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Lifestyle modification in the management of insulin resistance states in overweight/obesity: the role of exercise training

Tshidi Thaane^{a†*} , Ayesha A Motala^{b‡} and Andrew J Mckune^{a,c,d‡} 

^aDiscipline of Biokinetics, Exercise and Leisure Sciences, University of KwaZulu-Natal, Durban, South Africa;

^bDepartment of Diabetes and Endocrinology, University of KwaZulu-Natal, Durban, South Africa;

^cUniversity of Canberra Research Institute for Sport and Exercise Science, University of Canberra, Canberra, Australia;

^dCollaborative Research in Bioactives and Biomarkers (CRIBB) Group, University of Canberra, Canberra, Australia

*Corresponding author, email: t.thaane@gmail.com



Physical inactivity is a major contributor to overweight/obesity and associated disorders including cardiovascular diseases (CVDs), diabetes, and insulin resistance (IR). Intensive lifestyle modification (ILM) is recommended as first-line treatment for obese individuals at risk for IR. Exercise is considered to be a critical component of ILM. This narrative review discusses the role of exercise in the management of IR in overweight/obesity.

PubMed and Google Scholar were searched for articles published between January 1990 and January 2019 that examined mechanisms behind the effects of exercise on IR states associated with overweight/obesity. Studies examining and/ comparing effects of exercise mode, volume and/intensity on IR were also retrieved. Medical Subject Headings (MeSH) used were 'metabolic diseases' OR 'chronic diseases' AND 'exercise' and their related terms. Text words used in conjunction with the MeSH terms were 'aerobic training/exercise' OR 'resistance training/exercise' OR 'high intensity interval training/exercise', OR 'low volume training/exercise'. Reference lists of retrieved articles were also searched for appropriate studies.

Aerobic exercise training (AET) and resistance exercise training (RET) appear to produce comparable effects on obesity-induced IR states. RET, however, appears to be associated with greater improvements in glucose disposal in skeletal muscle, which is usually the primary site for IR. This is partly attributed to greater increases in key proteins involved in the insulin signalling pathway including protein content of glucose transporter 4 (GLUT-4) following RET. A study on individuals with impaired glucose tolerance (IGT) showed that RET improved glucose disposal by 23%, primarily due to a 27% increase in non-oxidative glucose metabolism, suggesting that RET may delay the manifestation of diabetes in patients with IGT. Furthermore, studies reviewed here show that components of exercise including the mode, volume and intensity of exercise training are an integral element in exercise prescription and must be recommended in accordance with the desired outcome.

Keywords: exercise, insulin resistance, lifestyle modification, overweight, obesity

Introduction

Lack of exercise and sedentary behaviour (prolonged sitting) are major risk factors for insulin resistance.^{1–3} Typically coupled with excessive intake of energy-dense foods, low-energy expenditure (physical inactivity) is associated with overweight/obesity.⁴ In the development of obesity, macrophages infiltrate adipose tissue and alter its endocrine and metabolic functions to produce abnormal levels of adipokines and cytokines such as leptin and interleukin 6 (IL-6).^{5, 6} This results in systemic inflammation, which is strongly associated with diminished response of liver, muscle and adipose tissue to cellular actions of insulin.⁷ Liver, muscle and adipose tissue play a critical role in glucose homeostasis, thus a defect in insulin action in these tissues results in impaired glucose uptake and storage.⁸ Consequences of impaired glucose homeostasis include dyslipidaemia, type 2 diabetes (diabetes) and cardiovascular diseases (CVDs).⁹

Lifestyle modification including cessation of tobacco smoking, changes in diet and exercise are recommended as non-pharmacological therapeutic approaches for the management of

obesity-associated diseases including cancer, diabetes and insulin resistance.¹⁰ Below we discuss therapeutic effects of exercise on impaired insulin signalling, impaired glucose metabolism, systemic inflammation and endothelial dysfunction; and clinical states of insulin resistance in overweight/obesity.

Impaired insulin signalling

Impaired insulin signalling as shown in [Figure 1](#) occurs at the level of insulin receptor substrate 1 (IRS-1), which leads to impaired glucose transport. Under normal physiological conditions, the insulin signalling pathway is initiated when insulin binds to its receptors located on the cell surface of insulin-sensitive tissue including skeletal muscle and adipose tissue. Activation of the insulin receptor leads to phosphorylation of IRS-1 which in turn activates the enzyme phosphatidylinositol 3-kinase (PI3 K).¹¹ Activation of PI3 K leads to the activation of protein kinase B/Akt, which is responsible for the phosphorylation of the substrate AS160 and activation of Rab proteins required for the translocation of vesicles containing glucose transporter 4 (GLUT4) to the cell membrane.¹² Once at the cell

[†]Denotes graduate student author

[‡]Denotes professional author

[‡]Denotes professional author

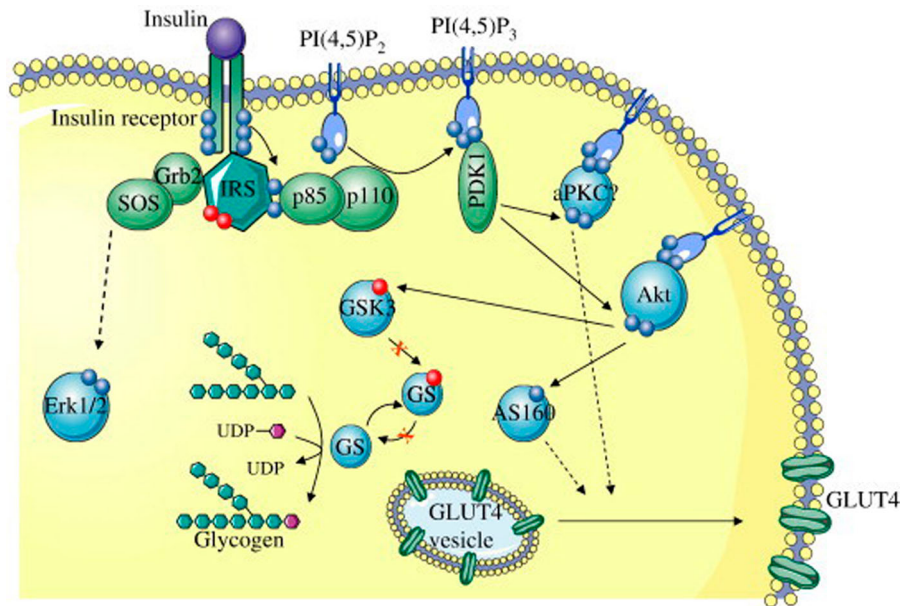


Figure 1. Schematic representation of the insulin signalling pathway showing defects in the signalling cascade in insulin resistance (Adapted from Fröjdö *et al.*).¹³ IRS: insulin receptor substrate; Grb2: growth factor receptor-bound protein 2; SOS: Son of Sevenless; Erk1/2: extracellular signal-regulated kinases 1/2; PIP₃: phosphatidylinositol 3 kinase; PDK1: phosphoinositide-dependent kinase-1; PKC: protein kinase C; Akt: serine-threonine protein kinase; GSK3: glycogen synthase kinase 3; UDP: uridine diphosphate; GLUT4-glucose transported 4.

surface, GLUT4 shuffles glucose into the cell where it is stored or metabolised.

Thus when insulin signalling is impaired, hyperglycaemia ensues. Chronic hyperglycaemia has been linked to diabetes-related micro- and macrovascular complications including neuropathy, retinopathy and nephropathy.^{14,15}

Impaired insulin signalling is caused by a variety of factors. In the skeletal muscle, it is attributed to the accumulation of fat in muscle fibres.¹⁶ Increased skeletal muscle fat content, particularly inside the muscle fibre (intramyocellular fat-IMCL) is strongly correlated with impaired glucose transport even though IMCL contributes a smaller portion (~1%) of the total fat content compared with fat accumulated outside the muscle cell (extramyocellular fat-EMCL).^{17,18} The mechanism behind accumulation of IMCL in the muscle is unclear. Some studies, however, have suggested that mitochondrial dysfunction contributes to increased IMCL fat content.^{19–21}

Skeletal muscle insulin resistance has been identified as a primary defect in insulin resistance and diabetes; the skeletal muscle therefore presents a critical target site for therapies aimed at controlling glycaemia.^{22,23} Therapeutic effects of exercise in the skeletal muscle are via acute and chronic adaptations. Acutely, exercise results in the translocation of GLUT 4, which results in improved glucose uptake by the muscle.²⁴ This exercise-induced GLUT 4 expression occurs via insulin-independent pathways including the calcium (Ca²⁺), 5'AMP-activated-kinase (AMPK) and nitric oxide synthase (NOS) kinases. Chronically, exercise results in increased mitochondrial content and muscle fibre transformation (from more glycolytic type IIb/IIc/x to more oxidative type IIa fibres), which are associated with increased oxidative capacity.^{25,26} A high muscle oxidative capacity is associated with optimal glucose metabolism and has been found to be predictive of metabolic health including low fat mass and optimal insulin sensitivity.^{27, 28}

Impaired glucose metabolism

Impaired glucose metabolism (pre-diabetes) is a transition state between normal glucose homeostasis and diabetes. This metabolic state is characterised by impaired glucose tolerance (IGT) and impaired fasting glucose (IFG), which are attributed to skeletal muscle and hepatic insulin resistance, respectively.^{29–31} Effects of exercise on human skeletal muscle are well elucidated and mechanisms have been highlighted in the preceding paragraph. Hepatocellular mechanisms, however, are unclear. Studies on animal models show that exercise reduces liver fat content, stimulates hepatic mitochondrial adaptations and increases 5' adenosine monophosphate-activated protein kinase (AMPK) activity.³² Increased AMPK activity inhibits transcription factors including hepatocyte nuclear factor 4 (HNF4) and CREB regulated transcription coactivator 2 (CRTC2) which maintain glucose homeostasis by inhibiting gluconeogenesis.^{33,34} Thus, exercise-induced AMPK activity may offer therapeutic benefit to patients with IFG who exhibit excessive rise in post-prandial glucose due to impaired hepatic glucose production.³⁵

Chronic systemic inflammation

The inflammatory process is a normal part of the body's natural defence to infection or trauma and results in the expression of inflammatory mediators such as IL-6, TNF- α and CRP. Although this process is pivotal in immunological response, chronic inflammation (persistent elevated levels of inflammatory markers), as seen in total and abdominal obesity, is a major risk factor for chronic diseases including insulin resistance.³⁶ Pharmacological interventions such as the use of statins have been shown to decrease obesity-induced inflammation.^{37, 38} Behavioural interventions including exercise (acute and chronic), however, are increasingly being shown to also have clinically significant benefits.^{39,40} It is important to note that, although exercise is associated with increased muscle-derived inflammatory cytokines acutely, these cytokines are of physiological benefit.⁴¹ IL-6 secreted after an acute bout of exercise has been found to initiate the secretion of the anti-inflammatory

cytokine (IL-10) from monocytes and lymphocytes.⁴¹ Chronic (regular, long-term) exercise has been shown to have an inverse, independent dose–response relation with inflammation.⁴² In a 12-month study, Marfella *et al.* reported that exercise decreased IL-6, CRP and TNF by 62%, 44% and 31%, respectively.⁴³ The mechanism by which exercise training mitigates inflammation has been suggested to be through the reduction of adipose tissue, which is the main secretory organ responsible for the production of inflammatory cytokines.^{7,43} Furthermore, exercise has been found to increase the expression of anti-inflammatory agents such IL-1 receptor antagonist (IL-1ra), IL-10 and adiponectin, which promote various physiological benefits including glucose metabolism and suppression of inflammatory markers such as TNF- α , which may reduce risk for insulin resistance.^{44–46}

Endothelial dysfunction

Obesity, particularly abdominal obesity, is a primary risk factor for impaired endothelial function, which results in abnormal regulation of vasoactive substances including nitric oxide (NO).⁴⁷ Nitric oxide is considered to be the most important endothelium-derived substance due to its antiatherogenic effects including the inhibition of inflammation and vascular smooth cell proliferation and migration. Endothelial dysfunction (ED), therefore, is strongly associated with chronically elevated levels of the pro-inflammatory markers including CRP.⁴⁸ Thus, ED is considered an initial step in the pathogenesis of insulin resistance and associated cardiovascular complications.⁴⁹ Research indicates that exercise training results in significant reduction in CRP and may produce cardioprotective effects. A recent meta-analysis of randomised controlled trials found that exercise was associated with a significant decrease in CRP (-0.66 mg/l (95% CI, -1.09 to -0.23 mg/l; -14% from baseline), suggesting that exercise could be a therapeutic alternative for the management of abnormal inflammation levels.⁵⁰

The effects of exercise on insulin resistance that are outlined in the preceding paragraphs are generally dependent on various components including the mode, volume and intensity of exercise training.⁵¹ These components are integrated with patient health characteristics identified from the exercise pre-participation screening process, which involves assessing the patient's level of physical activity and identifying any presence of signs or symptoms of cardiovascular and metabolic disease.⁵¹

Exercise mode

The mode of exercise refers to the type of exercise. Aerobic exercise training (AET), which includes exercise types such as walking, jogging, bicycling and rowing, is the most commonly studied mode of exercise in patients with obesity and related metabolic disorders.⁵² Long-duration AET has traditionally been prescribed to obese patients to aid in weight loss due to high energy demands associated with prolonged (> 60 minutes per day) exercise.⁵³ Recent studies, however, show that the effects of AET are amplified when it is combined with resistance exercise training (RET), which has previously not been recommended for obese patients.⁵⁴ In a 14-year study, Shiroma *et al.* reported that RET decreased the incidence of diabetes and cardiovascular disease by 30% and 17%, respectively.⁵⁴ Furthermore, the authors observed that people who performed RET reduced their risk of diabetes and CVDs by 30% and 17%, respectively.⁵⁴ This could be due to the fact that, unlike AET, RET maintains fat-free mass (FFM) and resting energy expenditure (REE), factors that are pivotal in weight loss and weight maintenance.⁵⁵ Resistance exercises included

shoulder press, squats, lunges and deadlifts, which are performed with progressive resistance machines or bands and/or free weights.^{56,57} These exercises were performed at ~ 70 –85% one-repetition maximum (1RM), which has been reported to preserve or improve FFM and REE while decreasing body fat.⁵⁸

Exercise volume and intensity

Exercise volume and intensity refer to the amount and effort required for the exercise. Exercise intensity (moderate, vigorous or high) is characterised by objective and subjective measures such as percentage of heart rate reserve (HRR) and rate of perceived exertion (Borg's 6–20 [RPE]), respectively.^{59,60} Exercise training at 40–60% of HRR or 12–13 RPE is considered moderate intensity training (MIT). Vigorous-intensity exercise is performed at 60–85% of HRR or RPE ≤ 14 while high-intensity training (HIT) is performed at near maximal to maximal effort, 90–100% HRR and 19–20 on the RPE scale.⁵¹

The intensity of exercise determines the volume (amount) of exercise. The lower the intensity or load the higher the volume of exercise required to achieve therapeutic effect and vice versa.⁶¹ High load (low volume) RET is traditionally considered to produce superior physiological adaptations including skeletal muscle hypertrophy when compared with low load (high volume) RET. A recent study by Morton *et al.* however, reported comparable increases in lean muscle mass in trained and untrained individuals following high and low load (high and low volume, respectively).⁶² The authors speculated that the similar increases may have been due to the fact that the participants who performed low load (high volume) RET achieved a greater exercise volume since they were able to exercise until volitional failure, which allowed for maximal activation of their motor units and ultimately led to the similar increases in skeletal muscle adaptation seen in the high load (low volume) group, suggesting that the gains in muscle mass are not dependent on the load when the exercise is performed to volitional fatigue.⁶²

There is general consensus that exercise training produces therapeutic effects on health outcomes including improvements in insulin sensitivity and cardiorespiratory fitness. Nonetheless, levels of physical inactivity continue to rise.⁶³ Time commitment (30–60 minutes) required for high-volume moderate-intensity training (HVMIT) has been cited as the most common barrier by people who are physically inactive.⁶⁴ Low-volume high-intensity training (LVHIT), which requires approximately 10% of the time required for HVMIT, is therefore increasingly being studied as a time-efficient alternative.⁶⁵

High-intensity interval training (HIIT) and sprint interval training (SIT) are the most commonly studied forms of LVHIT. Literature evidence shows that HIIT and SIT, which are characterised by brief periods of high-intensity exercise separated by active or complete rest, produce similar and sometimes superior benefits in patients with cardiometabolic disorders despite major differences in time commitment.^{66,67} In a 12-week study, Gillen *et al.* reported that three sets of 20-second SIT three times per week produced comparable improvements in cardiorespiratory fitness, insulin sensitivity and mitochondrial content as 45 minutes of MIT despite the fivefold lower exercise volume.⁶⁸ Studies have suggested that training at high intensity is associated with greater cardiac output and stroke volume as well as activation of peripheral factors that enhance the extraction of oxygen from the blood to tissues, factors associated with enhanced cardiorespiratory fitness.⁶⁹

Conclusion

In conclusion, studies discussed in this narrative review show that exercise improves insulin resistance by improving insulin signalling and glucose metabolism. These improvements, however, are generally dependent on various components including the mode, volume and intensity of the exercise. The beneficial effects of exercise, which have been studied thoroughly, provide support for current physical activity guidelines that recommend 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity aerobic physical activity per week, which are endorsed by diabetes organisations including the American Diabetes Association (ADA) and International Diabetes Federation (IDF). However, considering that 'lack of time' is the main contributor to the physical inactivity pandemic, public health guidelines ought to reflect time-efficient exercise training strategies for the prevention and management of insulin resistance and other metabolic disorders. Emerging research is increasingly showing that HIIT is a time-efficient and effective mode of exercise training that has potential to be an alternative strategy to encourage individuals to adopt and maintain a physically active lifestyle. However, comprehensive clinical trials are needed to advance knowledge on HIIT.

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ORCID

Tshidi Thaane  <http://orcid.org/0000-0002-2420-2905>

Andrew J Mckune  <http://orcid.org/0000-0002-5479-1544>

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