Chapter

The Role of Physical Activity on Insulin Resistance-Associated Endothelial Dysfunction

Shruti M. Gandhi, Eric S. Nylen and Sabyasachi Sen

Abstract

Enhanced physical activity and cardiorespiratory fitness significantly impact morbidity and mortality across the spectrum of noncommunicative chronic illnesses experienced by modern lifestyles. Physical activity itself prompts an intricate interplay of physiological responses across vital organ systems including microvascular adaptations to optimize nutrient, oxygen, and hormone delivery, some of which involves insulin-mediated regulation. Insulin has been known to act on the vasculature in multiple ways by its effects on endothelium and skeletal muscle blood flow. This is important to understand as it has implications for conditions associated with insulin resistance (IR) such as obesity, metabolic syndrome, prediabetes, diabetes, and polycystic ovarian syndrome among others. These conditions are associated with increased morbidity and mortality contributed by endothelial dysfunction via increased atherosclerosis, hypertension, and increased free fatty acid levels. In this chapter, we will discuss the effects of insulin on the vasculature, IR on the endothelium, and lastly, what impact physical activity may have on such processes.

Keywords: physical activity, insulin resistance (IR), endothelium

1. Introduction

The mechanisms behind the clinical improvements following exercise and the possible roles of endothelium and adipose tissue towards tissue re-modeling and regeneration are poorly understood.

The cellular changes resulting from exercise in overweight or obese population are not fully documented. However, the incidence of overweight and obese population who are insulin resistant is gradually increasing. There seems to be an intimate relationship between fat hypertrophy, fat inflammation, and vascular supply in metabolic syndrome states such as prediabetes. The vasculature and endothelium in metabolic syndrome or subjects with prediabetes and insulin resistance are prone to ROS accumulation and inflammation. Exercise appears to improve endothelial dysfunction in insulin resistant cohort though cell-based data is lacking. The favorable impact of exercise on cardio-metabolic health depends in part on the concomitant exercise-induced reduction of adiposity and fat-based inflammation and insulin resistance.

2. Insulin as a vascular hormone

Insulin acts as a vascular hormone, mediating its action by several mechanisms including its effect on cardiac output, endothelium, type and location of vessel, and skeletal muscle [1].

Cardiac output: it has been established that insulin combined with glucose infusion causes an increase in cardiac output (CO) [2]. High concentrations of insulin in humans of 70 μU/mL cause a 15% rise in CO by increasing heart rate and stroke volume [3]. The rise in CO is associated with a decrease in mean arterial pressure and in turn, a reduction in systemic vascular resistance.

Endothelium: insulin directly acts on the vascular endothelium by binding to insulin receptors, insulin-like growth factor I (IGF-I) receptors and hybrid insulin/IGF-I receptors [4]. With the binding of insulin to these endothelial receptors, both vasodilator (i.e., nitric oxide, NO) and vasoconstrictor (i.e., endothelin 1, ET-1) substances are released to balance vascular tone. NO causes vasodilation of the vessels via the activation of insulin receptor substrate-1 (IRS-1) leading to phosphatidylinositol 3-kinase (PI-3 kinase)/protein kinase B (Akt.) phosphorylation of

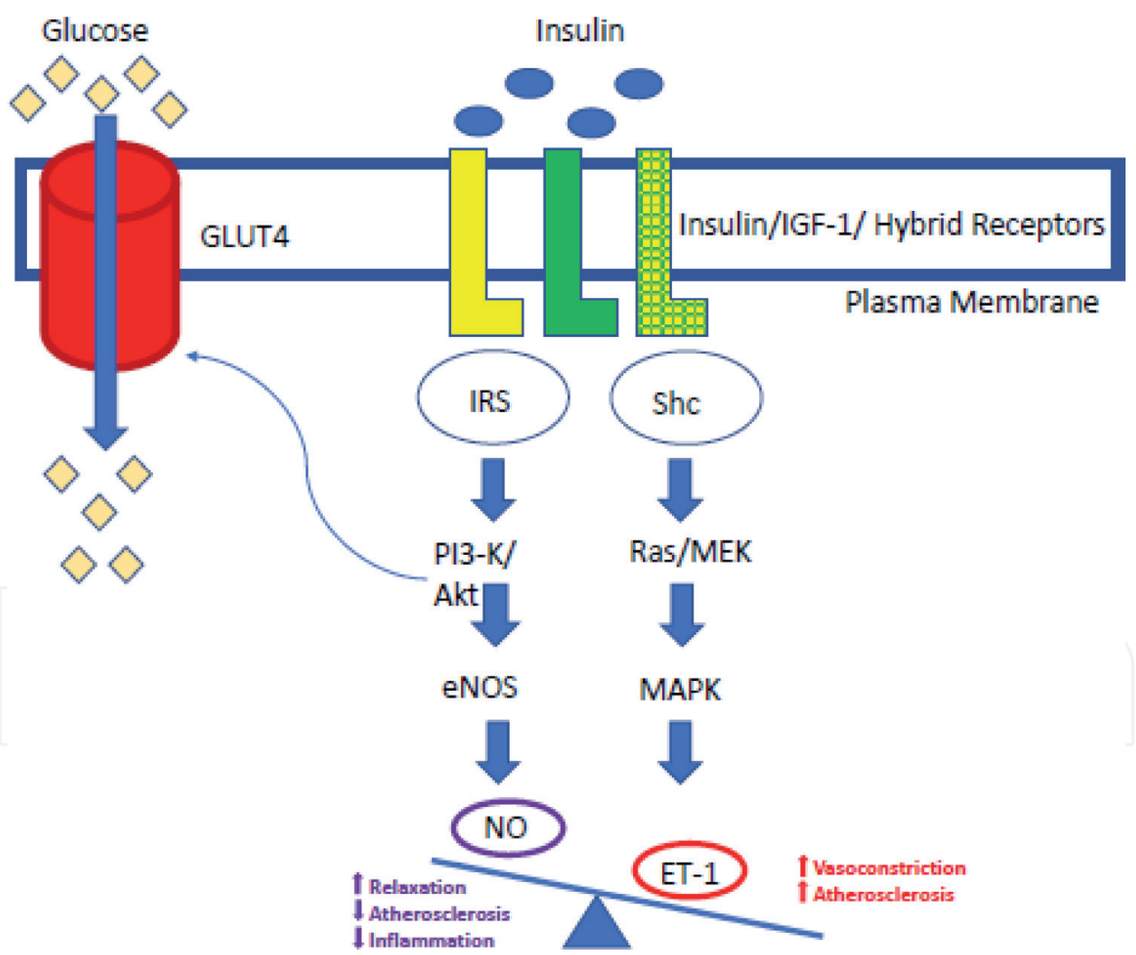

Figure 1.
Pathway of insulin-mediated release of nitric oxide (NO) and endothelin-1 (ET-1), two peptides that influence vasomotor tone and risk of atherosclerosis. Insulin directly affects the vascular endothelium by binding to receptors present on the endothelium which expresses not only insulin receptors but also insulin-like growth factor I (IGF-I) receptors and hybrid insulin/IGF-I receptors. These hybrid receptors are expressed 5- to 10-fold higher concentration than insulin receptors. Potentially, an over-abundance of IGF-1 receptor may result in vascular insulin resistance by promoting hybrid receptor formation which does not respond to physiological insulin concentrations while decreasing insulin receptor availability. As described in the text, insulin initiates an intracellular cascade of steps resulting in NO or ET-1. GLUT-4 transports glucose across the cellular membrane following insulin activation or muscle contraction via a complex of intermediary substrates. The former is initiated by the PI3K pathway, while muscle contraction by a PI3K independent pathway.

Vessel	Role	Insulin action	Mechanism
Conduit arteries	Regulate arterial compliance, blood pressure	Increases relaxation, increases compliance	Likely NO
Resistance arterioles	Determines vascular resistance	Dilation, decrease vascular resistance	NO
Terminal arterioles, capillaries	Regulate insulin delivery to muscle. Also exchange nutrients, oxygen and hormones with muscle	Muscle glucose uptake, recruit muscle microvasculature	Insulin, muscle contraction, angiotensin GLP1, adiponectin
Skeletal muscle	Muscle contraction	Increase blood flow, increase glucose uptake	NO, translocation of GLUT4 receptors

Table 1.
Role of insulin on various vessels and mechanism.

endothelial NO synthase (eNOS) whereas the ET-1 signaling pathway involves the mitogen activated protein kinase (MAPK) (**Figure 1**). During states of high insulin concentrations, as seen in euglycemic hyperinsulinemic clamp studies or postprandially, insulin's vasodilatory effect through NO predominates. NO not only decreases vascular tone but also decreases vascular smooth muscle cell (VSMC) proliferation and reduces binding of inflammatory cells and platelet aggregation [5].

Type and location of vessels: insulin's action on the vasculature varies depending on its site of action along the arterial tree which can include the conduit arteries, the resistance arterioles, precapillary arterioles and the capillaries (**Table 1**). It also acts on the skeletal muscle vasculature and can have effects locally.

The conduit arteries are large arteries which regulate arterial compliance in response to the ejection volume and stretch in order to maintain blood pressure. Insulin increases compliance by vasodilation of these vessels in response to NO release. In human studies with insulin infusion, the responsiveness of the femoral artery to methacholine-induced vasodilation is increased [4].

The resistance arterioles regulate blood pressure and total blood flow to tissues. They determine vascular resistance as a change in the size of the vessel (lumen size) can significantly increase or decrease resistance and thus the amount of blood supply to the tissues. Insulin via NO production causes dilation of these vessels, decreases resistance, and increases blood flow.

The microvasculature including the terminal arterioles, capillary networks and venules regulate insulin delivery to muscle tissues. Insulin action here promotes glucose uptake, recruitment of muscle vasculature and its own trans-endothelial transport [4]. This allows for exchange of nutrients, oxygen, and hormones to the muscle with removal of metabolic waste.

Skeletal muscle: during exercise, skeletal muscle blood flow, capillary recruitment, and GLUT4 translocation to the sarcolemma and T-tubules are augmented which is essential for glucose uptake and oxidation. Insulin targets the skeletal muscle by increasing blood flow and glucose uptake, the latter mediated by translocation of GLUT4 transporters to the sarcolemma and transverse tubules as well as to the surface of the cell (independent of insulin).

3. Insulin resistance (IR) and vasculature

Insulin resistance is characterized by a state of compensatory hyperinsulinemia due to changes in insulin secretion and/or insulin clearance [6] leading to mild forms of glucose intolerance, dyslipidemia (high triglycerides, low HDL, small

dense LDL), and hypertension termed the "insulin resistance syndrome". As discussed, during physiological conditions, insulin binding to endothelial receptors leads to phosphorylation of downstream substrates including activation of the IRS-1, PI3K pathway and subsequent recruitment of GLUT4 to mediate glucose transport into muscle and other tissues [7]. However, In the IR state, the IRS-1-PI3K-Akt-NO pathway is muted while the MAPK pathway remains intact [8]. The unopposed action of ET-1 leads to a shift towards vasoconstriction, increased arterial stiffness, hypertension, and tissue hypoxia. In addition to this decrease in NO bioavailability, increases in oxidative stress, inflammatory markers, and pro-thrombotic mediators (i.e., increased plasma von Willebrand factor, decreased lipoprotein lipase activity) are seen. More direct evidence for endothelial IR was shown in freshly isolated arterial endothelial cells where the insulin-induced eNOS-phosphorylation was negatively associated with oxidative stress markers [9].

During states of IR each vascular site becomes affected and contributes to an increase in atherosclerosis. At the level of the conduit arteries, IR causes decreased compliance with a concomitant increase in vessel stiffness, which is a predictor of coronary artery disease and stroke [10]. The impaired vasodilatory action of insulin on the resistance arterioles leads to decrease in blood flow to the tissues it supplies. For example, Baron et al. demonstrated that the inhibition of NO production (similar to states of IR) causes a decrease in blood flow and glucose uptake in the leg. The terminal arterioles in patients with IR showed a blunted response to mixed meal in brachial blood flow and forearm microvascular recruitment compared to lean subjects [3].

Oxidative stress: hyperglycemia due to IR also induces generation of reactive oxygen species (ROS) by activation of the NADPH oxidase system. ROS activates multiple pathways linked with cell growth, proliferation and modifies NO bioavailability. One such pathway includes the renin-angiotensin system which is inappropriately activated in settings of IR. Interestingly, during continuous insulin infusion, Angiotensin 2 receptor antagonism resulted in whole-body insulin resistance and attenuation of microvasculature recruitment [5]. The mechanism may involve increased binding to Angiotensin 1 receptors, which have been shown to increases oxidative stress and cause vasoconstriction through decreased bioavailability of *e*NOS and increased ROS. Chai et al. has shown that when AT2R is blocked, there is decreased microvascular blood flow by 80% along with reduced glucose extraction [11].

4. The effect of exercise on insulin resistance and vasculature

It is well established that exercise augments insulin signaling independent of PI3K, while the combination of skeletal muscle contraction and insulin additively enhances glucose transport via GLUT4 translocation. A plethora of studies have reported that regular physical activity is effective in patients with IR, such as type 2 diabetes, prediabetes and metabolic syndrome, in improving glucose tolerance, insulin sensitivity, glycosylated hemoglobin levels (HbA1c) and morbidity and mortality [12]. For instance, adults with IR were found to have improvements in hepatic and peripheral insulin sensitivity after 12 weeks of aerobic exercise. Shorter term studies (i.e., 7 days) have also demonstrated similar improvements in insulin sensitivity in obese patients [13]. Lifestyle interventions such as diet modifications added to 12 weeks exercise training showed further enhancements in addition to insulin sensitivity including fatty acid oxidation, post-prandial hyperinsulinemia and systolic resting blood pressure [14].

Exercise and the endothelium: exercise causes several adaptations to IR in the vasculature in both the skeletal muscle and endothelium. Vessel wall shear stress

generated by exercise activates the PI3k/Akt/NO signaling pathway resulting in increased expression of eNOS and improved endothelial vasodilation and vascular remodeling [15]. Vessels with high shear stress are considered anti-atherogenic (low ET-1, high NO bioavailability) as opposed to low shear stress environments (high ET-1, low NO bioavailability). In patients with Type 2 diabetes, 8 weeks of combined aerobic and resistance exercises improved flow mediated dilation (FMD) of the brachial artery suggesting increased shear stress and improved endothelial vasodilation [16]. Exercise improved FMD, microvascular perfusion in muscles of older adults relative to sedentary adults in nondiabetic subjects with metabolic syndrome [14]. Finally, insulin sensitization without exercise also augments FMD in prediabetes [17].

Skeletal muscle: during exercise, blood flow to the skeletal muscle increases up to 100-fold through vasodilation and recruitment of capillaries to help maximize oxygen extraction as well as insulin delivery to the skeletal muscle [5]. Pivotal studies investigated the vascular effects of exercise training on insulin [7, 15, 18]. Single leg cycle exercises over a 10-week period improved insulin stimulated glucose uptake and vasodilation in the trained limb post exercise training for both healthy and IR subjects. Moreover, insulin stimulated vasodilation in the lower limb is greater in endurance trained athletes compared to otherwise healthy sedentary controls [7].

5. Endothelium and endothelial progenitor cells

Endothelial cells constitute the innermost layer of blood vessel and promote vascular homeostasis and angiogenesis. Endothelial cells can secrete several mediators that can alternatively mediate vasoconstrictors, such as endothelin-1 and thromboxane A2, or vasodilators, such as NO, prostacyclin, and endothelium-derived hyperpolarizing factor. Since hyperglycemia and IR can negatively impact NO secretion from the endothelium, with vasoconstriction, vessel wall stiffness, platelet aggregation and diminished angiogenesis, there is a counter-regulatory reparatory cellular response by circulating endothelial progenitor cells (EPCs). These are immature bone marrow derived cells that can differentiate into mature endothelial cells. These cells home in on areas that experience vascular injury or ischemia by way of circulating growth factors and cytokines to initiate repair of the endothelial surface and stimulate neovascularization and angiogenesis. In conditions such as diabetes with vascular damage, the presence of diminished circulating EPCs constitute cellular biomarkers of compromised cardiovascular health [19]. In subjects with IR such as metabolic syndrome, decreased EPC number and impaired functionality prognosticates increased cardiovascular risk [20]. Interestingly, exercise promotes the production and numbers of EPCs [19, 21] putatively related to the anti-apoptotic effect of NO [22]. EPCs are also stimulated by exercise in aging studies. Moreover, the migratory function of EPCs is improved by exercise in subjects with IR [19, 23]. The degree of exercise dose appears to influence the overall EPC response [23]. In presence of insulin resistance but not overt diabetes, CPAP therapy improves endothelial health and EPC parameters [24].

Exercise, endothelium and fat derived mesenchymal stromal cells (MSCs): clinical trials are necessary to investigate the possible cellular and molecular pathways that may impact endothelium and fat metabolism. Identification of the pathways that influence crosstalk between endothelium and fat, and thereby improve cardiometabolic health in the elderly and young subjects is important to identify. The process will help to identify genes and cell differentiation pathways that may change fat derived stem cell differentiation, following exercise training in the elderly and the young subject cohorts, which will subsequently influence the mesenchymal

structures of our body. Our study [25] appears to indicate that exercise promotes osteogenic differentiation but not myogenic differentiation in the middle-aged veteran population with mean age of 51 years. However, whether osteogenic differentiation of adipose tissue derived mesenchymal stromal cells (MSCs) also occurs in young and the elderly is unknown. Myogenic differentiation in response to exercise is well documented [26], and different types of exercise appear to influence the differentiation depending on plasma-based differentiation factors [26]. However, the exact mechanism of how exercise modifies mesenchymal stromal cell (MSC) differentiation in the body needs further investigation. Prior to our recent studies, we would have hypothesized that exercise will promote myogenic differentiation in all age groups, however the differentiation of stem cells may be dependent upon the need of the body to regenerate a particular tissue lineage at a particular age. For example, exercise promotes myogenic differentiation in the young [26] whereas endothelial function improvement and bone regeneration may be more important in the elderly [27, 28].

6. Summary

Exercise is an important modifiable risk factor that significantly attenuates cardiovascular morbidity and mortality. Physical activity is associated with enhanced cardiorespiratory fitness which significantly attenuates IR, and some of these effects are mediated by augmented endothelial action of insulin. These vascular effects of exercise include an increase in endothelium-dependent vasodilation through increased NO bioavailability, suppression of ET-1, increased capillary density, and reduction in ROS.

Finally, exercise appears to rejuvenate endothelial function by recruitment of exercise responsive EPCs and influences MSC differentiation.

Disclosures

None.

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