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Review Article

Insulin resistance: vascular function and exercise

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ABSTRACT

Insulin resistance associated with metabolic syndrome and Type 2 diabetes mellitus is an epidemic metabolic disorder, which increases the risk of cardiovascular complications. Impaired vascular endothelial function is an early marker for atherosclerosis, which causes cardiovascular complications. Both experimental and clinical studies indicate that endothelial dysfunction in vasculatures occurs with insulin resistance. The associated physiological mechanisms are not fully appreciated yet, however, it seems that augmented oxidative stress, a physiological imbalance between oxidants and antioxidants, in vascular cells is a possible mechanism involved in various vascular beds with insulin resistance and hyperglycemia. Regardless of the inclusion of resistance exercise, aerobic exercise seems to be beneficial for vascular endothelial function in both large conduit and small resistance vessels in both clinical and experimental studies with insulin resistance. In clinical cases, aerobic exercise over 8 weeks with higher intensity seems more beneficial than the cases with shorter duration and lower intensity. However, more studies are needed in the future to elucidate the physiological mechanisms by which vascular endothelial function is impaired in insulin resistance and improved with aerobic exercise.

1. Introduction

Insulin resistance is a metabolic disorder that reflects low capability to wash glucose out of the bloodstream to target tissues. Unlike type 1 diabetes mellitus, which results from disrupted insulin secretion from pancreatic β cells, type 2 diabetes mellitus is a representative metabolic disease attributable to increased insulin resistance and decreased insulin sensitivity.[1] Type 2 diabetes mellitus comprises > 90% of all cases of diabetes and affected > 350 million people in 2011.[2] In particular, the population of diabetes mellitus is gradually increasing in Korea, and about 15,000 diabetic patients die every year owing to the associated complications.[2] Metabolic syndrome, a clinically prediabetic condition characterized by abdominal obesity, hypertension, hyperglycemia, and dyslipidemia, is closely associated with increased insulin resistance in etiology. Approximately 25% of the adult population is considered to be at risk of metabolic syndrome globally,[3] and about 35% of the adult population in

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the United States is reported to have metabolic syndrome.[4] In Korea, the population with metabolic syndrome increased from 25% in 1998 to 31% in 2007.[5] Metabolic syndrome and type 2 diabetes mellitus are etiologically similar because they share two common causes: insulin resistance and abdominal obesity.[6] Thus, patients with metabolic syndrome have about five times higher possibility to progress into type 2 diabetes mellitus compared with those without metabolic syndrome.[7]

Patients with type 2 diabetes mellitus or metabolic syndrome are usually at elevated risk of cardiovascular disease.[2,8,9] Degenerative alterations in vascular structure and function in the metabolic diseases result in atherosclerosis, a main cause of cardiovascular disease.[8] Atherosclerosis results from dysfunction of the vascular endothelium, which is closely related to decreased NO bioavailability and increased endothelium-derived contraction factors in blood vessels.[10] Previous studies have indicated that excessive oxidative stress in the vasculature of patients with with metabolic disease is a possible mechanism to cause reduction in NO bioavailability and to impair vascular endothelial function.[9,11–13] However, few studies have demonstrated the physiological mechanisms from vascular cells in patients with metabolic disease. Regular physical activity is known as a strategy to reverse vascular dysfunction and to prevent future cardiovascular disease. However, a few studies have investigated the effect of exercise training on vascular function in patients with type 2 diabetes mellitus and metabolic syndrome.[14–17] Thus, the purpose of this review is to introduce potential physiological mechanisms by which vascular function is impaired in augmented insulin resistance, to summarize previous studies to investigate the effects of exercise training on vascular function in type 2 diabetes mellitus and metabolic syndrome, and to facilitate related studies in the future.

2. Insulin resistance and oxidative stress: a putative physiological mechanism to cause vascular dysfunction

Increased insulin resistance leads to augmented glucose level in the bloodstream. Since vascular endothelium is the single innermost layer in the vascular structure, vascular endothelial cells are likely to be damaged by hyperglycemic stress, suggesting that metabolic dysfunction such as insulin resistance and type 2 diabetic mellitus may result in vascular dysfunction.[18] It has been demonstrated that the generation of reactive oxygen species (ROS) is increased in both large and small vascular beds collected from hyperglycemic animal models.[19] In a hyperglycemic environment, elevated ROS generation in vascular cells can be influenced by various biological signaling pathways. Aldose reductase, in hyperglycemic conditions, converts glucose to sorbitol by using nicotinamide adenine dinucleotide phosphate as a cofactor, thus the regeneration of reduced glutathione is reduced and intracellular oxidative stress level is increased.[2,20,21] Increased advanced glycation end-products lead to increased receptor activity, which facilitates ROS and inflammatory cytokine production.[2,22,23] Activation of the diacylglycerol–protein kinase C pathway also contributes to the elevated generation of ROS and inflammatory cytokines.[2,24–26] In the overloaded glycolytic pathway induced by hyperglycemia, uridine diphosphate N-acetyl glucosamine has a negative effect on endothelial NO synthase activity by obstructing its phosphorylation at serine 1177 and increases the expression of proinflammatory cytokines such as transforming growth factor-β1 and plasminogen activator inhibitor-1.[2,27–29] In the vascular endothelium, oxidative stress induced by increased ROS generation not only directly plays a pivotal role in reducing NO bioavailability, but also leads to increased expression of proinflammatory cytokines so that proatherogenic and prothrombotic processes are abnormally facilitated.[30] Thus, the structural and functional integrity of vascular endothelium is likely to be damaged with insulin resistance, which increases the risk of cardiovascular disease in those who are continuously exposed to hyperglycemia in the circulation.

3. Insulin resistance and exercise: effects on vascular function

Insulin signaling in local vascular cells is essential to promote vascular endothelial NO production.[31] Thus, the increase in insulin resistance in the vasculature has a negative effect on vascular endothelial function and cardiovascular morbidity and mortality. Regular physical activity and exercise are known to promote cardiovascular health in those with insulin resistance.

3.1. *Effect of exercise training on vascular function in individuals with insulin resistance*

There are no specific exercise guidelines for metabolic syndrome patients to preserve and promote their cardiovascular health. Even though their joint statements were published in both 2000 and 2010, the American College of Sport Medicine and the American Diabetes Association only provide generic exercise regimens for diabetic patients.[32,33] In the two previous position standards, the experts recommended aerobic exercise or aerobic exercise combined with resistance exercise to prevent and promote cardiovascular disease risk in patients with diabetes. However, the effect of either aerobic or combined exercise training on both micro- and macrovascular endothelial function is still in debate. Some studies presented positive results of exercise training,[17,34–36] but others did not show any positive effect of exercise on vascular health in type 2 diabetic patients.[37–39] For individuals with metabolic syndrome, a small number of studies have explored the effect of exercise training on vascular endothelial function, but the training effect has presented a positive tendency,[14,15,40,41] and had a close relationship with increased NO bioavailability.[42] It is established that insulin resistance contributes to impaired vascular endothelial function,[31] and either aerobic or combined exercise training programs might help to reverse endothelial dysfunction in those who have insulin resistance.[14,15,17,34–36,40,41] Exercise intensity also seems to be a main factor influencing exercise effects in people with insulin resistance. Although both moderate-intensity continuous training and high-intensity interval training have shown improvement in vascular endothelial function, in the same caloric

Table 1 – Effect of exercise training on vascular endothelial function in individuals with IR

Disease (*n*)	Age (y)	Sex	Ex mode	Ex intensity	Ex frequency	Ex time /duration	Vessel studied	Conclusion	Refs
IR (9) T2DM (14)	37 43	Both	Aerobic	Moderate	3–4 d/wk	20–40 min /8 wk	Conduit	ACh-induced vasorelaxation↑	34
T2DM (16)	–	–	Aerobic and resistance	Moderate	3 d/wk	1 h /8 wk	Conduit resistance	Flow-mediated vasodilation↑ ACh-induced vasorelaxation↑	35
T2DM (38)	62	Both	Aerobicand resistance	Moderate	3–5 d/wk	75 min /12 wk	Conduit	Flow-mediated vasodilation↑	17
T2DM (43)	62	Both	Aerobic	Moderate	3 d/wk	30–40 min /3 mo	Conduit	Flow-mediated vasodilation↑	36
T2DM (42)	67	Both	Aerobicand resistance	Moderate	3–5 d/wk	20–30 min /4 wk	Conduit	Flow-mediated vasodilation =	37
T2DM (59)	63	Both	Aerobic	Moderate	3 d/wk	30 min /6 mo	Micro (skin)	ACh-induced vasorelaxation =	38
T2DM (18)	60	Male	Aerobic and resistance	Moderate	3 d/wk	1 h /8 wk	Conduit	Flow-mediated vasodilation =	39
MS (29)	40–60	Male	Aerobic	Moderate	3 d/wk	50 min /12 wk	Conduit	Flow-mediated vasodilation↑	40
MS (28)	—	Both	Aerobic	Moderate High	3 d/wk	40–47min /16 wk	Conduit	Flow-mediated vasodilation↑ Flow-mediated vasodilation↑↑	14
MS (32)	50–55	Both	Aerobic	Moderate High	3 d/wk	40–47 min /16 wk	Conduit	Flow-mediated vasodilation↑ Flow-mediated vasodilation↑	15
MS (38)	50–70	Both	Aerobicand resistance	Not addressed	4–5 d/wk	90 min /6 mo	Micro (skin)	ACh-induced vasorelaxation↑	41

ACh, acetylcholine; Ex, exercise; IR, insulin resistance; MS, metabolic syndrome; T2DM, Type 2 diabetes mellitus; ↑, increase; ↑↑, more increase; =, no change.

expenditure, high-intensity interval training presents superior effect on vascular endothelial function and glycemic control.[15,36] The physiological mechanisms by which either aerobic or combined exercise training enhances vascular endothelial function in insulin resistance are not fully elucidated. Positive changes in oxidative stress and inflammatory biomarkers after exercise training are thought to be potential mechanisms from animal and systemic biomarker studies,[8,43–45] but no study has investigated the local alterations of potential biomarkers in human vasculature in response to acute or chronic exercise training in insulin resistance. Furthermore, it is also necessary to figure out a mechanistic linkage between exercise intensity and functional alteration of vascular endothelium. Table 1 shows a summary of studies examining the effect of exercise on endothelial function in individuals with insulin resistance.

3.2. *Effect of exercise on vascular dysfunction in experimental animal models*

Current evidence indicates that metabolic disease such as insulin resistance or metabolic syndrome induced vascular dysfunction in various animal models (Table 2). Even though a majority of previous studies have indicated that insulin resistance or metabolic syndrome induced vascular dysfunction, some studies also showed that these prediabetic conditions did not change endothelial function. These discrepant conclusions suggest that alteration of vascular function is affected by multiple factors including duration of certain diseases and vascular beds. For example, a number of studies showed that obesity (high-fat diet) induced insulin resistance caused acetylcholine-induced endothelial dysfunction in various blood vessels, including coronary arterioles, gracilis artery, femoral artery and aorta in mouse models,[46–49] whereas some studies indicated that insulin resistance did not induce vascular dysfunction in femoral artery, mesentery arterioles and aorta.[48,50,51] In addition, some studies showed that type of agonists induced inconsistent results in the same vascular beds.[50,52,53] For instance, insulin resistance caused impaired insulin-dependent vasorelaxation, however, acetylcholine-induced vasorelaxation was identical in mesenteric arterioles of C57Bl/6J mice.[50,52] By contrast, in the femoral artery of C57BL/6J mice, insulin resistance did not change insulin-induced vasorelaxation, but acetylcholine-induced vasorelaxation was reduced by insulin resistance.[53] Table 2 summarizes the effect of insulin resistance or metabolic syndrome on vasorelaxation in various vasculatures in experimental animal models.

It is well documented that exercise or regular physical activity has beneficial effects on metabolic diseases in animal models. Considering previous studies, most exercise protocols improved vascular function in various vascular beds such as coronary arterioles, arterioles, feed arteries from skeletal

Table 2 – Effect of insulin resistance or metabolic syndrome on vasorelaxation in various vasculatures in experimental animal models

Animals	Sex	Disease	Vessel studied	Conclusion	Refs
C57BL/6 mice	Female	IR	Coronary arteriole	ACh–induced vasorelaxation ↓ Flow-mediated vasorelaxation ↓	46
C57BL/6J mice	Female	IR	Aorta	ACh-induced vasorelaxation ↓ Insulin-induced vasorelaxation ↓	48
			Femoral artery	ACh-induced vasorelaxation =	
C57BL/6J mice	Male	IR	Aorta	ACh–induced vasorelaxation =	51
C57BL/6J mice	Male	IR	Aorta	ACh-induced vasorelaxation ↓	54
C57BL/6J mice	Male	IR	Femoral artery	ACh-induced vasorelaxation ↓ Insulin-induced vasorelaxation =	53
C57BL/6J mice	Male	IR	Coronary artery	ACh-induced vasorelaxation = Insulin-induced vasorelaxation =	49
			Aorta	ACh-induced vasorelaxation ↓	
C57BL/6J mice	Male	IR	Aorta	ACh-induced vasorelaxation =	55
C57BL/6J mice	Male	MS	Superior mesenteric artery	ACh-induced vasorelaxation ↓	56
C57BL/6J mice	Male	IR	Mesentery arteriole	ACh-induced vasorelaxation = Insulin-induced vasorelaxation ↓	50
C57BL/6J mice	Male	IR	Gracilis artery	ACh-induced vasorelaxation ↓	47
C57BL/6J mice	Not specified	Obesity	Femoral artery	ACh-induced vasorelaxation ↓	57
C57BL/6J mice	Not specified	IR	Mesentery arteriole	Insulin-induced vasorelaxation ↓ ACh–induced vasorelaxation =	52
B6D2F1 mice	Male	IR by aging	Artery from epididymal white adipose tissue	ACh-induced vasorelaxation ↓	58
New Zealand Obese Mice	Male	MS	Mesenteric artery	ACh-induced vasorelaxation ↓ Bradykinin-induced vasorelaxation ↓	59
Ossabaw swine	Male	MS	LAD	Coronary blood flow ↓	60

ACh, acetylcholine; IR, insulin resistance; LAD, left anterior descending; MS, metabolic syndrome; ↓, decrease; =, no change.

Table 3 – Effect of exercise on vascular dysfunction induced by IR or MS in experimental animal models

Animals	Sex	Disease	Vessel studied	Type of EX	Ex effect	Refs
C57BL/6 mice	Female	IR	Coronary arteriole	Voluntary wheel running	ACh-induced vasorelaxation ↑ Flow-mediated vasorelaxation ↑	46
C57BL/6 mice	Male	IR	Aorta	Treadmill exercise	ACh-induced vasorelaxation ↑	49
OLETF rats	Male	IR	Arteriole from white skeletal muscle	Voluntary wheel running	Insulin-induced vasorelaxation ↑	61
OLETF rats	Male	IR	Gastrocnemius feed artery	Voluntary wheel running	ACh-induced vasorelaxation ↑	62
			Soleus feed artery		ACh-induced vasorelaxation =	
Low intrinsic aerobic treadmill running capacity rats	Male	Metabolic syndrome	Aorta	Continuous moderate-intensity exercise, high-intensity aerobic interval training	ACh-induced vasorelaxation ↑	63

ACh, acetylcholine; Ex, exercise; IR, insulin resistance; MS, metabolic syndrome; OLETF, Otsuka Long–Evans Tokushima Fatty; ↑, increase; =, no change.

muscle and aorta (Table 3). However, it is still unclear which mechanisms are involved in these beneficial effects of exercise. Table 3 summarizes the effect of exercise on vascular dysfunction induced by insulin resistance or metabolic syndrome in experimental animal models.

4. Conclusion

There is no doubt that physical activity or regular exercise has beneficial effects on vascular function. However, it should

be noted that some discrepancies exist among these studies according to experimental design including type of exercise, intensity and duration of exercise, and heterogeneity of vascular beds. It seems that vascular function in smaller resistant arteries may be altered differently compared to larger vessels such as aorta and conduit arteries, based on the status of disease, exercise type, duration, and intensity. Further investigations are needed to explain mechanisms involved in these signaling pathways.

Conflicts of interest

All authors have no conflicts of interest to declare.

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