CORONARY HEART DISEASE (J FARMER, SECTION EDITOR)

Diabetes and Hypertension: Is There a Common Metabolic Pathway?

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Abstract Diabetes and hypertension frequently occur together. There is substantial overlap between diabetes and hypertension in etiology and disease mechanisms. Obesity, inflammation, oxidative stress, and insulin resistance are thought to be the common pathways. Recent advances in the understanding of these pathways have provided new insights and perspectives. Physical activity plays an important protective role in the two diseases. Knowing the common causes and disease mechanisms allows a more effective and proactive approach in their prevention and treatment.

Keywords Diabetes · Hypertension · Obesity · Metabolic syndrome · Metabolic pathway · Insulin resistance

Introduction

Hypertension and diabetes are two of the leading risk factors for atherosclerosis and its complications, including heart attacks and strokes. There is substantial overlap between diabetes and hypertension, reflecting substantial overlap in their etiology and disease mechanisms. In the Hong Kong Cardiovascular Risk Factor Prevalence Study, only 42% of people with diabetes had normal blood pressure and only

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56% of people with hypertension had normal glucose tolerance [1•]. In the US population, hypertension occurs in approximately 30% of patients with type 1 diabetes and in 50% to 80% of patients with type 2 diabetes [2]. A prospective cohort study in the United States reported that type 2 diabetes mellitus was almost 2.5 times as likely to develop in subjects with hypertension as in subjects with normal blood pressure [3]. In reality, diabetes and hypertension are found in the same individual more often than would occur by chance, whereas the overlap between dysglycemia and raised blood pressure is even more substantial than that between diabetes and hypertension [4]. This suggests either shared genetic or environmental factors in the etiology [1•].

Etiology

Genetics

Genome scans involving thousands of subjects and controls have revealed a large number of genes with small effects, as opposed to a small number of genes with large effects anticipated originally [5, 6]. Genetic variants in the gene encoding angiotensinogen, adrenomedullin, apolipoprotein, and α-adducin have been reported to be associated with common conditions such as diabetes, hypertension, dysglycemia, or metabolic syndrome [7–10].

In Hong Kong studies of single nucleotide polymorphisms (SNPs), SNPs that predict the development of diabetes were found also to predict the development of hypertension [11–14]. In genome scans in Hong Kong Chinese individuals, the region associated with diabetes was also associated with the metabolic syndrome, which includes hypertension as a component [15, 16]. A recent study at Columbia University on somatic gene conversion

and deletion suggested that multitudes of common SNPs are involved [17•].

Besides the genetic aspect, another very important aspect for the onset of diabetes and hypertension is environmental. Environmental factors include the period in utero and lifestyle factors such as diet and physical activity. Gestational diabetes, fetal malnutrition, and high birth weight are three factors that may predispose the fetus to cardiometabolic syndrome in adulthood [18, 19•, 20]. High intake of sodium, alcohol, and unsaturated fat, smoking, lack of physical activity, and mental stress are examples of an unhealthy lifestyle.

It is now realized that insulin resistance, which predicts type 2 diabetes, also has a role in the development of hypertension [21]. Indeed, hypertension and diabetes substantially share common pathways such as obesity, inflammation, oxidative stress, insulin resistance, and mental stress.

Obesity

Obesity, a global health problem, has been identified as the most important risk factor for hypertension and diabetes [22]. Obese persons have a significantly higher risk of hypertension and type 2 diabetes [23•]. Studies of obesity in Western countries where there is a high prevalence have led to a greater understanding of the phenomenon of risk factor clustering and of the pathophysiologic links among hypertension, obesity, diabetes. Obesity is generally considered as the combined result of dysfunction of feeding center in the brain, imbalance in energy intake and expenditure, and genetic variations. Obesity is largely determined by genes; approximately 50% to 90% of the variation in weight is the result of genetic predisposition according to twin studies [24, 25]

The obese (ob) gene that was discovered in 1950 was the first gene identified to be related to the onset of obesity [26]. From then on, researchers have sought to identify the genetic factors of obesity in addition to studying metabolic physiology. Genome-wide association studies have revealed a number of genes influencing the susceptibility to obesity [27–29]. The *FTO* gene, promoting obesity and overeating, was one of the key obesity susceptibility genes. Together with the *GNDPA 2* gene, they predict persistent central obesity in the Chinese population [10]. Other likely diabetes-related genes include *BCDIN3D/FAIM2*, *SH2B1*, and *KCTD15* [29–32] as well as *CRTC3*, which has been shown to slow down the speed of fat oxidation [33].

It is not surprising to find that diabetes and obesity share some common susceptibility genes. As obesity is a common factor in the etiology of hypertension and diabetes [1•], we would expect that hypertension, diabetes, and obesity not only share common pathophysiologic pathways but also common susceptibility genes.

Inflammation and Oxidative Stress

A low-grade inflammatory process occurs in both diabetes and hypertension [34–38]. Even chronic periodontitis is a latent factor in the development of diabetes, hypertension, cardiovascular diseases, and the metabolic syndrome [39–45]. In some ways, diabetes and hypertension could be considered as chronic inflammatory diseases.

Inflammatory markers (eg, C-reactive protein (CRP)) are increased in patients with diabetes, hypertension, and the metabolic syndrome, and also predict the development of these diseases [46–48]. The local renin-angiotensin-aldosterone system (RAAS) plays a very important role in vascular pathophysiology. Angiotensin-converting enzyme (ACE) is expressed in the shoulder of coronary artery plaques. Angiotensin II (Ang II) is to a large degree responsible for triggering vascular inflammation and inducing oxidative stress [49]. It stimulates NADH/NADPH oxidase, and activates Rho/Rho kinase, protein kinase C (PKC), and mitogen-activated protein kinase (MAPK) [50–53]. Also, Ang II down-regulates proinflammatory transcription factors such as nuclear factor-κB (NF-κB), resulting in the generation and secretion of reactive oxygen species (ROS), inflammatory cytokines (eg, interleukin-6 [IL-6]), chemokines, and adhesion molecules [54, 55]. These actions lead to endothelial dysfunction and vascular injury.

Gene regulatory network analysis has revealed oxidative stress as a key underlying molecular mechanism in diabetes and hypertension. The oxidative stress-mediated regulation cascade is the common mechanistic link among the pathogenesis of diabetes, hypertension, and other related inflammatory diseases [56].

Peroxisome proliferator-activated receptor (PPAR) activators lower blood pressure, induce favorable effects on the heart, and ameliorate endothelial dysfunction through antioxidant, anti-inflammatory, antiproliferative, antihypertrophic, and antifibrotic effects [57]. Ang II down-regulates the mRNA and protein of PPAR-α and PPAR-γ, resulting in the reduction of PPAR anti-inflammatory capacity and activation of inflammation. PPAR-α and PPAR-γ activators have been demonstrated to exert cardiovascular protective effects independent of their metabolic actions [58]. However, recent studies with dual PPAR activators have cast doubts on their clinical efficacy in cardiovascular prevention compared with the original PPAR activators currently marketed [59, 60].

Traditional pharmacologic approaches such as statins, ACE inhibitors, and Ang II receptor blockers (ARBs), which reduce cardiovascular events in randomized clinical trials, also reduce vascular inflammation in patients with diabetes and hypertension [61–63]. Optimization of lifestyle (eg, weight loss, exercise, and Mediterranean-style diet) also has the effect of reducing vascular inflammation [64, 65•].

Insulin Resistance

Insulin is a pleiotropic hormone that plays a pivotal role in the development of hypertension, diabetes, and the metabolic syndrome. The main metabolic actions of insulin are to stimulate glucose uptake in skeletal muscle and heart and to suppress the production of glucose and very low-density lipoprotein (VLDL) in the liver [66]. Under fasting conditions, insulin secretion is suppressed, leading to increased glucose synthesis in the liver and kidneys (gluconeogenesis) and increased conversion of glycogen to glucose in the liver (glycogenolysis) [67]. After a meal, insulin is released from pancreatic β-cells and inhibits gluconeogenesis and glycogenolysis [67]. Insulin stimulates the sympathetic nervous system (SNS) to increase cardiac output and the delivery and utilization of glucose in the peripheral tissues [68]. Other metabolic effects of insulin include inhibition of glucose release from the liver, inhibition of the release of free fatty acids (FFAs) from adipose tissue, and stimulation of the process by which amino acids are incorporated into protein [67].

Insulin resistance, a condition in which defects in the action of insulin are such that normal levels of insulin do not trigger the signal for glucose absorption, denotes an impaired response to insulin in skeletal muscle, liver, adipose, and cardiovascular tissue [67, 68]. Insulin resistance arises due to various genetic, acquired, and environmental factors, including obesity [69]. Increased RAAS activities may also cause insulin resistance via the stimulation of Ang II type 1 receptors, which trigger increased production of reactive oxygen species (ROS) in adipocytes, skeletal muscle, and cardiovascular tissue of obese individuals [70, 71]. FFAs are believed to induce insulin resistance and increase the level of oxidative stress [70, 72, 73], resulting in endothelial dysfunction and atherogenesis [69, 70].

Insulin resistance is associated with impaired insulin signaling, impaired fibrinolysis, and inflammation. Emerging evidence suggests that insulin resistance may result from abnormalities in key molecules of the insulin-signalling pathways, including overexpression of phosphatases and downregulation and/or activation of protein kinase cascades [74], leading to abnormalities in the expression and action of various cytokines, growth factors, and peptides, and overproduction of VLDL [75]. Insulin resistance may also result in impaired fibrinolysis, which is characterized by hypercoagulability and elevation of fibrinogen and plasminogen activator inhibitor (PAI)-1 [76, 77]. PAI-1 activity is elevated in a wide variety of insulin resistance patients. Even in patients with normal glucose tolerance, elevated levels of fasting insulin are associated with impaired fibrinolysis [76]. Therefore, insulin resistance is a prothrombotic state characterized by an elevation of PAI-1 and fibrinogen levels, leading to increased risk of cardiovascular events [75, 77].

Insulin resistance may be a result of an overproduction of proinflammatory cytokines (eg, IL-6, tumour necrosis factor (TNF), and CRP) and a relative deficiency of anti-inflammatory cytokines (eg, adiponectin) produced from adipose tissues due to obesity [78].

Insulin-mediated glucose uptake by muscle varies more than sixfold in apparently healthy individuals [79], with approximately half of the variability in insulin action being genetically determined and the other half resulting from differences in the degree of adiposity and physical fitness [80, 81]. Most patients with type 2 diabetes are insulin resistant, and about half of those with essential hypertension are insulin resistant [82]. Therefore, insulin resistance is an important common link between diabetes and hypertension.

Mental Stress and Sympathetic Nervous System

Stressors are intrinsic or extrinsic stimuli leading to disturbances in physiology and psychology, and may threaten health. Compared with physical stressors, modern stressors arising from psychological threat (eg, work stress, domestic violence, and natural disasters) are more sustained. Chronic mental stress, resulting from the modern lifestyle, is frequently associated with physiologic and psychological disturbances, and may indirectly lead to diabetes and hypertension [83–87].

Although epidemiologic investigations have demonstrated that mental stress is associated with hypertension, cardiovascular disease, obesity, and the metabolic syndrome (which includes diabetes as a component) [88–92], the effect of mental stress on the whole body is not completely understood. Animal experiments taught us that the mechanisms include renal sympathetic nerve activity (RSNA) [93, 94] and blood pressure control in which baroreflex function [95–97] is involved.

In the human body, stimulation of the sympathetic nervous system (SNS), caused by chronic stress, elevates pulse rate and cardiac minute output and also activates the RAAS, which is another important pressor mechanism [86]. Increased activity of the SNS also plays a part in the development of impaired glucose [87] and lipid metabolism [83, 98]. Studying the SNS and RAAS allows us to understand their roles in the etiology and treatment of hypertension, metabolic syndrome, and diabetes [84].

There is also a link between mental stress and obesity in patients with diabetes and hypertension. A high prevalence of hypertension in obese subjects has been related to psychosocial factors, including chronic stress [99–101]. The hypothalamic–pituitary–adrenal axis was suggested as a key mechanism linking obesity, hypertension, and chronic stress [101, 102]. Therefore, people should reduce stress to escape from the vicious cycle of mental stress, obesity, diabetes, and hypertension.

Physical Activity

In the Da Qing Impaired Glucose Tolerance and Diabetes Study, incident diabetes decreased by 46% in the exercise group [103]. In the nonrandomized Malmö Feasibility Study in 260 middle-aged men with impaired glucose tolerance, the incidence of diabetes was 50% lower in the intervention group after 5 years [104]. In the Finnish Diabetes Prevention Study, subjects with a change in moderate-to-vigorous leisure-time physical activity (LTPA) in the highest tertile were 49% to 65% less likely to develop diabetes than those in the lowest tertile [105]. In the Coronary Artery Risk Development in Young Adults study (CARDIA) with over 15 years of follow-up, there was a significant 17% reduction of risk of incident hypertension for every 300-exercise unit increment in average physical activity [106]. In the Athero-sclerosis Risk in Communities (ARIC) study, the highest quartile of leisure activity (primarily cycling and walking) had a 34% lower odds of developing hypertension over 6 years compared to the least active [107]. Thus, physical activity reduces the risk of developing diabetes and hyper-tension. The mechanism involves changes in body weight and glucose tolerance, as well as other factors [107].

The effect of obesity susceptibility genes on the onset of obesity is influenced by physical activity in the individual. The genotypic effect of *FTO* is more pronounced in inactive than active individuals [108•]. The former are more likely to carry risk alleles such as rs9939609 [109]. Nevertheless, individuals meeting the daily physical activity recommen-dations may overcome the effect of *FTO* genotype on obesity-related diseases such as diabetes, hypertension, and the metabolic syndrome [110–112].

The potential benefits of physical activity in the preven-tion and treatment of diabetes and hypertension are well recognized but regular physical activity is difficult and sometimes impossible to carry out in real life. Public health efforts should nevertheless still aim to raise public aware-ness and facilitate regular physical activity to prevent against diabetes, hypertension, and other related diseases.

Conclusions

Diabetes and hypertension share common pathways such as SNS, RAAS, oxidative stress, adipokines, insulin resistance, and PPARs (Fig. 1). These pathways interact and influence each other and may even cause a vicious cycle. Hypertension and diabetes are both end results of the metabolic syndrome. They may, therefore, develop one after the other in the same individual. Central obesity is the cause of the metabolic syn-drome. Only orlistat is currently available for the long-term treatment of obesity [114]. Therefore, optimization of lifestyle
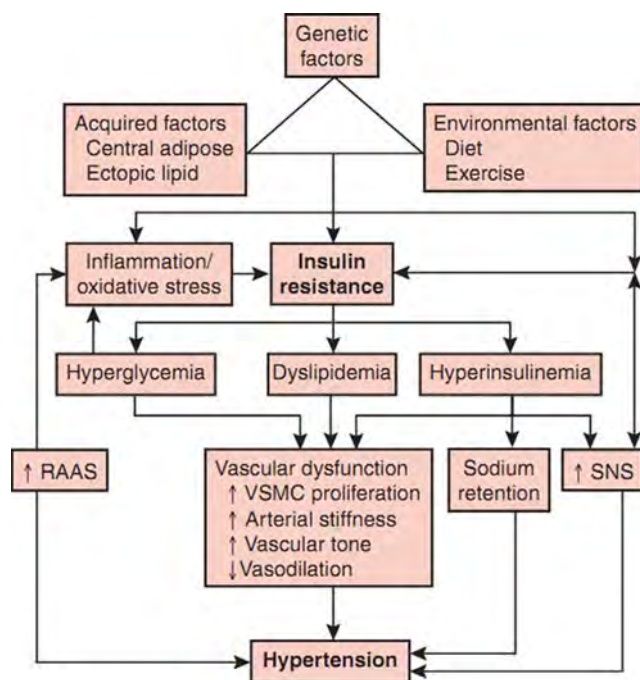

Fig. 1 Summary of putative pathophysiologic mechanisms in the development of hypertension in diabetes mellitus. RAAS—renin-an-giotensin-aldosterone system; SNS—sympathetic nervous system; VSMC—vascular smooth muscle cell. (*From* Mugo MN, Stump CS, Rao PG, Sowers JR. Chapter 34: Hypertension and Diabetes Mellitus. Hypertension: A Companion to Braunwald's Heart Disease. Copyright Elsevier, 2007 [113])

remains the cornerstone in the prevention and treatment of diabetes and hypertension.

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