

Improvement of Exercise Intervention on Vascular Endothelial Functions during Prediabetes Mellitus

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ABSTRACT. Prediabetes is considered to be an at a risk state, with an annualized 5-10% conversion rate of diabetes and the similiar proportion converting back to normoglycaemia. The global incidence of prediabetes is increasing and will reach to 471 million patients in 2030. The elevation of blood sugar is a continuum and hence prediabetes cannot be considered an entirely benign status and present insulin resistance (IR) and β -cell dysfunction, so that the development of prediabetic complications and vascular endothelial dysfunction. Therefore, it is crucial to early recognition and treatment of prediabetic individuals. For prediabetic individuals, lifestyle modification is the cornerstone of diabetes prevention with evidence of a 40-70% relative risk reduction. In the review, we include the possible mechanism of IR-induced vascular endothelial dysfunction, and exercise intervention improving the vascular endothelial dysfunction. These results showed clearly positive effects of physical exercise intervention and provided a direct

clinical evidence of the effectiveness of this approach for preventing early diabetes

KEY WORDS: Exercise Intervention, Vascular Endothelium, Endothelial Dysfunction, Impaired Glucose Tolerance, Insulin Resistance, Prediabetes Mellitus.

INTRODUCTION

Prediabetes represents an elevation of plasma glucose above the normal range but below that of clinical diabetes (Tabák et al., 2012). Prediabetes can be identified as either impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) (Grundy, 2012). During the IGT stage, insulin resistance (IR) and disorders of glucose metabolism commonly occur (Reaven, 2011). Excessive insulin secretion occurs in IR (Reaven, 2011). IR is affected by obesity, less physical activity and genetics (Mazzali et al., 2006). In modern life, sedentary lifestyle results in higher prevalence of IGT and diabetes with IR. Daqing trial in China (Pan et al., 1997), a diabetes prevention study in Finland (Tuomilehto et al., 2001) and a diabetes prevention program in America (Knowler et al., 2002) suggest that lifestyle modification in IGT patients obviously reduces the risk of diabetes. Therefore, treatment at the IGT stage may be the momentous way to diabetes prevention.

The cardiovascular morbidity in IGT is analogous to in diabetes (Schnell and Standl, 2006), so IGT develops into diabetes and increases the incidence of cardiovascular disease (Schnell and Standl, 2006). Endothelial dysfunction is a pivotal predictor of cardiovascular disease (Frick and Weidinger, 2007). Because of obesity is closely related to IR, endothelial dysfunction may lead to diabetic vasculopathy and is an important pathogenesis of cardiovascular disease (Schnell and Standl, 2006; Frick and Weidinger, 2007; Reaven, 2011). As a result, early detection and treatment of prediabetes is a great way to restore endothelial function and prevent diabetic cardiovascular complications.

Now, exercise has significant function on controlling IGT, diabetes and cardiovascular disease that make it the optimal choice for treating metabolic syndrome (Ryan, 2010; O'Gorman and Krook, 2011). Some researches demonstrate that exercise can bring many changes, such as much energy consumption, muscle mass growth, loss of body fat and affecting the endocrine system (Ryan, 2010; Haque et al., 2011; O'Gorman and Krook, 2011). In recent years, people have focused on the characteristics of exercise intervention relative to other methods: simple, safe, low cost and easy implementation (Ryan, 2010; Haque et al., 2011; O'Gorman and Krook, 2011).

Therefore, in this review, we summarize the possible mechanisms of IR-induced vascular endothelial dysfunction and the effects of exercise intervention on vascular endothelial function.

Definition of prediabetes

Various organizations have defined prediabetes with criteria that are not uniform. The World Health Organization defines prediabetes as a state of intermediate hyperglycemia using two specific parameters, IFG defined as fasting plasma glucose of 110-125 mg/dL and IGT defined as postload plasma glucose of 140-200 mg/dL based on 2h oral glucose tolerance test or a combination of both (WHO and IDF, 2006). The American Diabetes Association's prediabetic definition is as follows: the same IGT threshold, IFG cut-off value of 100-125 mg/dL and hemoglobin A1c 5.7- 6.4% (ADA, 2014).

In 2010, the global prevalence of IGT is about 343 million and the International Diabetes Federation predicts that prediabetic patients will reach 471 million by 2035 (IDF, 2015). Furthermore, the annual probability of prediabetes converted to diabetes is about 5-10%, with similar proportion converting back to normoglycaemia (Gupta et al., 2016).

Definition of endothelial dysfunction

The intact vascular endothelium prevents the injury of blood vessel under physiological conditions and has many biological functions: blood vessel reconstruction, vasculogenesis, and so on (Altaany et al., 2014). The normal endothelium can resist vascular inflammation (Agarwal et al., 2016; Zhang et al., 2016). In endothelial cells, leukocyte adhesion relies mainly on proinflammatory cytokines which are subject to nitric oxide (NO) (Hartge et al., 2007). The consensus is that endothelial injury can launch the inflammatory cascade reaction in vessels (Su, 2015; Castellon and Bogdanova, 2016). The main characters of endothelial dysfunction include reactive oxygen species (ROS) accumulation, activation of proinflammatory factors and decreased NO bioavailability (Widlansky and Gutterman, 2011). Endothelial dysfunction results from the imbalance of

vasodilators and vasoconstrictors and closely related with atherosclerosis, diabetes, obesity, etc (Skrypnik et al., 2014).

The possible mechanism of causing vascular dysfunction

IR promotes a rise of glucose level in the blood flow. The vascular endothelium is the single layer in the innermost zone of blood vessel so that hyperglycemic stress may impair the vascular endothelial cells, suggesting that metabolic syndrome such as IR and diabetes may result in vascular dysfunction (Kaiser et al., 1993). It has been demonstrated that the production of ROS is increased in both large and small vascular beds from hyperglycemic animal models (Brownlee, 2005). In the hyperglycemic environment, various biological signaling pathways regulate elevated ROS generation in vascular cells. For example, with help of a cofactor nicotinamide adenine dinucleotide phosphate, Aldose reductase converts glucose to sorbitol, thus the regeneration of reduced glutathione is reduced, and intracellular oxidative stress level is increased (Vikramadithyan et al., 2005; Giacco and Brownlee, 2010; Hwang and Kim, 2014). Increased advanced glycation end-products activate corresponding receptor, which facilitates ROS and inflammatory cytokine production (Goldin et al., 2006; Yao and Brownlee, 2010). Activation of the diacylglycerol–protein kinase C pathway also contributes to the elevated generation of ROS and inflammatory cytokines (Pieper and Riaz-ul-Haq, 1997; Geraldles and King, 2010). In the overloaded glycolytic pathway induced by hyperglycemia, uridine diphosphate N-acetyl glucosamine inhibits endothelial NO synthase activity by phosphorylation of serine 1177 and increases the expression of proinflammatory factors, such as transforming growth factor-beta 1 and plasminogen activator inhibitor-1 (Sayeski and Kudlow, 1996; Du et al., 2000). In the vascular endothelium, activated oxidative stress directly reduced NO bioavailability, but also increased expression of proinflammatory cytokines, so that proatherogenic and prothrombotic processes are abnormally initiated (Pierce et al., 2009). Thus, the structural and functional integrity of vascular endothelium is likely to be damaged by IR, which increases the risk of cardiovascular disease in the condition that continuously exposed to hyperglycemia in the circulation.

Effects of exercise training on vascular endothelial dysfunction in prediabetic patients

At present, patients with metabolic syndrome can't enjoy the specific exercise guidelines which protect and improve their cardiovascular health. The American College of Sport Medicine and the American Diabetes Association only provide universal exercise programs for diabetic patients in their issued joint statements, and recommend aerobic exercise or aerobic plus resistance exercise to reduce the risk of cardiovascular disease in patients with diabetes (Albright et al., 2000; Colberg et al., 2010). However, some studies indicate positive effect of exercise on vascular endothelial function (Maiorana et al., 2001; De Filippis et al., 2006; Okada et al., 2010; Mitranun et al., 2014), while others may be ineffective for diabetic patients (Miche et al., 2006; Middlebrooke et al., 2006; Schreuder et al., 2014). A few researches present exercise intervention can improve vascular endothelial dysfunction in individuals with metabolic syndrome (Tjønnå et al., 2008; Vinet et al., 2015). It is established that insulin signal regulates NO production in vascular endothelial cells and IR facilitates vascular endothelial dysfunction in the vasculature (Manrique et al., 2014). As you know, IR is common pathogenesis of prediabetes, diabetes and metabolic syndrome, exercise promotes cardiovascular health in those with IR. Now, some studies show that aerobic exercise training contributes to reverse endothelial dysfunction of the conduit vessel in individuals with IR (De Filippis et al., 2006; Tjønnå et al., 2008; Mitranun et al., 2014), and combination of aerobic and resistance exercise has the same effect in the conduit vessel (Maiorana et al., 2001; Okada et al., 2010), the resistance vessel (Maiorana et al., 2001) and arteriole (Vinet et al., 2015). Our study team also demonstrate that after two intervention types (aerobic exercise and aerobic plus resistance exercise) are administered to prediabetic patients for 24 weeks, endothelial dysfunction of brachial artery is obviously improved, and the combination type is more effective (Liu et al., 2013). Otherwise, it seems that exercise performance is mainly affected by exercise intensity in IR state. Abnormal vascular endothelial function can be improved by moderate-intensity continuous training or high-intensity interval training, if the energy consumption is equal, high-intensity interval training presents superior effect on vascular endothelial function (Tjønnå et al., 2008; Mitranun et al., 2014).

At present, it is not fully understood the internal mechanism of exercise intervention improving IR-induced vascular endothelial dysfunction. Positive changes in oxidative stress and inflammatory indices after exercise training are thought to be underlying mechanisms from animal and systemic biomarker studies (Ostergård et al., 2006; Zoppini et al., 2006), but no exploring the local alterations of potential biomarkers in IR human vasculature in response to acute or chronic exercise training. Furthermore, it is also necessary to figure out a mechanistic linkage between exercise intensity and functional alteration of vascular endothelium.

Effects of exercise intervention on IR-induced vascular dysfunction in animal models

Currently, many researches show that IR or metabolic syndrome induced vascular dysfunction in animal model, but some studies demonstrate that endothelial function don't change in prediabetic state. These inconsistent results indicate multiple factors affect vascular function, such as duration of disease and vascular beds. A lot of studies find that IR result in endothelial dysfunction in various blood vessels, including coronary arteriole (Park et al., 2012), gracilis artery (Lamping et al., 2013), femoral artery (DeMarco et al., 2015) and aorta (Xu et al., 2011) in mouse model, nevertheless, some studies reveal IR no inducing vascular dysfunction in femoral artery (DeMarco et al., 2015), mesentery arterioles (Jang et al., 2013) and aorta (Lee et al., 2012).

We know that exercise intervention has the positive effect on animal models with metabolic diseases. Considering previous studies, most exercise program promotes vascular function in various blood vessels. Voluntary wheel running improves IR-induced vascular endothelial dysfunction in mouse coronary arteriole (Park et al., 2012), rat arteriole (Mikus et al., 2012) and rat feed artery (Bender et al., 2011). Treadmill exercise has the same effect in mouse aorta (Xu et al., 2011).

CONCLUSION

Prediabetes is a heterogeneous state that is characterized by coexistence of IR and β -cell dysfunction, and increase the risks of converting to diabetes or causing its complications. Therefore, it is crucial to early recognition and treatment of prediabetic individuals. It is generally accepted that physical activity or regular exercise has beneficial effects on vascular function. However, prediabetic subjects are few in experiment studies. Design experiment from exercise type, intensity and duration, heterogeneity of vascular beds and disease status, etc. Otherwise, currently there are little data assessing different prediabetes screening and treatment strategies in terms of cost-effectiveness and health benefits. Meanwhile, it is necessary to further explore its regulatory mechanism.

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DISCLOSURE OF CONFLICT OF INTEREST

None.

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