldown (-14.3 lbs) and leg extension (-15.6 lbs) compared to increments between 4 and 5 months.

There was no significant effect of age on strength development over time. The effect of group was also not influenced by age or sex. Sex however was a significant factor in models for absolute changes in workload on the seated row ($P=0.006$), bench press ($P=0.004$), biceps curl ($P=0.049$), shoulder press ($P=0.015$), lateral pulldown ($P=0.029$), chest press ($P=0.049$), leg extension ($P=0.005$) and leg curl ($P=0.01$) with men averaging greater workload increments over time than women. When expressed as a percent change from baseline, the effect of sex only remained significant for changes in workload on the seated row ($P=0.008$), bench press ($P=0.002$), shoulder press ($P=0.019$) and leg extension ($P=0.013$) with men showing greater percent increases in workload from baseline than women.

Monthly workload improvements for upper body exercises were comparable to monthly improvements in lower body exercises. Specifically, in the resistance training and combined training groups, the largest upper body workload increments (51% and 42% respectively) and lower body workload increments (45% and 42% respectively) were measured between month 1 and 2 of training. Subsequently, upper body and lower body workload increments were less than the first two months but were nonetheless similar between both training groups. Upper and lower body workload increments over 6 months are displayed in Figure 3.

DISCUSSION

Our findings demonstrate that muscular strength, as represented by increments in workload over time, significantly improved with resistance exercise training in individuals with T2DM. We also found that the rate of strength development was similar with resistance training alone and with combined aerobic and resistance training. There was, however, a clear trend

towards a slowing in strength development over time and this tendency was similar between upper body and lower body exercises. Greater workload increments occurred within the first two months of training whereas smaller strength gains were found in subsequent months. There was also a tendency for workload increments to decrease more in the combined training group between 5 and 6 months than in the resistance training group.

We show that the interaction between training modality and strength increments over time was not significant for any of the strength exercises suggesting that similar increases in workload occurred in both training groups. In the combined training group however, we found that in the final month of training, workload increments decreased for several strength exercises. Other studies have reported reductions in strength over time with a combined aerobic and resistance training program (Hickson 1980; Chtara et al. 2008). Hickson (1980) for example, found that strength development was either attenuated or decreased when resistance training was combined with aerobic training. Participants in that study were young healthy individuals (mean age of 25) assigned to either a strength training group, endurance training group or a combined strength and endurance training group. The strength training group had a consistent rate of strength development throughout the 10 week training period whereas in the combined group, strength development leveled off and subsequently decreased after the 7th week. The participants in the combined training group, however, were required to perform heavy resistance training and endurance training 6 days per week. Therefore, it is conceivable that a high training frequency and residual fatigue compromised strength development. In the present study, although exercise training was only performed 3 times weekly, our participants were previously sedentary individuals with low physical fitness. Thus fatigue from performing both aerobic and resistance

training could be a factor contributing to the observed reduction in strength performance over time. In a more recent study by Chtara et al. (2008), 48 male subjects (mean age of 21.4) trained twice a week for a period of 12 weeks. The endurance training program involved high intensity interval running and the resistance training program consisted of a circuit program including strength endurance exercises and explosive strength and power exercises. The results from this study show that circuit training alone led to greater improvements in 1 RM half squat ($P<0.01$), right and left 1-leg half squat ($P<0.02$), 5-jump test ($P<0.01$), peak jumping force ($P<0.05$), peak jumping power ($P<0.02$) and peak jumping height ($P<0.05$) than combined endurance and circuit training. However, since this type of program and the strength exercises involved are not typically prescribed to older adults it is difficult to compare our results to the ones from this study.

In contrast to the studies by Hickson (1980) and Chtara et al. (2008), McCarthy et al. (1995) found that 3 days per week of combined strength and endurance training over 10 weeks in sedentary young adult males (mean age: 26.5-27.9 across groups) led to similar improvements in 1-RM on the squat and bench press with strength training alone. Endurance training involved 50 minutes of cycling at 70% of heart rate reserve and the resistance training program included 3 sets of 6 repetitions targeting several large muscle groups. Among healthy older adults (≥ 60 years), Wood et al. (2001) found that 3 days per week of concurrent aerobic and resistance exercise training led to similar improvements in strength as resistance exercise training only. In this study, the aerobic component included a maximum of 45 minutes of exercise on a treadmill or cycle ergometer at 60-70% of estimated heart rate. Resistance training involved 8 exercises for 2 sets of 8-12 repetitions. The training regimens used in these two studies are similar to the

training programs performed by DARE participants. These studies, however, did not evaluate training progression and only compared strength at baseline and at the end of the intervention. Thus it is not possible to determine whether strength progression was the same with resistance training only and combined training. In the present study, strength improvements from 0 to 6 months were also comparable between both training groups. However, evaluating monthly training progressions revealed that strength development with combined training had a tendency to decrease in the last month of training whereas in the resistance group, workload increments were smaller in magnitude but did not decrease from the previous month.

Previous studies have examined the rate of strength development in healthy individuals. Morganti et al. (1994) showed that strength continued to develop over time in 39 healthy older women (59.5 ± 0.9 yr) who were randomized to a control group or to a resistance training group over a 12-month period. The women in the resistance training group exercised twice weekly at ~80% of 1-RM and experienced significant strength gains over the entire 12 months of training. A greater proportion of overall gains, nonetheless, were seen in the first 3 months. In this study, the training intensity was relatively high (80% 1-RM) and frequent adjustments (i.e. based on weekly or biweekly 1-RM testing) of training intensity were made in order to maintain a load corresponding to 80% of 1-RM. This may explain why strength continued to increase significantly over time. Another study by Frontera et al. (1988) also did not report a plateau in strength gains but rather a gradual improvement in strength each week over 12 weeks of high intensity resistance training in men 60-72 years of age. Similarly, Fiatarone et al. (1990) did not observe a plateau in the strength development of the knee extensors over 8 weeks of resistance training in frail elderly (86-96 yrs) men. In the present study, workload increments were greater

between the first and second month of training for lower and upper body exercises. Thereafter, workload increments were consistently lower than the previous month, especially between the final 2 months of training which suggests that participants were reaching a plateau in strength development. Similar trends in strength development have been reported previously in young, middle aged and elderly healthy individuals. In a study by Hickson et al. (1994) 10 young subjects performed heavy resistance training 3 days per week for 8 weeks and another 8 weeks at a higher workload. During the first training period, week-to-week improvements were seen in the first 4 weeks of training. However, no changes in strength in the last 3 weeks were reported. During the second training period, training loads were increased to meet the most recent 1-RM but overall strength improvements were much less than observed during the first period (21% vs. 7%). Hakkinen et al. (2000) showed that a 12 week progressive resistance training program improved strength in middle aged (43-57 years) and elderly (64-73 years) men and women. Strength, however, ceased to increase and actually decreased in the last 4 weeks of training in middle-aged women and elderly men and women.

The absence of a plateau has been associated with such factors as higher training intensities, frequent load adjustments (based on weekly or biweekly 1-RM testing) and longer training periods (Morganti et al. 1994). In the studies that did not report a plateau in strength development, training intensity was relatively high (80% 1RM) and frequent 1-RM testing were performed to maintain workloads corresponding to 80% of the most recent 1-RM load. This may explain why strength continued to increase significantly over time as shown in the study by Morganti et al. (1994) which reported significant improvements in strength over 52 weeks. In the studies of relatively shorter duration (<12 weeks) (Frontera et al. 1988; Fiatarone et al. 1990) it is possible that neurological adaptations to strength training which are mainly responsible for early

improvements in strength, were still playing an important role in strength development. Hence, had these studies been longer in duration (i.e., > 12 weeks), it is possible that a leveling off in strength gains may have occurred. However, Frontera et al. (1988) performed weekly 1-RM measurements over 12 weeks and Fiatarone et al. (1990) conducted bi-weekly 1-RM testing over 8 weeks and adjusted the workload accordingly. As such, participants were consistently lifting heavier loads which may have avoided a plateau in strength development. Conversely, Hickson et al. (1994) kept workloads constant during the first 8 weeks of training and found a leveling off in strength development after only 4 weeks. Strength increased slightly in the second 8-week training period after the load was increased again but, the new load remained constant and strength ceased to increase in the last couple of weeks. In the current study, although the resistance training program was designed to be progressive, workload increased only when the participant could lift the weight more than 8 times while maintaining proper forms.

Significance

In recent years, resistance exercise training has been highly recommended for individuals with T2DM to improve glycemic control and increase muscular strength. While we assume that our training program was designed to induce progressive increases in strength, we showed in this study that there is a clear slowing in performance improvements after 6 months of training. A greater emphasis should be put on increasing the training intensity to ensure that individuals taking part in resistance training programs are provided with a sufficient stimulus to ensure a progressive increase in strength. Previous studies have already demonstrated that high intensity resistance training is safe for individuals with T2DM (Castaneda et al. 2002; Dunstan et al. 2002) and that higher training intensities and frequent load adjustments seem to offset the leveling off

in strength development (Frontera et al. 1988; Fiatarone et al. 1990; Morganti et al. 1994). Current recommendations for resistance exercise training consist of performing 3 sets of 8-10 repetitions targeting all major muscle groups 3 times weekly. It could be argued that if reductions in strength improvements are observed after a few months of training, despite continued adjustment in workload, it may be unnecessary to require that individuals continue to perform the same number of sets or number of training sessions per week. Previous studies have shown that a reduced number of sets and/or number of training sessions per week can provide a sufficient stimulus to maintain strength (Morganti et al. 1994; Honkola et al. 1997; Ibanez et al. 2005). However, it is important to consider that there are underlying benefits associated with the greater work volume, notably important improvements in A1C, which appear to occur up to 6 months and are necessary in order to maintain adequate glucose control in individuals with T2DM (Sigal et al. 2007). In the DARE trial for example, although workload increments had a tendency to level off in the last months of training in both training groups, A1C improvements were maintained in the final 3 months relative to the first three months of training albeit the magnitude of change was greater in the combined exercise training group (i.e., resistance training only: 0 to 3 months, -0.13% and 3 to 6 months, -0.17%; combined exercise training: 0 to 3 months, -0.47% and 3 to 6, -0.43%).

In summary, our findings demonstrate that strength gains can be derived from 3 days a week of progressive resistance training alone or in combination with aerobic exercise training in individuals with T2DM which is consistent with reports among middle-aged and older non diabetic individuals. Strength development had a tendency to level off between the 5th and 6th month of training in our participants and this was more prominent in the combined exercise

training group where workload increments decreased at 6 months. It is important to consider, however, that additional metabolic benefits occurred between 3 and 6 months with resistance training and were even greater with combined training.

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Table 1. Participant's baseline characteristics

Characteristic	Resistance Training (N = 59)	Combined Training (N = 60)	P-Value
Age (yr)	54.6 ± 0.9	53.48 ± 0.9	0.397
Men/women	38/21	39/21	
Age group 39-54/55-70	27/32	31/29	
Seated Row (lbs)	1494 ± 105	1402 ± 104	0.535
Bench Press (lbs)	1115 ± 75	1032 ± 75	0.439
Leg Press (lbs)	2533 ± 213	2798 ± 211	0.380
Biceps Curl (lbs)	704 ± 53	778 ± 53	0.324
Shoulder Press (lbs)	752 ± 65	791 ± 65	0.677
Leg Extension (lbs)	1108 ± 74	1127 ± 73	0.861
Lateral Pulldown (lbs)	1297 ± 86	1443 ± 85	0.232
Chest Press (lbs)	984 ± 67	985 ± 67	0.995
Triceps Pushdown (lbs)	956 ± 135	852 ± 133	0.586
Upright Row (lbs)	758 ± 66	845 ± 66	0.355
Leg Curl (lbs)	1100 ± 62	1116 ± 61	0.856

Values are presented as means ± SE. lbs=pounds; yr = year. Weight represents the sum of the weight lifted for 3 sets.

Table 2-a. Upper body workload increments (lbs) at monthly intervals over 6 months.

	Seated Row	Bench Press	Biceps Curl	Shoulder Press	Lateral Pulldown	Chest Press	Triceps Pushdown	Upright Row
1-2 mo								
	RT	461 (67)	211 (69)	234 (39)	294 (54)	260 (57)	116 (171)	335 (55)
	A+R	376 (63)	297 (49)	272 (48)	321 (65)	286 (55)	188 (37)	277 (57)
2-3 mo								
	RT	214 (47)	181 (37)	117 (27)	240 (48)	189 (31)	122 (35)	96 (33)
	A+R	276 (77)	187 (48)	164 (48)	221 (56)	115 (35)	97 (24)	159 (37)
3-4 mo								
	RT	233 (36)	102 (32)	100 (36)	117 (26)	117 (27)	82 (29)	164 (34)
	A+R	115 (40)	75 (43)	25 (40)	131 (28)	190 (48)	110 (32)	104 (36)
4-5 mo								
	RT	132 (28)	99 (22)	58 (22)	41 (46)	82 (25)	54 (16)	74 (27)
	A+R	94 (59)	60 (42)	25 (46)	49 (28)	38 (33)	-11 (44)	16 (39)
5-6 mo								
	RT	79 (23)	11 (22)	37 (23)	8 (63)	53 (26)	41 (30)	65 (23)
	A+R	-8 (41)	-28 (29)	-9 (24)	-14 (42)	16 (35)	46 (31)	42 (28)
	*P-values	0.436	0.522	0.435	0.970	0.326	0.656	0.437

Data are presented as means (SE). *Using repeated measures analysis of variance time x group interactions, mo = month. Weight represents the sum of the weight lifted for 3 sets.

Table 2-b. Lower body workload increments (lbs) at monthly intervals over 6 months.

	Leg Press	Leg Extension	Leg Curl
1-2 mo			
RT	810 (121)	353 (52)	333 (62)
A+R	835 (120)	286 (52)	234 (59)
2-3 mo			
RT	686 (101)	263 (37)	208 (42)
A+R	663 (195)	248 (58)	132 (27)
3-4 mo			
RT	461 (90)	118 (28)	98 (24)
A+R	260 (135)	67 (59)	129 (52)
4-5 mo			
RT	419 (86)	87 (28)	73 (26)
A+R	256 (113)	45 (55)	-8 (45)
5-6 mo			
RT	47 (79)	27 (2)	36 (20)
A+R	1 (96)	-15 (38)	53 (34)
*P-values	0.830	0.979	0.416

Data are presented as means (SE). *Using repeated measures analysis of variance time x group interactions, mo = month. Weight represents the sum of the weight lifted for 3 sets

FIGURE CAPTIONS

Figure 1. Upper body workload increments (%) at monthly intervals in the combined aerobic and resistance training group (grey bars) and the resistance exercise training groups (black bars). The values represent mean \pm SE for upper body strength exercises: seated row, panel A; bench press, panel B; biceps curl, panel C; shoulder press, panel D; lateral pulldown, panel E; chest press, panel F; triceps pushdown, panel G, and upright row, panel H.

Figure 2. Lower body workload increments (%) at monthly intervals in the combined aerobic and resistance training group (grey bars) and the resistance exercise training groups (black bars). The values represent mean \pm SE for lower body strength exercises: leg press, panel A; leg extension, panel B; and leg curl, panel C.

Figure 3. Upper body workload increments (%) between months over 6 months with resistance training and combined training, panel A. Lower body workload increments (%) between months over 6 months with resistance and combined training, panel B.

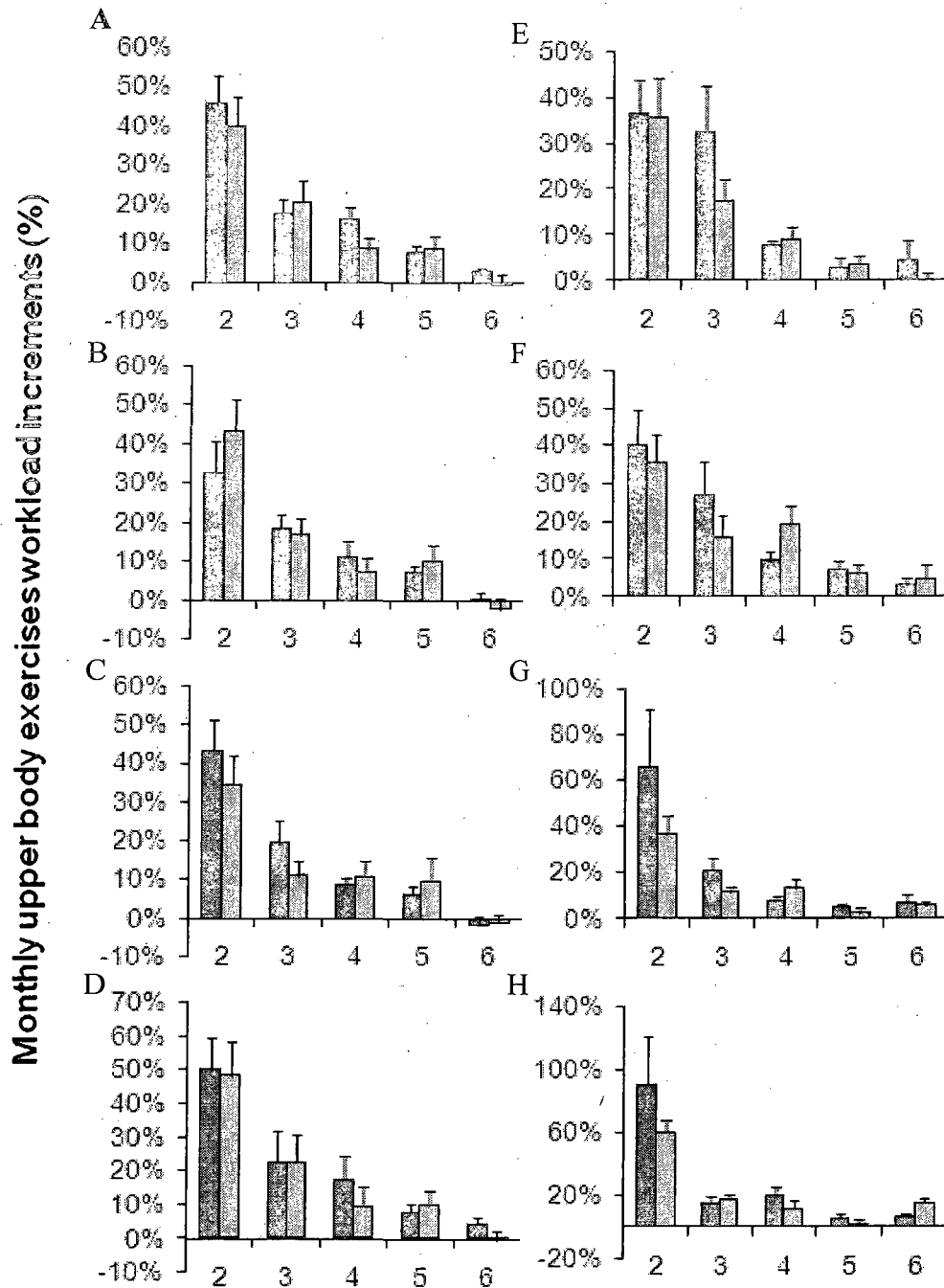


Figure 1. Upper body workload increments (%) at monthly intervals in the combined aerobic and resistance training group (grey bars) and the resistance exercise training groups (black bars). The values represent mean \pm SE for upper body strength exercises: seated row, panel A; bench press, panel B; biceps curl, panel C; shoulder press, panel D; lateral pulldown, panel E; chest press, panel F; triceps pushdown, panel G, and upright row, panel H.

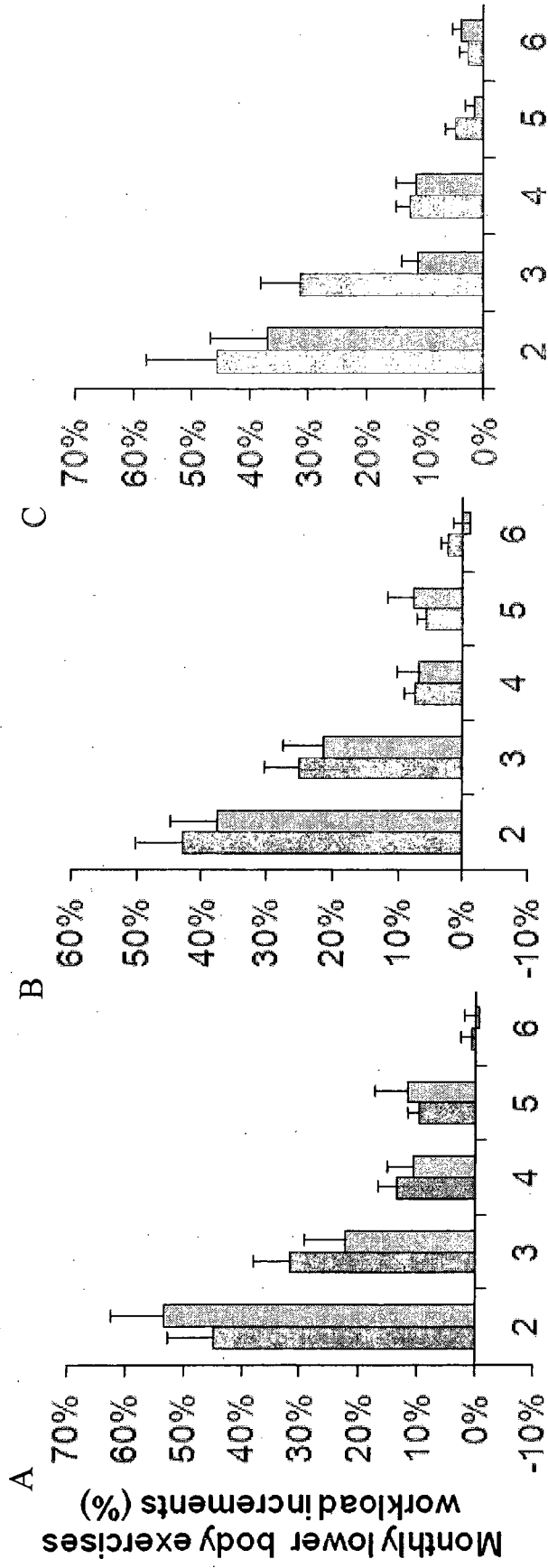


Figure 2. Lower body workload increments (%) at monthly intervals in the combined aerobic and resistance training group (grey bars) and the resistance exercise training groups (black bars). The values represent mean \pm SE for lower body strength exercises: leg press, panel A; leg extension, panel B; and leg curl, panel C.

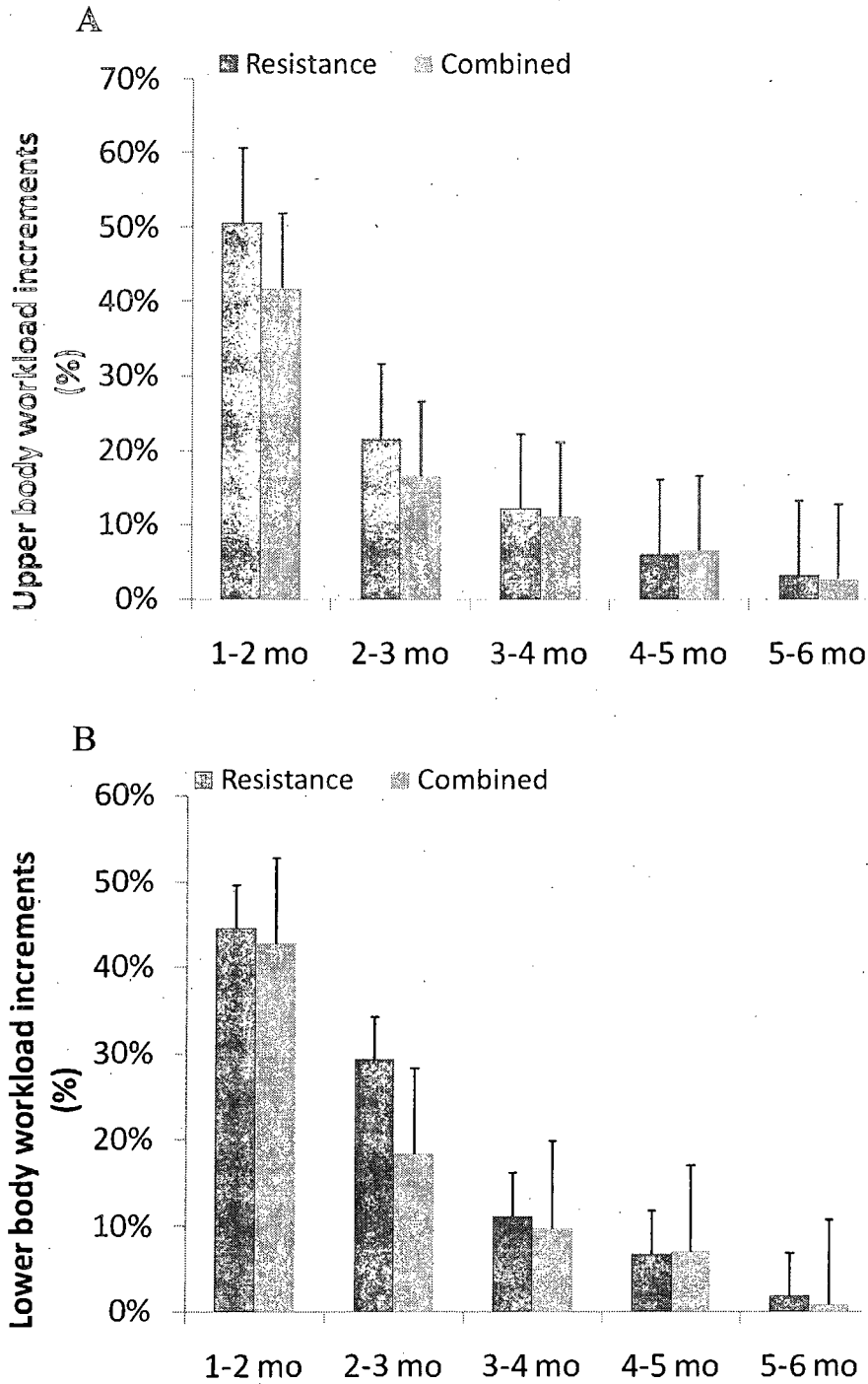


Figure 3. Upper body workload increments (%) between months over 6 months with resistance training and combined training, panel A. Lower body workload increments (%) between months over 6 months with resistance and combined training, panel B.

GENERAL CONCLUSION

Low physical fitness in T2DM has been associated with a higher risk of functional disability, cardiovascular disease as well as cardiac and all-cause mortality compared to individuals with higher levels of fitness. The DARE study reinforced the importance of both aerobic and resistance training, in particular when resistance training is combined with aerobic training, to improve A1C. Exercise programs for people with T2DM should include aerobic and resistance exercise for developing and maintaining cardiorespiratory fitness and muscular strength. Current exercise recommendations include accumulating at least 150 minutes of moderate intensity (50-70% HR_{max}) aerobic activity and/or 90 minutes of vigorous (>70% HR_{max}) aerobic exercise over at least 3-5 days a week (107, 118). Recommendations in terms of resistance exercise training for individuals with diabetes consist of 3 sets of 8-10 repetitions targeting all major muscle groups. In this trial, participants in the aerobic training group progressed from 15 to 45 minutes of aerobic exercise training 3 times per week at 60-75% of maximal heart rate and those in the resistance training group performed 3 sets of 8 repetitions targeting 12 muscles groups. Participants in the combined aerobic and resistance training group performed both training programs. Our study showed that strength and cardiorespiratory fitness improved with combined exercise training to a similar extent as either mode of training alone. Although aerobic exercise training also led to significant improvements in strength, these improvements were greater with combined aerobic and resistance training and resistance training alone. Conversely, resistance training did not induce significant changes in cardiorespiratory fitness. With evidence from the results of the DARE trial and this sub study, the combination of both exercise modes seems optimal to simultaneously improve cardiorespiratory fitness, muscular strength and A1C in individuals with T2DM.

APPENDIX A

Table 1. Clinical trials involving aerobic exercise with people with type 2 diabetes mellitus. Exercise program details and effects on A1C and fitness are presented.

Source	n/design	Age (yrs)	Diabetes duration (yrs)	Study length	Exercise prescription	Intensity	Primary finding	Changes in fitness
(Sigal, Kenny et al. 2007)	AR: 60 RT: 64 AR: 64 CT: 63 10	AR: 53.9±6.6 RT: 54.7±7.5 AR: 53.5±7.3 CT: 54.8±5.0 44±/±3	AR: 5.1±3.5 RT: 6.1±4.7 AR: 5.2±4.8 CT: 5.0±4.5 n/a	3x/week for 24 weeks Most days of the week for 16-20 weeks	AT: 15-45 treadmill or bicycle RT: 3 sets, 8 repetitions, 12 exercises Walking on treadmill 1 m - 30 min session After - 40 min sessions Exercise on most days of the week 1 weekly session supervised 10 minute warm up 30-45 min (60 min/session) by the end of the program of aerobic activity (running, walking on treadmill, cycling) 5 minute cool down	60-75% HRmax Mod: 60-70% HR max	HbA _{1c} AT: ↓ 7.46±1.5 to 6.98±1.5 ↓ with physical activity and weight loss (7.9+/-0.5 to 6.5+/-0.3)	VO2max ↑ by 12+/-1.6% (43.5+/-1.6 to 48.6+/-1.6 ml/kg/min)
(Kadoglou, Iliadis et al. 2007)	60: 30 exercise group, 30 control group	Exercise group: 59.3 (4.76) Control: 63.8 (7.03)	Exercise group: 6.9 (4.24) Control: 6.71 (3.9)	4x/week for 6 months	10 minute warm up 30-45 min (60 min/session) by the end of the program of aerobic activity (running, walking on treadmill, cycling) 5 minute cool down	Low initial intensity and progression towards higher intensity training 50-75% VO2peak ET: 60% VO2 max	10.63±0.41 with exercise vs. 0.31±0.10 increase in controls	VO2peak 15.8% increase in exercise vs. 3% decrease in controls Test duration increased by 0.79 min in exercise vs. 0.39 min reduction in controls
(Cauza, Hanusch-Enserer et al. 2005)	43: 22 strength training, 17 endurance training	ET: 57.9+/- 1.4	ET 9.2 +/- 1.71	3x/wk for 4 months	ET: Wk 1-4: 15 min + 5 min every 4 wks Last 4 wks 90 min	ET: ET: 7.7 +/- 0.3 to 7.4 +/- 0.3		ET: ↑ 8% (16.33+/-1.1 to 17.82+/-1.2 ml/kg/min) Strength (kg) Leg press ↑ 15% (93.2+/-8.7 to 107.2+/-10.2) Bench press No change (40.4+/-3.8 to 40.2+/-3.5) Pull sitting No change (47.4+/-3.8 to 49.7+/-4.2) Workload (W) ↑ 12%(106+/-9 to 118+/-10) Time on treadmill ↑ 423+/-207 s to 471+/-230 s
(Tessier, Ménarda et al. 2000)	39: 19 Experimental group, 20 control group	Experimental group: 69.3+/- 4.2 Control group: 69.5+/-5.1	Experimental group: 51.3+/-51 months Control: 101.5+/-84.2 months	3x/wk for 16 wks	3x/wk 10 min warm up 20 min rapid walk 20 min strength training: 2 sets 20 reps of major muscle groups 10 min stretching	Baseline: 35-59% HRmax Wk 4: ↑ 60-79% HRmax	No change after training (7.5+/-1.2 to 7.6+/-1.2)	T2DM: ↑ VO2max 18.7+/-3.2 to 21.8+/-4.9 Walk time on 1.6 km walk ↓ 18.4+/-0.7 to 16.9+/-1.6 min Normoglycemic women: ↑ VO2max 20.7+/-5.4 to 25.7+/-6.3 Walk time on 1.6 km walk ↓ 18+/-0.8 to 15.9+/-1.3
(Walker, Piers et al. 1999)	31 women: 11 T2DM, 20 normoglycemic	T2DM: 58+/-6 Normoglycemi: 56+/-5	n/a	At least 5x/wk for 12 wks	Walking program Self-paced walk 60 min (self reported)	Not reported, self paced	↓ in women with diabetes after walking program (7.78+/-1.37 to 7.19+/-1.59)	

Table 1. Continued

Source	n/design	Age (yrs)	Diabetes duration (yrs)	Study length	Exercise prescription	Intensity	Primary finding	Changes in fitness
(Brandenburg, Reusch et al. 1999)	27: 10 Lean control subjects, 9 overweight control subjects, 8 T2DM subjects	Lean group: 37+/-6, Overweight group: 37+/-6, T2DM: 43+/-7	T2DM: 3+/-2	3x/wk for 3 months	Treadmill, rowing machine, bicycle ergometer Each session: 5 min warm-up, 50 min moderate intensity exercise, 5 min cool-down	70-85% HRmax	HbA _{1c} Baseline: Lean group: 6.3+/-2.8, Overweight group: 5.4+/-0.5, T2DM 9.5+/-1.9 Changes with exercise training not reported	VO2max: T2DM ↑ 17.7+/-4.0 to 22.4+/-5.5 Overweight: ↑ 21.8+/-2.9 to 23+/-1.8 Lean: No change with training (25.1+/-4.7 to 26.1+/-6.0)
(Dunstan, Mori et al. 1997)	Fish + moderate exercise (14) Fish + light exercise (12) Moderate exercise (11) Light exercise (12)	30-65 yrs Fish + moderate exercise (52.6) Fish + light exercise (54.1) Moderate exercise (52.3) Light exercise (53)	Fish + moderate exercise (6.8) Fish + light exercise (3.7) Moderate exercise (3.8) Light exercise (4.4)	3x/week for 8 weeks	Moderate exercise: 5 min warm-up/cool down 30 min stationary cycling at 60 rpm Light exercise: 10 min stationary cycling 30 min stretching/flexibility exercises	Moderate exercise: WK 1: 50-55% VO2max 55-65% VO2max Light exercise: HR upper limit: 100 bpm	Moderate exercise 0.66% decrease with moderate exercise vs. light exercise Moderate exercise attenuated increase in A1C accompanied with eating fish	T2DM improved VO2 kinetics at 20, 30 and 80 W VO2max: 12% increase (1.87 to 2.07 L/min) with moderate exercise
(Mourier, Gautier et al. 1997)	21: 10 Training group, 11 sedentary group	Training group: 45+/-2, Control group 46+/-3	n/a	Pre-training period: 3x/wk for 2 wks Training: 3x/wk for 8 wks	Pre-training: Braked cycle ergometer Training: Progressed to training when able to perform 45 min @ 75% VO2 peak	Continuous exercise: 45 min 75% VO2peak 2x/wk Intermittent exercise 1x/wk 5 exercises 85% VO2peak for 2 min 3 min at 50% VO2peak between 5 exercises Low impact	↓ with training (8.5+/-0.6 to 6.2+/-0.2)	VO2 peak ↑ 41% (23.0+/-1.2 to 32.4+/-1.3 ml/kg/min) Max workload ↑ 37% (161+/-6 to 220+/-13 W)
(Argus-Collins, Kumanyika et al. 1997)	58 participants; 31 exercise + diet 27 control	61.6±5.8	8.0±8.5	3x/week for 6 months	5 min warm-up 20 minutes of low impact aerobics(treadmill, stationary bicycles, rowing machine) 5 min cool-down 30-45 minutes Bicycle, rowing, skipping rope, walking, jogging, stair climbing, gymnastics, interval training	50-70% of maximal baseline effort	↔ (7.5±0.4 to 7.5±0.4)	Maximal heart rate ↓ 151±12 to 135±11 Resting heart rate ↓ 81±3 to 67±3
(Lehmann, Vokac et al. 1995)	Intervention n=16 Control n = 13	Intervention: 54 Control: 59	Intervention: 7.1 Control: 8.7	Weekly supervised training for 3 months				

Table 1. Continued

Source	n/design	Age (yrs)	Diabetes duration (yrs)	Study length	Exercise prescription	Intensity	Primary finding	Changes in fitness
(Raz, Hauser et al. 1994)	38 participants 19 exercise group 19 control	56.6±6.6	n/a	3x/week for 12 weeks	45 minutes Cycling, rowing, swimming, treadmill	65% VO _{2max}	HbA _{1c} ↓ 12.5±2.9 to 11.7±2.6	
(Vanninen, Uusitupa et al. 1992)	78: 45 men (24 conventional group, 21 intervention group), 33 women (16 conventional group, 17 intervention group)	Men: 53+/-7, women: 54+/-6	n/a	Goal was to perform 3-4 sessions/wk for 12 months Conventional Intervention (encouraged physical activity)	Encouraged ↑ in physical activity Walking, jogging, cycling, swimming, cross country skiing Goal: 3-4 sessions/wk 30-60 min	HR between 110-140bpm	No change in both conventional and intervention group for the men (C): 7.3+/-1.7 to 7.4+/-1.6, I: 7.1+/-1.5 to 7.0+/-1.9 ↓ in women intervention group (7.1+/-1.5 to 6.2+/-1.0)	VO _{2max} : Men intervention group: No change (24.1+/-5.8 to 24.8+/-6.9) Intervention women: no change (18.9+/-3.9 to 19.4+/-3.6) VO ₂ at anaerobic threshold Intervention men: no change (14.5+/-3.4 to 15.1+/-4.1) Intervention women: no change (12.7+/-2.5 to 12.8+/-2.4)
(Wing, Epstein et al. 1988)	Study 1: Diet + moderate exercise (12) Diet + placebo exercise (13) Study 2: Diet + exercise (15) Diet only (15)	30-65 yrs Study 1: Diet + moderate exercise (56.2) Diet + placebo exercise (52.5) Study 2: Diet + exercise (56.1) Diet only (55.1)	Study 1: Diet + moderate exercise (9.8) Diet + placebo exercise (9.6) Study 2: Diet + exercise (10.7) Diet only (10.9)	Study 1 10 wks: Diet + ME 2x/week as a group 1x/week on their own Diet + PE 1x/week at home Study 2 3x/week as a group for 10 weeks 1x/week for additional 10 weeks 1x/month for a year as group and the rest was done on their own 2x/week supervised and 1x/week on their own for 2 years	Diet + ME Moderate intensity walking Diet + PE Light flexibility exercises for one hour	Diet + ME Gradually increase speed and distance until they could walk 3 miles in one hour Diet + PE Low intensity	Study 1 Pre to 10 weeks Diet + ME 9.7±0.5 to 8.0±0.4 Diet + PE 9.4±0.5 to 7.9±0.5 Changes not sustained between pre and 1 yr follow up Study 2 Diet + exercise Pre 10.6±0.5 Post 8.2±0.3 1 yr 9.2±0.5 n/a	VO _{2max} : 15.7% (range -6.6 to 28.6%) 20% if drop outs excluded
(Skarfors, Wegener et al. 1987)	T2DM exercise group: 6 T2DM sedentary controls: 8	T2DM exercise group: 59 (1.4) T2DM sedentary controls: 59.3 (1.6)	T2DM exercise group: 2.9 (2.8) T2DM sedentary controls: 2.3 (3.1)	6x/week for 4 months	45 minutes of jogging or cycling	75% of VO _{2max}	↓ 9.6 to 8.6	
(Ronnemaa, Mattila et al. 1986)	25 participants 13 exercise group 12 control	52.5 (range 45-60)	7.1 (range 1-13)	3x/wk for 6 wks (in laboratory supervised)	45 minutes Walking, jogging Aerobic exercise: (bicycles, ergometers, treadmill, rowing) Eight 4 min periods with 1.5 min rest in between	Wk 1-2 50% VO _{2max} Wk 3+ ↑70-75% VO _{2max}	Diabetic group: VO _{2max} ↑ 26.2+/-1.1 to 28.4+/-1.0 ml/kg/min HR at 100 w ↓ 138+/-4 to 124+/-4 bpm Non diabetic control group: ↑ 32.6+/-1.7 to 37.6 +/-2.3 HR at 100 W ↓ 132 +/-5 to 124+/-8	
(Schneider, Amorosa et al. 1984)	31: 20 Diabetic patients, 11 non diabetic control subjects	Diabetic patients: 51+/-2 Control: 46+/-4	n/a					

Table 2. Clinical trials involving resistance exercise with people with type 2 diabetes mellitus. Exercise program details and effects on A1C and fitness are presented.

Source	n/design	Age (Yrs)	Diabetes duration (Yrs)	Study length	Exercise prescription	Intensity	Primary finding	Changes in fitness
(Sigal, Kenny et al. 2007)	AR : 60 RT : 64 AR : 64 CT : 63	AR : 53.9±6.6 RT : 54.7±7.5 AR : 53.5±7.3 CT : 54.8±5.0	AR : 5.1±3.5 RT : 6.1±4.7 AR : 5.2±4.8 CT : 5.0±4.5	3x/week for 24 weeks	AT: 15-45 treadmill or bicycle RT: 3 sets, 8 repetitions, 12 exercises 10 min warm-up (bike-low resistance) Wk 1-2 minimal weight Wk 3+: 3 sets (1, 4, 5 and 6 sets) 10-15 reps All major groups	60-75% HRmax	RT: ↓ 7.48±1.47 to 7.18 ±1.52	
(Cauza, Hanusch-Enserer et al. 2005)	43: 22 strength training, 17 endurance training	56.4 +/- 1.1	8.83 +/- 3.5	3x/wk for 4 months		progressively ↑ to keep max reps/set between 10-15	↓ with ST (8.3 +/- 1.7 to 7.1 +/- 0.2)	VO2peak No change (20.71 +/- 1.1 to 20.95 +/- 1.4 ml/kg/min) Strength (kg) Leg press ↑ 48% (113.6 +/- 7.8 to 167.9 +/- 9.7) Bench press ↑ 29% (52.3 +/- 3.1 to 67.4 +/- 4.0) Pull sitting ↑ 22% (56.9 +/- 3.6 to 69.7 +/- 4.0) Workload (W) ↑ 12% (132 +/- 9 to 147 +/- 10) ↑ max strength Leg: ↑ 17.1% (104.5 +/- 8.0 to 124.2 +/- 8.0 kg) Arm: ↑ 18.2% (63.3 +/- 6.9 to 74.1 +/- 7.6 kg)
(Ibanez, Izquierdo et al. 2005)	9	66.6 +/- 3.1	n/a	2x/wk for 16 wks	45-60min/session Wk 1-8: 3-4 sets 10-15 reps Wk 9-16: 3-5 sets 5-6 reps Leg extensors - 2 exercises Arm extensor - 1 exercise Main muscles groups - 4-5 exercises	Wk 1-8 : 50-70% 1 RM Wk 9-16 : 70-80% 1RM 20% of training : 30-50% 1RM	No change with RT (6.2 +/- 0.9 to 6.2 +/- 0.9)	
(Baldi and Snowling 2003)	18; 9 RT and 9 control			3x/wk for 10 weeks	20% of training : 3-4 sets 6-8 reps as rapidly as possible	Progressive intensity	↓ with RT (8.9 +/- 0.8 to 8.4 +/- 0.6%)	Muscular strength and endurance ↑ 25 to 52%
(Castaneda, Layne et al. 2002)	31: PRT group (standard care + resistance training) 31: Control group (standard care)	PRT: 66 +/- 2 Control: 66 +/- 1	PRT: 8 +/- 1 Control: 11 +/- 1	3x/wk for 16 wks	10 exercises 15 reps (upper body) 5 min warm-up 35 min PRT 5 cool-down 3 sets 8 reps 5 exercises	Progressive: Wk 1-8 60-80% (1RM) Wk 10-14 70-80% 1 RM Wk 9 and 15 intensity ↓ 10%	↓ with RT (8.7 +/- 0.3 to 7.6 +/- 0.2)	Strength ↑ 33 +/- 7% whole body strength (389 +/- 30 to 518 +/- 48 kg)

Table 2. Continued

Source	n/design	Age (yrs)	Diabetes duration (yrs)	Study length	Exercise prescription	Intensity	Primary finding	Changes in fitness
(Dunstan, Daly et al. 2002)	29: 16 RT + WL, 13 WL only	RT + WL: 67.6 +/- 5.2 WL: 66.9 +/- 5.3	RT + WL: 7.6 +/- 5.4 WL: 8.8 +/- 7.9	3x/wk for 6 months	RT+WL: 5 min warm up + cool down on bike (low intensity) 45 min high intensity RT 3 sets 8-10 reps 9 exercises	Wk 1-2: 50-60% IRM Wk 3+: goal is to achieve 75-85% IRM Progressive ↑ in workload when 3 sets of 10 reps can be performed	HbA _{1c} ↓ with RT+WL (1.2 +/- 0.9), no change with WL only	Strength Upper body: 3 m - ↑ 22.9% 6 m - ↑ 41.7% Lower body: 3 m - ↑ 5.8% 6 m - ↑ 28%
(Dunstan, Puddey et al. 1998)	21: 11 CWT and 10 control	CWT: 50.3 +/- 2.0 Control: 51.1 +/- 1.2	CWT: 5.3 +/- 1.4 Control: 5.1 +/- 1.2	3x/wk for 8 wks	CWT Warm up Cool down (cycling 5 min) Flexibility exercises Wk 1-2: 2 sets or circuit Wk 3-8: 3 sets of circuit 60 min 10-15 reps 9 exercises + abs curls	50-55% IRM	No change with RT (8.2 +/- 0.5 to 8.0 +/- 0.5)	↑ range from 15+/-6% for rowing pulley to 43+/-12% for leg extension
(Honkola, Forsén et al. 1997)	38: 18 RT, 20 control	RT: 62 +/- 2 Control: 67 +/- 2	RT: 8 +/- 2 Control: 8 +/- 2	2x/wk for 5 months	Circuit type resistance training 8-10 mvts per circuit of major muscle groups 2 sets 12-15 reps	Modest intensity to being - progressive ↑ in load	No change with RT (7.5 +/- 0.3 to 7.4 +/- 0.2)	↑ number of reps: Abs: 18+/-2 to 26+/-3, Back: 23+/-11 to 30+/-14, Biceps: reps x load (kg): Left: 33+/-44 to 167+/-22, Right: 32+/-4 to 104+/-21, Quads: 20+/-14 to 28+/-14

Table 3. Clinical trials involving combined aerobic and resistance exercises with people with type 2 diabetes mellitus. Exercise program details and effects on A1C and fitness are presented.

Source	n/design	Age (yrs)	Diabetes duration (yrs)	Study length	Exercise prescription	Intensity	Primary finding	Changes in fitness
(Sigal, Kenny et al. 2007)	AR: 60 RT: 64 AR: 64 CT: 63	AR: 53.9±6.6 RT: 54.7±7.5 AR: 53.5±7.3 CT: 54.8±5.0	AR: 5.1±3.5 RT: 6.1±4.7 AR: 5.2±4.8 CT: 5.0±4.5	3x/week for 24 weeks	AT: 15-45 treadmill or bicycle RT: 3 sets, 8 repetitions, 12 exercises AT: 30 min RT: 30 min 3 sets 12 reps - 6 exercises Ae: cycle ergometer 30-55 min RT: 3 sets 10-15 reps 7 exercises: large muscle groups	60-75% HRmax AT: 40-80% HRres RT: 40-60% 1RM ↑ weekly Ae: 65-75% HR reserve max 55 min at 75% HR reserve in final week RT: 50-65% 1RM Max 3 sets of 10 reps at 65-70% 1RM Ae: 1-2 m 60-70% HRmax ↑ to 70-80% HRmax RT: 60% 1RM	AR: ↓ 7.46±1.48 to 6.99 ±1.54 ↓ with RT + AT (8.3 ±/- 1.7 to 7.1 ±/- 1.2)	Not reported
(Balducci, Leonetti et al. 2004)	120: 62 RT + AT and 58 control subjects	69±/- 8.9	9.8±/- 7.3	3x/wk for 1 year				
(McGavock, Mandic et al. 2004)	24: 17 RT + AT, 7 control	RT+AT: 58±/- 7, Control: 59±/- 5	n/a	3x/wk for 10 wks			No change with RT+AT (6.6±/-0.9 to 6.4±/-0.6)	VO2 peak ↑ 15% (21.3±/-3.3 to 24.5±/-4.2 ml/kg/min) Strength gains not reported
(Tokmakidis, Zois et al. 2004)	9 post-menopausal women	55.2±/-6.7	n/a	Familiarization period: 2 wks Training: 2x/wk for 16 wks	Aerobic: Walking/jogging 75 min. 5-10 min warm up/cool down 10 min stretching 40-45 min treadmill Resistance: 2x/wk 3 sets 12 reps Six exercises 75 mins Ae: treadmills, bikes, steppers, elliptical, rowing RT: 2 sets 12 reps 5 exercises	↓ with RT+AT (7.7±/- 1.7 to 6.9±/-1)	Exercise time ↑ 8.2±/-1.2 min to 9.1±/-0.9 Strength: Upper body ↑ 150.5±/-21.4 kg to 197.8±/-15.8 kg Lower body ↑ 48.3 ±/-10.6 kg to 67.5±/-11.1 kg	
(Cuff, Menelly et al. 2003)	28 women 9: AT, 10 RT + AT, 9 control	Control 60 ±/- 2.9 AT + RT: 63.4±/- 2.2 AT only: 59.4±/- 1.9	Control: 4.7±/- 1.2 AT + RT: 3.7 ±/- 0.9 AT only: 3.2 ±/- 0.5	3x/wk for 16 wks		AT: 60-75% HR reserve RT: lights weights with progression to heavier loads	No change in any group (Control: -0.03±/-0.2, AT+RT: -0.1±/-0.22, AT only: -0.1±/-0.11)	AT+RT VO2 peak (L/min) ↑ 10.2±/-3.7% (0.17±/-0.06 l/min) Upper body load ↑ 49% Lower body load ↑ 42% AT only VO2 peak (L/min) ↑ 13.1±/-6.5% (0.22±/-0.11 l/min)

Table 3. Continued

Source	n/design	Age (yrs)	Diabetes duration (yrs)	Study length	Exercise prescription	Intensity	Primary finding	Changes in fitness
(Loimaala, Huikuri et al. 2003)	49: 24 Exercise group, 25 control group	Exercise group: 53.6+/-6.2, control group: 54.0+/-5.0	n/a	2x/wk for 52 wks	Minimum 30 min Aerobic: Jog or walk 2x/wk Resistance: Eight exercises 3 sets 10-12 reps 3x/wk Circuit training 10 min warm up and cool down Aerobic: Cycle ergometry, treadmill walking 8 cycling stations 45 sec 5 min treadmill walking to end circuit Resistance: 7 stations 1 complete lift in 3 sec 15 reps in 45 sec	Ae: 65-75% HRmax RT: Progressive 70-80% 1RM 1 circuit and progress to 3 Ae: 70% HR peak ↑ to 85 % by wk 6 RT: 55% 1 RM to begin ↑ 65% by wk 4	HbA _{1c} ↓ with exercise training (8.2+/-2.1 to 7.6+/-1.4)	VO ₂ max ↑ 31.9+/-5.1 to 33.8+/-5.5 ml/kg/min Strength: Sit up. ↑ 12.7+/-7.3 to 20.8+/-6.8 Leg extension: ↑ 202+/-38 to 293+/-73 Sum of max contractions: (kg) ↑ 403+/-30 to 456+/-31 VO ₂ peak: M/kg/min ↑ 23.1+/-1.2 to 24.8+/-1.4 L/min ↑ 2.0+/-0.1 to 2.2+/-0.2 Exercise time ↑ 12.6+/-1.2 to 14.8+/-1.3
(Maiorana, O'Driscolla et al. 2002)	16/randomize cross-over design	52+/-2	n/a	3x/wk for 8 wks				