Review Article

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Effect of Physical activity on Insulin Resistance, Inflammation and Oxidative Stress in Diabetes Mellitus

Internal Medicine Section

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ABSTRACT

Diabetes Mellitus is a growing health concern projected to affect 366 million people worldwide by around 2030. Multiple approaches to address this health concern are documented; amongst which increased the habitual physical activity has been shown to be beneficial. Various mechanisms demonstrated show improvement of cellular insulin sensitivity. The interplay between insulin sensitivity and insulin resistance plays a key role in development and persistence of the diabetic state, which can be directly linked to the levels of physical activity. Regulation of adiponectin and leptin levels are also linked to physical activity via reduction of central obesity. Inflammatory markers, free radical reduction and up-regulation of physiological antioxidant processes are also observed in subjects with increased physical activity schedules, all of which play a significant role in the pathogenesis of Diabetes Mellitus.

Key words: Inflammation, Insulin, Oxidative stress, Insulin Resistance, Obesity

INTRODUCTION

Diabetes Mellitus (DM) has affected millions of people worldwide and this count continues to increase at an alarming rate. Estimates show that that the number of diabetics in the world will reach upto 366 million in 2030 [1]. In the US alone, about 9% of the adult population are affected with type 2 diabetes [2]. Many studies have emphasized the importance of physical exercise in preventing type 2 diabetes [3,4,5]. Physical activity along with diet change inhibit or at least postpone the progression of impaired glucose tolerance to overt type 2 diabetes [6]. A meta-analysis of 14 studies showed a clinically significant reduction in glycosylated hemoglobin (HbA1c) in response to exercise in type 2 diabetic population [7]. In type 1 diabetes physical exercise restores insulin sensitivity thus affords better glycaemic control [8,9]. In fact, evidence shows that risk of developing diabetes can be lowered by moderate aerobic exercise [10,11]. In existing diabetics, regular physical exercise combined with diet modifications demonstrate reduction in Body Mass Index (BMI), Increase High Density Lipoprotein (HDL) levels, Decrease Triglyceride (TGL) levels and normalized blood pressure [12,13]. Habitual physical activity also reduces all-cause mortality by reducing the risk of coronary heart disease, stroke and colon cancer [14]. Physical activity also reduces inflammation and protects tissues from oxidative stress both of which play a contributory role in the diabetics. This paper will review the effects of physical exercise on insulin resistance, inflammation and oxidative stress in type 2 diabetes mellitus.

Physical Exercise and Insulin Resistance

Insulin resistance is a characteristic of type 2 diabetes, but it can exist in Type 1 diabetes as well. Insulin resistance describes the inability of a known quantity of exogenous or endogenous insulin to increase glucose uptake and utilization in an individual as much as it does in a normal population [15]. The exact molecular action leads to insulin resistance is not yet understood. Several mechanisms have been proposed to be the underlying cause of insulin resistance. These include: (1) genetic abnormalities of proteins involved in insulin action cascade (2) fatal malnutrition (3) high visceral adiposity. In most patients, Insulin resistance occurs as part of a cluster of cardiovascular and metabolic abnormalities commonly referred to as “The Metabolic Syndrome”, which may contribute to the development of type 2 diabetes. It is well established that acute exercise is associated with substantial improvement in insulin sensitivity. A single bout of moderate intensity exercise can increase the glucose uptake by at least 40% [16]. Several of the early studies observed significant improvements in glucose tolerance [17] and insulin sensitivity [18] in response to exercise training obtained post-training measurements within 12 to 48 hours of the last exercise session. This is supported by the fact that cessation of exercise in trained persons is associated with a marked and rapid decrease in insulin sensitivity [19]. Perseghin G et al., demonstrated that a single bout of moderate intensity exercise could increase glucose uptake by at least 40% [20]. Furthermore, exercise promotes weight loss, which reverses the insulin resistance which is the characteristic of obesity. So the beneficial impact of daily exercise on insulin resistance would be magnified if associated with diminished body fat. Indeed, combined with the fact that modest exercise reduces the morbidity and mortality associated with cardiovascular disease and diabetes, it is an effective therapeutic strategy for reducing insulin resistance and, more importantly, improving overall quality of life and wellbeing [21]. Individuals with diabetes due to insulin resistance can be reversed by habitual physical exercise. As excess adiposity in the waistline contributes to insulin resistance, regular exercise assists in reduction of body fat, thus increasing cellular insulin sensitivity. Glucose uptake remains elevated for up to 120 minutes after physical activity, due to increase in GLUT4 (Glucose Transporter type 4) presence in plasma membranes and T-tubules. Insulin sensitivity increases for at least 16 hours post-exercise. This is observed in healthy individuals as well as subjects with type 2 diabetes [22]. Physical training may also make favorable changes in lipid metabolism and regulate hepatic glucose output, which is important in the type 2 diabetes.

Exercise and Inflammation in Type 2 DM

Inflammation may plays a crucial intermediary role in pathogenesis of diabetes mellitus. Interleukin 6 (IL-6) and C-Reactive Protein (CRP), are two sensitive physiological markers of subclinical systemic inflammation associated with hyperglycaemia, insulin resistance, and overt type 2 DM [23]. Cross-sectional studies have reported increased concentrations of these inflammatory markers

in both the insulin resistance syndrome and overt type 2 DM [24-27]. In a prospective study done with a sample size 1,047 subjects without diabetes, it was found that over five years, there was linear increase in the incidence of new onset diabetes and in the levels of inflammatory markers like fibrinogen, CRP and plasminogen activator inhibitor [28]. Another inflammatory marker, which is thought to play an important role in diabetes, is Interlaeukin 1 (IL-1). IL-1 is a pro inflammatory cytokine proposed to be involved in the autoimmune destruction of Beta cells of pancreas of type 1 diabetes [29]. IL-1 inhibits beta cell function and activates the transcription factor nuclear factor NF kB (nuclear factor kappa-light-chain-enhancer of activated B cells) thus inhibiting beta cell function and promoting apoptosis [30]. IL-1 has also been implicated in the pathogenesis of type 2 diabetes as chronic inflammation contributes to the failure of beta cells to secrete sufficient amount of insulin. Discrete insulitis in type 2 diabetes is thought to be due to the pathological activation of innate inflammatory systems by metabolic stress which is regulated by IL-1 signaling. Interlaeukin 1 production has been noticed in pancreatic secretions obtained from subjects with type 2 diabetes. High glucose levels in the blood increase beta cell production and increased levels of IL-1, which in turn causes functional impairment and causes apoptosis. Role of IL-1 in type 2 diabetes was further confirmed by a study by Claus et al., who demonstrated that IL 1 antagonism resulted in improved glycaemic control in subjects' type 2 diabetes [31]. Adipose tissue increases production of TNF-α (Tumor necrosis factor alpha), which contributes to the insulin resistance. TNF-α and IL-1 also stimulate the production of IL-6 [32]. Regular exercise increases the secretion of anti-inflammatory cytokines rather than pro-inflammatory cytokines like TNF-alpha and IL-1 Beta, which are, contributors to development of diabetes [33-36]. Other anti-inflammatory cytokines that are increased in circulation during exercise are IL-1 ra and s-TNF-R [37,38]. A multi-disciplinary study to reduce body weight in obese women through low calorie diet and increased physical activity demonstrated reduced levels of IL 6, IL 18, CRP (C-reactive protein) and increased levels of adiponectin which has anti-inflammatory and insulin–sensitizing properties [39,40]. Physically active individuals have also reduced leptin levels which is associated with CRP [41]. In obese individuals, omental adipocytes produce more IL-6 and TNF-alpha than do abdominal sub–cutaneous adipocytes consequently causing reduced levels of resting IL-6 and TNF-α, ultimately CRP production [42]. Physical activity also reduces inflammation by improving endothelial function. Exercise reduces peripheral inflammatory markers of endothelial dysfunction such as soluble intra–cellular and vascular adhesion molecules, granulocyte-macrophage colony-stimulating factor [43]. Physical exercise also preserves nitric oxide availability thus improving endothelial function [44].

Exercise and Oxidative stress in Type 2 DM

Oxidative stress occurs when there is imbalance between production of Reactive Oxygen and Nitrogen Species (RONS), often referred to as "free radicals, "exceeds body's antioxidant defense [45]. Oxidative stress has been implicated in causing insulin resistance and β-cell dysfunction. The onset and progression of diabetes is strongly associated with increased production of Reactive Oxygen and Nitrogen Species (RONS). Oxidative stress also plays an important role in pathogenesis of micro and macro vascular complications of diabetes [46,47]. Increased RONS in the circulation promotes oxidation of lipids, proteins and DNA leading to exacerbation of Micro and Macro vascular complications of diabetes [48]. Physical activity plays a key role in regulating the balance between reactive species formation and antioxidant mechanisms thus reducing oxidative stress leads to reduced risk of chronic disease. Interestingly acute exercise causes transient elevations of RONS but provides the necessary stimulus needed for up regulation in endogenous antioxidant defenses [49]. This is confirmed by studies in untrained animals, which demonstrates increased oxidant levels in response to acute exercise [50,51] but long-term exercise counteracts this by causing elevated anti-oxidant enzymes and thus reducing free radicals production [52-57]. Studies on rats also proved that endurance training increases levels of anti-oxidants and antioxidant enzymes in skeletal and cardiac muscles thus protecting from oxidative stress [52-55]. In another study in rats, endurance training produced a 33% increase in glutathione content of muscle. Increase in levels of glutathione peroxidase and superoxide dismutase activity was also noted [53]. In addition to combating oxidative stress, antioxidants also improve insulin sensitivity [57]. Evidence from clinical trials suggests that treatment with vitamin E, Vitamin C, or glutathione improves insulin sensitivity in insulin resistant individuals [58,59]. In summary regular physical exercise may be an effective way in combating oxidative stress in subjects with diabetes and could also delay micro and macro vascular complications of diabetes mellitus.

CONCLUSION

To summarize, physical activity provides tremendous benefit to the diabetic population and is an irreplaceable part of the overall strategy against diabetes. The information reviewed in this article clearly demonstrates multiple mechanisms through which physical exercise has the potential to reduce obesity, reduce inflammation, up-regulate mechanisms governing physiological anti-oxidant generation and drastically increase cellular sensitivity to endogenous, or exogenous insulin. A multi–faceted approach in which patients use a combination of pharmaceutical therapy in conjunction with diet modification with emphasis on nutrition, and controlled caloric intake resulting in decreased body fat percentage is essential. Increased level of habitual physical activity in moderate measure is suggested, which through safe and adequate application has potential to positively impact the health of those with full blown diabetes, insulin resistance and pre-diabetes.

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