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ACADEMIC LITERATURE REVIEW

# Diabetes, aging and physical activity

**Bruce Frier · Pearl Yang · Albert W. Taylor**

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**Abstract** Diabetes mellitus (DM) is a metabolic disease affecting the regulation of insulin and glucose causing a disruption in the normal control of counterregulatory hormones and macronutrients, resulting in blood glucose accumulation. Metabolic deregulation leads to the production of noxious substances that have a particular propensity for damaging vascular and nervous structures. Physiological changes observed with aging are correlated with a concomitant increase in DM and its associated complications. Long-term complications, including peripheral and central neuropathies, micro- and macrovascular damage, retinopathy, and nephropathy are the major causes of mortality in diabetics [cardiovascular disease (CVD) being the primary complication causing death in this population]. All-cause mortality is three to four times greater in the DM population; hence, management of DM is of timely importance, particularly with a projected prevalence increase of 134% within the next 25 years among individuals over the age of 65 years. Exercise modalities, including endurance and resistance training, were employed to improve glycemic/metabolic control and to ameliorate the progression of DM-related complications. Several risk factors, including glucose levels, blood pressure, lipid/cholesterol profile, and BMI, are reportedly improved with these modes of exercise. However, not all studies demonstrate an improvement in risk factors, but consistently note improvement in complications and a reduction of DM incidence. There is convincing evidence that exercise, with or without specific improvements to traditional DM-related risk factors, is an effective therapy for the management of DM.

**Keywords** Exercise · Diabetes mellitus · Type 1 · Type 2 · Diabetes complications

The Canadian Centre for Activity and Aging is affiliated with St. Joseph's Health Care and The University of Western Ontario, London, Ontario, Canada.

B. Frier
School of Kinesiology, The University of Western Ontario,
London, Ontario, Canada

P. Yang
Graduate Department of Rehabilitation Science,
University of Toronto,
Toronto, Canada

A. W. Taylor
Faculty of Health Sciences, The University of Western Ontario,
London, Ontario, Canada

A. W. Taylor
Faculty of Medicine and Dentistry,
The University of Western Ontario,
London, Ontario, Canada

A. W. Taylor (✉)
The Canadian Centre for Activity and Aging,
London, Ontario, Canada
e-mail: ataylor2@uwo.ca

## Introduction

Diabetes mellitus (DM) is a metabolic pathology characterized by systemic circulatory glucose accrual, accompanied by diminishing cellular glucose uptake and metabolism. Diabetic metabolism is also evidenced by elevated counterregulatory hormones, which alters lipid metabolism and increases protein catabolism [34]. Sequelae of diabetes may include microvascular complications involving retinopathy, nephropathy, and neuropathy (distal symmetric polyneuropathy and autonomic neuropathy), and macrovascular complications culminating in coronary ar-

tery disease. All-cause mortality is three to four times greater in patients with DM, with CVD accounting for the majority of deaths [93]. The senior population demonstrates a particular susceptibility to DM with a prevalence rate of more than half of all DM cases. With one in five seniors suffering from DM and the deleterious impairments attributed to its pathophysiology, a clear need for treatment and prevention is evident in this growing population. In 2000, the World Health Organization [106] estimated 177 million people suffered from DM. This was a 31% increase over 5 years, up from 135 million in 1995, and an astonishing 490% increase over the 1985 estimate of 30 million. The WHO projects 350 million people will suffer from diabetes by 2030, and that DM may account for ~9% of the total global causes of death [107].

DM is one of the most extensively studied pathologies, spanning centuries. Moreover, the observation that DM was a condition that indicated elevated glucose in urine led to the recommendation, over 2000 years ago, that exercise be used as a treatment [96]. The present review is not comprehensive, but will attempt to delineate some of the current perspectives on DM and will focus on the numerous physiological effects of DM and the potential for aerobic and resistance exercise to ameliorate and prevent the disease and its various accompanying pestilence within the senior demographic.

## Diabetes and aging

Age-associated decline of personal vitality is generally accepted as a congenital axiom. Increased susceptibility to disease with increasing age is likewise axiomatic. Hence, age-associated physical discompositions, such as DM, heart disease, cancer, and stroke, ranging in degree from asymptomatic to death, may be perceived as immutable and intrinsically human. Comorbidity increases with age (from ~35% of patients over 65 to ~70% of patients over 80), as does the cost of treating patients who present with comorbidity [35]. In addition, comorbidity leads to an underreporting of deaths attributed to DM, as fatal events attributed to heart disease and stroke, for example, may not be ascribed to DM. Not surprisingly, decreased life expectancy of ~4 years among individuals diagnosed with DM aged 65–74 was reported [40]. The fact that all-cause mortality is three to four times greater in the DM population attests to its principal role in the lives of seniors. Not only does this amount to massive health care expenditures, but also represents a significant individual financial burden (direct and indirect costs totaling ~132 billion US dollars or ~111 billion euros in 2002 in the United States [46]). It is predicted that by the year 2030 the number of individuals over 65 who suffer from DM will increase by 134%. The progressive nature of DM suggests that the more senior elderly demographic will suffer; between the years 2000 and 2050 the largest increase in DM prevalence is predicted to be among the elderly with the more represented senior demographic being above 75 years (271% increase in women and 437% increase in men) [12]. The prevalence of DM in adults older than 60 years is estimated at ~25% [41].

Imperative to a full account of the impact of accumulating comorbid infirmities, in addition to recognizing the direct metabolic stress of DM, is accounting for the potential for a given intervention to affect the progress and manifestation of the disease. For example, aging is associated with a mortality-related decline in muscle strength [80], a decline in muscle mass [17], decreased oxygen consumption capacity ($VO_{2max}$), and a concomitant increase in fat mass [86], along with increased disability [10]. DM is coincidently related to increased adiposity [5], decreased muscle mass [94], and an elevated waist circumference (associated with both DM [79] and metabolic syndrome [59]). Curiously, DM is also associated with altered mitochondrial function relative to normal individuals, suggesting diminished $VO_{2max}$, and exercise capacity associated with DM may be related to a unique mitochondrial phenotype [68]. Therefore, it is logical to propose that therapies aimed at reducing these age-related anthropomorphic and physiological changes (for example, via exercise intervention) may provide a stimulus, which is able to reverse or prevent age- and disuse-associated physiological changes and, thereby, reduce DM and its comorbidities. However, aging may also be inherently associated with progressive physiological changes, including those leading to an increased incidence of DM, which may remain unaffected by exercise (reviewed by Degens and Alway [26] and Karakelides and Sreekumaran Nair [58]). In light of the predictive statistics for DM and the economic and personal cost of the disease, it seems an intuitive responsibility to seek out etiologies and treatment for this sweeping threat.

## DM symptoms

Primarily, DM is a metabolic disorder that manifests through its varied effects on levels of circulatory and intracellular energy substrates with the inherent characteristic of high plasma glucose levels. Individuals are considered normal with a fasting plasma glucose (FPG) of <100 mg/dl (5.6 mmol/l). A positive DM diagnosis is contingent upon obtaining a FPG level ≥126 mg/dl (7.0 mmol/l) [4]. This measurement must be repeated on a subsequent day to confirm the diagnosis. A casual measure (regardless of time of day or time between meals) of plasma glucose ≥200 mg/dl (11.1 mmol/l) is also suspect for DM

when combined with additional symptoms, which may include unexplained weight loss, increased appetite, frequent urination (polyuria), excessive thirst (polydipsia), blurred vision, nausea, mental confusion, and fatigue. A third test frequently employed to determine hyperglycemia is an oral glucose tolerance test (OGTT). An OGTT is the oral administration of ~75 g of water-solubilized glucose: 2 h postingestion, a blood glucose ≥200 mg/dl (11.1 mmol/l) is provisionally indicative of DM. The essence of these tests is to confirm consistent hyperglycemia resulting from the inability to dispose of glucose due to insulin insufficiency and/or insulin resistance and/or decreased receptor sensitivity. Therefore, any one of these tests needs to be repeated to confirm the glucose profile inherent to DM. Because hyperglycemia is a hallmark symptom of DM it may also be a monolithic miscreant singularly responsible for the multifarious maladies observed with disease progression. Indeed, insulin resistance and numerous micro- and macrovascular abnormalities can be correlated with hyperglycemia, but hyperlipidemia was also proposed as a contributor to DM-associated cellular dysfunction. Moreover, the clinical and biochemical summary list of symptoms and characteristics does not conclusively elucidate the inciting incident inevitably leading to the chronic disease. Prudence dictates and current knowledge limits us to an examination of pathophysiology and potential mechanisms of cellular injury proposed in the published literature. Ideally, examining DM symptoms and pathophysiology could expose the potential for exercise and physical activity as a therapy and method of prevention in the lives of seniors.

## Etiology

Central to glucose metabolism is (1) a proportional pancreatic release of insulin that (2) effects insulin receptor agonization leading to (3) intracellular glucose transporter-4 (GLUT4) translocation resulting in (4) subsequent cellular glucose uptake. DM may be represented by impairment at all four levels of glucose metabolism. DM is generally characterized by one of two types (gestational diabetes will not be discussed and is, in all likelihood, irrelevant in this review). Primarily, DM type 1 (DM1) is the complete absence of pancreatic insulin secretion due to beta cell autoimmune destruction resulting in insufficient cellular glucose uptake. Disease progression proceeds through the inability to regulate and dispose of excess glucose and glucose by-products and via elevated catabolism and lipid metabolism. DM type 2 (DM2) typically includes relatively insufficient insulin secretion with compounded cellular insulin resistance. DM2 is represented in 90–95% of all cases of DM [4]. A common perception is that DM1 originates at the level of pancreatic function whereas DM2 originates at the level of insulin receptor function. Therefore, the former is a disease of prima organum (first organ) whereas the later is finalis portus (final port). However, this distinction may not be borne out through closer pathophysiological examination of each disease, i.e., a great similarity exists between the two disease states. Functionally, the long-term and acute complications of DM (retinopathy, nephropathy, neuropathy, CVD, ketoacidosis, hyperglycemic hyperosmolar nonketotic syndrome, and hypoglycemia) can be sequelae of either phenotype.

Beta cell dysfunction vs insulin resistance is often perceived as the pillar supporting the division between DM1 and DM2. It is generally accepted that DM1 is the result of autoimmune destruction of insulin-secreting pancreatic beta cells. Hence, a singular crime, albeit with multiple suspects, leads to DM1. It was suggested that beta cell destruction and dysfunction might be central to initiating the progression of DM2 (reviewed by Khan and Chakrabarti [62] and Rhodes [89]). An estimated 41 to 63% lower beta cell volume was observed in lean and obese individuals with DM2, respectively [15], with a selective decrease of beta cell mass and alpha cell increase, which correlated with BMI [108].

It is not clear whether beta cell destruction is an initiating factor leading to hyperglycemia and dyslipidemia in DM2 or an increasing variable responding to hyperglycemia, dyslipidemia, and insulin resistance. For instance, intracellular palmitate was shown to directly induce insulin resistance/impaired glucose uptake by downregulating GLUT4 via protein kinase C (PKC) activation [56], indicating a possible mechanism for hyperglycemia and hyperinsulinemia, independent of beta cell function and insulin quality. Nonetheless, both hyperglycemia [71] and elevated levels of free fatty acids [45] were shown to induce beta cell destruction, although through different mechanisms. Moreover, the mechanism of free fatty acid-induced beta cell destruction appears to be different than cytokine-induced apoptosis [64], which may indicate a unique etiology for DM1 autoimmune beta cell destruction and DM2. Regardless, both DM1 and DM2 similarly present with insulin quality and secretion abnormalities [3], hyperglycemia, hyperlipidemia, and hyperglucagonemia [9, 19], possibly due to beta cell destruction and/or alpha and beta cell miscommunication [67].

## Genetics of DM

Genetic factors exist for the development of both DM1 and DM2, although DM2 demonstrates a greater inheritability than DM1. The susceptibility of pancreatic beta cells to cytokine-, fatty acid-, glucose-, or lipoprotein-induced

destruction may be partly genetically influenced, as the concordance (probandwise) for the DM1 phenotype in monozygotic twins was reported to be 42.9% and only 3.8% in dizygotic twins [52]. Twins (median age of 55 years) with only one member originally diagnosed with DM2 showed a concordance (pairwise) rate of 76% within 15 years of initial assessment; the additional variable of impaired glucose tolerance increased the DM2 concordance rate to 96% [76]. Although susceptibility to the disease state may be partly inheritable, there exists an undeniable link between life style and disease progression, as evidenced by the previously mentioned DM link to body compositional changes, which are correlated with behavioral activities and disease interventions, such as diet and exercise. Current abilities to control genetic susceptibility to DM are lacking. Hence, the ability to control overall exposure of the internal environment to abnormal levels of provocative substances, such as glucose and glucose by-products, is an immediate goal of disease control and prevention.

## Disease progression and complications

The clinical assessment of general exposure to glucose is accomplished by measuring glycation of the A1(c) form of hemoglobin (A1C). A nonenzymatically produced ketoamine or glycation (rather than the enzyme-induced glycosylation) accumulates on A1C over time. Measuring A1C will indicate the average exposure of hemoglobin to glucose over the ~120-day life span of the red blood cell, while principally estimating mean blood glucose over the past 30 days [78]. Clinical tests report A1C as a percentage of total glycated hemoglobin. The current standard target is an A1C measurement <7% in non-DM individuals. Although DM generally leads to A1C above 7%, the measurement per se is not indicative of DM; rather, it is specific for exposure to high glucose, which is associated with micro- and macrovascular complications. Ergo, the American Diabetes Association (ADA) [4] does not consider an A1C measurement a definitive test for DM.

Glycemic control and the interruption of hyperglycemia-induced damage pathways have long been recognized as the most important goals of treatment; inhibition of the micro- and macrovascular damage pathways is frequently the target of DM complication intervention studies. However, not all investigations report significant benefit from interrupting the activation of these (reviewed by Khan et al. [63]) and other [28] pathways. Nonetheless, there is convincing evidence that controlling hyperglycemia and A1C in DM does confer benefit and reduces micro- and macrovascular complications (reviewed by Olansky [81] and Davidson [23]). For example, [90] reported that a high level of A1C was associated with carotid intima-media thickness and other CVD risk factors (e.g., lipid profile and waist circumference). In addition, the joint Canadian–American *Diabetes Control and Complications Trial* (DCCT) (the effect of intensive diabetes therapy, 1995) and the *United Kingdom Prospective Diabetes Study* (UKPDS) have demonstrated that glucose control leads to significant reduction in micro- and macrovascular (heart disease) complications (~30% reduction per 1% reduction in A1C) [24, 25]. Moreover, the ability to control DM-associated high blood pressure has also demonstrated macrovascular/cardiovascular benefit [99].

Several investigations have reported specific biochemical reactions associated with hyperglycemia that may be at the heart of vascular complications in DM (reviewed by Olansky [81]). Conformational changes to red blood cells via glycation may affect movement through the microvasculature and cause damage directly. Possible pestilent pathways include the polyol pathway [11], the advanced glycation end-product pathway [36], the diacylglycerol-stimulated PKC pathway [22], and oxidative stress (reviewed by Pacher and Szabo [82]). The object of their biochemical affections appears to be the endothelium: elevated vascular permeability and basement membrane thickening related to endothelial dysfunction in DM appear to be the result of these adversarial actions (reviewed by Khan and Chakrabarti [62]). As such, latent DM-related complications, including diabetic autonomic neuropathy (sympathetic and parasympathetic nerve degeneration) and especially distal symmetric polyneuropathy (axonal degeneration causing numbness and other paresthesias, often leading to injury and infection and potentially culminating in amputation), may have a common etiology.

Each DM-related complication has unique and staid consequences. Some of the more sinister corollaries, even while manifesting obtrusively, may not always be perceived as a consequence of DM. For instance, half of all amputations are performed in individuals with DM [77]. Seniors are at exceptional risk for DM-related amputation with a threefold increase between the ages of 45–74 and a sevenfold increase for those over 75 years [88]. It was projected that up to 65% of diabetic patients will die from CVD [95]. Moreover, a four- and twofold increased risk for CVD mortality in diabetic women and men compared with nondiabetic women and men, respectively, has long been observed in the scientific community [57]. In younger individuals, the second most common cause of death is acute complications (hypoglycemia, hyperglycemic hyperosmolar nonketotic syndrome, and ketoacidosis), but this is shown to decrease with age, accounting for as little as 2% of mortality between the ages of 40 and 85 years [97]. These data suggest that the vast majority of people diagnosed with DM (including those receiving treatment)

will die from the disease. Hence, the massive accumulation of literature over several centuries has revealed DM to be exceptionally difficult to manage, in spite of clearly delineated, partly controllable mechanisms of glucose regulation. Although DM sequelae are varied and acerbic, common etiology may provide some insight into potentially successful interventions.

## DM and exercise

Physical activity and physical parameters of fitness (muscle mass, fat-free mass, strength, and maximum oxygen consumption) typically decline with age [55], but exercise demonstrates a clear capacity to improve these parameters in seniors [49]. Elderly individuals who show greater fitness levels also demonstrate fewer negative health problems [91]. A previous review has revealed an inverse linear dose–response between exercise volume and all-cause mortality [61]. Similarly, exercise was shown to reduce CVD and all-cause mortality in people with DM in an inverse dose–response manner [60]. Several extensive studies have examined the positive effects of glycemic control on health profiles in DM, including the *Framingham Study* [57], *DCCT* [25], the *UKPDS* [74], the *Kumamoto Study* [92], the *Finnish Diabetes Prevention Study* [69], and the *Wisconsin Epidemiological Study* [66] (the reader is directed to the original publications and to additional reviews [39]). The mechanisms of benefit may include (1) augmented glucose uptake, (2) improved postprandial insulin secretion, (3) lowered hepatic glucose production, (4) increased cellular respiration, (5) elevated resting metabolism via increased muscle mass, and (6) improved lipid profile. Studies examining the effect of exercise on DM in the elderly are remarkably sparse when compared with the extent of DM research in general. In addition, more exercise and diabetes researches conducted in older adults regard prevention rather than treatment. Nonetheless, effects of exercise in the elderly generally follow the same pattern as the effects seen in younger adults, including improved glycemic control, cellular respiration, strength, and blood pressure, increased muscle mass, and greater fat loss. In addition, documented improvements of glycemic control in the aforementioned studies demonstrate that benefits are conferred upon representatives of both younger adults and the senior demographic.

However, not all studies illustrate changes to known risk factors, despite an observed decrease in CVD mortality. Therefore, the protective mechanism of exercise is unclear. Nonetheless, certain variables are correlated with disease progression and therapeutic intervention, such as glycemic control, and should be considered when searching for evidence that exercise may influence disease status. For example, the *UKPDS* and *DCCT* reported that a reduction of A1C of only 1% conferred significant reduction in risk of progression and the development of micro- and macrovascular complications in the entire cohort of subjects (a previous review of these studies suggested up to ~30% reduction per percentage decrease of A1C [85]). Therefore, in spite of the modest number of studies specifically examining exercise-induced prevention and improvements in seniors with DM, it is important to review those studies that measured glycemia and other traditionally related variables and report any changes to DM-related complications in a multitude of study populations.

## Endurance exercise

Several studies revealed a relationship between DM complications and reduced risk factors derived from endurance exercise. A recent study in an aged DM population demonstrated that 1 year of moderate-intensity aerobic exercise led to a decline in BMI, total cholesterol, triglycerides, percent body fat, waist circumference, FPG, A1C, leptin, adiponectin, and C-reactive protein [49]. The magnitude of change was similar in both the aged group and a younger cohort and the beneficial changes were suggested to be derived primarily from weight loss. Endurance exercise in DM patients was also shown to improve exercise tolerance, $VO_{2max}$, A1C (~1%), in addition to improving baroreceptor sensitivity (autonomic function) [70]. Hersey et al. [44] reported increased capacity of oxygen consumption in elderly men and women (70–79 years) after 6 months of endurance training at 75–85% $VO_{2max}$ three times per week.

The subjects in the study by Hersey et al. [43] demonstrated a lowered plasma insulin response to an OGTT and decreased body fat compared with control subjects. In support, Wannamethee et al. [104] reported an inverse relationship between serum insulin levels and physical activity in a prospective study involving over 5,000 individuals (age 40–59 years, employing a ~17-year follow-up) from 24 towns in England, Scotland, and Wales. These investigators also demonstrated an inverse relationship between moderate physical activities, such as sports, once a week or less and more frequent activities (walking or gardening) with CVD and DM. Rahimi et al. [87] noted that another CVD marker (C-reactive protein) was inversely related to exercise capacity in elderly subjects. These researchers also reported that low exercise capacity appeared more frequently in older individuals with DM. It is interesting to note that exercise intolerance was report-

edly symptomatic of cardiovascular neuropathy in DM patients [103].

## Obesity and CVD mortality

Not all exercise studies showed significant changes in body composition or glycemic control. Prediction of CVD mortality in diabetic patients may be better correlated to fitness. Fitness assessment of over 1,200 men with DM (mean age 50±10) demonstrated that low cardiorespiratory fitness and low physical activity were associated with greater all-cause mortality regardless of normally associated risk factors, such as body composition, glucose levels, and baseline CVD [105]. Similarly, in prediabetics, when baseline values for FPG and BMI were adjusted, Pan et al. [83] observed that exercise intervention was able to prevent DM by almost 50%.

Even though a relationship appears between specific risk factors for both CVD mortality and diabetic complications, there appears to be a consistent effect of exercise with or without an observable change to some or all of these risk factors. A recent study of more than 2,300 individuals with both DM1 and DM2 examined the influence of cardiorespiratory fitness on CVD mortality [20]. This study noted that higher levels of fat mass and BMI were associated with lower levels of cardiorespiratory fitness. Even though there appeared to be an association between CVD mortality and traditional risk factors (high blood pressure, plasma glucose, cholesterol, and parental history), at each varying level of body composition (stratified BMI), cardiorespiratory fitness was independently predictive of CVD mortality. Hence, not all studies demonstrate a requisite exercise-induced reduction of all risk factors to positively influence disease progression. Indeed, some trials demonstrate that the effects of exercise on DM are independent of additional risk factors.

It seems reasonable that disease control traditionally attempted to reduce risk factors associated with the multitude of complications inherent in its progression, such as by improving lipid profiles in CVD and glycemic control for micro- and macrovascular complications. As such, nutritional intervention was intuitively incorporated into patient management; hence, exercise intervention studies frequently employed both physical activity and nutritional recommendations, further confounding the effects of exercise on DM treatment and prevention. Regardless, even these studies are equivocal on the beneficial mechanism of intervention. For example, an exercise intervention with the addition of diet control revealed reduced mortality independent of any changes in glucose tolerance or BMI [32]. In contrast, a 1-year study employing moderate aerobic exercise (three to four times a week) and nutritional intervention revealed an improved cholesterol profile (elevated HDL) and a slight decrease of A1C ($\Delta$=0.5%) in insulin-resistant individuals [101]. Therefore, the literature demonstrates that when aerobic exercise is incorporated into a program designed to treat or prevent DM, there is generally a reduction in complications, disease progression, and incidence of DM. However, not all studies report a reduction of risk factors associated with DM complications. Nonetheless, endurance exercise remains intimated with decreased CVD mortality and a reduction in all-cause mortality in DM, while keeping the source of its potency clandestine. Other exercise modalities employed in DM intervention studies may help uncover the consistency of exercise to alter associated risk factors, disease incidence, and progression.

## Resistance exercise

For DM1 and DM2, physical activity and exercise training are beneficial in the facilitation of glucose from within the blood into muscles without the mediation of insulin, thus helping to alleviate the need for exogenous insulin or oral hypoglycemic agents [8]. Resistance training (RT) studies in diabetics started as an alternative modality of training to the precedent aerobic exercise program and were later used in combination with aerobic exercise to seek an optimal training strategy. RT in the older adult is an important training modality useful for combating age-associated, functional declines in muscle strength and endurance (associated with decreased muscle mass and resting metabolic activity) [37, 38], increased insulin resistance [84], decreased flexibility and range of motion [14], and decreased maximal aerobic capacity [42, 50, 51, 109, 110]. Randomized RT and combined aerobic and resistance training (CT) studies with DM2 over the last decade have examined measures of diabetes management (glycated hemoglobin [6, 7, 16, 18, 21, 29–31, 42, 48, 53, 54, 73, 98], FPG [6, 7, 16, 18, 21, 29–31, 42, 47, 53, 73, 98], plasma insulin, and insulin sensitivity [6, 27, 30, 31, 47, 54, 98]), anthropometrical markers of diabetic risk (BMI or weight) [6, 13, 16, 18, 21, 29–31, 42, 48, 53, 54, 72, 98], the response of cellular proteins involved in glucose regulation [27, 47], and indicators of cardiovascular risk (LDL, HDL, triglycerides, and blood pressure [6, 7, 16, 18, 21, 30, 47, 48, 73]).

## RT in the elderly

Of the 13 RT studies reviewed, eight were conducted in older adults with average age between 60 and 80 years [13, 16, 27, 30, 31, 47, 48, 53]. Similarly, among the four CT

studies, two used older adults with DM2 as their sample population [7, 21]. The most commonly measured outcomes were strength (11 out of 13 studies), glycated hemoglobin (11 out of 13), weight (11 out of 13), fasting glucose (8 out of 13), and plasma insulin (7 out of 13). It is interesting to note that despite all of the RT studies demonstrating significant increases in muscular strength, there was a low incidence of significant findings for traditional risk factors for DM-related risk factors. For instance, only four studies found significant decreases in A1C after RT [16, 18, 30, 48]; one study found a significant decrease in weight [30]; three studies found decreased fasting glucose [6, 18, 53]; and only one study found significant changes in plasma insulin levels [6]. Moreover, there were no changes in BMI [6, 29, 31, 42, 53] or aerobic capacity in the studies measuring these parameters [18, 42, 54]. It is of clinical concern that A1C was not significantly decreased in the majority of RT studies. It should be noted that those studies with significant differences in glycated hemoglobin were at least 16 weeks in duration. Within the four CT studies in diabetics considered here [7, 21, 73, 98], three found significant decreases in A1C and fasting glucose [7, 73, 98]. Proportionately, the CT studies were more effective at managing glucose and significantly decreasing A1C.

## CVD risk and RT

As mentioned previously, decreasing the risk of cardiovascular events with exercise is an important part of diabetes management. Unfortunately, the markers of cardiovascular risk are not uniformly improved within the reviewed RT studies. Two of the five studies reported significant decreases of LDL and triglycerides posttraining [18, 48], while one of the five studies found an increase in HDL [18]. Similarly, only two studies found significant decreases in blood pressure after RT [16, 18]. Of the CT studies reviewed, three measured cholesterol and triglycerides, while only one found significant improvement in these measures [7]. This would lead to question whether the training stimulus for the majority of these RT and CT studies was sufficient to elicit beneficial adaptations to the lipid profile and triglycerides, or whether dietary control was inadequate among subjects.

However, there is evidence that a combined endurance and RT program may be an adequate stimulus to affect CVD-related and other DM complication-related risk factors. Balducci et al. [7] were successful at significantly improving both diabetic management and cardiovascular markers. Their yearlong study, using a CT protocol with 62 subjects, found the greatest significant decreases in all examined parameters ($p<0.0001$) of managing glucose and cardiovascular risk factors. The participants exercised aerobically for 30 min at 40–80% of heart rate reserve and performed three sets of 12 repetitions of resistance exercises using free weights and machines at 40 to 60% of the one-repetition maximum (1-RM). Cauza et al. [18] and Honkola et al. [48] were similarly successful in improving glucose control and cardiovascular parameters.

In summary, the effects conferred upon DM progression by endurance and resistance exercise are numerous, and myriad benefits are consistently reported. There are no enough consistent reports that indicate that the positive effects of exercise on DM are directed at any one or more associated risk factors. Nonetheless, there are no apparent reports demonstrating that a well-designed randomized control trial resulted in no reduction of incidence or micro- and macrovascular complications due to DM. Ergo, it is important to emphasize that exercise generally improves health and increases longevity within the diabetic population, and the lack of an unequivocally demonstrable mechanism does not diminish its inherent potency.

## Exercise recommendations

Exercise potency is supported by professional organizations, such as the American College of Sports Medicine (ACSM) and the ADA. The ACSM's *Position Stand* on endurance exercise and DM2 [2] currently recommends that exercise should approximate the volume and intensity recommended for healthy individuals after appropriately progressing from existing levels [61]; that is, progression to moderate intensity aerobic activity leading to the expenditure of approximately 1,000 kcal/week. Similarly, the ADA's *Position Statement* [33] indicates that previous reports showed positive effects on DM with exercise intensities between 50 and 80% $VO_{2max}$, three to four times a week for 30–60 min/session. Moreover, the ADA recommends exercise as a valid DM intervention in the elderly to improve fitness and insulin resistance via endurance training, and for increasing strength and muscle mass via RT.

In support, the ACSM recommends RT as part of a diabetes management strategy to help decrease the risk of associated complications [2]. The ACSM outlines a minimum frequency of twice a week; one set of 10 to 15 repetitions of 8 to 10 exercises incorporating larger muscle groups. The training protocols used within these studies have varied in the number of resistance exercises (3 to 10), repetitions (8 to 20), sets (2 to 6), frequency per week (2 to 5), and intensity (40 to 80% 1-RM). The RT studies showing significantly decreased A1C [16, 18, 30, 48] have used 2 to 3 bouts per week, 2 to 3 sets of 8 to 15 repetitions in 5 to 10 whole body exercises up to 85% of 1-RM

intensity or 10 to 15 repetition maximums for each exercise. The ACSM statement notes that greater intensity and volume of exercise may be of greater benefit for the individual. Based on the reviewed RT studies and the ACSM guidelines for intensity, this may indicate that the maximal intensity achievable, considering adherence to exercise and safety, would provide the greatest training benefit in managing diabetes.

## Considerations

Individuals with DM demonstrate a repertoire of complications and conditions necessitating careful consideration before prescribing an exercise intervention. Blood glucose should be carefully monitored to avoid hypoglycemia during and after exercise. Neuropathies may prevent the detection of lacerations or pressure injuries, which may lead to infection. Hence, properly fitted footwear is imperative. Older DM patients demonstrate diminished postural control [65], which may precipitate balance-related falls. Autonomic disruption may lead to orthostatic hypotension [75], requiring care when moving from prone to supine positions during exercise. Advanced diabetic retinopathy may be exacerbated by high-intensity exercise employing the Valsalva maneuver [1]. In addition, because individuals with DM are more likely to suffer from CVD, a stress test should be performed before prescribing any exercise regimen, whether endurance or resistance. Because both endurance and resistance training are indicated and favorable in the progress and treatment of DM [102], their incorporation into a regular routine seems efficacious.

## Conclusion

The ease with which pernicious diabetic complications manifest alerts the public and scientific communities to the attitudinal and physiological inherency of DM. Statistics reported by the UN [100] project that the world's population will increase from 6.5 billion today to 9.1 billion in 2050 with the senior demographic being the largest growing segment of the population. Thus, as DM prevalence grows with increasing age, the call to arms becomes decidedly urgent and bitter. Although some natural and unalterable propensity toward elevated susceptibility exists with aging, it seems unlikely that all attempts to improve our health and alter our fates will be met with an unforgiving and implacable adversary. Clearly, exercise (the very activity limited by diabetes) reveals that diabetes is a disease willing to be placated. The role of pancreatic beta cells in disease progression is becoming defined; the known biochemical pathways activated by the effects of hyperglycemia, hyperlipidemia, and oxidative stress within the DM patient population are increasingly controllable; and dysfunctions at the level of the insulin receptor and intracellular signaling are becoming progressively delineated. The ability of exercise to improve health and confer physical fitness in a DM environment, in spite of a multitude of injurious sequelae, is evidenced by its reduction of all-cause mortality, CVD mortality, and incidence and progression of complications. Still, the volume of evidence required for our complete understanding of DM and the contribution of exercise to the attenuation of its complications is legion. The mechanistic action on DM attributable to exercise remains opaque and provocatively clandestine, but, by virtue of evidence, remains steadfastly beneficial.

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