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Obesity, impaired glucose tolerance, and diabetes mellitus are associated with a substantially increased prevalence of hypertension, cardiovascular (CVD), and chronic renal disease. The prevalence of hypertension in patients who have type 2 diabetes mellitus is up to 3 times higher than in patients without diabetes mellitus. Further, the coexistence of hypertension in diabetic patients greatly enhances their likelihood of developing CVD and chronic kidney disease.[1–4] Indeed, studies conducted in the Framingham population with diabetes mellitus[1] indicated that the presence of hypertension in these participants was a resulting risk factor for the presence of CVD. This data and other studies suggest a 2-fold increased risk of CVD events and deaths in diabetic persons with hypertension compared with those with normal blood pressures. The increased association between hypertension and diabetes mellitus can be explained, in part, by the presence of a maladaptive interaction of factors, such as excessive caloric intake/decreased activity and associated insulin resistance (IR), chronic activation of the renin–angiotensin (Ang II)–aldosterone system (RAAS), the sympathetic nervous system, and abnormalities of innate immunity, inflammation, and oxidative stress[1–21] (Figure). The epidemic of obesity and sedentary lifestyle, and the aging of populations worldwide have contributed to the current high prevalence of diabetes mellitus and hypertension.

Role of Increasing Overweight and IR in Promoting Both Diabetes Mellitus and Hypertension

Hypertension is more common in diabetic patients than in the general population.[1–4] In the Strong Heart Study, baseline measurements which independently predicted incident hypertension, included waist circumference, elevations in baseline systolic blood pressure, and left ventricular mass and diabetes mellitus.[2] Further, a recent longitudinal Japanese study of 5198 subjects showed that parental hypertension has an age-independent impact on both male and female offspring in elevations in blood pressure, plasma glucose, and triglyceride levels.[5] The authors of this study suggested that IR was the underlying pathophysiologic factor contributing to this array of abnormalities in the offspring, as suggested in prior publications in *Hypertension* regarding the relationship between IR and hypertension.[3,6] In a longitudinal study of a northern Italian population, it was reported that an increase in body mass index and waist circumference was associated with a linearly increased adjusted risk of developing impaired fasting glucose, diabetes mellitus, blood pressure, and left ventricular hypertrophy.[7]

The risk of developing diabetes mellitus, hypertension, and associated CVD risk factors is increased with obesity and inactivity.[4–16] Indeed, the prevalence of childhood obesity is increasingly prevalent and is associated with metabolic abnormalities and CVD risk factors in childhood, as well as during adulthood.[12–16] For example, using carotid-femoral pulse wave velocity as an index of arterial stiffness in children, investigators found that pulse wave velocity was positively correlated with body mass index, waist circumference, and percentage body fat, and negatively correlated with cardiorespiratory fitness.[12] In another study, Canadian adult[13] waist circumference was associated with greater elevations of systolic blood pressure during exercise. In a recent study,[14] an inverse association was shown between exercise capacity and the rate of progression from prehypertension to hypertension in middle aged and older men. Other significant factors predicting the progression from prehypertension to hypertension included systolic blood pressure, age, body mass index, and the presence of diabetes mellitus. These observations are important, as it is increasingly recognized that prehypertension is a CVD risk factor. Recent findings in young diet or genetically induced obese rats, and rats selectively bred for low aerobic capacity, indicate the exhibition of increased myocardial fibrosis and diastolic dysfunction in a prehypertension state.[11–13] The translational relevance of these studies is highlighted by the fact that it is estimated that 37% of the adult US population has prehypertension, and 40% of these people will progress to hypertension within a 2-year time frame.[10] Collectively, these studies suggest that improved cardiorespiratory fitness in the young may greatly reduce the development of diabetes mellitus, hypertension, and associated CVD.

Role of Hormonal/Neuroendocrine Factors in Promotion of Hypertension and Diabetes Mellitus

Excessive caloric intake and a sedentary lifestyle promote IR, a condition in which the insulin metabolic signaling response in skeletal muscle, liver, and adipose tissue is impaired.[6,15,16] This alteration in insulin metabolic signaling leads to increased vascular adhesion molecule expression, oxidative stress, inflammation, and decreased vascular
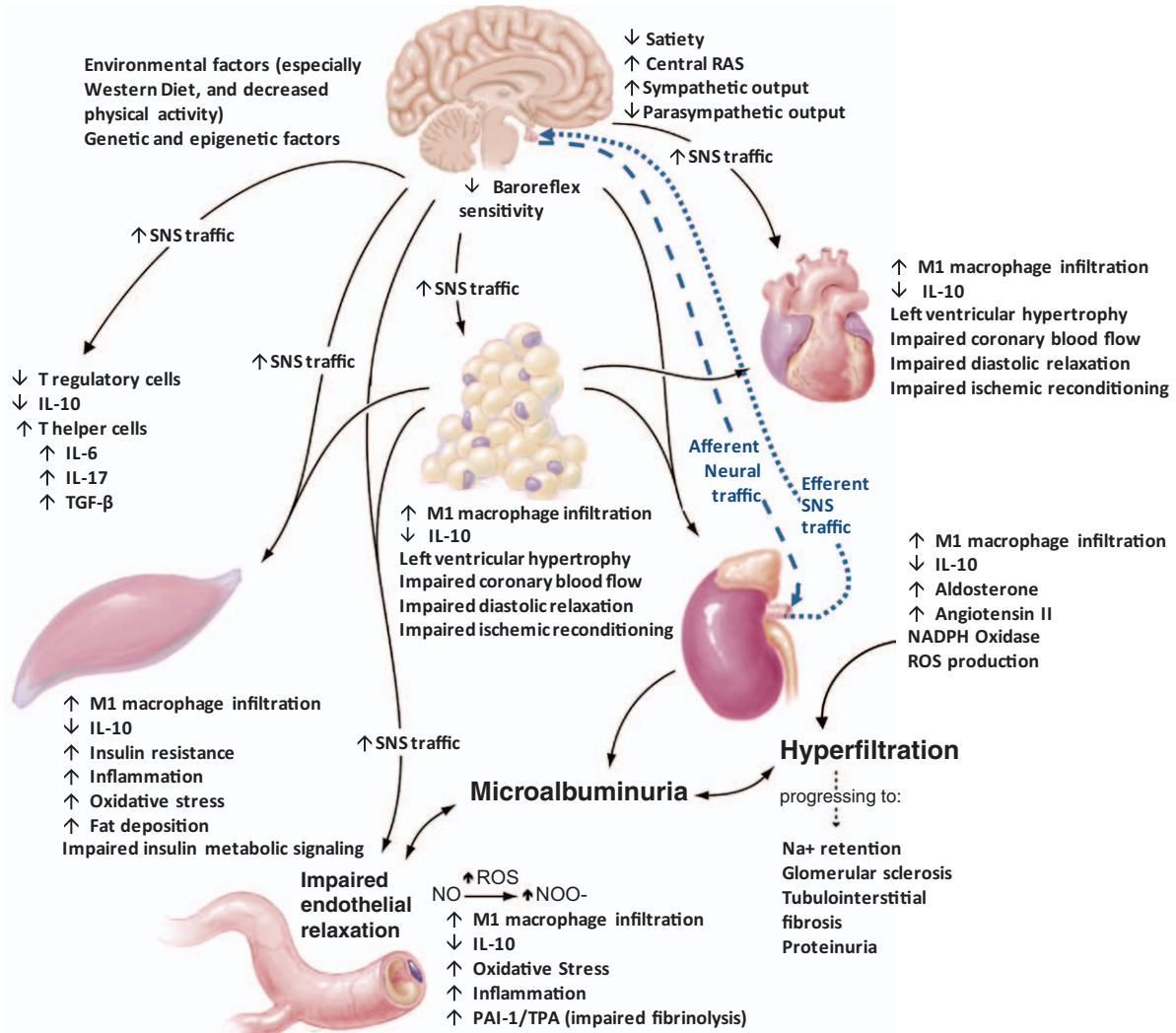
Figure. Systemic and metabolic factors that promote coexistent diabetes mellitus, hypertension, cardiovascular, and chronic kidney disease.

bioavailable nitric oxide.[15–19] The decreased bioavailability of nitric oxide reduces endothelial-mediated vascular relaxation and promotes vascular stiffness.[19] Obesity and IR are also associated with inappropriate activation of the RAAS and the sympathetic nervous system.[20–32] A recent study[20] highlights the role of adipose tissue in promoting activity of the RAAS. This investigation was based on previous observations that adipocyte angiotensinogen is important in the formation of Ang II. This study demonstrated that, whereas a high-fat diet substantially increased plasma levels of Ang II and blood pressure in wild-type mice, it did not do so in adipocyte-specific angiotensinogen knockout mice showing the importance of adipose tissue angiotensinogen production in the development of hypertension in obesity. Increased adiposity has also been associated with high levels of plasma aldosterone,[21–23] suggesting that obesity is a condition characterized by and activated in RAAS. Activation of the RAAS in obesity may, in turn, increase the propensity to IR, hypertension, diabetes mellitus, and associated CVD.[21,24] Ang II and aldosterone have been shown to inhibit insulin metabolic signaling in cardiovascular and classical insulin-sensitive tissue,[23–27]

and this likely plays a role in reduced endothelial-mediated vascular relaxation and development of hypertension. There is emerging evidence that Ang II and aldosterone, acting through nongenomic mechanisms, may promote IR through activation of serine kinases, and increased serine phosphorylation of the critical insulin signaling/docking molecule, insulin receptor substrate protein 1, leading to impaired phosphoinositol 3 kinase engagement and protein kinase B stimulation, diminished insulin metabolic signaling, and biological consequences, such as impaired nitric oxide-mediated vascular relaxation.[23,25–27]

There is emerging evidence that innate and adaptive immunity are involved in Ang II and aldosterone-induced hypertension and vascular disease.[28–30] Infusion of both hormones has been shown to increase blood pressure, cause increases in vascular inflammation, oxidative stress, remodeling, and endothelial dysfunction in wild-type, but not in mice deficient in T-cells. These T-cell–mediated effects are accompanied by infiltration of T-cells and macrophage, and increases in NADPH oxidase in vessels, kidney, and heart tissue. These studies also showed that Ang II and aldosterone reduced

T-regulatory cells, in part, by increasing the apoptosis of these cells. These adverse vascular responses to Ang II and aldosterone have been shown to be prevented by adoptive transfer of T-regulatory cells.[28–30] Data from one of these studies[29] showed that interleukin-10 released from these T-regulatory cells reduced NADPH oxidase activity in vascular tissue. These data collectively suggest that adoptive transfer of T-regulatory cells could be a mechanism for reducing vascular disease associated with diabetes mellitus.

There is an emerging body of evidence that central obesity, IR, sleep apnea, and resistant hypertension are often accompanied by increased sympathetic nervous system activity.[31,32] Further, activation of the sympathetic nervous system promotes IR, and the risk of developing diabetes mellitus.[31,32] A percutaneous catheter-based procedure has been developed for therapeutic renal denervation. This involves the application of low-dose radiofrequency energy to the renal artery endothelial surface, causing selective reduction in renal sympathetic afferent and efferent signaling.[31,32] This intervention is associated with reduced central sympathetic outflow, as evidenced by attenuation of muscle sympathetic nerve activity and plasma levels of norepinephrine.[31] In recent studies, this procedure has been reported to reduce fasting and postprandial glucose levels and to improve insulin sensitivity, in addition to having substantial blood pressure-lowering effects.[31,32] Collectively, these data suggest that this method of reducing sympathetic output has considerable utility in patients with IR, impaired glucose tolerance, and resistant hypertension, who are at high risk for CVD and chronic renal disease. Other prospective therapeutic targets for treatment in diabetic patients with hypertension include reductions in the urotensin system,[33] uric acid,[34] and endoplasmic reticulum stress.[35]

Treatment of Hypertension in Diabetic Patients

There are evolving notions regarding the optimal treatment strategies for patients with hypertension and diabetes mellitus. Some of the controversies include the optimal blood pressure target in diabetic patients, the rapidity of achieving that target, the impact of various blood pressure-lowering medications on cerebral perfusion, metabolism and progression of diabetes mellitus, CVD, and renal disease progression.[36–40] Although there is evidence that lowering blood pressures <140/90 mm Hg goal decreases stroke, there remains concerns about adequate cerebral perfusion in diabetic patients with microvascular disease and impaired cerebrovascular autoregulation.[38] Thus, the optimal blood pressure goal for diabetic patients should be individualized, just as for glycemic control. Various strategies such as more frequent patient visits[41] and home blood pressure monitoring[42] have been reported to improve achievement of blood pressure goals in patients with diabetes mellitus and hypertension.

One of the factors that may influence the choice of blood pressure–lowering agents in diabetes mellitus is the influence of the agents on metabolic parameters, especially glucose metabolism. In this regard, thiazide diuretics and conventional β-blockers may worsen insulin sensitivity and glucose tolerance, especially in the setting of obesity.[36,43,44] The impact of various predisposing factors on the worsening of glucose control is different for diuretics versus β-blockers. For example,

hypokalemia and hypomagnesemia have been attributed to worsening of glucose control with thiazide therapy.[43] Low serum levels of these divalent cations have been observed to be associated with both impaired β-cell insulin secretion and insulin metabolic signaling in adipose tissue, liver, and skeletal muscle tissue.[43] Hyperuricemia has also been associated with development of worsening glucose metabolism in obese patients treated with diuretics and β-blockers.[36] There is also evidence that treatment with conventional β-blockers is also associated with weight gain which, in turn, worsens glucose tolerance.[43,44] In contrast to conventional β-blockers, vasodilating β-blockers, such as nebivolol, are not associated with weight gain and do not worsen glucose tolerance in states of obesity and impaired glucose tolerance.[44–46]

There is evidence in experimental animals and man that angiotensin receptor blockers (ARBs) may have beneficial effects on insulin secretion from β-cells and insulin sensitivity.[47,48] For example, treatment with an ARB was shown to protect against the adverse metabolic effects of a high-fat diet in mice.[47] Indeed, ARB treatment not only improved glucose tolerance and insulin sensitivity, but it also protected against islet β-cell destruction and improved glucose-induced insulin secretion. These beneficial metabolic effects of ARB treatment were accompanied by reduced systemic and tissue inflammation. In a study conducted in hypertensive patients with central obesity, adding an ARB to thiazide therapy attenuated the negative effects of thiazide treatment on pancreatic β-cell glucose-induced insulin secretion.[48] Collectively, these studies suggest that ARBs have beneficial metabolic effects when used alone or in combination with thiazide therapy in states of obesity and hypertension.

Another mechanism by which thiazide diuretics may worsen insulin sensitivity and glucose tolerance is by activation of the RAAS and the sympathetic nervous system. In a recently reported study,[49] chlorthalidone therapy was associated with activation of the sympathetic nervous system as measured by recordings of sympathetic nerve traffic. This therapy was also associated with reduced insulin sensitivity as determined using a homeostasis model assessment of IR. However, the addition of the mineralocorticoid receptor antagonist spironolactone attenuated both the chlorthalidone-induced sympathetic activation and IR in hypertensive patients. Thus, thiazide diuretic therapy appears to worsen glucose metabolism via activation of the RAAS and sympathetic nervous system and via effects of islet β-cells, as well as insulin-sensitive tissues. Recently, it has been observed that dipeptidyl peptidase 4 inhibition, used in treating hyperglycemia, lowers blood pressure and improves endothelial function in hypertensive rodents.[50] It will be interesting to see whether these agents lower blood pressure while improving glucose tolerance in hypertensive patients with diabetes mellitus. It will also be important to determine whether these agents also abrogate the negative metabolic effects of conventional β-blockers and diuretics in hypertensive patients with diabetes mellitus.

Despite the differential effects of various antihypertensive agents on glucose metabolism, it is unclear which agents or combination of agents have the most beneficial effects on CVD and renal outcomes in patients with diabetes mellitus and hypertension. In the Nagoya Heart Study composite, CVD

outcomes were comparable between valsartan- and amlodip-ine-based treatments in Japanese patients with glucose intolerance.[51] However, admission to hospitals because of heart failure was significantly less in the valsartan-treated group. The combination of angiotensin-converting enzyme inhibitors and dihydropyridine calcium channel blockers was assessed in Italian patients with hypertension and type 2 diabetes mellitus. In these patients, combined therapy did not slow glomerular filtration rate decline, but lessened CVD, retinopathy, neuropathy, and stabilized insulin sensitivity. These results suggest that this may be an excellent combination therapy for treating hypertension in diabetic patients. Thus, RAAS blockers with either thiazide diuretics or dihydropyridine blockers appear to be a good combination to achieve optimal metabolic and CVD outcomes in this group of patients.[50,51]

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