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Jameela Banu
The University of Texas Rio Grande Valley

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Diabetes and Physical Activity

Jameela Banu*

Coordinated Program in Dietetics, Department of Health and Biomedical Sciences, College of Health Affairs and Department of Biology, College of Sciences, University of Texas Rio Grande Valley, 1201 W University Dr, Edinburg, TX 78539-2999, USA

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***Corresponding author:** *Jameela Banu, Coordinated Program in Dietetics, Department of Health and Biomedical Sciences, College of Health Affairs and Department of Biology, College of Sciences, University of Texas Rio Grande Valley, 1201 W University Dr, Edinburg, TX 78539-2999, USA, Tel: +956-665-3222; Fax: +956-665-5253; E-mail ID: jameela.banu@utrgv.edu*

Abstract

Diabetes has been on the rise globally. Although many factors contribute to the increasing risk and manifestation of this disease lack and decreased physical activity/ exercise stands out as one of the major factors. Treatment interventions for prediabetic and diabetic patients include diet and lifestyle changes with enhanced physical activity/ exercise. Several types of physical activity are available for these patients but, recommendations have to be made on an individual basis after giving due consideration to the co morbidities and other risks and barriers. Implementation of progressive resistance therapy may be successful in maintaining glucose homeostasis in diabetic patients.

Keywords: Diabetes; Aerobic exercise; Resistance exercise; Myostatin; miRNA; Osteocalcin

Introduction

Recently, there is an increase in the number of individuals diagnosed with diabetes- A medical disorder associated with an imbalance in glucose homeostasis. Many factors contribute to this condition and one of the most important factors, in addition to diet, is a lack of Physical Activity (PA)/ Exercise (EX) and adoption of partial or complete sedentary lifestyle. PA is the daily activities an individual performs in addition to planned EX regimens. Interventions that include increased physical activity/ exercise along with medications are highly recommended. However, with several different options available for EX regimens, it is important to select the most beneficial form of EX for individuals, considering the existing lifestyle and co-morbidities. This review focuses on the various factors and mechanisms that are affected by diabetes and physical activity. PubMed and Medline were the databases used to collect relevant literature, and they are compiled and discussed. In addition, the risks and barriers associated with the different types of PA are also discussed.

Diabetes

Diabetes is a medical condition that affects 347 million people around the world. In 2014, the global prevalence of diabetes was estimated to be 9% among adults aged 18 and above [1]. In the United States, in 2012, 29.1 million people (9.3% of the population) had diabetes [2] and diabetes remained the 7th leading cause of death in the US, in 2010. The total cost of diagnosed diabetes is $245 billion in 2012. This included $176 billion in direct medical expenses for emergency care, hospitalization, office visits and medications and $69 billion as indirect costs such as days absent from work, reduced productivity, unemployment due to diabetes-related disability and lost productivity due to early mortality [3].

There are two major types of chronic diabetic conditions identified – Type I Diabetes Mellitus (T1DM) and Type II Diabetes Mellitus (T2DM). A temporary diabetic condition is also seen during pregnancy in some women and is termed gestational diabetes mellitus. Diabetes, in general, is characterized by increased circulating blood sugar and uncontrolled diabetes. These adverse effects lead to many complications that affect several organs like skin, eye, kidney, heart, nerves, bone, etc. resulting in ketoacidosis, high blood pressure, stroke and severe Diabetic Neuropathy (DPN) of the extremities [4-7]. DPN affects predominantly the distal segments of the lower limbs impairing walking and daily activities [4,7]. In addition, diabetic patients have decreased skin thickness, increased skin hardness, thickened tendons, muscle atrophy, impairment and activation delays, and decreased bone mineral density, limited mobility at joints, less thick fat pad and gait changes [8-14]. The severity of the complications advances with age and adds to the complications of the normal aging process.

Muscle strength of the upper and lower body correlated with measures of diabetic complications especially with sensory and autonomic functions [6]. Loss of muscle strength is associated with atrophy of ankle and foot muscles due to denervation caused by loss of motor axons combined with insufficient innervations [15]. Also, Peripheral Arterial Disease (PAD), due to diabetes, may aggravate muscle weakness and atrophy of limbs including the upper limbs [16] where handgrip strength decreased with age [8].

T1DM is usually diagnosed in children and is characterized by

a lack of insulin due to non-functional or destroyed pancreatic β cells. The auto-destruction of β cells [17] is controlled genetically. In addition, T1DM patients have greater utilization of fatty acid and oxidation as well as, decreased glucose utilization [18]. The kidneys are overworked in T1DM patients, as these patients have higher hyperfiltration rate due to increasing glomerular hypertension in the kidneys [19] and undergo diabetic nephropathy [20]. However, only 5% of all the individuals diagnosed with diabetes are diagnosed with T1DM, which is about 1.25 millions of Americans [21].

T2DM, on the other hand, is seen in adults and older individuals. These patients usually develop insulin resistance (IR) as underutilization of insulin leads to increased circulation in the blood resulting in decreased production of insulin, and eventual failure of β cells [2]. A Majority of the total number of patients diagnosed with diabetes 90-95% is T2DM [2].

Actually, IR starts before β cell damage and shut down of the pancreas [22-27]. For insulin-dependent glucose transport, insulin first binds to the insulin receptor on the plasma membrane and triggers the signaling pathway to mobilize glucose from the cells. After insulin binds to its receptor, Insulin Receptor Substrate-I (IRS-I) is phosphorylated and this activates Phosphoinositide-3 Kinase (PI3K) and protein kinase B (Akt), leading to translocation of glucose transporter 4 (GLUT4) to the membrane and subsequent transportation of glucose into the cells. In the case of IR, IRS-1 phosphorylation is defective so is the activation of PI3K and Akt [2], therefore, GLUT4 is not translocated to the membrane, thus, decreasing the uptake of glucose into the cells. This leads to dysfunction in skeletal muscle with (a) IR in the muscles [28]; (b) buildup of intramuscular triglycerides [29,30]; (c) impaired mitochondrial function [2,31]; (d) impaired glycogen synthesis; and (e) lipid accumulation around and within the muscles [2]. Several factors cause IR, such as inflammation, reduced mitochondrial content or dysfunction mainly by accumulation of lipid intermediates in skeletal muscle [32]; reduced insulin signaling leading to decreased insulin-stimulated GLUT4 translocation and aging [33].

In diabetic individuals, muscle function is compromised. Muscles are influenced greatly, by the levels of Myostatin, a protein that inhibits muscle differentiation and growth [34-37] and attenuates muscle fiber protein accretion [38-40]. Myostatin has direct metabolic effects on other tissues like adipose and liver as well [41]. In T2DM, there is an increase in the mRNA levels of Myostatin [42], and this is inversely related to insulin sensitivity which directly influences glucose uptake and utilization in a cell-specific manner [41]. Myostatin also affects glucose uptake indirectly, through Tumor Necrosis Factor-α (TNF-α) expression, which antagonizes insulin-mediated glucose uptake [43]. In addition, mutations in Myostatin gene and impaired Myostatin protein leads to increase in muscle mass in animals and humans [39, 44-46].

Diet plays an important role in manifestation, establishment, and progression of diabetes. As glucose metabolism is affected, it is very logical to focus on carbohydrate intake in diabetic patients and has been the practice for a long time. Interventions on regulating carbohydrate intake reduced circulating glucose levels. However, there is increasing evidence pointing towards the role of excessive intake of fats also leading to IR. T2DM patients show increased levels of fat uptake soon after meals [47]. Lipid accumulates in adipocytes within muscle tissues and fibers [48] which are one more factor that can cause IR [30,49]. In addition, chronic overload of calories with increased adiposity also leads to IR [50] and hypocaloric diet reduces both fat and lean mass [51]. IR, in the skeletal muscles, also develops when there is increased H_2O_2 production in the mitochondria as a result of acute and chronic intake of high-fat diet [52]. Moreover, high-fat diet-induced IR and glucose intolerance was decreased in mice that had mutated Myostatin along with decreased TNF-α level in muscle and adipose tissue [53]. Therefore, myostatin down-regulation may be beneficial to diabetic patients.

Diabetic patients also exhibit a faulty energy balance. This is attributed to decreased mitochondrial density, size and ultrastructure [54], and impairment of the oxidative capacity of mitochondria in the skeletal muscle [55]. The Electron Transport System (ETS) housed in the mitochondria, and responsible for producing most of the energy molecules-Adenosine Triphosphate (ATP), is also impaired [56]. The hydrogen molecules that are necessary for ATP production enter the ETS from the TCA cycle and β oxidation through Nicotinamide Adenine Dinucleotide (NAD). Higher levels of reduced Nicotinamide Adenine Dinucleotide (NADH) production from the Tricarboxylic Cycle (TCA) and β oxidation are reported from muscle cells of T2DM patients [57]. This results in a buildup of high reducing equivalents in energy metabolism, leading to the accumulation of acetyl-CoA, ceramides, and diacylglycerols which correlate with IR and altered insulin cascades [58].

Oxidative stress is one more factor that may play a role in the development of diabetes [59,60]. Oxidative stress increases with aging [61] and a combination of low intake of antioxidants with decreased PA contributed to the escalation of oxidative stress [52,62]. One of the molecules that contribute to oxidative stress is nitric oxide (NO). Many metabolic reactions in the body are mediated by NO, which is produced with the help of the enzyme Nitric Oxide Synthase (NOS). NOS are produced in several different organs of the body including pancreatic β cells [63]. In T1DM, β cell degradation is associated with NOS, which is associated with increased pro-inflammatory cytokines that induce apoptosis of cells [64]. However, dual effects of NO have been reported. Depending on the NO concentration, anti-apoptotic or pro-apoptotic effects may occur [65]. At high concentrations, excessive NO is detrimental to the β cells and at low concentrations NO protects these cells. It is also important to note that under IR and T2DM conditions, there is increased circulation of NOS inhibitor in the plasma which results in decreased NO production – a natural adaptation of the body to reduce NO production. On the other hand, when there is impaired glucose-stimulated insulin secretion (GSIS), NO production is enhanced [66]. Therefore, normal functioning of the GSIS is necessary, to avoid the deleterious effects of NO. Moreover, insulin can also increase NOS activity [67].

During the last decade, the importance of microRNA (miRNA) in the regulation of metabolism had been brought to light. miRNA are small molecules that play an important role in the eventual expression and translation of mRNA and proteins. They have been implicated in glucose homeostasis and IR as well. Interestingly, miRNAs' are associated with changes in fat mass and IR in children [68]. Silencing certain miRNA's like miR103 and miR107 improved glucose homeostasis and insulin sensitivity while other miRNA's like miR103 and miR107 impaired glucose homeostasis [69]. Glucose tolerance and IR is also modulated by Let-7. Overexpression of Let-7 led to IR [70] and has been found at higher levels in T2DM patients [71]. miRNA's such as miR133a and miR206 were downregulated in T2DM patients and an inverse relationship between IR and miR133a exists [72].

Recently, Osteocalcin (OC), a protein secreted by bone cells and important for bone formation has been shown to play an endocrine role in influencing insulin secretion and sensitivity. Undercarboxylated OC (UnOC) fraction increased insulin secretion and sensitivity and decreased visceral fat in males and females [73]. Increase in serum OC and UnOC levels, improved insulin secretion and/or sensitivity in humans [74,75]. Lack of OC led to glucose intolerance in muscles [76]. Mice, genetically modified to increase UnOC are protected from T2DM and obesity [76]. Injection of OC improved glucose tolerance and insulin sensitivity in high fat fed mice [76]. Mice treated with intermittent OC injections displayed more mitochondria in their skeletal muscles and increased energy utilization. In addition, they were protected from diet-induced obesity, improved glucose handling, prevented the development of T2DM, and liver steatosis [76]. Interestingly, mice lacking OC have decreased β cell proliferation [75]. Therefore, OC may be used as treatment option along with medications, diet modifications, and PA interventions.

Physical activity/ Exercise

Global industrialization is responsible for drastic lifestyle changes in humans. One major drawback is the lack and/or reduction of PA, which is essential for maintaining health and healthy aging. Lack of sufficient daily PA is an underappreciated primary cause of most chronic conditions [77]. Therefore, there is increasing emphasis on maintaining PA and EX regimen throughout an individual's lifetime. PA/EX during childhood influences many organ systems in the body to function and develop normally, in addition to reducing obesity and complications that arise from diabetes. In adults, also PA/ EX is encouraged to reduce the risk of developing several health issues that may arise, during and after middle age. The elderly are more susceptible to frailty, and a daily EX regimen is emphasized to maintain better health, thereby, improving the quality of their life [78]. There are reports of age-related decreases in muscle mass, and EX regimen increased muscle mass and strength as one age [79]. Convincing evidence suggests that sedentary lifestyle increased the risk of cardiovascular disease (CVD) in T1DM patients [80]. In addition, inactive muscles are not capable of removing oxidative intermediates due to insufficient electron transport and results in lipid toxicity [81,82]. Moreover, continued long-term reductions in PA/EX and inactivity are the primary causes of IR [52,83]. Daily PA reversed the risk of development of diabetes in prediabetic patients [52]. Furthermore, muscle loss occurs with aging and there is a decline in aerobic capacity with a dramatic decrease in PA/EX [51,84]. A Normal function of an individual is dependent on sufficient aerobic capacity and muscle strength [51]. Therefore, an increase daily PA and a continuous EX regimen are important to avoid several medical complications including diabetes.

There are several benefits of EX-(a) decreased mortality up to 40%and lower utilization of health care services [85-94]; (b) prevention of Coronary Heart Disease (CHD) [95,96]; (c) decreased lipid levels [97,98]; and (d) body composition [99]. With regular EX, primary and secondary prevention of several chronic conditions including diabetes has been reported [51]. Regular EX also decreased glucose levels and increased insulin receptors effectiveness [100].

EX can be of different types-aerobic EX-involves a large group of muscles. This EX regimen is for extended periods of time and includes multiple repetitions. It also includes endurance EX for both the muscles and heart and is reported to increase mitochondrial abundance and aerobic capacity [101]. On the other hand, resistance EX (REX) involves a movement of high loads using machines or weights or both and the number of repetitions is relatively less [102,103]. This is reported to increase muscle mass in middle-aged and elderly [101]. Both aerobic EX and REX are associated with decreased risk of T2DM. Even a single bout of muscle contraction increased insulin sensitivity in animals and humans [104-113].

Another important fact is that EX can also induce non-insulin dependent uptake of glucose. For example, IR patients show contraction mediated uptake of glucose through calcium and adenosine monophosphate-activated protein kinase (AMPK) [114,115] with an increase in AMPK α 2 mediated glucose uptake after EX [116]. The intensity of EX controls the uptake of glucose and sometimes both pathways may be involved in this. Whole body strength training for 16 weeks shows improved homeostatic model assessment-IR (HOMA-IR) in T2DM Hispanic adults [117] and increased hepatic insulin sensitivity [28].

EX influences NOS, a membrane protein found in the muscle fibers, and is increased in many disease conditions [118,119]. There are three kinds of NOS-eNOS which is co-localized with mitochondrial markers in muscle fibers [118]; iNOS that increased under conditions of inflammation and the presence of pro-inflammatory cytokines [120,121]; and nNOS that is found in the outer membrane of muscle fibers and neuromuscular junctions [119]. During EX, NO production is increased initially due to a burst of the NOS activity [122]. NO production is induced by an increase in pro-inflammatory cytokines due to EX, which supplies oxygen during vigorous EX [123]. Prolonged treadmill EX, also increased protein expression of nNOS and eNOS and the contractile activity of skeletal muscles [122,124,125].

EX is also influenced by miRNA's as they control muscle proliferation, differentiation and apoptosis [126] and regulate the aging process and changes in skeletal muscles [127-129].

During aging, in mice, the quadriceps muscles expressed upregulated miR7, miR206; miR468, miR542, and miR698 while miR124a, miR181a, miR221, miR382, miR434, miR455 were downregulated [130]. In Rhesus monkeys, miR15a, miR18a, miR144, and miR451 were up-regulated and miR181a/b was downregulated with aging [131]. Both aerobic EX and REX influenced the expression of different miRNAs. During aerobic EX miR181, miR1 and miR107 are up-regulated and miR23 is downregulated in mice [132]. But in humans, miR1 and miR133 increased before EX, rather than after EX [133] in several muscles. REX down regulated muscle specific miR-1 and miR133a, in mice [134]. In humans, miRNA up-regulation and downregulation was reported based on responders with reference to hypertrophy of vastus lateralis muscles [135]. Downregulation of miR26a, miR29a and miR378 was reported in low responders with upregulation of miR451. There were 15 other miRNAs' that were not affected by REX. These miRNA's may modulate yet another pathway-the mammalian target of rapamycin (mTOR) signaling pathway, which is activated during muscle protein anabolism and REX [135]. REX also increased insulin-like growth factor-I (IGF-I) and decreased miR1 which may result in increased muscle cross-sectional area, in elderly men and women after EX [136]. In addition, EX also increased UnOC this had potentially positive effects on glucose tolerance [73].

Impact of exercise on diabetes

T1DM: In T1DM individuals, aerobic EX maintained glycemic control and decreased the amount of insulin required to maintain circulating glucose levels, although HbA1cdid not change [17]. After EX, insulin in pancreatic β cells increased and insulin secretion by the pancreas also enhanced. It also stimulated the uptake of glucose by muscles and supported muscle contraction. In addition, muscle cells were protected from oxidative damage [137-142]. Short term and long term aerobic EX also increased GLUT4 [142,143] which is required for glucose transport into the cells.

NOS is highly influenced by EX. Interestingly, although GLUT4 mediated transport of glucose is independent of NO, NOS activity enhanced glucose transport and the NOS inhibitor-L-NG-Monomethyl Arginine (L-NMMA) attenuated glucose uptake [124]. At low concentrations, NOS can positively influence insulin secretions while at high concentrations it may have a negative influence on pancreatic β cells and inhibit insulin secretion [63]. Therefore, TIDM patients may have to increase the intake of the diet containing anti-oxidants, before EX, to counter the production of NO.

EX is an indispensable component of treatment for patients with T1DM [144]. Even low-intensity EX helps [17] and Stretching EX decreased T1DM neuropathy and pain [145]. However, it has been reported that moderate EX helped in declining glucose levels rapidly during the exercise and slowly reversed back after the exercise when compared to high-intensity EX and REX [146]. High-intensity EX programs showed great improvements in insulin response to oral glucose load compared to lower intensity aerobic EX [147]. Therefore, the overall impact on circulating glucose levels were attained more with intermittent moderate EX and some high-intensity EX.

T2DM: In insulin resistant middle-aged men, aerobic EX decreased muscle and plasma myostatin and this strongly correlated with insulin sensitivity and diabetic patients [148]. In mice, there was decreased the circulation of myostatin, insulin and glucose levels [148] after EX, which decreased IR. Aerobic training increased insulin sensitivity in T2DM patients [149,150]. In addition, aerobic EX in T2DM patients reversed advanced glycation in kidney and ameliorated the early signs of diabetic nephropathy [151]. Kidney function is also influenced by EX. There are reports that there is reduced glomerular mesangial volume and decreased albumin excretion, a level of lipid peroxidation and fibrogenesis in glomerular mesangium [152-154]. Moreover, improved cardiac function may also protect kidney function after EX [155]. Aerobic EX showed increased glucose disposal rate in these patients [156]. In addition, treadmill EX in rats increased insulin sensitivity, improved insulin-mediated capillary recruitment in combination with augmented muscle glucose uptake [137].

Endurance training in T2DM individuals increased the expression of GLUT4 protein and mRNA [157,158]. EX also decreased glucose-stimulated insulin levels [159] and myostatin [41]; especially high bouts of Endurance EX decreased myostatin mRNA levels [160,161]. Furthermore, myostatin null mice displayed decreased endurance performance and energy is regulated by increased mitochondrial enzymes such as citric synthase and succinate dehydrogenase [162,163]. An important fact is that levels of myostatin mRNA is different depending on the time after EX [164]. Another way REX can influence muscle maybe by decreasing skeletal muscle myostatin mRNA expression and plasma protein levels [165-170]. However, some reports on REX did not show the same benefits [171,172] and this may be due to differences in the experimental protocols such as - terms of rest, repetition, a number of contractions, intensity, training state and biopsy sampling time.

Many benefits of REX have been reported in T2DM patients. In addition, to decreasing neuropathy and pain, REX improved the glycemic index, HbA1C, adiposity and muscle strength [145,173,174], it also reduced fasting insulin, increased insulin sensitivity, glucose disposal rates and improved glucose tolerance [175-179]. REX increased glucose uptake in muscles by increasing and translocating GLUT4 to the plasma membrane [180]. In addition, REX also increased skeletal muscle cross-sectional area, muscle cell mitochondria [181] and improved mitochondrial function [182-184].

Risks and barriers of EX: Many patients have reported several difficulties in fulfilling the EX regimens recommended to them. Some of the problems they face may include allocation of time; work schedule, weather, proximity and access to facilities, lack of motivation [185]. Among those who have low economic status, several psychological factors, like embarrassment and fear of failure, negative body image and chronic disease stigma that needs vigilance during PA/EX (especially among T1DM

patients with fear of hypoglycemia) [186] are also barriers that contribute to non-compliance. Other obstacles include numerous intrapersonal reasons like lack of energy, lack of time due to other leisure activities and perceived competencies, as well as interpersonal reasons such as family, friend peer support, environmental/organizational factors, opportunity, resources, etc. [77,187-189].

Although PA/EX is recommended for healthy living, it is associated with several risks as well. Usually high intensity, as well as rapid increase in intensity is detrimental for the patients. One very dangerous side-effect is the late onset of hypoglycemia after EX, especially in T1DM individuals. Aerobic EX caused acute risk of hypoglycemia [190], while intermittent and REX had the lowest likelihood of hypoglycemia [185,191]. Another important physiological change is that moderate and exhaustive EX may generate oxidative stress, which can enhance IR [192]. Therefore, when interventional methods are recommended, a combination of several factors such as intensity of EX and co-morbidities including CVD, stroke, etc. should be taken into consideration.

Summary

In order to successfully reduce the risks of diabetes in humans and maintain a healthy life with diabetes, significant multiple lifestyle changes seems to be the best approach [193-199]. These changes include diet modifications and PA/EX with medicines [200,201]. Consumption of decreased carbohydrates and fats, with the inclusion of moderate to high amounts of fiber, will be the major dietary changes for prediabetic and diabetic patients.

Diet adjustments should accompany changes in PA/EX as well. Both T1DM and T2DM will benefit from these changes. Although T1DM patients may have to continue taking insulin, the amount of insulin can be reduced significantly. Regular EX is important as it reduced HbA1C in T1DM [185], however, moderate caloric restriction intake with PA reduced fat mass [202] can be beneficial too.

T2DM patients may benefit more extensively with diet and lifestyle changes. Non-diabetic children of T2DM and IR T2DM patients showed decreased insulin sensitivity, muscle mitochondrial density, mitochondrial electron transport and insulin-mediated skeletal muscle glucose uptake [22,23,56,203], putting them at high risk of developing diabetes. Such individuals can delay the onset of diabetes by increasing their PA/ EX. Independent of the type of EX, both prediabetic and diabetic patients showed benefits with increased PA by improving insulin sensitivity and maintaining glucose homeostasis. Moreover, the habitual physical activity may prevent and postpone non-insulin dependent diabetes [100]. Aerobic EX is good, so is repetitive EX [204]. The overall an increase in PA, increased post-receptor insulin signaling increase in GLUT4 mRNA and protein levels [63,157], glucose synthase [205], hexokinase [206], β cell function [146], An influx of glucose to muscles, enhanced muscle capillarization and blood flow [207,208]. Increased blood flow, stimulated NO which induced smooth muscle relaxation and vasodilation [209]. However, REX may be better than aerobic EX, and may result in program retention and success of the interventional objectives [185].

As mentioned earlier, EX can affect several pathways to maintain glucose homeostasis. Apart from increasing insulin sensitivity and mobilizing glucose into the cells, it can influence the insulin signaling pathway through miRNAs' to stimulate glucose uptake. Another protein that is impacted due to EX is OC, which increased insulin secretion, sensitivity, and mitochondria in the muscles, thereby, affecting the energy balance which is disrupted in diabetes [75].

Conclusion

In conclusion, it is established that people with moderate to high levels of EX have lower mortality rate and utilization of health care services. However, physical fitness is dependent on nutritional status, dietary and smoking, genetics, socio-economic factors and PA. In addition, it also depends on pulmonary and muscle function health status of other organ systems, medications, and orthopedic limitations [77,210]. To have attainable goals, which may be more pleasant and an inspiring experience [211], graduated physical activity with small increments and long term goals on the health is recommended [61]. Therefore, progressive resistant therapy (PRT) is safe and an effective EX regimen, which [212] promotes favorable energy balance and decreased visceral fat deposition with an increase in basal metabolism and activity will be more beneficial. It also improved insulin sensitivity and glycemic control. More importantly, it is safe for frail elderly individuals and patients with co-morbidities like CVD and obesity. Moreover, PRT increased glucose disposal rates, glycogen storage capacity, GLUT4 receptors in skeletal muscle and insulin sensitivity [212]. However, it is important to have good glycemic control for EX to benefit [17].

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Declarations

The author does not have any conflict of interest. This is a review and did not involve animals or humans.

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