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Physical Activity in the Prevention and Treatment of Type-2 Diabetes Mellitus and its Complications- A Critical Review Of Reviews

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ABSTRACT

Background: Physical inactivity was one of the leading risk factors for development of diabetes mellitus. Type-2 diabetes mellitus (T2DM) accounts for 80-90% of persons with diabetes, and is most prevalent in developing countries. **Objective:** The objective of this review paper was to describe the role of physical activity in prevention and treatment of T2DM and its complications. **Methods:** Systematic independent literature search of Pubmed, CINAHL and Scopus was done using keywords physical AND activity and diabetes or diabetic IN title by two testers. Consensus was achieved in presence of the third tester. The suitable citations were identified and selected studies were grouped under prevention, treatment and prevention and treatment, of T2DM. Under each of the three categories, it was further sub grouped into diabetes alone, its associated risk factors or comorbidities and complications. **Results:** Thirty-two reviews were identified and a final 25 were considered suitable for review. Of these, 14 studies were on prevention only; 7 were on treatment only; 2 were on both prevention and treatment; and 2 were guidelines/ consensus statements. From the prevention studies, physical activity reduced the risk of T2DM by 25-35%. From the treatment studies, physical activity not only reduced HbA1c levels but also enhanced social participation and quality of life. **Conclusion:** Regular physical activity such as simple walking for 30min per day for all/most days of the week was shown to prevent and manage T2DM effectively. Physical therapists in developing countries are faced with greater demands for individualizing physical activity prescription for T2DM patients.

Key words: Physical activity; Sedentary lifestyle; Non-insulin dependent diabetes mellitus; Rehabilitation; Physical therapy.

Key Messages: Walking for just 30 min/day was shown to be beneficial in preventing and treating type-2 diabetes from this review of reviews.

INTRODUCTION

The term diabetes mellitus describes a metabolic disorder of multiple aetiology characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both [1,2]. The prevalence of diabetes for all age-groups worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030. The urban population in developing countries is projected to double between 2000 and 2030 [3].

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The microvascular complications of diabetes are termed collectively as "triopathy" which includes retinopathy, neuropathy and nephropathy and the macrovascular complications include peripheral vascular disease, cerebrovascular disease and cardiovascular disease [4].

Four types of diabetes have been recognized; type-1 (beta cell destruction- autoimmune/idiopathic), type-2 (defect in insulin resistance/ insulin secretion), impaired glucose tolerance and gestational diabetes mellitus, type-3 diabetes from specific etiologies and type-4 gestational diabetes [1,2].

Type 1 diabetes accounts for 5% to 10% of all cases of diabetes. Its risk factors include autoimmune, genetic, and environmental factors. Type 2 diabetes accounts for 90% to 95% of all diagnosed diabetes cases [4]. There is a higher prevalence of DM in India (4.3%) compared with the West (1%–2%).5 Prevalence of type II diabetes in India in 1951 was estimated to be <1.5% in urban and <1.0% in rural population. The figures rose to 2.3% and 1.5% respectively by 1975 and to 8.5% and 2.5% by 19916.

Physical inactivity was shown to be an independent risk factor shown to be highly associated with development of diabetes mellitus and associated mortality [7-12]. The etiological factors for physical inactivity involve complex biopsychosocial interaction of anthropometric, cultural and demographic factors [13,14]. Physical activity prescription was considered an inherent therapeutic and preventive strategy in diabetic patient care irrespective of the age [15-17], type [18,19] or presence/absence of complications [20].

Physical activity was part of ancient medicine for generations and one of the primary goals of asanas in therapeutic yoga is to be physically active. The objective of this review paper is to provide evidence for physical activity in prevention and treatment of T2DM and its complications through a systematic literature search of published reviews.

MATERIALS AND METHODS:

Study design: Systematic review of reviews.

Search methods: Independent search was done by two testers using specific search strategy and consensus was obtained on discussion with the third tester.

Search strategy: Search was conducted using keywords 'physical AND activity AND type 2 AND diabetes OR diabetic IN title' in Pubmed, CINAHL and Scopus. Initial screening of obtained citations was done by title and then by abstract to assign suitability for review.

Selection criteria: Reviews on prevention and/or treatment of T2DM by physical activity published in English from 1992 to 2010 that included studies on humans were included. Non-English papers, other types of diabetes and assessment studies were excluded.

Main Findings

A search method for this review was shown in figure-1. Our first-level search yielded 112 citations. After elimination of duplicate citations, we got 32 potentially eligible citations. Of the final total 32 citations [7], were non-English papers and were excluded. The final list of 25 selected reviews was then categorized into three: prevention [21-34], treatment [35-41], prevention and treatment [42,43] and guideline/consensus statement [44,45].

Prevention

Burr et al in their narrative review opined that individualized physical activity prescription as part of a lifestyle modification program was successful resulting from adaptations that occur in multiple tissues like adipose, skeletal muscle, liver and pancreas. Increased insulin sensitivity was an important physiological mechanism that linked changes in body composition leading to improved metabolic health. Additionally regular physical activity also had cardioprotective effects. Physical activity can either be aerobic or resistance types [21].

Qin et al in their systematic review of cohort studies calculated statistical and biological interaction between obesity and physical activity and the risk of type-2 diabetes. All studies showed positive bio-

logical interaction, with inconsistent statistical interaction. They also found that obesity and physical inactivity interacted on an additive scale. This meant that prevention of either obesity or physical inactivity, not only reduced the risk of diabetes by taking away the independent effect of this factor, but also by preventing the cases that were caused by the interaction between both factors [22].

Gill and Cooper reviewed 20 longitudinal cohort studies and presented a consistent picture indicating that regular physical activity substantially reduces risk of type 2 diabetes with a high level of physical activity being associated with a 20-30% reduction in diabetes risk. Data from 6 studies indicated that increasing moderate physical activity by approximately 150 minutes per week reduced the risk of progression among those with impaired glucose tolerance and cardiovascular risk factors to develop diabetes, with this effect being greater if it was accompanied by weight loss [23].

Qi et al reviewed studies that consistently indicated that the regular physical activity during occupation, commuting, leisure time or daily life reduced the risk of type 2 diabetes by 15-60%; and lifestyle intervention, including counseling for physical activity, nutrition, and body weight, can reduce the risk of type 2 diabetes by 40-60% among adults with impaired glucose tolerance and by about 20% among general individuals. Studies also reported genetic association in predisposition to develop diabetes and named genes such as TCF7L2, PPARG, CAPN10, and KCNJ11 [24].

The evidence linking physical inactivity to the future risk of type 2 diabetes is strong, and modification of behaviour is a critical and effective element of strategies aimed at the prevention of this increasingly prevalent disorder. Subgroups that might respond differently could be defined on the basis of characteristics such as age, degree of obesity, family history, ethnicity, and genetic risk. The identification of such subgroups could aid in the targeting of preventive interventions [25].

Jeon et al identified 10 prospective cohort studies of physical activity of moderate intensity and type-2 diabetes, including a total of 301,221 participants and 9,367 incident cases. Five of these studies specifically investigated the role of walking. The summary RR of type-2 diabetes was 0.69 for regular participation in physical activity of moderate intensity as compared with being sedentary. Similarly, the RR was 0.70 for regular walking (typically > or = 2.5 h/week brisk walking) as compared with almost no walkin [26].

Exercise stimulates PGC-1alpha gene expression and increases V O2max, the latter of which relates inversely with type 2 diabetes risk. Consistently, low levels of PGC-1alpha mRNA and nucleotide sequence variation at PGC-1alpha associate with lower level of V O2max and increased diabetes risk. Thus, PGC-1alpha sequence variation may interact with physical activity to modify diabetes risk via changes in oxidative energy metabolism [27].

Epidemiological studies suggest that physically active individuals have a 30-50% lower risk of developing type 2 diabetes than do sedentary persons and that physical activity confers a similar risk reduction for coronary heart disease. Risk reductions are observed with as little as 30 min of moderate-intensity activity per day. Protective mechanisms of physical activity include the regulation of body weight; the reduction of insulin resistance, hypertension, atherogenic dyslipidemia, and inflammation; and the enhancement of insulin sensitivity, glycemic control, and fibrinolytic and endothelial function [28].

Moderate changes in both body weight and physical activity improve the control of hyperglycemia associated with diabetes [29]. To prevent obesity and diabetes there are grounds for recommending the combination of increasing daily physical activity level to a PAL-value of at least 1.8 and reducing dietary fat content to 20-25 energy-% in sedentary subjects, and to 25-35% in more physically active individuals [30].

Recent studies have shown that cardiorespiratory fitness--an objective measurement of physical activity--is a strong predictor of type 2 diabetes. Self-reported physical activity is also associated with decreased risk of developing diabetes [31]. Lei-

sure-time physical activity, expressed in kilocalories (kcal) was inversely related to the development of NIDDM. Incidence rates declined as energy expenditure increased. For each 2000-kcal increment in energy expenditure, the risk of NIDDM was reduced by 24% [relative risk (RR) 0.76, 95% confidence interval (CI) 0.63-0.92] [32].

To maximize success of a diabetes prevention trial, both diet and physical activity should be part of the intervention. The relative importance of diet or physical activity as components of the intervention will vary, depending upon the participant. However, it is critical that compliance with the physical activity and diet intervention be maintained, for this question to be answered. If the intervention is successful, the participants will have made lifestyle changes that have the potential of lasting beyond the closure of the clinical trial [33,34].

Treatment

Balducci et al in their systematic review found that both aerobic and resistance training were shown to produce beneficial effects by reducing HbA(1c), inducing weight loss and improving fat distribution, lipid profile and blood pressure in patients with type 2 diabetes. Mixed aerobic and resistance training was recently shown to be more effective than either one alone in ameliorating HbA(1c) levels [35].

Yates et al in their systematic review found that physical activity and weight loss programs had beneficial effects in preventing type-2 diabetes. The authors also suggested the importance of physical activity behavior change [36].

Johnson et al was involved in a multidisciplinary group towards development, implementation and evaluation of a practical, inexpensive, easy-to-deliver physical activity intervention programs for adults with type-2 diabetes. Their programs used the principles of social cognitive theory (self-efficacy, social support, goal setting, and self monitoring and pedometric feedback). Walking as a physical activity was introduced through "first step program" which was 12-16 weeks in length.

Approximately 6000-9500 steps per day on average (1000 steps in 10 min). They observed that heart rate responses during walking were moderate to vigorous intensity and suggested that walking can be an acceptable form of physical activity as laid out by Canadian diabetes association clinical practice guidelines expert committee in 2003 [37].

Glucose transport into the skeletal muscle is primarily mediated by a membrane-associated glucose transport protein, GLUT4. Physical activity was effective in preventing vascular complications in diabetes through a cascade of events that mainly involves GLUT4, lipids metabolism and endothelial function. GLUT4 activity is enhanced through different metabolic pathways that involve the activation of peroxisome proliferator-activated receptor c coactivator 1a (PGC1a), myocyte enhancer factor 2 (MEF2), GLUT4-enhancing factor (GEF), nitric oxide (NO), insulin and a protein kinase Ca-dependent (cPKC). 5¢-AMP activated protein kinase (AMPK) plays a regulatory role on both PGC1 and NO activity, the latter in turn acts on endothelial function. Glycogen muscle content plays a role of modulator for both AMPK and insulin action. Physical activity is also effective in improving the lipids profile both reducing the level of triglycerides, low density lipoproteins, free fatty acids and enhancing high density lipoproteins with a consequent stimulation of insulin action [38].

Strategies to reduce sedentary behaviours appear to have potential for reducing obesity among children and adolescents. Among adults, strategies that combine diet and PA are more effective than PA strategies alone. Combined lifestyle strategies are most successful for maintained weight loss, although most programs are unsuccessful in producing long-term changes. Evidence suggests that interventions can lead to small but clinically meaningful improvements in glycaemic control, even in the absence of weight loss. A recent study demonstrated that a multifactorial intervention (diet, PA and pharmaceutical) can reduce the risk of diabetes complications in individuals with type 2 diabetes [39]

There is a growing appreciation for the role of

diverse types of exercise, such as strength training, in type 2 diabetes. Although people with diabetes-related complications have been discouraged from exercising in the past, there are a variety of activities that allow for safe exercise in a supervised setting [40].

The effects of resistance training on cardiovascular risk factors to date likely limit its application as an adjunctive therapy for individuals with Type 2 diabetes. The question is no longer "can exercise/ physical activity benefit the individual with Type 2 diabetes?" The answer is yes. Future research needs to refine questions regarding type, dose, and magnitude of effects of physical activity (and its subcategory exercise) on glycemic control, insulin sensitivity, and on risk factors for cardiovascular disease within the context of program acceptability and feasibility [41].

Prevention and Treatment

McGavock et al suggested that daily targets of 60-90 minutes of physical activity and less than 60 minutes of screen time (i.e. time spent in front of a television, computer or video games) were required for the prevention and management of T2DM in youth [42].

Obesity and type-2 diabetes can be considered diseases of physical inactivity. Physically activity protects against type-2 diabetes through its positive effects on weight management and on the metabolic pathways involved in glycemic control that are not weight-dependent. Increasing physical activity is one of the most effective strategies both for preventing type-2 diabetes and for managing it once it is present. A promising strategy is to get people walking more, starting small and increasing gradually over time [43].

Guidelines and/or Consensus Statements

There were two such reviews; one was a guideline44 and other was a consensus/ position statement [45]. Both of these recommend physical activity as a preventive and therapeutic strategy for individuals with T2DM.

DISCUSSION

The review was the first of its kind-review of reviews which provided an extensive information and evidence for physical activity in T2DM. The mechanism by which physical activity leads to glycemic control and prevention of vascular complications was described by Jeon et al [26], LaMonte et al [46] and Agostie et al [38] and could be summarised as follows;

Exercise has been shown to increase insulin-stimulated glycogen synthesis through an increased rate of insulin-stimulated glucose transport by GLUT4 glucose transporters and increased glycogen synthase activity. In addition, elevated capillary proliferation in muscles, increased muscle mass, and a higher proportion of more insulin sensitive types of muscle fibers may contribute to beneficial effects of physical activity on insulin Guidelines and/or consensus statements:

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sensitivity [26].

Biological mechanisms by which physical activity may enhance glucose homeostasis and confer protection against diabetes [46].

Structural changes in skeletal muscle

- 1 fiber size
- 1 percentage of Type IIa fibers (possibly Type I fibers)
- 1 capillary density and blood flow

Biochemical changes in skeletal muscle

- 1 insulin signaling kinetics (1 phosphatidylinositol 3-kinase and GLUT4 activity)
- 1 non-insulin signaling kinetics (1 5_-AMP-activated protein kinase activity)
- 1 enzymes related to glucose metabolism [hexokinase, glycogen synthase, and key oxidative en-

zymes (e.g., citrate synthase, aconitase, succinate dehydrogenase)]
- 1 myoglobin

Systemic influences of physical activity
- 1 oxygen uptake and functional capacity at submaximal and maximal workloads
- 1 lipoprotein lipase and other key enzymes to improve lipemic control
- 2 excessive hepatic secretion of glucose and VLDL
- Improvements in counter-regulatory hormone levels/activity (e.g., cortisol, IGF-I)
- Improvements in comorbid conditions (e.g., hypertension, visceral obesity, systemic inflammation, dyslipidemia).

LIMITATIONS OF THE REVIEW

Lack of quantitative synthesis of the reviews' findings and meta-analysis which may be acceptable due to a huge heterogeneity in included studies in patient characteristics, intervention methods, dosage description and outcomes assessment.

The included reviews used the terms, 'physical activity' and 'exercise' interchangeably. Physical activity- bodily movement produced by the contraction of skeletal muscle that requires energy expenditure in excess of resting energy expenditure. Exercise- a subset of physical activity: planned, structured, and repetitive bodily movement performed to improve or maintain one or more components of physical fitness [47].

According to a well-known epidemiological axiom, the overall disease burden in a given population generally undergoes a more dramatic reduction when a large segment of the population adopts small improvements in health behaviors than when a small segment of the population adopts large improvements [48].

Implications for Practice

Regular physical activity and exercise are important components in the prevention of diabetes. In addition to lowering blood glucose, exercise improves insulin action, contributes to weight loss, and reduces several risk factors for cardiovascular disease. In which physical activity in the form of walking for 30 minutes/day on most days of the week was encouraged [49].

Role of physical therapists

Physical therapists evaluate and treat most patients with diabetes for their comorbid musculoskeletal-related conditions, of the 52, 447 patients referred for physical therapy treatments, approximately 80% had either diabetes, pre-diabetes or diabetes-associated risk factors. The prevalence of diabetes was 13.2% among patients who visited physical therapists [50]. Physical therapists are highly trained and well competent [51] in individualizing exercise and activity prescription for patients towards physical activity prescription [52]. Such an individualized physical activity prescription would facilitate increased patient motivation [53], thereby facilitating a positive behavior change [54] In developing countries like India, physical therapists have a huge responsibility and role to play in improving quality of life of type-2 diabetes patients by providing physical activity programs [55] However, strategic initiatives [56] and progressive policy changes [57] are required for successful implementation of such preventive programs at national level.

Implications for Research

Though few studies showed direct association between physical inactivity and diabetic complications [58], no review was found in our search in the three main databases, which relatively indicate the lesser importance given by researchers worldwide. Studies in our population would provide valuable data for applicability of physical activity programs in such populations.

CONCLUSION

Regular physical activity such as simple walking for 30min per day for all/most days of the week was shown to prevent and manage T2DM and its asso-

ciated cardiovascular risk factors and comorbidities like stroke and obesity effectively

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