# EXERCISE: A POWERFUL TOOL TO MANAGE TYPE 2 DIABETES IN THE AGEING POPULATION

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## ABSTRACT

The aim of this paper is to highlight the evidence on the interrelationships between exercise and Type 2 diabetes mellitus (T2DM) in the ageing population. The evidence addressed in the specific literature is presented in three domains: aerobic exercise, resistance exercise, and combined aerobic and resistance exercise. The effects of aerobic exercise are well established, but in the ageing population resistance training could be considered a superior intervention to help glycaemic control; the effects of resistance training on insulin sensitivity are attributable to an increase in muscle mass. Thus, although with resistance training body weight does not change much, the main effect of resistance training on body composition of the elderly should be a shift from fat to muscle mass, and the maintenance of a large muscle mass may reduce obesity related risk factors. Fewer studies have investigated the effects of combined resistance and aerobic training, but from the available evidences it would appear that combined exercise training seems to offer additional benefits if compared with aerobic training alone and resistance training alone.

Keywords: Diabetes, ageing, resistance exercice, aerobic exercise.

## INTRODUCTION

In Western society, both medical and social institutions are paying increased attention to the health and well-being of the elderly and the impact that their growing numbers will have on society in future years. Both Europe and the US are facing major changes in population age-balance which is likely to reshape its demographic structure over the next 20 years. In fact, by the year 2050, one-tenth of the world's population will be over 65, and people over 80 are the fastest growing segment of the population, both in the US[1] and in Europe, where the population is projected to reach 517 million in the year 2060. Nearly one-third of the citizens will then be aged 65 or over.[2] According to the importance of this population segment, in recent years a significant amount of new evidence has accumulated regarding the benefits of regular exercise and physical activity for older adults. Among this, there is now a growing body of knowledge supporting the prescription of exercise and physical activity for older adults with chronic diseases and disabilities that started since the publication of the American College of Sports Medicine (ACSM) guidelines on exercise and physical activity for older adults.[3]

Amongst the elderly population, Type 2 diabetes mellitus (T2DM) is a growing problem; this is a metabolic disorder that results in hyperglycaemia due to the body being unable to produce enough insulin or to insulin resistance, and a larger proportion of newly diagnosed diabetics are elderly subjects. Physical activity and exercise are fundamental in preventing and treating T2DM, and since the publication of the American Diabetes Association (ADA) consensus statement,[4] it was highlighted that health benefits occur according to a dose/response relationship: to maximise benefits, diabetic patients should partake in physical activity/exercise programmes that far exceed the minimum level of physical activity recommendations (e.g. 150 minutes per week of moderate intensity physical activity); in fact, additional benefits occur as the amount of physical activity increases through higher intensity, greater frequency, and/or longer duration. On the other hand, the ACSM guidelines[3] stress the fact that if older adults cannot do 150 minutes of moderate-intensity aerobic activity per week because of chronic conditions, they should be as physically active as their abilities and conditions allow. The aim of this paper is to critically review the recent literature on the effects of exercise and T2DM, with a specific focus on the ageing population.

### Structural and Functional Decline with Ageing

Ageing is associated with a number of modifications that encompass the physical, physiological, and psychological domains. We will focus on the physiological domain, considering the age-related modifications that have a relationship with T2DM: specifically, the loss of lean body mass, particularly skeletal muscle, and the progressive increase of body fat mass and those modifications that are due to T2DM, represented by motor nerve impairments. The fact that muscle mass decreases with age has long been known, and this age-related loss of muscle mass appears to be fairly consistent - at a rate of approximately 1–2% per year - over the age of 50 years.[5] This decline in muscle mass occurs in both sedentary and active ageing adults, whilst in healthy young adults, no net change occurs in skeletal muscle due to balance in skeletal muscle protein synthesis and degradation. This age-related reduction in muscle mass and strength is accompanied by a reduction in motor unit number[6,7] by atrophy of muscle fibres, especially the Type 2a, and an associated decline in protein synthesis, particularly myosin heavy chains.[8]

The loss of muscle mass with ageing is clinically important for a number or reasons: it leads to diminished strength and exercise capacity, consequently producing a decline in function, but more importantly in the context of this paper, it is related to a decrease in glucose uptake due to a diminished capacity of glucose storage and an impairment on insulin signalling. Due to the metabolic consequences of reduced muscle mass, it is understood that normal ageing and/or decreased physical activity may lead to a higher prevalence of T2DM. Thus, the greater an individual's total muscle mass, the lower the person's risk of having insulin resistance, the major precursor of T2DM.[9] Biological ageing is also associated with a progressive increase in body fat mass and a loss of lean body mass, particularly skeletal muscle. Visceral fat increases by >300% between the ages of 25 and 65 years, increasing the risk for the development of both T2DM and cardiovascular disease (CVD) in adults with normal body mass index.[10] The distribution of excess fat in the abdominal region modifies the health risk profile, whilst the excess adiposity in the periphery does not appear to increase CVDs.[11]

The above-mentioned modifications have an important role in the progression of T2DM, but they are basically age-related changes in body composition; however, there are also some physiological modifications that could be determined by diabetes itself, specifically the reduced muscle strength associated not only to decreased muscle mass but to muscle quality,[12] leading to diabetic polyneuropathy (DPN). In fact, several reports have shown a relationship between reduced muscle strength and presence and severity of DPN,[13-15] thus suggesting that muscle weakness is a late complication of DPN with motor nerve impairment.[16] It was recently hypothesised that strength deficit with diabetes and the effect of motor nerve impairment are related to contraction speed and to a reduced muscle fibre conduction velocity, and that exercise training may counteract the impairment of neuromuscular function induced by the disease.[17]

## THE ROLE OF PHYSICAL ACTIVITY AND EXERCISE

In recent years, the clinical importance of physical activity has become extremely important, both in the general population as well as in the elderly. However, the terms 'physical activity' and 'exercise' denote two different concepts.[18] 'Physical activity' refers to any bodily movement produced by skeletal muscles that results in an expenditure of energy and includes a broad range of occupational, leisure, and daily activities. 'Exercise' refers to planned or structured physical activity. It involves repetitive bodily movements performed to improve or maintain one or more of the components of physical fitness: aerobic capacity (or endurance capacity), muscular strength, muscular endurance, flexibility, and body composition. A considerable amount of literature has been published recently to attempt to identify safe and effective exercise programmes for subjects with T2DM. There are no position stands specifically developed for the elderly with T2DM, but assuming that this is a pathology that is generally developed later in life, even though the onset is now occurring earlier, we can consider as a reference the latest ACSM-ADA position stand.[19] The most relevant research questions addressed in the recent specific literature, specifically on the benefits of structured exercise and not on those of general physical activity, will be presented in the following sections.

## Aerobic Exercise

Numerous studies have been published in the past on the effects of aerobic exercise on patients with T2DM, and some specifically involved elderly subjects. Exercise interventions were generally found to reduce glycosylated haemoglobin (HbA1c). In a meta-analysis reviewing exercise intervention of supervised exercise in T2DM individuals,[20] aerobic exercise was seen to have a significant effect on $VO_{2max}$, and on glycaemic control, while having little effect on body weight. We could say that the effects of aerobic exercise on HbA1c are well established and supported by solid literature, as reported in the latest ACSM-ADA joint position stand.[19] However, the most interesting question to be addressed is not the effect of aerobic exercise itself, but the effects of exercise intensity: vigorous exercise versus moderate physical activity.

To address this, of particular interest is the research undertaken by Mourier et al.[21] In this study, subjects trained for 8 weeks at high-intensity on a cycle ergometer, combining training at 75% of $VO_{2\ peak}$ (continuous for 45 minutes) and interval training (5 cycles of 2 minutes at 85% of $VO_{2\ peak}$ alternating with 3 minutes at 50% of $VO_{2\ peak}$). The results showed a statistically significant elevated effect versus the sedentary control group on: increase in $VO_{2\ peak}$, decrease of HbA1c %, decrease of subcutaneous and visceral abdominal fat, and increase of mid-tight muscle. The effect of exercise intensity was also evaluated on insulin sensitivity; three randomised controlled trials (RCTs)[22-24] and a review[25] compared the effects on insulin sensitivity of different intensities of aerobic exercise training with the same total energy expenditure on exercise. We can conclude by stating that interventions with more vigorous aerobic exercise programmes resulted in greater reductions in HbA1c, greater increase in $VO_{2max}$, and greater increase in insulin sensitivity.

## Resistance Exercise

Skeletal muscle mass is the primary site of glucose disposal, and skeletal muscle that declines each decade after the age of 30[26] may lead to an increasing risk of developing glucose intolerance and T2DM.[27] As mentioned above, the other significant modification that occurs with age is an increase of body fat, specifically of intra-abdominal fat that, if compared to total body fat, correlates better with systolic and diastolic blood pressure, triglycerides, and decreased insulin sensitivity.[27,28] It is also important to consider that intra-abdominal obesity is a well-recognised risk factor for low-grade inflammation.[29,30] Overall, those modifications generate a state of metabolic dysfunction in the skeletal muscle of elderly subjects with T2DM. However, even though ageing has an influence on skeletal muscle loss and all its related consequences, those can be counteracted by exercise training, and mainly by resistance training. Emerging research suggests that resistance training may influence age-related physiological changes and may impose potent and unique benefits in T2DM.

The early studies offering preliminary evidence for the benefits of resistance training with T2DM patients were published 15 years ago, and generally on ageing patients. Eriksson et al.[31] demonstrated that 3 months of moderate-intensity circuit resistance training significantly decreased HbA1c, a reduction mainly due to improvements in lean body mass, as a strong inverse correlation between HbA1c and muscle cross-sectional area post-training. Dunstan et al.[32] randomised 36 overweight older men and women into a progressive resistance training plus moderate weight loss group or a moderate weight loss group which did not execute any specific exercise training. A greater reduction in HbA1c was observed in the training group compared to weight loss alone in the absence of difference for waist circumference or total fat mass between groups.

Similar findings on older adults were reported by Castaneda et al.[33] who randomised 62 patients into either supervised high-intensity progressive resistance training or a nonexercising control group, showing a mean increase in lean tissue mass of 1.2 kg. Also Baldi et al.[34] in another RCT, reported a significant reduction in HbA1c, fasting glucose, and insulin, as well as a significant increase in fat-free mass. Dunstan et al.,[32] Castanedaet al.,[33] and Baldi et al.[34] agree that increases in skeletal muscle mass are related to decreases in HbA1c, and support the hypothesis that resistance training improves glycaemic control by increasing the skeletal muscle storage of glucose. Ibanez et al.[35] demonstrated that, in elderly subjects, resistance exercise reduces visceral fat. This was followed by numerous other studies highlighting the fact that resistance training has the power to combat musculoskeletal dysfunction in patients with T2DM and improve the overall metabolic health. Recently, a well written review was published[36] that provided an overview on the biochemical mechanistic effects of resistance training on glucose metabolism and discussed the molecular mechanisms that lead to adaptation in skeletal muscle in response to resistance training.

### Combined Aerobic and Resistance Exercise

Whether combined resistance and aerobic training offers a synergistic and incremental effect on glycaemic control in individuals with T2DM is an issue that has been addressed by a number of studies,[37-39] even though not specifically designed to address this question with the elderly. Moreover, whether there is an incremental value to combine aerobic and resistance training, as opposed to aerobic or resistance separately, has been addressed in the studies by Cuff et al.[40] and more recently by Sigal and Church.[41,42] Maiorana et al.[37] investigated the effects of an 8-week circuit training programme, combining aerobic and resistance exercise, compared with a non-training period. Muscular strength, oxygen uptake, and exercise test duration increased with training while HbA1c, fasting blood glucose, skin folds, the percentage of body fat, and the waist-hip ratio significantly decreased.

Balducci et al.[38] demonstrated that even low-to-moderate intensity resistance training, combined with moderate aerobic exercise three times a week for a year significantly improved metabolic and lipid profiles, adiposity, and blood pressure. More specifically, compared with a non-exercising comparison group, HbA1c and fat mass was significantly reduced while fat-free mass increased. Additionally, fasting blood glucose, low-density lipoprotein cholesterol, and total cholesterol were significantly reduced, while high-density lipoprotein cholesterol was increased. The findings of this study demonstrate a global improvement in cardiovascular (CV) risk factors with a marked improvement in HbA1c, and highlight the potential benefits of combined training for individuals with T2DM.

Furthermore, these findings also identify that longer-duration and more moderate resistance training may be as efficient as short-term high-intensity programmes at maintaining glucose homeostasis and reducing CV risk factors. The first well designed RCT that aimed to evaluate whether combined resistance and aerobic training offers an incremental value versus either alone or versus a sedentary control group, was DARE (Diabetes Aerobic and Resistance Exercise)[41] followed by HART-D (Health Benefits of Aerobic and Resistance Training in Individuals With Type 2 Diabetes).[42] The primary outcome of both studies was a change in HbA1c from baseline to termination. The hypothesis of the studies was that the decrease in HbA1c would have been greater in the aerobic and resistance training groups than the control group, and would be even greater in the combined exercise training group than the aerobic or resistance training group.

In the DARE study the absolute change in HbA1c was significantly higher in both the aerobic and the resistance training group compared with the control group. Combined exercise training resulted in an additional change in HbA1c that achieved statistical significance if compared with aerobic training alone and with resistance training alone. In the HART-D study, only the combined group showed a significant decrease of HbA1c. One of the most interesting studies was the IDES (Italian Diabetes and Exercise Study),[43] aimed at assessing the efficacy of an intensive exercise intervention strategy in promoting physical activity and improving HbA1c and other modifiable CV risk factors in patients with T2DM. Sedentary patients with T2DM and metabolic syndrome were enrolled in 22 outpatient diabetes clinics across Italy and randomised by centre, age, and diabetes. Interestingly, the experimental group exercised twice a week (combined aerobic and resistance exercise), whilst the control group received structured exercise counselling, which aimed to improve their activity. This exercise intervention strategy was effective in promoting physical activity and improving HbA1c and CV risk profile. Conversely, counselling alone, though successful in achieving the currently recommended amount of activity, was of limited efficacy on CV risk factors, suggesting the need for a larger volume of physical activity in these high-risk subjects.

## CONCLUSIONS

Clinical trials and cohort studies have highlighted the role of physical activity in the prevention and treatment of T2DM. Even though the vast majority of the studies were not specifically designed to evaluate the effects of exercise with the elderly, nevertheless, the targeted population involved in those studies was often constituted by elderly subjects. As a result, a considerable amount of literature has been published in recent years trying to identify safe and effective exercise programmes. The benefits of aerobic exercise are well documented and their effects in patients with T2DM are widely perceived to be beneficial for glycaemic control, weight loss, and the control of lipids and lipoproteins. Some meta-analyses have been particularly useful in summarising and analysing prior research, and the effects of aerobic exercise on HbA1c - the major marker of glycaemic control - have become well established. Well conducted meta-analyses have shown that intensity is a better predictor than exercise volume of both the difference in HbA1c and $VO_{2max}$ between the exercise and the control group. The effect of exercise intensity was also evaluated on insulin sensitivity by means of RCTs that compared the effects on insulin sensitivity of different intensities of aerobic exercise training, with the same total energy expenditure on exercise.

In conclusion, we can say that interventions with more vigorous aerobic exercise programmes resulted in greater reductions in HbA1c, greater increase in $VO_{2max}$, and greater increase in insulin sensitivity. Considering that ageing is associated with a reduction in muscle mass, a progressive increase in body fat mass, and a loss of lean body mass (particularly skeletal muscle), resistance training seems to play a fundamental role. Considering the available evidence, it appears that resistance training could be an effective intervention to help glycaemic control, especially considering that the effects of this form of intervention, as reported in the major RCTs, are comparable with aerobic exercise in terms of metabolic control; but in addition, it provides significant advantages in terms of muscle mass improvement and loss of visceral fat. Thus, although with resistance training body weight does not change much, the main effect of resistance training on body composition of the elderly should be a shift from fat to muscle mass, and the maintenance of a large muscle mass may reduce obesity-related risk factors. Resistance training may serve as a countermeasure of age-associated mitochondrial dysfunction by reducing potentially damaging compounds to mitochondria, and this has important implications for T2DM and the metabolic syndrome.

Whether combined resistance and aerobic training offers a synergistic and incremental effect on glycaemic control in individuals with T2DM is an issue that has been addressed by a number of studies; in general, the results indicate that a combined training programme of strength and aerobics could induce positive adaptations on glucose control, insulin action, muscular strength, and exercise tolerance. Moreover, whether there is an incremental value to combining aerobic and resistance training, as opposed to either separately, is another interesting question that has been addressed by research recently. Combined exercise training seems to determine additional change in HbA1c, which can be seen as significant if compared with aerobic training alone and resistance training alone.

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