2.1. Role of Hyperglycemia in the Pathogenesis of Hypertension

Chronic hyperglycemia likely contributes to the genesis of hypertension in diabetic individuals through several mechanisms. One such hypertensive effect engendered by hyperglycemia is that of sodium retention and the increase in exchangeable body sodium that has been observed in diabetic hypertensive individuals (Weidmann & Ferrari, 1991). Hyperglycemia results in glomerular hyperfiltration of glucose, which in turn, stimulates the proximal tubular glucose-Na\(^+\) cotransporter (Ulbrich, 1976). This mechanism is insulin independent and is rapidly operative, as evidenced by elevated proximal tubular cell Na\(^+\) concentration and Na\(^+\),K\(^+\)-ATPase activity within 4 days of streptozotocin-induced hyperglycemia in rats (Kumar et al., 1988). Thus, sodium retention occurs in association with mild-to-moderate hyperglycemia and likely contributes to increased total exchangeable Na\(^+\) and blood pressure elevations in diabetic hypertensive patients. Chronic hyperglycemia may also contribute to increased vascular rigidity by promoting vascular structural changes. At high concentrations, glucose appears to have a direct toxic effect on endothelial cells (Lorcnczi et al., 1985) which may result in decreased endothelial-mediated vascular relaxation, increased constriction, promotion of vascular smooth muscle cell hyperplasia, and vascular remodeling. High glucose levels mimicking the diabetic hyperglycemic state have also been shown to induce fibronectin and collagen IV overexpression in cultured human vascular endothelial cells. Enhanced expression of fibronectin and collagen IV may further contribute to endothelial dysfunction. Fibronectin is a gh/coprotein that has a complex role in cell matrix interactions, and its increased expression has been associated with thickened glomerular basement membranes and mesangium (Roy et al., 1990). Thus, hyperglycemia-induced local synthesis of fibronectin by endothelial cells may contribute directly to endothelial dysfunction as well as indirectly to increase in basement membrane production. There is considerable evidence that hyperglycemia accelerates formation of nonenzymatic advanced glycosylation products, which accumulate in vessel wall proteins (Brownlee et al., 1988). The rate of this accumulation is proportional to the time-integrated blood glucose level over long periods of time. A highly significant correlation has been noted between accumulation of increased levels of advanced glycosylation end products and vascular complications. Vlassara et al., (1986) have identified a membrane- associated macrophage receptor that specifically recognizes proteins to which advanced glycosylated end products are bound. The binding of proteins with advanced glycosylation end products to macrophage receptors induces the synthesis and secretion of tumor necrosis factors and interleukin-1. These cytokines, in turn, stimulate other cells to increase protein synthesis and to proliferate. Interleukin-1 causes
vascular smooth muscle cells, mesangial cells, and endothelial cells to proliferate and increases glomerular Type IV collagen synthesis. Interleukin-1 and tumor necrosis factors induce the expression of the protooncogenes c-myc and c-fos. Further, the growth-promoting effects of tumor necrosis factors and insulin are synergistic. Tumor necrosis factors appear to stimulate platelet-derived growth factor-like mitogens from both aggregating platelets and endothelial cells by causing thrombosis-promoting alterations in the endothelial cell surface (Le J, Vilcek, 1987). As extensively reviewed (Brownlee et al., 1988) these alterations include induction of a tissue factor-like procoagulant, suppression of the anticoagulant protein C pathway, and synthesis of an inhibitor of plasminogen activator. The thrombotic changes may then induce release of platelet-derived growth factor from aggregating platelets and from endothelial cells through receptor-mediated thrombin stimulation. Thus, prolonged hyperglycemia could lead to excessive production of extracellular matrix and proliferation of vascular smooth muscle cells as a result of an increase in the number of highly cross-linked proteins with advanced glycosylated end products, with resulting hypertrophy and vascular remodeling. This could, in turn, contribute to the enhanced vascular constriction and accelerated atherosclerosis characteristic of diabetic vasculature. The observation that chronic hyperglycemia is associated with decreased elasticity of connective tissues in arterial walls may also be related, in part, to increased advanced glycosylation. In addition to irreversible nonenzymatic glycosylation of structural protein, hyperglycemia leads to glycosylation of apolipoproteins, which may increase the atherogenicity of lipoprotein molecules (Blankenhorn & Kramah, 1989).

2.2. Characteristics of hypertension in obesity and type 2 diabetes: insulin resistance, elevated sympathetic nervous activity, and stimulated the reninangiotensin-aldosterone system (RAAS)

Data from many epidemiological and clinical studies has identified a close relationship between elevated sympathetic nervous system activity and insulin resistance/hyperinsulinemia in obesity (Straznicky et al., 2011; Esler et al., 2006). Several studies of longitudinal design have examined the effect of body weight changes (weight loss or weight gain) on sympathetic nervous system activity and insulin sensitivity (fasting plasma insulin levels and homeostatic model assessments of insulin resistance (HOMA-IR)). Elevations in sympathetic nervous activity and insulin levels during weight gain (Masuo et al., 2005) and reductions of sympathetic nerve activity and insulin levels during weight loss (Masuo et al., 2001) have been observed. These longitudinal studies have clearly shown that elevated
sympathetic activity and insulin resistance are closely linked to obesity (weight gain), the onset of obesity and the maintenance of obesity. Similarly, sympathetic activation and insulin resistance are strongly linked to the onset and development of hypertension and diabetes (Huggett et al., 2003). Furthermore, stimulation of the renin-angiotensin-aldosterone system (RAAS) is frequently demonstrated in obesity and hypertension and may be related to insulin resistance either via direct or indirect mechanisms (Matayoshi et al., 2007; Kamide et al., 2004).

![Diagram](image)

**Fig. 27.** Relationships between insulin resistance, sympathetic activation and stimulated renin-angiotensin-aldosterone system (RAA) in type 2 diabetes and hypertension (Masuo et al., 2010)