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Review

Exercise and type 2 diabetes: New prescription for an old problem

Stephen R. Bird, John A. Hawley*

Exercise Metabolism Group, School of Medical Sciences, RMIT University, P.O. Box 71, Bundoora, Victoria 3083, Australia

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ABSTRACT

During the past 50 years, the prevalence of a cluster of chronic, inactivity-related diseases including obesity, insulin resistance and type 2 diabetes mellitus (T2DM), collectively referred to as 'metabolic syndrome' (MetS) has reached global epidemic proportions. Appropriate exercise training is a clinically proven, cost-effective, primary intervention that delays and in many cases prevents the health burdens associated with MetS. Indeed, there is no single intervention with greater efficacy than physical exercise to reduce the risk of virtually all chronic diseases simultaneously. However compliance to National guidelines for physical activity remains low, with "a lack of time" the most frequently cited barrier to exercise participation by adults, irrespective of age, sex and ethnic background. Part of the growing apathy to modify lifestyle habits is that current public health recommendations may be unrealistic and unattainable for the majority of the populace. Hence, there is an urgent need for innovations in exercise prescription that can be incorporated into daily living and induce clinically beneficial health outcomes. Here we focus attention on a novel form of exercise prescription, high-intensity interval training (HIT), and provide evidence that HIT is a time-efficient and well-tolerated therapeutic intervention to improve cardio-metabolic health in a number of pre-clinical and clinical populations.

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1. Introduction

During the past 50 years the prevalence of a cluster of interrelated chronic metabolic disease states including obesity, insulin resistance and type 2 diabetes mellitus (T2DM) (collectively referred to as the metabolic syndrome [MetS]) has reached epidemic proportions. The aetiological basis of these disorders is polygenic and highly dependent on the environment (i.e., existing genes interact with environmental factors to result in phenotypic expression of these diseases). One environmental factor that is strongly associated with a plethora of chronic metabolic disorders and has changed dramatically in this time is a decline in daily physical activity. Yet despite an overwhelming body of evidence demonstrating the efficacy of exercise training to improve insulin

* Corresponding author. Tel.: +61 3 9925 7353; fax: +61 3 9467 8181.
E-mail address: john.hawley@rmit.edu.au (J.A. Hawley).

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resistance and treat or prevent T2DM, coupled with robust endorsements from national and international public health authorities, the vast majority of individuals fail to undertake sufficient daily activity. The objectives of this brief review are: (1) to present evidence to demonstrate that appropriate exercise training is a clinically proven, primary intervention that delays and in many cases prevents the health burdens associated with MetS, and (2) to focus attention on a novel form of exercise prescription, high-intensity interval training (HIT), and show that HIT is a time-efficient and well-tolerated therapeutic intervention to improve cardio-metabolic health in a number of pre-clinical and clinical populations.

2. Blood glucose homeostasis

The control of blood glucose concentration is essential for good health as both sustained high (hyperglycaemia, >7 mM) and low (hypoglycaemia, <4 mM) circulating levels lead to serious medical complications and potentially fatal consequences. In healthy humans there is a tightly regulated process that maintains blood glucose concentration at ~5 mM throughout the majority of the day and night. Such glucose homeostasis depends on a precise balance between the rate of glucose appearance in the blood (Ra) due to recently digested food and hepatic glucose output, and the rate of disappearance of glucose from the blood (Rd) due to glucose uptake by insulin-dependent tissues such as skeletal muscle and adipocytes, and insulin-independent tissues such as the brain and splanchnic organs. When Ra approximates Rd, euglycaemia prevails and systemic glucose concentrations remain constant at between 4 and 5 mM. This tightly coordinated homeostasis, is enabled by the secretion of pancreatic hormones including: (i) insulin (from the β-cells), which promotes glucose uptake from the blood, thereby reducing blood glucose levels, and (ii) glucagon (from the α-cells), which promotes glucose release from the liver, thereby increasing blood glucose levels. Consequently these hormones regulate the pattern of glucose uptake and utilisation by peripheral tissues (primarily muscle and to a lesser extent adipose tissue) as well as its uptake and release by the liver. Of the two insulin-sensitive tissues involved in peripheral glucose uptake and oxidation, skeletal muscle accounts for up to 80% of glucose disposal following ingestion or infusion [1,2], whereas adipose tissue only accounts for 3–4% of insulin-mediated glucose uptake [3]. Hence this makes skeletal muscle quantitatively the most important tissue involved in maintaining glucose homeostasis under both insulin-stimulated and resting conditions [1,2,4].

3. Insulin resistance: the precursor to type 2 diabetes mellitus

T2DM is characterised by an inability to maintain glucose homeostasis during rest and most daily activities. A precursor to T2DM is insulin resistance, in which major tissues such as the muscle become desensitised to insulin, thereby resulting in elevated fasting and basal levels of blood glucose and/or excursions into hyperglycaemia. Accordingly, the best predictors of increased diabetes risk and progression to T2DM are hyperglycaemia, abnormal glucose tolerance and a reduced insulin-stimulated glucose uptake into skeletal muscle [2]. With regard to hyperglycaemia, ambulatory postprandial and/or nocturnal glucose excursions, so-called 'hyperglycaemic spikes', (>11.1 mM) are an early and often undetected feature of the insulin resistant state [5]. In fact these 'hyperglycaemic spikes' are more predictive of the onset of cardiovascular disease (CVD) complications than elevated fasting plasma glucose [6] and are strongly associated with glycated haemoglobin (HbA_{1c}) content in both pre-diabetic individuals and patients with T2DM [7].

4. T2DM as part of the increasing health problem of metabolic syndrome

During the past 50 years there has been a dramatic increase in the prevalence of a cluster of interrelated chronic metabolic disease states, including: insulin resistance, T2DM, obesity and coronary heart disease (CHD). Specifically, the prevalence of T2DM has increased to epidemic levels over the past two decades, affecting 366 million people world-wide in 2011 and predicted to increase to 552 million by 2030 [8]. This recent and dramatic increase in the prevalence of T2DM is most notable in 'developed' countries such as the U.S.A., the United Kingdom and Australia where the increase has paralleled the rise in obesity [9].

As noted, T2DM is a progressive metabolic disorder that develops from a loss of insulin sensitivity. The risk factors for its onset and progression include environmental, behavioural and undefined genetic influences [10]. With the behavioural and environmental risk factors also being common to many of the other chronic diseases within the sphere of metabolic syndrome, therefore, strategies to improve insulin resistance before the onset of diabetes and its debilitating secondary complications are paramount, as they have far reaching consequences affecting many of the most prevalent chronic diseases in society today. To this end an overwhelming body of evidence supports the role of exercise as the intervention with the greatest potential benefit.

5. Exercise for the prevention of T2DM

In addition to the epidemiological evidence demonstrating that a lifestyle that includes appropriate levels of physical activity reduces the risk of insulin resistance and T2DM developing in 'healthy people', there is irrefutable proof that appropriate exercise training is an effective therapeutic intervention for those at high risk of T2DM. In numerous studies exercise has been demonstrated to increase insulin action in skeletal muscle from obese and insulin resistant individuals, and halve the risk of progressing to T2DM over a 5-year period (for reviews see [11–13]). Indeed, there is no single intervention with greater efficacy than physical exercise to reduce the risk of virtually all chronic diseases simultaneously [14]. Of direct clinical significance to T2DM is that the reductions in HbA1c levels induced by long-term exercise programmes are of a similar magnitude to those produced by long-term drug or insulin therapy [15]. Additionally, it should be noted that physical inactivity and excess energy intake leading to obesity, which are key risk factors for a number of diseases, exert an independent and additive risk [16]. Hence advocating exercising for health is not solely about 'losing weight'.

6. Metabolic syndrome: the result of an 'exercise deficient' phenotype

6.1. The case for exercise

The case for a causal link between the rise in physical inactivity during the past century and the increase in a cluster of chronic metabolic diseases is compelling. An individual's level of habitual physical activity is directly related to the degree of insulin resistance [17], with as little as two weeks of reduced ambulatory activity sufficient to significantly reduce peripheral insulin sensitivity, cardiovascular fitness, and lean leg mass in healthy, non-exercising young men [18]. Physical inactivity elevates the risk of T2DM in both 'normal' weight [19] and obese individuals [20],