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COMMENT

Optimizing antihypertensive therapy in patients with diabetes mellitus

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Hypertension is a common morbidity in patients with diabetes mellitus (DM) [1]. The coexistence of DM and hypertension synergistically increases the risk for macrovascular and microvascular complications, including coronary heart disease, peripheral artery disease, stroke, retinopathy, and nephropathy, as well as left ventricular hypertrophy and congestive heart failure, compared with DM or hypertension alone [2]. Clinical trials have demonstrated that adequate control of blood pressure (BP) significantly reduces the risk of these complications in diabetic patients [2]. On the other hand, it has been reported that many hypertensive patients with DM do not achieve optimal BP targets, which might be attributable to the pathophysiology of DM, therapeutic inertia, or patient-related factors, including poor medication adherence and difficulties in accessing specialist care [2]. Since the prevalence of hypertension and DM has been increasing worldwide [1], especially in the aged population, the management of hypertension in diabetic patients is an important topic in public health and clinical practice.

In this issue of *Hypertension Research*, Gnanenthiran et al. provided important information on the efficacy of BP-lowering therapies in hypertensive patients with DM [3]. The authors analyzed the data from the Triple Pill vs. Usual Care Management for Patients with Mild-to-Moderate Hypertension (TRIUMPH) study, a randomized, controlled, open-label trial of 700 patients with mild or moderate hypertension who required an initiation or escalation of antihypertensive therapy [4]. The TRIUMPH trial demonstrated that in patients with mild or moderate hypertension, treatment with a low-dose triple combination pill, which contained half the standard dose of telmisartan (20 mg), amlodipine (2.5 mg), and chlorthalidone (12.5 mg), significantly improved the achievement of the BP target at the 6-month follow-up compared with usual care at the discretion of treating physicians. In this post hoc analysis of the TRIUMPH trial, the authors found that the triple combination pill achieved greater BP reduction than usual care after 6 months of follow-up, regardless of the presence or absence of DM. In addition, the observed BP reduction was lower in patients with DM than in those without DM regardless whether the triple combination pill or usual care was administered, although there was no difference in the number of drugs prescribed or the predicted efficacy of treatment between patients with and without DM. Multivariate analysis revealed that DM was a negative predictor of the change in BP. Although detailed information on DM control status and medications was lacking, the findings of this study suggest that DM might reduce the efficacy of antihypertensive drugs, indicating that more aggressive BP-lowering therapies might be necessary for the treatment of mild or moderate hypertension in patients with DM than in those without DM.

Hypertension and DM share common pathophysiologies that interact with each other, including neurohumoral activation, such as the overactivity of the sympathetic nervous system, renin-angiotensin-aldosterone system (RAAS) activation, abnormal renal sodium handling and volume overload; vascular remodeling, such as endothelial dysfunction, arterial stiffness and increased peripheral vascular resistance; oxidative stress; and inflammation, although detailed initiating mechanisms remain unknown (Fig. 1) [5]. Consistently, more than 50% of diabetic patients are reported to have hypertension; approximately 20% of hypertensive patients have DM [1]. These common pathophysiologies might be affected by genetic and environmental factors. Hyperinsulinemia and

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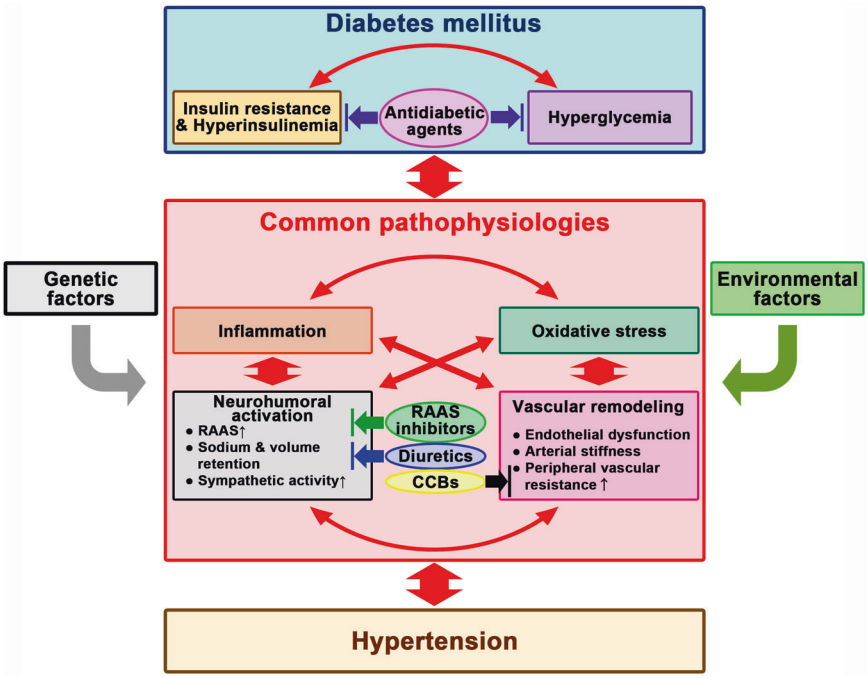

Fig. 1 Common pathophysiologies in hypertension and diabetes mellitus and medical treatment. Hypertension and diabetes mellitus share common pathophysiologies, such as neurohumoral activation, vascular remodeling, oxidative stress and inflammation, that form complex vicious cycles. These pathophysiologies might be affected by genetic and environmental factors. Insulin resistance and hyperglycemia drive these vicious cycles, which might reduce responsiveness to blood pressure-lowering drugs, including renin-angiotensin-aldosterone system (RAAS) inhibitors, calcium channel blockers (CCBs) and diuretics, in hypertensive patients with diabetes mellitus

insulin resistance precede the development of type 2 DM and are associated with selective impairment of insulin signaling, in which the phosphoinositide 3-kinase/Akt pathway is suppressed, whereas the extracellular signal-regulated mitogen-activated protein kinase pathway is overstimulated [6]. Hyperglycemia induces the activation of the aldose reductase pathway and protein kinase C and the production of advanced glycation end-products that activate their receptors [6]. These changes in signaling pathways cause suppressed endothelial nitric oxide synthase activity and production of nitric oxide, the activation of vascular smooth muscle cells, RAAS and sympathetic activation, oxidative stress, and inflammation, which might raise BP through endothelial dysfunction, arterial stiffness, and sodium and volume retention. Elevated BP increases mechanical stress on the vasculature and exacerbates the common pathophysiologies. Impaired endothelium-dependent vasodilation is suggested to deteriorate insulin resistance by limiting the delivery of glucose to target tissues [7]. Collectively, the common pathophysiologies in hypertension and DM form vicious cycles that accelerate cardiovascular complications. Since first-line antihypertensive drugs, such as RAAS inhibitors, calcium channel blockers and diuretics, target these pathophysiologies, more aggressive suppression with higher titrations of drugs might be necessary to counter the driving force of these vicious cycles by insulin resistance and hyperglycemia in patients with DM than in those without DM.

There are three therapeutic strategies that could improve BP control in hypertensive patients with DM that are not mutually exclusive: the uptitration of antihypertensive drugs, the improvement of DM control through lifestyle interventions or diabetes medications, and the targeting of the common pathophysiologies in hypertension and DM that are not directly targeted by antihypertensive or antidiabetic medications, such as inflammation. Based on the multifactorial nature of hypertension in patients with DM, the combination of first-line antihypertensive drugs from different classes might be a rational strategy to achieve BP targets. In fact, the current hypertension guidelines recommend starting pharmacological treatment of hypertension with a single-pill combination [8]. In the present study, patients in the triple combination pill group achieved better BP lowering than those in the usual care group with a smaller number of antihypertensive drug classes. On the other hand, it remains unknown whether treatment with a higher number of different classes of BP-lowering drugs would result in better long-term clinical outcomes, including cardiovascular complications and DM control status, when optimal BP control is achieved in patients with DM. For example, diuretics might have a negative impact on insulin resistance, the lipid profile, and electrolyte balance and might affect long-term clinical outcomes, although the impact might be minimal when used in low or moderate dosages. Further studies will be necessary to examine the effect of various combinations of BP-lowering drugs on long-term clinical outcomes in patients with DM. These studies might add important information on whether physicians should treat diabetic patients with inadequate BP control by dosage titration of an initial drug or sequential addition of drugs from different classes as the next step if they started with monotherapy.

Obesity is a common risk factor for both DM and hypertension. A recent meta-analysis found that lifestyle

interventions, such as the reduction of excess body weight through caloric restriction, sodium restriction, and physical activity, can help lower BP in patients with type 2 DM [9]. Sodium glucose cotransporter-2 inhibitors reduce BP through diuresis, nephron remodeling, reduced arterial stiffness, and weight loss [10]. Glucagon-like peptide-1 receptor agonists also have a mild reduction effect on BP [11]. However, it remains unclear whether DM control status or medications affect responsiveness to BP-lowering drugs. Further studies with detailed information on DM control status and DM medications will be necessary to clarify whether the combination of antihypertensive drugs and lifestyle interventions or antidiabetic medications would have synergistic, rather than additive, effects on BP control.

Hypertension and DM are both low-grade chronic inflammatory diseases. Inflammation significantly contributes to the pathophysiology of their complications, such as atherosclerosis and cardiac remodeling [12]. Recently, anti-inflammatory therapies, including neutralizing antibodies against proinflammatory cytokines and inhibitors targeting pattern recognition receptors, have shown therapeutic potential for the treatment of atherosclerosis and heart disease [13]. Although a secondary analysis of the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) demonstrated that treatment with an anti-interleukin-1β neutralizing antibody did not reduce BP [14], pharmacological inhibition of the NLRP3 inflammasome showed the potential to reduce BP in mice with established hypertension [15]. The effect of anti-inflammatory therapies on BP and glycemic control in diabetic patients with cardiovascular complications might be worth investigation in future studies.

The TRIUMPH study demonstrated that the initiation of antihypertensive drugs from three different classes at once in a single pill did not cause a higher rate of serious adverse events or the withdrawal of any BP-lowering medications due to adverse events compared with usual care in a relatively young population with mild or moderate hypertension [4]. However, it is unclear whether the initiation of a triple combination pill is safe for diabetic patients, especially in the elderly population with progressive atherosclerosis, compared to the initiation of two-drug combinations or monotherapy with sequential addition of other classes of drugs. Single-pill combination therapy might improve medication adherence. It might be important to clarify specific subpopulations of diabetic patients for whom triple combination pill therapy would be beneficial or harmful.

In conclusion, hypertensive patients with DM might be less responsive to antihypertensive medications than those without DM. Further basic and clinical knowledge will be necessary to establish optimal individualized BP-lowering strategies in hypertensive patients with DM.

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Compliance with ethical standards

Conflict of interest MS has received speaking honoraria from Bayer Yakuhin, Ltd., Mitsubishi Tanabe Pharma Corporation, Takeda Pharmaceutical Company, Ltd., Daiichi Sankyo Company, Ltd., and Nippon Boehringer Ingelheim Company, Ltd. MS has also received clinical research funding from Bayer Yakuhin, Ltd. and scholarship grants from Mitsubishi Tanabe Pharma Corporation, Takeda Pharmaceutical Company, Ltd., and Daiichi Sankyo Company, Ltd. MS is involved with the Department of Cardio-Diabetes Medicine funded partly by Boehringer Ingelheim Company, Ltd. The other authors declare no conflicts of interest.

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