REVIEW ARTICLE

Review Series-Hypertension with Diabetes Mellitus

Hypertension with diabetes mellitus: physiology and pathology

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Abstract

Elevated blood pressure is closely related to increased circulatory fluid volume and peripheral vascular resistance. Patients with diabetes mellitus experience increased peripheral artery resistance caused by vascular remodeling and increased body fluid volume associated with insulin resistance-induced hyperinsulinemia and hyperglycemia. Both of these mechanisms elevate systemic blood pressure. Thus, fully understanding the pathophysiology of hypertension in diabetes mellitus requires knowing the natural history of type 2 diabetes. Patients exhibit hyperinsulinemia with insulin resistance due to impaired glucose tolerance and early-stage diabetes. Hypertension occurs because of increased body fluid volume. After reaching mid-stage diabetes the vascular remodeling has progressed and peripheral vascular resistance also contributes to hypertension. Moreover, vascular remodeling strongly influences diabetic complications. Specifically, afferent arteriolar remodeling during diabetic nephropathy leads to increased glomerular pressure. Thus, treatment with a renin-angiotensin system inhibitor that promotes renal damage regression is critical to lowering the systemic blood pressure and dilating efferent arterioles to reduce glomerular pressure.

Introduction

Hypertension is a well-known complication of diabetes mellitus and diabetes is a well-known complication of hypertension [1]. In Japan, there are approximately 43 million patients with hypertension and 20.5 million patients with diabetes mellitus, including subjects with impaired glucose tolerance. Patients with diabetes can have elevated blood pressure and 40–60% of diabetes cases exhibit high blood pressure. Either diabetes or hypertension can present various complications without symptoms. The interaction between hypertension and diabetes can lead to the development of stroke and myocardial infarction, which represent major causes of death in Japan due to the progression of arteriosclerosis. Diabetic nephropathy also progresses rapidly as a result of blood pressure elevation. These findings suggest that considering the physiology and pathology of diabetes and hypertension are critical.

Pathology and physiology of blood pressure elevation

Figure 1 presents the current understanding of hypertension pathophysiology. Briefly, blood pressure is controlled by the relationship between circulatory fluid volume and peripheral vascular resistance [2]. The circulatory fluid volume is regulated by blood fluid volume and cardiac contractile force. The blood fluid volume is influenced by the sodium store/excretion balance (reflecting salt sensitivity and sodium intake). The cardiac contractile force is controlled by both sympathetic nervous activity and cardiac function. Peripheral vascular resistance is regulated by vascular tone,
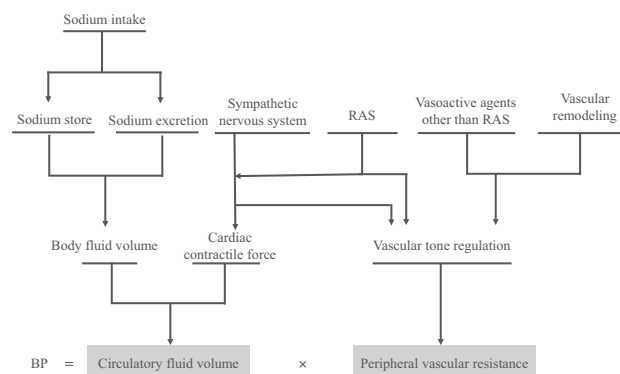
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Fig. 1 Hypertension pathophysiology

which is influenced by both vascular remodeling and vasoactive agents including the renin-angiotensin system.

High salt intake with salt sensitivity can lead to elevated blood pressure. This relationship can be understood by examining Guyton's pressure–natriuresis relationship curve [3], which shows that sodium excretion is promoted at a blood pressure level higher than the threshold in the kidney. Under strongly salt-sensitive conditions a higher blood pressure is required to excrete sodium via urine. Moreover, hypertension itself shifts the threshold to a higher level. Salt sensitivity is influenced by salt excreting dysfunctions that are common in aging patients, chronic kidney disease cases, and by salt accumulation observed in obesity, diabetes, and menopause. A diet with high salt intake combined with salt sensitivity reportedly leads to nocturnal hypertension [4], and this condition overlaps with morning hypertension in patients with chronic kidney disease [5]. Notably, patients with diabetes and nocturnal high blood pressure show a greater than 16-fold higher risk of cardiovascular events [6].

Resistance vessel narrowing via vascular remodeling promotes increased vascular resistance and blood pressure elevation. The endothelial dysfunction and vascular remodeling precede an increase in blood pressure. The development of arteriosclerosis involves oxidation stress, inflammation, vasoactive materials, cytokines, chemokines, and growth factors that can affect each other. If the functional vasoconstriction remains at a constant level, then there is blood pressure elevation observed in resistance vessels that undergo vascular remodeling. A cycle can develop and advanced vascular endothelial dysfunction promotes progression of vascular remodeling. The presence of coexisting risk factors (e.g., hypertension, diabetes, and dyslipidemia) promotes more advanced vascular endothelial dysfunction and ultimately produces damage to various organs [7].

The relationship between insulin and blood pressure elevation

Insulin lowers plasma glucose levels and is a key hormone in diabetes mellitus development. Insulin has several functions, including the following: facilitates glucose uptake by organs, promotes glycogen storage in liver and muscle tissue, controls the breakdown of stored glycogen, promotes adipose tissue development, and controls fat resolution [8]. Additionally, the insulin receptor is part of the receptor tyrosine kinase family that includes platelet-derived growth factor receptor and heparin-binding epidermal growth factor-like receptor. Thus, insulin also stimulates vascular smooth muscle cell migration and proliferation [9].

Insulin translocates Na^+/K^+-ATPase from the cytoplasm to the cell membrane to open the Na^+/H^+ channel that passively transports hydrogen ions out of the cell and sodium ions into the cell. This process also increases the cellular calcium ion concentration and decreases pH [10]. The Na^+/H^+ exchange transporter opens following the reduction of intracellular sodium, and this is caused by an insulin-induced increase of Na^+/K^+-ATPase. The action of Na^+/K^+-ATPase leads to sodium ion transport into blood vessels through renal tubule cells [11]. When an insulin deficiency leads to diabetic ketoacidosis the Na^+/K^+-ATPase activity decreases, which increases the transport of sodium and hydrogen into the cell and potassium out of the cell. These changes increase the cellular sodium ion density and lead to symptoms of high serum potassium [12]. However, when insulin resistance induces hyperinsulinemia the sodium reabsorption from renal tubules is increased and leads to high blood pressure [13].

The circulatory fluid volume can also increase relative to hyperglycemia-induced hyperosmolarity [14]. The prolonged high plasma glucose levels in diabetes cases alter the extracellular osmotic pressure on the side with higher glucose concentration, which increases relative to the intracellular osmotic pressure. Water exits the tissue (into the vasculature) to reduce the difference between the intracellular and extracellular osmotic pressure and this flow increases the extracellular amount of body fluid and blood (i.e., circulatory blood volume). Therefore, hyperglycemia also leads to systemic blood pressure elevation by increasing the circulatory fluid volume.

Hyperinsulinemia stimulates sympathetic nervous activity and increases renin excretion [15]. The increase in renin activates the sympathetic nervous system and increases cardiac output and peripheral vascular resistance. These changes ultimately elevate blood pressure by increasing both the circulatory fluid volume and peripheral vascular resistance. Moreover, insulin stimulates obesity through fat accumulation and this leads to obesity-induced hypertension in association with type 2 diabetes mellitus [16].

Hypertension and natural history of diabetes mellitus

It is critical to understand the natural history of diabetes and the pathophysiology that gives rise to this disease [17]. Type 2 diabetes is a complex metabolic disorder characterized by elevated blood glucose and a markedly increased risk of cardiovascular disease due to a cluster of metabolic and vascular abnormalities that include hyperglycemia, dyslipidemia, and hypertension. Tissue insulin resistance is an important part of the pathophysiology of type 2 diabetes and is often tied to obesity and/or adiposity. Insulin resistance and defective insulin secretion (relative insulin deficiency) are considered the key factors that
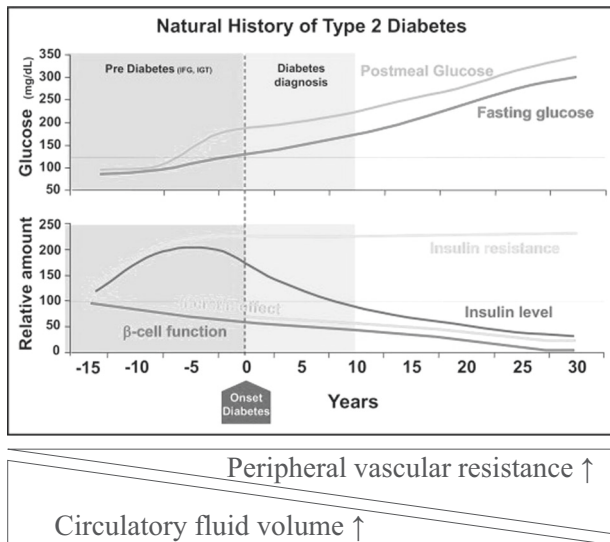
Fig. 2 Natural history of type 2 diabetes mellitus. *Source*: Ref. [18]

promote hyperglycemia, which is a characteristic of type 2 diabetes [18].

In the natural history of type 2 diabetes, insulin resistance prompts β-cells to secrete additional insulin, which initially increases the insulin levels (Fig. 2). However, the increased insulin secretion actually represents a relative insulin deficiency because β-cell function begins to deteriorate during the early course of type 2 diabetes. Impaired β-cell function is both necessary and sufficient for the development of pre-diabetes and diabetes onset. At the onset of diabetes, the level of insulin secretion no longer keeps pace with insulin resistance and β-cell function is already significantly reduced. According to the UKPDS, diabetes is often not clinically diagnosed until 10 years after its onset and at this time β-cell function may be reduced by over 50% [19]. It is now recognized that β-cell impairment arises and worsens several years before diabetes onset and the initial manifestation of postprandial hyperglycemia [20].

It is interesting that the pathophysiology of patients with hypertension and type 2 diabetes involves the natural history of type 2 diabetes and the above-described mechanisms of blood pressure elevation. The period from the initial impairment of glucose tolerance to diabetes onset is characterized by both hyperglycemia and hyperinsulinemia with insulin resistance. During this period the main pathologies causing blood pressure elevation are the promotion of sodium reabsorption due to higher insulin levels and excessive body fluid due to hyperglycemia-induced osmolar adjustment.

In the early stage of diabetes, both hyperglycemia and hyperinsulinemia can promote vascular remodeling. The gradual progression of vascular remodeling leads to increased peripheral artery resistance and eventually contributes to hypertension. The stages involving advanced vascular remodeling lead to pancreatic β-cell loss and attenuation of insulin secretion with a corresponding reduction of sodium reabsorption by insulin. At this time, the main mechanism causing blood pressure elevation is increased peripheral artery resistance because the increase of body fluid is stable with only osmolar adjustment due to hyperglycemia.

Vascular remodeling proceeds through all stages of diabetes and treatment with renin-angiotensin system inhibitors should be administered early in the disease course to prevent vascular remodeling [2, 21]. From a pathophysiological viewpoint, both sodium restriction and thiazide diuretics are useful treatments during early-stage diabetes involving hyperinsulinemia. Additionally, calcium antagonist treatment is advisable in the middle-to-late stage of diabetes when insulin production is lower. It is preferable to manage diabetes without insulin elevation to avoid increased fluid retention and vascular remodeling [22].

Hypertension and diabetic complications

The diabetic complications of macroangiopathy [23] and microangiopathy [24] are largely caused by vascular remodeling and are influenced by various components of metabolic syndrome including hypertension, diabetes, dyslipidemia, and obesity. The coexistence of hypertension with diabetes is associated with a 6-fold increase in the risk of cardiovascular events compared to in healthy subjects [25]. White coat and masked hypertension also increase cardiovascular risk in patients with diabetes and chronic kidney diseases [26].

Hypertension influences the development of diabetic nephropathy [27], which pathologically consists of the following: thickening of the glomerulus and renal tubule basement membrane, mesangial and interstitial proliferation, endothelium denaturation, and interstitial changes involving exudative lesions in small vessels [28, 29]. Diabetic nephropathy also involves smooth muscle cell proliferation with medial and intimal thickening of afferent arterioles [30]. There are also proinflammatory reactions such as T lymphocyte permeation and small vessel hyperplasia [31]. These changes are caused by hyperglycemia-induced glomerular circulation and renin-angiotensin system stimulation [32], glycation [33], and oxidative stress [34]. There are also intracellular metabolic abnormalities such as polyol and protein kinase activation [35], microinflammation, cytokine production [36], and extracellular matrix production or resolution [37]. Blood pressure elevation influences these mechanisms and diabetic nephropathy is worsened by glomerular hypertension due to afferent arteriole medial and intimal thickening with systemic hypertension [38].

Hyperglycemia and hyperinsulinemia induce medial and intimal thickening in afferent arterioles, which causes dysfunction of contraction and dilation and leads to failure of optimal control of glomerular pressure. In healthy individuals without diabetes or obesity the afferent arterioles contract to maintain glomerular pressure at 50 mmHg against systemic hypertension. However, diabetes-induced afferent arteriole dysfunction can allow glomerular pressure to increase to over 70 mmHg. The high glomerular pressure promotes hyperfiltration and lowers the serum creatinine concentration and leads to albuminuria. Continuous high glomerular pressure results in more dominant proteinuria and ultimately leads to decreased glomerular filtration due to mesangial denaturation or glomerular necrosis, which can progress to end-stage renal damage [39].

The reduction of glomerular high pressure is one possible means of avoiding end-stage renal failure. However, maintenance of optimal glomerular pressure requires strict systemic blood pressure control and dilation of efferent arterioles via renin-angiotensin inhibition [40]. Proper glomerular pressure control can reduce the hyperfiltration and glomerular filtration rate and increase serum creatinine. These changes should be monitored to achieve glomerular pressure adjustment without worsening renal function. The guidelines of the Japanese Society of Hypertension suggest that patients with diabetic nephropathy and hypertension should be treated with angiotensin receptor antagonists or an angiotensin-converting enzyme inhibitor to maintain a blood pressure of below 130/80 mmHg [2].

Compliance with ethical standards

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