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ORIGINAL RESEARCH

# THE ROLE OF PHYSICAL ACTIVITY IN THE PRIMARY PREVENTION OF TYPE 2 DIABETES VIA THE AMELIORATION OF INSULIN RESISTANCE

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**Abstract**
Type 2 diabetes is the most common endocrine disease in our society, affecting around 5% of Western populations, whilst showing a steady rise in prevalence. The complications that arise from the disease are known to cause morbidity and mortality, and are associated with long-term damage, dysfunction, and failure of various organs. These complications include atherosclerosis in the micro and macro vasculature, kidney dysfunction, nerve problems, hypertension; and eye problems such as retinopathy. Epidemiological evidence suggests regular physical activity improves insulin sensitivity. This review presents the case for physical activity as a tool of primary prevention, in the population of non-diabetics and high risk individuals (IFG & IGT), in reference to obesity related insulin resistance. Cross-sectional, prospective cohort and randomised control trials clearly show that moderate-intensity physical activity can improve insulin sensitivity; this can be improved further by undertaking vigorous-intensity physical activity.

**Keywords:** exercise, metabolic, disease, risk,

## Introduction

Diabetes mellitus is an umbrella term referring to a group of metabolic diseases characterized by high blood glucose levels (hyperglycaemia) resulting from defects in insulin secretion, insulin action, or the two combined (American Diabetes Association, 2006). Diagnosis of diabetes is made on display of fasting blood glucose levels of >7mmol/l. There is also a recognised classification which is considered as abnormally high blood glucose levels; between 5.6-6.9mmol/l. Such individuals are categorised as having impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) has been referred to as 'pre-diabetes' due to the increased risk of developing full blown diabetes (American Diabetes Association, 2006).

There are two predominant types of diabetes Type 1 and Type 2. Type 1 is characterised by the auto-immune destruction of insulin-secreting ß-cells of the islets of Langerhans located in the pancreas, and by the production of little or no insulin. This form of diabetes often develops in children, although it may occur at any age and often, but not always, requires insulin treatment. Type 2 develops in adult age and is characterized by insufficient insulin secretion with or without insulin resistance. This form of diabetes usually, but not always, does not require insulin treatment (Pozzilli et al., 2001).

The chronic hyperglycaemia of diabetes is attributed to cause long-term damage, dysfunction, and failure of various organs. These complications include atherosclerosis in micro and macro vasculature, kidney dysfunction, nerve problems, hypertension and eye problems such as retinopathy (Freeman et al., 2006; Kaushik et al., 2007; Park et al., 2008). Additionally the global economic and disease burden associated with diabetes is large and continues to escalate (Zimmet, 2003). In terms of the human cost, nearly 1 million deaths were associated with diabetes worldwide in 2002 (Yach et al., 2004). In the United Kingdom alone it was attributed as the cause of 69,000 deaths per year as of 2002 (WHO, 2004). It is clear from the above that type 2 diabetes is a condition of the upmost concern, in accordance with increasing prevalence, preventative measures are of paramount importance.

**Aetiology of Type 2 Diabetes**

Understanding type 2 diabetes requires an examination at the cellular level. To maintain glucose homeostasis the metabolic action of insulin secretion by pancreatic ß cells, suppression of hepatic glucose production and stimulation of glucose uptake by insulin sensitive tissue is coordinated (Sigal et al., 2004). The major stimulant of glucose uptake is insulin secretion; this process has recently been identified as the insulin signalling cascade, as shown in Figure 1. In response to fluctuations in blood glucose level, insulin is secreted and binds to the transmembrane (α-subunit) insulin receptor of a skeletal muscle cell (the predominant organ in glucose disposal), leading to the phosphorylation of a protein called insulin receptor substrate (IRS). Following activation IRS transduces the signal via activation of the PI3-K enzyme, which results in the production of a lipid termed $PIP_3$. Further activation of the membrane associated enzyme PDK1 stimulates the protein kinase Akt. The final step of the cascade is the passing of the insulin signal to glucose transporter 4 (GLUT4). On receipt of the signal GLUT4 translocates from intracellular vescicles to the cell membrane, resulting in glucose transport into the cell, and thus disposal from the blood (Baudler et al., 2003).

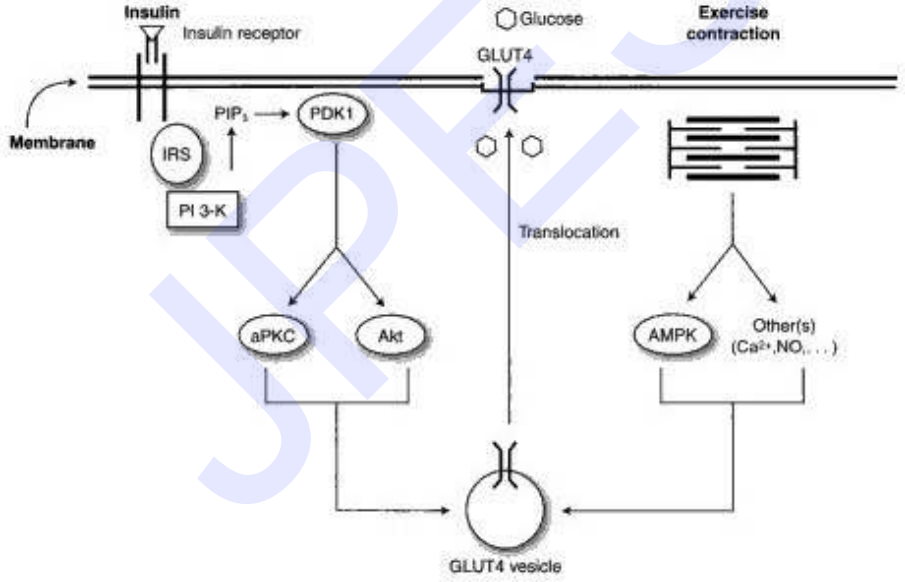


Figure 1. Schematic representation of the Insulin signalling cascade (Bouchard et al., 2006).

Patients with type 2 diabetes or those with 'pre diabetes' display defects in the IRS signalling pathway and the signalling of GLUT4 translocation, thus leading to decreased glucose disposal and a state of hyperglycaemia (Houmard et al., 2004).The pathogenesis of the disease involves a large number of risk factors. Figure 2 illustrates a conceptual model of the processes that lead to the expression of diabetes. At a given level of genetic susceptibility, changes in the regulation of carbohydrate and lipid metabolism are fundamental antecedents to the progression of diabetes. Impaired substrate clearance by skeletal muscle and adipose tissue has been identified as a key aspect of metabolic dysfunction that is associated with insulin resistance and impaired insulin secretion (LaMonte et al., 2005).

This review will present the case for physical activity as a tool of primary prevention, in the population of non-diabetics and high risk individuals (IFG & IGT), in reference to obesity related insulin resistance.

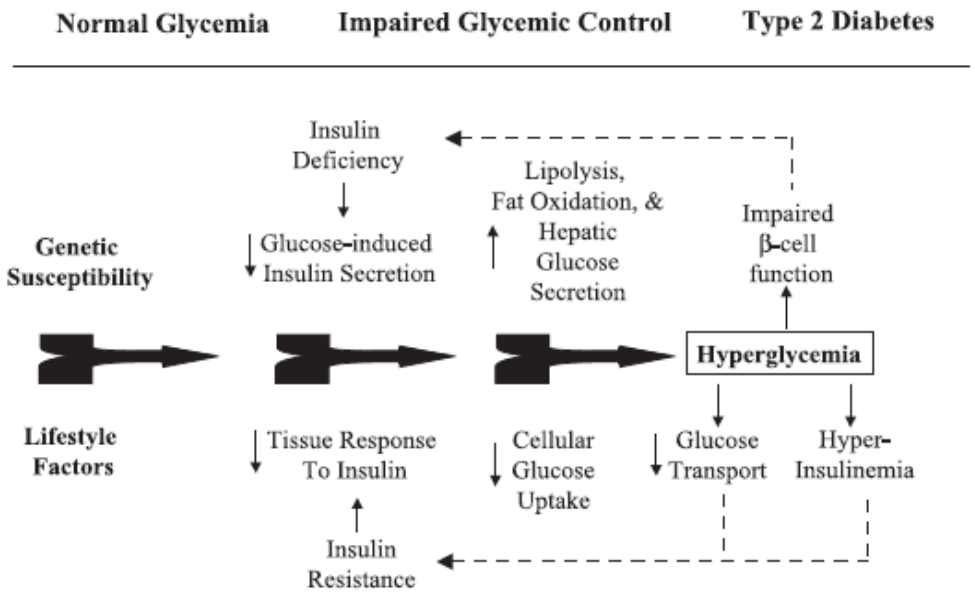


Figure 2. Pathogenesis of Diabetes (La Monte et al., 2005).

**Epidemiological Evidence: Obesity and Diabetes**

Several epidemiological studies report obesity as the central risk factor for diabetes (Mokdad et al., 2003; Rana et al., 2007). A large prospective cohort study (Hu et al., 2001) followed 84,941 female nurses for 16 years. All participants were free of related disease. Data upon their dietary habits, lifestyle and physical activity status was updated periodically. The resultant analysis found that the relative risk (RR) of diabetes increased in a linear fashion with increasing Body Mass Index (BMI) as outlined in Table 1. The study concluded that obesity was the single most important predictor of diabetes.

Table 1. Relative Risk of Type 2 Diabetes in Relation to BMI (Hu et al., 2001).

| Body Mass Index ($kg/m^{-2}$) | Relative Risk (95% CI) * |
|---|---|
| <23.0 | 1.0 |
| 23.0-24.9 | 2.67 (2.13-3.34) |
| 25.0-29.0 | 7.59 (6.27-9.19) |
| 30.0-34.9 | 20.1 (16.6-24.4) |
| ≥ 35 | 38.8 (31.9-47.2) |

* RR adjusted for age, time, family history, menopause, menopause hormone therapy.

Furthermore a recent meta-analysis of 32 studies utilised a random effects model to pool RR scores for all of the studies. This revealed that the RR for diabetes was 1.87 (1.67- 2.10), 1.87 (1.58-2.20), and 1.88 (1.61, 2.19) per standard deviation of body mass index, waist circumference, and waist/hip ratio. This demonstrates a strong association between measures of obesity and the relative risk of type 2 diabetes (Vazquez et al., 2007).

**Obesity and Insulin Resistance**

Higher levels of adiposity contribute to insulin resistance in muscle, liver and adipose cells (Barnard et al., 1992). Recent literature purports that inflammatory responses are associated with obesity and the pathogenesis of type 2 diabetes (Dandona et al., 2004). Indeed recent research shows that prolonged inflammation known as 'low-grade' or 'meta-inflammation' may alter insulin sensitivity (Hotamisligil, 2006). Strong evidence suggests that adipose tissue produces adipokines which modulate glucose homeostasis. The most discussed is tumour necrosis factor-α (TNFα) a pro inflammatory cytokine (signalling protein), produced by adipocytes (adipose tissue cells). TNFα is said to increase the phosphorylation of IRS-1 and inhibit the translocation of GLUT-4 contributing to a disruption of insulin signalling in surrounding skeletal muscle, and ultimately insulin resistance (Schinner et al., 2005).

**Physical Activity and Insulin Resistance**

Current guidelines (Sigal et al., 2004) suggest that to improve glycaemic control at least 150 min/week of moderate-intensity aerobic physical activity (40–60% of $VO_{2max}$ or 50–70% of maximum heart rate) and/or at least 90 min/week of vigorous aerobic exercise (60% of $VO_{2max}$ or 70% of maximum heart rate) is required. Epidemiological evidence suggests regular physical activity improves insulin sensitivity (Skerret et al., 2002). A limited number of studies have been conducted in non-diabetic individuals. One such cross-sectional study reported an inverse relationship ($p$ <.001) between both moderate intensity physical activity and insulin sensitivity (1467 middle aged men and women with and without insulin deficiency). Increases in moderate intensity physical activity of 200k/cal per day were associated with increases in sensitivity of 2.6% in the healthy subjects. After adjustment for BMI and waist-to-hip ratio the relationship was attenuated (1.9%) but still significant ($p$ <.001) (Mayer-Davis et al., 1998). Similarly a cross-sectional study of 142 (40-83 yr old healthy) women found that 30-min increases in moderate-vigorous and moderate physical activity per day were associated with 6.7 and 6.6% lower fasting insulin levels. After adjustment for BMI and central obesity the effect was lowered to 3.4 and 5.2% ($p$ <.05) respectively (Irwin et al., 2000). Saliently exercise contributes to glycaemic control, through increased insulin sensitivity. Interestingly the decreased strength of the relationship upon adjustment for obesity in both studies, suggests that weight loss through increased physical activity may well explain much of the variance in insulin sensitivity levels (Buemann et al., 1996).

However interpreting the inverse relationship detailed in cross-sectional studies is open to the possibility of confounding factors such as disease misclassification and reverse causality (Bassuk et al., 2005). In addition activity questionnaires may more accurately capture actual levels in some groups than others (e.g. normal vs. overweight); clearly altering recorded physical activity data. Finally cross-sectional studies lack the temporal sequence to infer cause and effect, thus prospective cohort and randomised control trials need to be examined. In terms of primary prevention, experimental studies provide the most methodologically robust site for investigation. A study that randomly assigned 154 middle aged non-diabetic men and women to various exercise regimens or to a non-exercising control (over 6 months), found equivalent durations of moderate and vigorous exercise were associated with similar improvements in insulin sensitivity. Compared with sedentary controls, participants who performed 170 min/wk of moderate intensity exercise and those who spent the same time in vigorous activity experienced an 88 and 83% ($p$ <.05) increase in insulin sensitivity; yet these were not adjusted for weight loss (Houmard et al., 2004). In addition those who exercised for 170 min/wk regardless of intensity improved insulin sensitivity compared to those who undertook 115 min/wk, suggesting activity duration may be more important than intensity. These findings are congruent with the guidelines of at least 150 min/wk of moderate activity (Sigal et al., 2004).

Another study randomly allocated 63 apparently healthy sedentary men to a non-exercise control group, a moderate-intensity exercise group (three 400-kcal sessions per week at 60% of $VO_{2max}$) or a high-intensity exercise group (three 400-kcal sessions per week at 80% of $VO_{2max}$). A follow up of 36 subjects found that after 24 weeks insulin concentration decreased by 2.54 (+/-4.09) and 2.37 mU l(-1), (+/-3.35), insulin sensitivity score increased by 0.91 (+/-1.52) and 0.79 (+/-1.37) in the moderate and high intensity groups respectively. Furthermore when data from both groups was combined it revealed that these changes were significantly greater than the control ($p$ <.05) (O'Donovan et al., 2005). The study concluded moderate intensity exercise was actually as effective as high intensity exercise, provided a total of 400kcal were expended. It can be ascertained that total energy expenditure may well have a significant bearing upon insulin sensitivity. Thus similar studies are needed to specify a graded dose response relationship between physical activity and insulin sensitivity.

In relation to the biological plausibility of this evidence, there is significant literature outlining the intracellular effect of physical activity upon insulin sensitivity and glucose disposal. Exercise is associated with increased insulin action on skeletal muscle glucose transport, specifically with increased GLUT-4 expression, possibly related to increased AMPK (Figure 1.) activity (Goodyear et al., 1992; Henriksen et al., 1994; Saengsirisuwan et al., 2002); this facilitates glycogen synthesis by increasing glucose availability. Furthermore hemodynamic adjustments increase capillary surface area in working muscle, increasing the availability of insulin. Few studies have systematically examined the effects of intensity, duration, and pattern of exercise in relation to the acute effects on insulin-glucose dynamics. This mechanism has been addressed in a study of exercise induced GLUT-4 translocation in Type 2 diabetics (Kennedy et al., 1999). Immediately following 45–60 min of cycling at 60–70% of $VO_{2max}$, there was a 74% (+/- 20) increase in plasma membrane GLUT-4 protein in the vastus lateralis muscle, which was nearly identical to the post-exercise increase (71 +/-18%) seen in non-diabetic subjects.

In light of these observations, exercise represents a potent mode of improving an individual's metabolic status. A variety of studies (outlined in Table 2, below) have detailed the protective effects in high risk individuals. For example an experimental study, of 522 middle aged overweight men and women with IGT were assigned to a lifestyle intervention program or control. Those in the intervention achieved a loss of more than 5% body weight, reduced fat intake to less than 30% of baseline and importantly were performing the equivalent of

150 min of moderate exercise per week. The resultant exercise only risk reduction was 46% ($p$ <0.005) as compared with ~40% in the control group. Importantly intravenous glucose tolerance tests (small sub sample, post trial) suggested improved insulin sensitivity explained the reduction in diabetes incidence in the cohort (Tuomilehto et al., 2001).

Table 2. Randomised control trials of multicomponent interventions in high risk populations.

| Study | Study Population | Intervention(s) | Length (yr) | Reduction in risk (%) |
|---|---|---|---|---|
| Da Qing Impaired Glucose Tolerance & Diabetes Study (Pan et al., 1997) | 577 men/women with IGT, mean age 45; mean BMI 25.8 kg/m$^2$ | Diet only; exercise only; diet plus exercise; control. | 6 | Diet only: 31% ($p$ < 0.03). Exercise only: 46% ($p$ <0.005). Diet plus exercise: 42% ($p$ <0.005). |
| Finnish Diabetes Prevention Trial (Tuomilehto et al., 2001) | 522 men/women with IGT; mean age 55, mean BMI 31 kg/m$^2$ | Lifestyle modification (goal of weight loss, diet & moderate-intensity exercise) or control. | 3.2 | 58% ($p$ <0.001). |
| US Diabetes Prevention Program (Knowler et al., 2002) | 3,234 men/women with elevated glucose; mean age 51, mean BMI 34 kg/m$^2$ | Lifestyle modification (weight loss, exercise, or Metformin) or placebo. | 2.8 | Lifestyle modification: 58% (48-66%). Metformin: 31% (17-43%). |

On evaluation of the presented data, it is clear that increased physical activity is associated with increased insulin sensitivity. In both non-diabetic and high risk individuals, this is apparent; suggesting that physical activity should be used as a tool of both primary and secondary prevention. However there are not enough controlled clinical studies to permit a clear consensus on the dose of physical activity that improves glycaemic control (Kelley et al., 2001).

Further, the case for vigorous physical activity must not be ignored. Clear evidence suggests that vigorous intensity activity, increases insulin sensitivity further; due to induced glucose turnover (Perseghin et al., 1996; Romijn et al., 1993). Less is known however upon metabolic indices and vigorous activity. On balance of efficacy and feasibility, the current health recommendations should remain unchanged until a distinct graded dose-response relationship is pinpointed. As a well-known epidemiological axiom purports, the overall disease burden in a population undergoes a more dramatic reduction when a large segment of the population adopts small improvements in health behaviour than when a small segment adopts large improvements (Rose, 1992).

**Conclusion**

This study has reviewed a small cross-section of the available data detailing the effect of physical activity upon insulin sensitivity, in relation to type 2 diabetes. Numerous cross-sectional studies have clearly elucidated an inverse relationship between physical activity status, insulin resistance and metabolic risk factors in healthy individuals. The strength of such evidence is limited by the pitfalls of cross-sectional data, therefore prospective cohort and clinical trial studies should be the focal point of any evidence based preventative strategy. Further, much of the intervention data has been drawn from high risk populations (i.e. impaired fasting glucose). It is suggested that more experimental intervention studies need to be conducted upon healthy individuals. Such studies should be large in number and have significant statistical power, as many of the studies reviewed have utilised small sample sizes, and short follow up periods.

Nevertheless a number of conclusions can be made:

- Cross-sectional, prospective cohort and randomised control trials clearly show that moderate-intensity physical activity can improve insulin sensitivity with this can be improved further by undertaking vigorous-intensity physical activity.
- The duration of activity may be more important than intensity, in the primary prevention of insulin resistance.
- Weight loss may well be the significant factor for increased insulin sensitivity, and reduced metabolic risk, however when adjusting for weight, the prophylactic benefit of exercise remains.

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