REVIEW ARTICLE

Common metabolic features of hypertension and type 2 diabetes

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Abstract

Hypertension and type 2 diabetes frequently coexist, suggesting that the two diseases have common pathophysiological bases. This review describes the pathophysiological mechanisms of how type 2 diabetes is frequently associated with hypertension. Multiple common factors mediate between both diseases. Factors that induce both type 2 diabetes and hypertension include obesity-induced hyperinsulinemia, activation of the sympathetic nervous system, chronic inflammation, and changes in adipokines. Vascular complications resulting from type 2 diabetes and hypertension include endothelial dysfunction, vasodilation/constriction dysfunction of peripheral vessels and increased peripheral vascular resistance, arteriosclerosis, and chronic kidney disease. While many of these vascular complications are caused by hypertension, they also exacerbate the pathology of hypertension. In addition, insulin resistance in the vasculature blunts insulin-induced vasodilation and blood flow to skeletal muscle, which contributes to impaired glucose uptake to skeletal muscle and glucose intolerance. In obese and insulin-resistant patients, increase in the circulating fluid volume forms the major pathophysiology of elevated blood pressure. On the other hand, in non-obese and/or insulin-deficient patients, especially those in the middle- or later stages of diabetes, peripheral vascular resistance is the major pathophysiology of hypertension.

Keywords Hypertension · Type 2 diabetes · Obesity · Insulin resistance · Sympathetic nerve

Introduction

Type 2 diabetes and hypertension are both common diseases. For example, according to the 2019 National Health and Nutrition Survey Report in Japan, 19.7% of men and 10.8% of women were strongly suspected of having diabetes (defined as hemoglobin A1c greater than 6.5%) and 29.9% of men and 24.9% of women had a systolic blood pressure of 140 mm Hg or higher. Furthermore, diabetes and hypertension frequently coexist. The rate of hypertension in patients with diabetes is ~50%, which is about twice that in non-diabetic patients [1–4]. Conversely, the rate of diabetes in patients with hypertension is two to three times higher than in non-hypertensive individuals [1, 4–6]. In addition, the prevalence of concomitant diabetes and hypertension is even higher in patients with factors such as

older age, obesity, and renal dysfunction. The frequent coexistence of diabetes and hypertension suggests not only that they are common diseases but also that they have common pathophysiological bases. Genetic predisposition is one such common base [7], and patients with type 2 diabetes have characteristics that enhance the risk of developing hypertension. For example, a recent study identified a combination of 14 single nucleotide polymorphisms (SNPs) for hypertension in patients with type 2 diabetes and found that the number of SNPs was dose-dependently associated with the risk of hypertension [8]. However, acquired and modifiable factors such as excessive energy intake, alcohol consumption, smoking, and lack of physical activity are considered to be more strongly involved in the development and coexistence of both diseases. In particular, when obesity occurs as a result of these genetic and/or acquired factors, the risk of developing diabetes and hypertension increases further, as evidenced by their inclusion as components of metabolic syndrome [9].

Another important implication regarding the coexistence of diabetes and hypertension is that their coexistence further increases the risk of micro- and macrovascular complications [3, 10–13], e.g., the risk for cardiovascular diseases is

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Graphical Abstract

The relationship between various factors involved in the pathogenesis of type 2 diabetes and hypertension. It should be noted that all the factors shown in the figure are not necessarily present simultaneously in every patient.
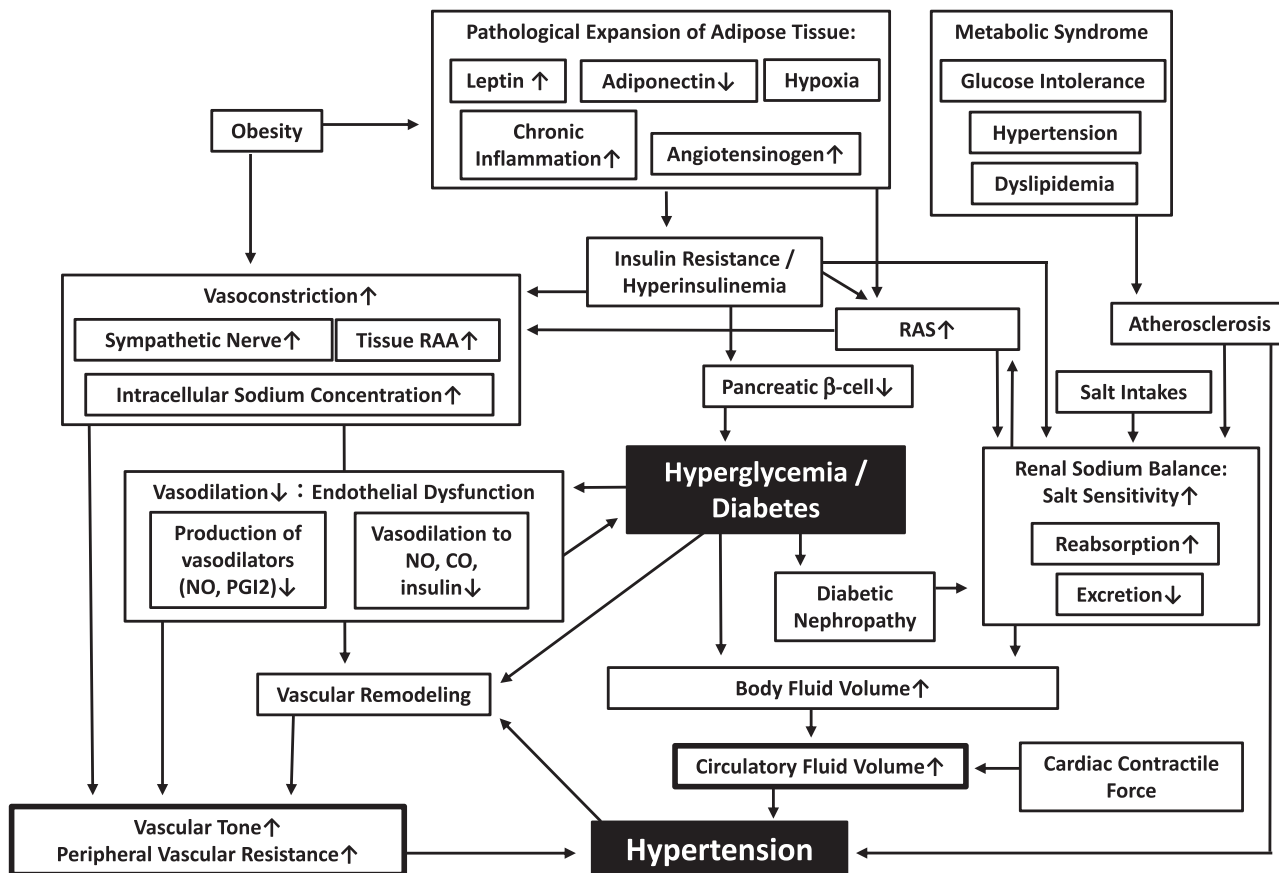
about fourfold higher in individuals with both diabetes and hypertension than in those without either disease [3, 10]. Consequently, it is recommended that blood pressure should be strictly controlled in patients with diabetes [13, 14]. In this review, we first outline the pathologies of type 2 diabetes and hypertension, which are closely related as mentioned above. I would like to review the relationship between these factors in pathology and consider how diabetes and hypertension coexist and whether there is a causal relationship between them.

Classification and pathophysiology of type 2 diabetes

All cases of type 2 diabetes have chronic hyperglycemia as a common feature, but the etiology and pathophysiology of the disease are diverse. The American Diabetes Association classifies the etiology into type 1 diabetes, type 2 diabetes, specific types of diabetes due to other causes, and gestational diabetes [15]. In addition, type 2 diabetes is often divided into a type in which obesity and insulin resistance are the main pathologies and another type in which obesity is not present and insulin secretion deficiency is the main pathology. This review explains the typical features of these two types below. However, the actual pathophysiologies of individual patients with type 2 diabetes cannot be explained only by being obese with insulin resistance or non-obese with insulin secretory deficiency, and most patients exhibit varying proportions of both features and are somewhere between these pathological classifications [15].

Type 2 diabetes with obesity and insulin resistance as the main pathology

As obesity progresses, adipocytes become larger and adipose tissue becomes hypertrophied. Such adipose tissue, especially visceral adipose tissue, undergoes histological and functional changes, referred to as "pathological expansion" or "unhealthy expansion", which include chronic inflammation, increased oxidative stress, hypoxia, tissue fibrosis, and alterations in adipocyte-derived

bioactive substances called adipokines in both human and rodent [16–19]. Among the features of pathological expansion, in particular a decrease in adiponectin and increase in the production of inflammatory cytokines such as tumor necrosis factor alpha (TNFα) and interleukin-6 (IL-6) are involved in the induction of whole-body insulin resistance. Hypertrophic adipose tissue is infiltrated by inflammatory M1 macrophages, which produce more inflammatory cytokines than enlarged adipocytes do [16, 19–21].

In non-obese individuals, fat is found mainly in subcutaneous adipose tissue, and adipocytes exert physiological functions such as producing and secreting adiponectin. However, as people gain weight, fat ectopically accumulates in visceral adipose tissue, liver (resulting in fatty liver), skeletal muscle, heart, kidney, perivascular, and pericardial spaces. This so-called ectopic fat accumulation impairs physiological tissue function. In the pathogenesis of obesity-associated glucose intolerance, some types of ectopic fat, such as visceral and hepatic fat, are involved in the induction of insulin resistance [21]. In addition, ectopic fat is also seen in the pancreas as interlobular or intralobular infiltration of adipocytes and accumulation of intracellular lipid droplets. The effect of pancreatic fat accumulation on glucose metabolism is still controversial, but research has suggested that fat-cell infiltration is involved in the deterioration of the insulin-secreting capacity through islet inflammation [22, 23].

The type of diabetes with strong insulin resistance is predominant in Western countries, and its etiology is related to lifestyle habits and environmental factors. In this context, it is important that although East Asian people, including Japanese, and Asian American people are less obese than people of other ethnicities, most of them also have varying degrees of insulin resistance before the onset of type 2 diabetes [15, 24]. Hyperinsulinemia occurs to compensate for insulin resistance, especially around the time of onset of type 2 diabetes. After long-lasting insulin resistance, the compensatory hypersecretion of insulin fails to match the resistance. As a result, insulin action is relatively deficient, blood glucose levels rise, and type 2 diabetes develops [15]. In addition, when insulin resistance is the underlying pathology and glucose intolerance is accompanied by metabolic abnormalities such as hypertension and dyslipidemia, metabolic syndrome or insulin resistance syndrome is diagnosed.

Type 2 diabetes with insulin deficiency as the main pathology

The mean body mass index (BMI) of Japanese patients with type 2 diabetes is about 25 to 26 kg/m^2 [25], which is clearly lower than the mean BMI of patients with type 2 diabetes in Western countries (30–32 kg/m^2) [26, 27]. The Japanese Society for the Study of Obesity defines obesity as a BMI of 25 or higher (in contrast, the WHO defines obesity as a BMI of 30 or higher), but one in two Japanese people with type 2 diabetes does not have obesity as defined by this criterion. On the other hand, the prevalence of diabetes is fairly similar in Japan and the United States, which is related to the fact that people in East Asian countries, including Japan, have a genetically lower ability to secrete insulin than people in Western countries [28]. Type 2 diabetes is generally caused by genetic and environmental factors. Whereas insulin resistance is associated more strongly with lifestyle and environmental factors, insulin secretion is more closely related to a genetic predisposition or family history in first-degree relatives (even more so than type 1 diabetes). However, the genetics of type 2 diabetes are not fully clarified, and they are under intense investigation in the context of precision medicine [9].

Type 2 diabetes in which the main pathology is hyposecretion of insulin is often not accompanied by obesity from the early stage of diabetes onset. Furthermore, even in patients with type 2 diabetes whose main pathologies were initially obesity and insulin resistance/hyperinsulinemia, over time pancreatic β-cell function decreases (so-called exhaustion of pancreatic β-cells), as do blood insulin levels. The ultimate result may be insulin dependence, in which patients require insulin injections to survive [15, 29].

It should be noted that the two typical features described above not only represent the different types of patients with type 2 diabetes but also may change over the course of an individual's medical history.

Pathophysiology of hypertension

The pathology of hypertension is primarily explained by increased circulatory fluid volume and increased peripheral vascular resistance [30]. The former is related to body fluid volume and cardiac contractile force. Body fluid volume is determined to a large extent by the balance between sodium excretion and reabsorption in the kidney, and this balance is affected by the renin-angiotensin-aldosterone system (RAS), salt intake, and salt sensitivity, among other things. Salt is excreted into the urine when blood pressure exceeds a certain threshold as classically described by Guyton's pressure–natriuresis relationship curve [31]. When the threshold is elevated, i.e., when increased blood pressure is required for urinary sodium excretion, the condition is defined as being strongly salt sensitive. Salt sensitivity is influenced by impaired sodium excretion from the kidneys, as is seen in older people and patients with chronic kidney disease, and excess sodium accumulation, as is seen in people with obesity and diabetes. Excess salt intake

combined with salt sensitivity leads to hypertension by increasing the volume of body fluid.

On the other hand, peripheral vascular resistance is related to vasoconstriction, vasodilation, and vascular remodeling. Vascular smooth muscle is the main effector of vascular constriction and dilation responses. The vasoconstrictive response is regulated by humoral factors such as RAS, catecholamines, and endothelin-1 and by neural regulation via sympathetic nerve activity, whereas the vasodilatory response is regulated by the release of vasodilators from vascular endothelial cells and responses to exogenous vasodilators such as nitric oxide (NO).

Insulin also has a vasodilatory effect that increases the delivery of insulin and glucose to target tissues, such as skeletal muscle [32]. In isolated arteries, the vasomotor effects of insulin are dependent on the balance between endothelial-derived NO-mediated vasodilation and endothelin-1-mediated vasoconstriction [33, 34]. The net effect of insulin is typically vasodilation in healthy subjects [35, 36]. Importantly, insulin also has effects that centrally activate the sympathetic nervous system and adrenergic receptor-mediated vasoconstriction, resulting in the limitation of NO-mediated vasodilation [32, 37, 38].

Vascular remodeling of resistance vessels (arterioles) increases peripheral vascular resistance because it constricts the lumen, and these changes increase intra-arterial blood pressure. Conversely, hypertension itself also induces several functional vessel abnormalities, such as impaired vasodilation due to endothelial dysfunction, remodeling of resistance vessels, and atherosclerosis of arteries. When hypertension coexists with other metabolic disorders, such as diabetes and dyslipidemia (e.g., in metabolic syndrome or insulin resistance syndrome), these changes progress further. Thus, hypertension and vascular functional and morphological abnormalities are mutually facilitative and lead to a vicious circle [30].

Pathophysiology of hypertension complicated with diabetes

Patients with diabetes have a high rate of comorbidity with hypertension, and vice versa. One reason for this relationship is that the two diseases have some common background factors and some disease mechanisms promote each other. The relationship between various factors involved in the pathogenesis of diabetes and hypertension is summarized in Fig. 1. However, it should be noted that all the factors shown in the figure are not necessarily present simultaneously in one patient. For example, among patients with type 2 diabetes, the major factors leading to hypertension are different in obese/insulin-resistant and non-

obese/insulin-deficient patients and in patients in different disease stages, as discussed below.

Most patients with type 2 diabetes have insulin resistance before plasma glucose levels become elevated. Compensatory hypersecretion of insulin by pancreatic β-cells can lead to hyperinsulinemia, especially before and after the onset of diabetes [15]. Hyperinsulinemia contributes to elevated blood pressure through several mechanisms; for example, insulin promotes sodium reabsorption and increases body fluid volume by opening the Na+/H+ transporter expressed in renal tubular cells [39, 40]. In addition, hyperinsulinemia activates the sympathetic nervous system and increases renin secretion, which elevates blood pressure by increasing peripheral vascular resistance and cardiac output [41]. Hyperinsulinemia is also involved in a mechanism for hypertension via sympathetic nerve activation in obesity even in the absence of diabetes. Furthermore, accelerated arteriosclerosis due to hyperinsulinemia also contributes to elevated blood pressure [21, 42].

Similar to insulin resistance, the pathological expansion of adipose tissue can predate the onset of type 2 diabetes [17, 18]. Changes in adipokines and increases in inflammatory cytokines in hypertrophied adipose tissue are also involved in the pathology of hypertension and cause glucose intolerance. In particular, the adipokine angiotensinogen, which is produced and released from enlarged adipocytes, activates RAS and enhances both body fluid retention and vasoconstriction, causing an elevation of blood pressure [43]. Although insulin acts to promote vascular remodeling, this process takes time and is milder in the earlier stages of diabetes than in the middle and later stages. Thus, during the earlier stages of diabetes, when insulin resistance is the predominant pathology, an increase in the circulating fluid volume is considered to be the major pathophysiology leading to hypertension [29].

As diabetes progresses, insulin secretion decreases because of the exhaustion of pancreatic β-cells (not because of an improvement in insulin resistance), and as a result, the direct effects of hyperinsulinemia are weakened. On the other hand, persistent hyperglycemia and oxidative stress impair vascular endothelial function, resulting in reduced production of endogenous vasodilators, such as NO and prostaglandin I2, and decreased reactivity to vasodilators, such as exogenous NO, and a reduced vasodilatory response. Vasoconstriction is also enhanced through the diabetes-associated enhancement of the sympathetic nervous system and tissue RAS [41]. Thus, increased peripheral vascular resistance is considered to be the major pathophysiology of hypertension in the middle and later stages of diabetes [29].

Furthermore, the development of chronic kidney disease because of diabetic kidney disease decreases the glomerular
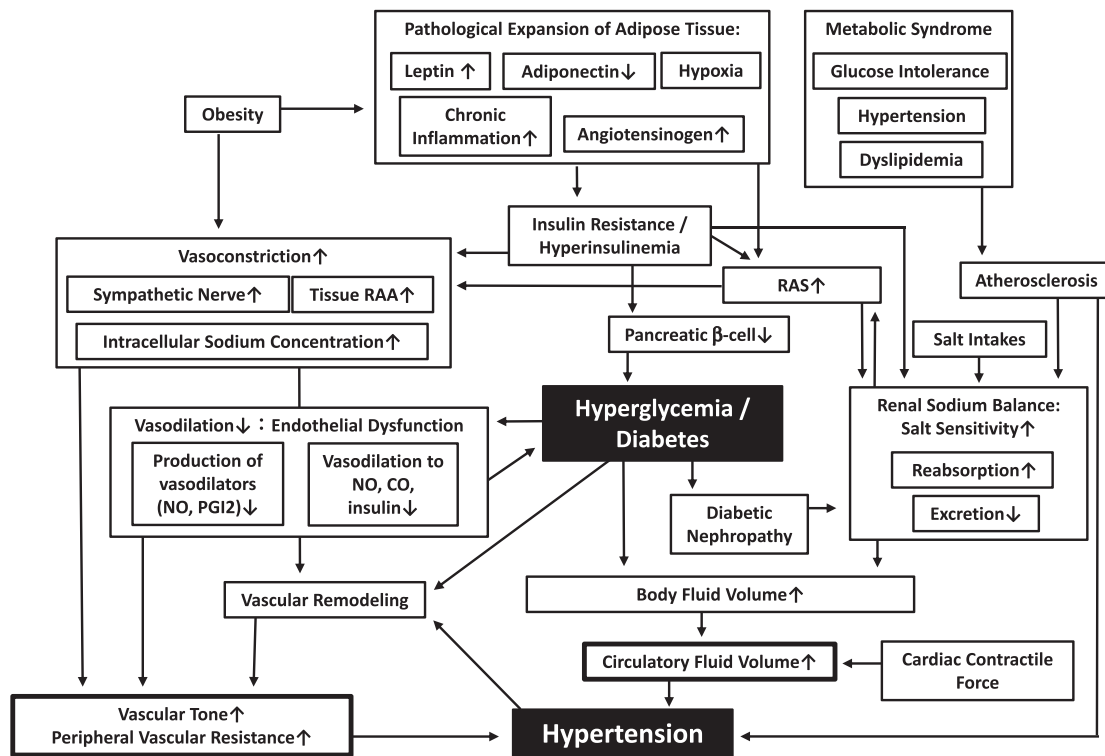
Fig. 1 The relationship between various factors involved in the pathogenesis of type 2 diabetes and hypertension. It should be noted that all the factors shown in the figure are not necessarily present simultaneously in every patient

filtration rate and sodium excretion from the kidney, further elevating blood pressure [44]. Concomitant arteriosclerosis also promotes an increase in blood pressure (Fig. 1) [21, 42]. In this review, detailed explanation about the involvement of these well-documented vascular complications in pathophysiology of hypertension will be avoided.

Conclusion

In this review, the pathophysiological mechanisms of how type 2 diabetes is frequently associated with hypertension were described. As described above, multiple common factors mediate between both diseases. They are not involved in the development of hypertension in all diabetic patients, and the factors involved differ for each patient, such as the presence or absence of obesity and the disease stage of diabetes. That is, in patients with obesity/insulin resistance as the main pathologies and in the early stages of diabetes, retention of body fluid forms the main pathology of hypertension. On the other hand, in non-obesity patients whose main pathology is insulin secretion deficiency or in the middle stage of diabetes or later, increased vascular resistance forms the main pathology of hypertension. These are not completely dichotomous, and there is a gradation between the two typical mechanisms (Fig. 1).
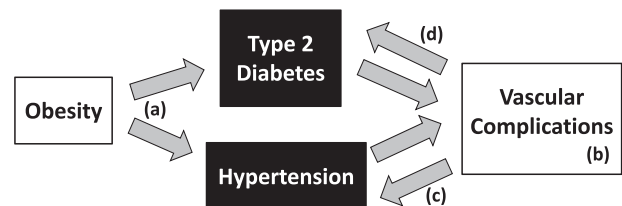

Fig. 2 Causal relationship of the factors between hypertension and type 2 diabetes. The causal relationship between various factors involved in the pathogenesis of diabetes and hypertension is summarized. **a** common factors that induce both type 2 diabetes and hypertension, **b** vascular complications resulting from type 2 diabetes and hypertension, **c** vascular complications which exacerbate hypertension, **d** vascular dysfunction which deteriorate glucose metabolism. It should be noted that all factors in this figure do not necessarily apply simultaneously to every patient

In addition, the causal relationships of these multiple factors are simplified and shown in Fig. 2. Factors that induce both type 2 diabetes and hypertension include obesity-induced hyperinsulinemia, activation of the sympathetic nervous system, and changes in adipokines (Fig. 2a). Vascular complications resulting from type 2 diabetes and hypertension, either alone or coexisting, include endothelial dysfunction, vasodilation/constriction dysfunction of peripheral blood vessels and increased peripheral vascular resistance, arteriosclerosis, and chronic kidney disease. (Fig. 2b). Many of these vascular

complications are caused by hypertension, but they also work to exacerbate the pathology of hypertension (Fig. 2c).

Finally, I will discuss only one point about whether vascular dysfunction is involved in the deterioration of glucose metabolism (Fig. 2d). Insulin signaling in vascular endothelial cells dilates blood vessels through the production of NO [32–36, 45]. Insulin resistance in the vasculature, which is observed in obesity and type 2 diabetes, blunts insulin-induced dilation in resistance arteries across vascular beds. Reduced insulin-stimulated vasodilation and blood flow to skeletal muscle limits glucose uptake and contributes to impaired glucose control in type 2 diabetes [32].

Compliance with ethical standards

Conflict of interest The author declares no competing interests.

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