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Review Article

Physical Activity and Its Impact on Diabetes

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Abstract: The current wave of the diabetes epidemic has become a global public health issue. Multiple strategies have been studied in trying to curb the menace and promising among these is lifestyle intervention which includes regular physical activity. During physical activity there is an accelerated utilization of substrates particularly stored triglycerides by the muscles thereby improving insulin sensitivity and this is valuable in the prevention of diabetes. On prolonged exercise blood glucose is derived from the breakdown of glycogen and from non carbohydrate substrates via gluconeogenesis. Exercise has a positive effect on diabetes co-morbidities e.g. obesity, hypertension, dyslipidemia as well as all-cause mortality. Regular physical activity mediates molecular events in the various pathways of diabetic complications like exerting anti-inflammatory effects to combat the chronic subclinical inflammation, fortifying the body antioxidant defense systems and reducing the formation and effects of advanced glycation end-products. The maximum health benefits of exercise are obtainable when done regularly and guidelines are available for the general public and individuals with diabetes on how to achieve these benefits. Finally, the emphasis on the importance of physical activity does not exclude the principle that patients with diabetic complications should seek expert counseling before embarking on an exercise program because some activities might be risky for this group of patients.

Keywords: Diabetes, Exercise, Physical Activity, Complications

1. Introduction

The emergence of the diabetes epidemic is linked to the enduring physical inactivity that is prevalent in modern human societies. The diabetes burden has more than tripled in the last three decades largely due to the unfolding environmental modification that is increasingly becoming antithetical to human energy expenditure. Technological advancement has engendered a sophisticated built environment that by necessity relegates physical exertion in occupation, transportation, leisure and domestic activities; hence the proliferation of lifestyle diseases. Inactivity is an unequivocal risk factor for diabetes and the antidote remains physical activity, yet individuals with diabetes are less physically active. The growing realization of the fundamental role of exercise in managing diabetes is a delightful development and seemingly indicates a potential pathway for the eventual decline in prevalence of diabetes. This article is an effort to reinforce the existing knowledge of how physical activity aids the prevention of diabetes, improve glycemic control and exerts inhibitory effects on the pathways of diabetic complications.

Definitions

The terms physical activity and exercise are often used inter-changeably and that will be the approach in this article. Physical activity refers to the summation of the entire activities requiring the movement of skeletal muscles which includes occupational, domestic, recreational and others. It is defined as any bodily movement produced by skeletal muscles that require energy expenditure [1]. Exercise is a form of physical activity that is planned, structured and repetitive for the purpose of improving or maintaining physical fitness [1, 2]. It is used to improve health, fitness and as a means of physical rehabilitation [3]. The conditioning provided by exercise has both physical and physiological dimensions.

2. Substrate Utilization During Physical Activity

The major sources of energy for the exercising muscles are fatty acids and carbohydrates (CHO) [4]. The contribution from protein is minimal [4]. Free fatty acids (FFAs) utilization starts with commencement of a bout of exercise and continues as long as the activity is submaximal in intensity and duration [5, 6]. As the activity approaches maximum intensity (VO_2 Max) and prolonged duration there is a shift towards CHO as the major substrate [5]. Serum FFAs are readily oxidized in the muscle mitochondria for ATP production. FFAs are equally mobilized from triglycerides stored in the muscle and adipose tissues [6]. The adipose tissue is a major reserve for triglycerides. Lipolysis of triglycerides provides a stream of FFAs for muscle utilization during physical activity and preserves glycogen stores to prevent early exhaustion [7]. As the intensity of the activity becomes maximum or the duration becomes prolonged, blood glucose is maintained by gluconeogenesis in addition to hepatic and muscle glycogenolysis [8, 9]. This allows strenuous activity to continue without hypoglycemia. Gluconeogenesis essentially entails the synthesis of glucose from non CHO precursors i.e. glycerol, amino acids (e.g. alanine) as well as lactate that accumulates from anaerobic glycolysis. In the liver and muscle, glycogen phosphorylase is activated which is the rate limiting enzyme in glycogenolysis [10]. At rest this enzyme exists in the inactive b form but it is phosphorylated to the active a form during exercise by phosphorylase kinase [5]. Depletion of glycogen stores inevitably results in fatigue. Endogenous insulin production progressively reduces during exercise [11] while blood levels of glucagon and cathecolamines are increased [12, 13]. These counter regulatory hormones stimulate lipolysis, gluconeogenesis and glycogenolysis by acting on key enzymes involved in these metabolic pathways e.g. activating glycogen phosphorylase while inhibiting glycogen synthase. Besides intensity and duration, substrate utilization also depends on training adaptation. Regular endurance exercise conditions the body to a more gradual utilization of stored CHO with the tendency to successively prolong the onset of exhaustion in subsequent episodes.

3. Exercise and Insulin Sensitivity

Insulin resistance is the fundamental physiological alteration in type 2 diabetes because insulin is produced by the pancreatic beta cells but the target tissues i.e. muscles and adipose tissues fail to respond and undertake insulin mediated actions. Insulin promotes glycolysis by stimulating hexokinase/glucokinase and enhances glycogen formation by activating glycogen synthase. It promotes lipogenesis in the adipose tissues by activating lipoprotein lipase [14]. Skeletal muscles account for a major proportion of body energy expenditure and hence glucose disposal. Thus, insulin sensitivity is a cardinal physiologic characteristic of muscles functioning optimally. Exercise promotes insulin sensitivity by provoking glucose uptake in the muscles. Muscles contain Glucose transporter type 4 (GLUT-4) [15], an insulin stimulated glucose transporter that carries glucose into the cells by facilitated diffusion. The expression and subsequent translocation of GLUT 4 to the cell membrane where it takes up glucose and transports it into the cells is upregulated by exercise [16]. The quantitative aggregate of the GLUT 4 molecules present in the cells correlates directly with the glucose uptake ability [5] and insulin sensitivity. GLUT 1 is also involved in the transport of glucose in the muscles but its contribution is modest [5].

During exercise, the elevation of AMP (Adenosine monophosphate) activated protein kinase (AMPK) results in inactivating phosphorylation of the TBC1D1 which is an inhibitory molecule [17]. This inactivation ensures that GTP (Guanosine triphosphate) reacts with Rab proteins in the GLUT 4 vesicles which lead to amplification of vesicular translocation [18]. AMPK is also thought to play a role in fatty acid oxidation and enhanced mitochondria oxidative capacity [19]. Studies focusing on the molecular mechanisms of exercise induced insulin sensitivity have identified insulin receptor substrate 1 & 2 (IRS 1&2), adiponectin and IL-6 as potential molecules of interest [17, 20]. Postulated physiological mechanisms for exercise induced insulin sensitivity include increased skeletal muscle cappilarization, enhancement of beta cell activity as well as exercise induced reduction in intracellular adhesion molecule 1(ICAM 1), C-reactive protein (CRP) and serum amyloid A (SAA) [19].

The effectiveness of exercise as a means improving insulin sensitivity is extensively documented. However, research findings in regards to the persistence of this occurrence in the post exercise period are equivocal. The length of time that insulin sensitivity lasts after a single or cumulative bouts of exercise is variable. An accelerated insulin independent glucose uptake which lasts for about two hours [21] occurs following a bout of exercise and it is believed to be due to increased presence of GLUT 4 in the plasma membrane and T-tubules [22]. This observation can be replicated with electrical stimulation of skeletal muscles. The waning of this transient phase is followed by a more prolonged sensitivity of glucose transport to insulin which also gradually declines as glycogen supercompensation builds up [5]. Another exercise induced adaptive response of skeletal muscles to glucose utilization is increased muscle mitochondria which improves glucose and fatty acid oxidizing capacity [23]. Newsom et. al. demonstrated increased insulin sensitivity a day after a single episode of modest exercise in a group of sedentary obese adults [24]. Both Heath et. al. and King et. al. had initially reported a reversal of increased insulin action after ten days of inactivity in trained individuals [25, 26]. Although, insulin sensitivity was restored to initial level after the resumption of training. However, Bajpeyi et. al. showed that insulin sensitivity was still increased 15 days after cessation of moderate intensity exercise in a cohort of previously sedentary obese individuals who participated in an eight-month exercise program [27]. In the presence of weight loss, insulin

sensitivity can be maintained for two to three years provided the weight is not regained [28].

4. Physical Activity and Diabetes Prevention

The Diabetes Prevention Program (DPP) was a landmark randomized control trial that investigated the relationship between lifestyle intervention i.e. physical activity and diet, and development of diabetes [29]. The physical activity schedule was 150 minutes of moderate intensity for high risk groups. Conducted across 27 centers in the US, participants were randomly assigned to lifestyle intervention, metformin and placebo groups. The results showed a 58% reduced risk of diabetes in the lifestyle intervention group, followed by 31% in the metformin group and only 11% in the placebo group [29]. The same result (58% reduced risk of DM) was recorded in the Finnish Diabetes Prevention Study [30] after a follow up of three years. The follow up study to the DPP i.e. DPP outcome study (DPPOS) revealed that the lifestyle intervention arm of the DPP continued to have a delay in developing diabetes by 34% after ten years [29]. The Da Qing Diabetes Prevention Study also randomly assigned individuals with prediabetes into lifestyle intervention and control groups. The result was a 51% lower incidence of diabetes during active intervention and 43% lower incidence over 20 years [31]. The result entertains the possibility that an active lifestyle intervention for a given period can prevent diabetes for a longer period. Another similarly designed Japanese trial involving individuals with impaired glucose tolerance recorded a 67.4% reduced risk in the lifestyle intervention group after four years of follow up [32]. Indeed, these are overwhelming evidences that physical activity plays a remarkable role in the prevention of diabetes.

Enormous metabolic benefits could be achieved in the absence of vigorous activity or so called “gym workout.” A prospective cohort study involving women participating in the Nurses’ Health Study estimated that standing or walking at home for 2 hours a day was associated with 12% reduction in diabetes (95% CI, 7-16%) [33] and each one hour per day of brisk walking was associated with a 34% reduction in diabetes (95% CI, 27-41%) [33]. It further estimated that 43% of new cases of diabetes can be prevented by adopting an active lifestyle. The investigators in the University of Pennsylvania Alumni health study reported an adjusted T2DM risk reduction of 6% for every 500 kcal increment in leisure time physical activity (LTPA) [34]. The protective effect was strongest in those with highest risk for T2DM e.g. obese and hypertensive.

4.1. Glycemic Control

As stated above, both exercise and insulin increase muscle glucose uptake by promoting the translocation of GLUT-4. Although, this is achieved through different pathways. The insulin mediated pathway is impaired in diabetes while the exercise pathway is functional [35]. Hence, it is rational to suggest that regular exercise can partly compensate for the defect in insulin action. Blood glucose (BG) levels and insulin sensitivity improve with moderate intensity aerobic exercise in diabetes and the risk of hypoglycemia is minimal without the use of insulin or secretagouges [36]. Resistance training increases muscle mass and strength which is equally beneficial for BG levels particularly in older people due to age-related decrease in muscle bulk. A sixteen weeks’ resistance training study for older men with T2DM achieved a 46.3% increase in insulin action and 7.1% reduction in fasting blood glucose [37]. Both aerobic and resistance training have been well documented to reduce HBA1c [36]. The American College of Sports Medicine (ACSM) has recommended combined aerobic and resistance training for improved insulin action and BG control [36].

4.2. Cardiovascular Diseases and Mortality

Frequent and intense physical activity has been linked with reduced cardiovascular events in T1DM. In the Finnish diabetic nephropathy study, a higher LTPA, intensity, frequency and duration significantly correlated with reduced cardiovascular events [38]. Gregg et. al. reported that walking for at least 2 hours/week was associated with 39% lower all-cause mortality and 34% lower CV mortality in people with DM [39]. Further reduction in mortality was achieved in those whose walking was enough to increase heart and respiratory rates. Physical inactivity and low cardiorespiratory fitness are independent predictors of mortality in men with DM [40]. In both cases, the risk is almost doubled when compared to physically active men [40].

4.3. Metabolic Syndrome

Multiple studies have demonstrated the positive impact of exercise on the various components of the metabolic syndrome. Regular physical activity is associated with reduced BMI [41], Blood pressure [42, 43] and improvement in serum lipids [43].

5. Effects on the Pathways of Diabetic Complications

5.1. Oxidative Stress

It occurs due to cellular accumulation of reactive oxygen species, a phenomenon that is central to the pathogenesis of diabetic complications. Oxidative stress acts as a converging process for the different pathways implicated in hyperglycemia induced tissue damage [44]. Possible mechanisms for the generation of oxidative stress are influx through the polyol pathway, impaired superoxide dismutase and catalase activity, advanced glycation end products (AGEs) and altered glutathione activity [45, 46]. Although, exercise is linked with acute increase in reactive oxygen species (ROS); regular exercise is nevertheless a proven mechanism by which endogenous antioxidant defenses are upregulated [47]. Hence, the transient increase in ROS is obviated by the sustained

improvement in antioxidant protection. It is noteworthy that oxidative stress promotes lipid peroxidation, protein oxidation and oxidative DNA damage [48], processes that are not peculiar to diabetes but extend to ageing and other chronic diseases. Exercise reduces mitochondria oxidative damage and exerts prominent anti-inflammatory effects which attenuate the generation of ROS. In a rather fascinating manner, the initial increase in ROS during exercise stimulates transcription factors e.g. NF-kB and AP-1 (activator protein-1) which in turn leads to increased expression of enzymes (catalase and superoxide dismutase), repair proteins (Heat Shock Protein {HSP}) and NO by Nitric oxide synthase (NOS) which collectively establish a formidable antioxidant defense [47]. Exercise also stimulates PGC-1α signaling, a transcription factor that is involved in increasing mitochondria oxidative capacity and expression of antioxidant proteins e.g. glutathione perioxidase and SOD-2 [47].

5.2. Advanced Glycation End-Products (AGEs)

AGEs are products of non enzymatic reaction between sugars and protein, lipids or nucleic acids [49]. They play a role in the development of diabetic complications. AGEs also contribute to the ageing process and could be ingested via food or cigarette smoke [49]. Their accumulation is associated with both macrovascular and microvascular complications by enhancing cross linking of matrix proteins e.g. collagen, interaction with renin angiotensin aldosterone system (RAAS) in diabetic kidney disease (DKD); induction of cytokines, adhesion molecules, growth factors and chemokines [49]. Studies evaluating the relationship between AGEs and exercise are scanty. Choi et. al. evaluated the effect of exercise on soluble receptor for AGE (sRAGE) which acts to eliminate AGEs or inhibit ligands that activate RAGE [50]. After twelve weeks of aerobic training sRAGE level was increased along with improvement in several cardiometabolic risk factors[50]. The increased sRAGE also correlated negatively with highly sensitive CRP. Sponder et. al. also demonstrated that long term physical activity increased sRAGE levels [51]. Decreased AGEs in non diabetic females after twelve weeks of lifestyle intervention has also been reported [52]. Given the enormous attention AGEs have attracted in investigating the pathogenesis of diabetes complications, it is crucial that more studies evaluating their relationship with exercise are undertaken.

5.3. Chronic Inflammation

A chronic subclinical inflammatory process occurs in diabetes, a feature that is shared with obesity and atherosclerosis. The serum levels of pro-inflammatory cytokines e.g. IL-1, IL-6 and TNF-α are elevated [53]. In prediabetes, an increased level of inflammatory markers is associated with development of overt DM [54]. These cytokines inhibit processes in the insulin signaling cascade causing insulin resistance and are also involved in pathogenesis of diabetic complications. They act on the liver to increase the production of VLDL and fibrinogen [53]. In addition, the production of acute phase proteins e.g. C-reactive protein (CRP), plasminogen activator inhibitor-1 (PAI-1), serum amyloid A (SAA) e.t.c. is also enhanced by the action of these cytokines on the liver [53]. CRP, a biomarker of systemic inflammation, is a reliable predictor of cardiovascular events [55] and it is elevated in diabetes [56]. Skeletal muscle contraction during exercise releases a certain group of cytokines known as myokines [57]. Prominent among these is IL-6 which in contrast to that of the adipose tissues has a vast array of anti-inflammatory effects [57, 58]. It promotes the release of other anti-inflammatory cytokines e.g. IL-10, IL-1ra while inhibiting the production of IL-1β and TNF-α. It also acts in a sequence that leads to the activation of AMPK with subsequent increase in glucose uptake and FFA oxidation [58]. Moreover, it is thought to play a role in stimulating hepatic glycogenolysis and gluconeogenesis [58]. Multiple large scale epidemiological studies have consistently reported a reduction in CRP in individuals who exercise regularly. Some of such studies are British Regional Heart study, National Health and Nutrition Examination Survey III (NHANES III), Multiethnic Study of Atherosclerosis (MESA), Nurses' Health Study e.t.c [59]. However, the findings indicated that the inverse relationship was dose dependent. Other studies which have examined a broader panel of inflammatory markers including fibrinogen, IL-6, TNF-α e.t.c have further strengthened the evidence that regular physical activity reduces subclinical inflammation [59].

6. Physical Activity Guidelines

6.1. General Guidelines

The United States Department of Health and Human Services recommend that adults engage in at least 150 minutes of moderate intensity or 75 minutes of high intensity exercise or equivalent combination of both moderate and high intensity activity per week [60]. This should be spread out over 3 or 4 days preferably on alternate days. For additional or more extensive benefits, the target should be 300 minutes per week of moderate intensity or 150 minutes per week of high intensity activity or an equivalent combination of both [60]. These guidelines are essentially the same with those of the Australian Government Department of health [61] and the United Kingdom Department of Health and Social care [62]. All the guidelines emphasize the importance of avoiding sedentary behaviors.

6.2. Guidelines for Individuals with Diabetes

The American Diabetes Association (ADA) has released physical activity guidelines specifically for individuals with diabetes [63]. These recommendations are in multiple categories.

(a) Reduced sedentary time: as a principle the amount of time spent on sedentary activities should be reduced. Prolonged sitting should be frequently interrupted with bouts of light activity at least every 30 minutes to improve blood glucose control.

(b) Physical activity recommendation: These are similar to the general guidelines above. In addition, Pre-exercise medical clearance is unnecessary for asymptomatic individuals before embarking on low to moderate intensity activity. Also, supervised exercise programs are preferable to non-supervised.

(c) Pregnancy: Women with pre-existing diabetes are encouraged to participate in regular physical activity before and during pregnancy and those with gestational diabetes should engage in 20-30 minutes of moderate intensity exercise daily or in most days of the week.

(d) Maintenance of activity: behavioral change strategies are required to increase physical activity. Easy targets are initially set and achieved before progressing to high goals. Internet driven interventions may help in achieving required outcome.

6.3. Exercising with Chronic Complications

(a) Neuropathy: Peripheral neuropathy is the most common form in diabetes [64]. It is associated with numbness, parasthesia and varying degree of loss of temperature, pain, touch or pressure sensation [64]. Patients with neuropathy are at risk of diabetic foot ulcer which may lead to amputation [65]. It is thought that patients in this category should avoid high impact activities [66] e.g. running or jogging. Activities like swimming, stationary biking and sitting based exercises appear safer [67]. However, the ACSM have recently recommended that individuals without acute foot ulcers can undertake moderate weight bearing exercises and that moderate walking does not increase the risk of foot ulcer or recurrent ulceration in patients with neuropathy [36]. Particular attention to footwears and feet examination still remains primary while engaging in exercise.

(b) Retinopathy: Physical activities that greatly increase blood pressure, intraabdominal or intraocular pressure [36] like lifting heavy objects are not recommended for patients with proliferative retinopathy. They carry a risk of intraocular hemorrhage or retinal detachment [67]. Low intensity activities like walking or moderate intensity biking are advised.

(c) Nephropathy: Patients with overt nephropathy should avoid vigorous activities due to reduced aerobic capacity and muscle function. Exercise is started at a low intensity and gradually increased to moderate intensity aerobic activity [36].

7. Conclusions

Exercise is an indispensible strategy in the prevention and management of diabetes. The understanding of its efficacy is necessary for health care givers and educators so as to help patients avail themselves of the inherent benefits. The ease with which exercise can be commenced and the fact that it does have variety of positive effects in multiple systems of the body are attractive points to be highlighted. To achieve maximum benefit exercise will have to be done in a consistent manner. Although the inability to sustain motivation is an identified factor militating against exercise adherence, interventions like group or supervised activities have been shown to improve the consistency. Also, well structured health education programs with emphasis on lifestyle modification should be developed and implemented in healthcare facilities in an attempt to prevent chronic diseases.

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