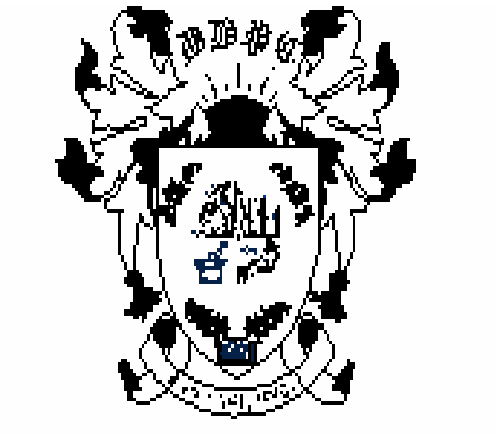
CARDIOVASCULAR COMPLICATIONS OF DIABETES - REVIEW

Jagdish L Kakadiya, Dr. Nehal J Shah

Department of Pharmacology, Dharmaj degree Pharmacy College,
Petlad-Khambhat road, Dharmaj,
Dist: Anand, Gujarat, India.



ADDRESS FOR CORRESPONDENCE
Mr. Jagdish L. Kakadiya
Dharmaj degree pharmacy college,
Amrapali Township, Petlad-Khambhat road,
Dharmaj, Dist: Anand-388430,
Gujarat, India.
jagdishkakadiya@yahoo.co.in

The cardiovascular complications of diabetes were previously considered to be caused by structural changes with very slow progression. Historically, with the available methodology, abnormal deposition of extracellular material was studied more extensively than were changes in cellular function. It is now recognized that, on the functional level, cardiovascular dysfunction during deregulated metabolism occurs soon after the onset of metabolic abnormalities, long before the appearance of histopathological changes, and that such dysfunction is regulated by dynamic and complex mechanisms on the cellular and molecular levels. This gives hope that intervention with preventive therapies is possible at a stage before atherosclerosis and heart failure are manifest. Both type 1 and type 2 diabetes are precipitated by failing function of the pancreatic beta cell. In addition, they are characterized by peripheral insulin resistance, which may be both a cause and effect of the disordered metabolic state. As the prominent general features of diabetes, hyperglycaemia and insulin resistance are probable causes of diabetic cardiovascular complications. Below, the mechanisms at the cellular and molecular levels that potentially explain the pathogenesis of atherosclerosis and cardiac dysfunction are outlined. Based on this understanding, potential new treatment strategies are then discussed.

INSULIN SENSITIVE AND INSULIN RESISTANT CARDIOVASCULAR MECHANISMS

Because resistance to insulin-stimulated glucose uptake and metabolism in non-vascular tissues is central to the pathogenesis of type 2 diabetes (and is a common feature in type 1 diabetes), resistance to insulin stimulated effects in the cardiovascular system is an obvious candidate for a general mechanism to explain the development of diabetic complications in the heart and blood vessels. Below, various insulin sensitive mechanisms are outlined that, when altered in insulin resistance and diabetes, may have relevance to atherogenesis and the occurrence of cardiac dysfunction.

Mediators of vasomotion: nitric oxide and endothelin-1

One of the currently best known vascular actions of insulin is to increase the production of endothelium-derived nitric oxide (NO). Apart from its role in mediating vasodilatation, NO inhibits monocyte adhesion, proliferation of vascular smooth muscle cells, and platelet adhesion and activation in the intrinsic coagulation pathway (1). Because all of these effects are potentially important for the development of atherosclerosis, a decrease in NO production in

insulin resistance and diabetes is believed to be of central importance to the development of diabetic vascular complications. This may occur either because of NO breakdown by reactive oxygen species produced in the vessel wall, or be due to decreased activity caused by glucose induced post-translational modification of endothelial nitric oxide synthase (NOS) (2). Decreased NO availability may occur despite compensatory increased expression of endothelial NOS (3, 4). Insulin-stimulated vasodilatation is dependent on endothelium-derived NO (5–8). Both endothelial NOS expression and activity are mediated through the insulin signalling pathway that involves activation of phosphatidylinositol 3-kinase (PI3K). Thus, in endothelial cells, insulin stimulates insulin receptor autophosphorylation (9,10), tyrosine phosphorylation of insulin receptor substrate-1 (9–11) and -2 (9), insulin receptor substrate associated PI3K activity(9,10), phosphoinositide dependent kinase-1 activity (11), and subsequent serine phosphorylation(9,10) and activation (12,13) of Akt, causing serine phosphorylation (10,13) and activation(10,12–15) of endothelial NOS. The PI3K pathway also mediates insulin stimulated endothelial NOS gene expression (15).

In obesity-associated insulin resistance, insulin stimulation of the PI3K pathway is blunted (9, 15). When signalling through the PI3K pathway is decreased, the supposedly beneficial effect of other hormones and growth factors on endothelial NOS function (including oestrogen and vascular endothelial growth factor [VEGF], which are also activators of this pathway) may potentially also be compromised. Local regulation of vasodilator tone is regulated as the result of the balance between vasodilator and vasoconstrictor signalling molecules. Endothelin-1 is the most potent vasoconstrictor known and its importance in coronary artery disease is increasingly being recognized, for example by the demonstration that the majority of basal vascular tone in atherosclerotic arteries is mediated by endothelin-1, which accounts completely for the vascular tone at stenoses (16).

Endothelin-1, like NO, is primarily synthesized in the endothelium, and mediates its vasoconstrictor effects after binding to G-coupled receptors on vascular smooth muscle cells (17). It also has mitogenic effects in vascular smooth muscle cells (18). Plasma levels are increased in diabetes (17), perhaps because high glucose concentrations induce endothelin-1 expression through activation of protein kinase C (PKC) (19). Insulin stimulation of NO mediated vasodilatation may be counteracted by insulin stimulated endothelin-1 production (20,21). In vascular cells, insulin induces endothelin-1 expression (22), but conversely

endothelin-1 inhibits insulin signaling (23). Thus, endothelin-1 decreases insulin-stimulated glucose uptake (24). Little is known about how insulin and endothelin-1 signalling interact in vivo in normal physiology and in insulin resistant states.

In the myocardium, NO may modulate heart rate andcontractility (25), and regulates glucose uptake (26) and mitochondrial respiration (27). The inhibitory effect of cardiac NO on oxygen consumption is depressed in diabetes (28). Endothelin-1 potently increases cardiac contractility (29) and, although myocardial endothelin-1 expression and endothelin-1 receptor affinity is increased in diabetes, the inotropic effect of endothelin-1 appears to be blunted (30). Much more work is needed if we are to understand how these signalling molecules affect cardiac function in diabetes.

Vascular endothelial growth factor: a mediator of angiogenesis

VEGF regulates vascular permeability and angiogenesis, but may also inhibit vascular smooth muscle cell proliferation and thrombosis (31). In diabetes and insulin resistance, cardiac VEGF expression is decreased (32). The relevance of these data for cardiac angiogenesis has recently been emphasized by clinical trial data showing that endocardial injection of VEGF complementary DNA can improve clinical outcomes in patients with ischaemic heart disease(33). It is important to note that in diabetes and insulin resistance the opposite finding, that of increased VEGF expression, is observed in the retina and in renal glomeruli (32); this is in accord with increased retinal and glomerular angiogenesis as elements of diabetic microvascular complications. Insulin stimulates VEGF expression in myocardium (32), but in diabetes and insulin resistance this effect is blunted (34).

Proliferation and apoptosis

In tissues in which glucose uptake depends on insulin stimulation, insulin signalling transduction follows the PI3K pathway described above. Mediation of the mitogenic effects of insulin, however, is facilitated by a pathway involving mitogen-activated protein kinase (MAPK). In insulin resistance, the MAPK pathway is unaffected in vascular (9) and non-vascular (35) tissues, thus promoting mitogenic effects of insulin during the hyperinsulinaemia that is characteristic of insulin resistance. Insulin has an antiapoptotic effect in endothelial cell culture(36). A similar effect in cardiomyocytes has been described after ischaemia/reperfusion. In both cell types, the antiapoptotic effect involves signalling through Akt (36, 37). In patients with type 2 diabetes and in healthy people after 2 hours of induction of hyperglycaemia, the

plasma concentration of soluble adhesion molecules are elevated (38). Insulin, on the other hand, decreases levels of intercellular adhesion molecule-1 in endothelial cells (39). Clinically, insulin treatment decreases levels of circulating soluble adhesion molecules (40) as soon as after 12 h (38).

Cardiac substrate metabolism

Cardiomyocyte phenotypes, including maturation of contractile protein isoforms, are dependent on insulin signalling, as evidenced by observations in mice with cardiomycyte-selective insulin receptor knockout (41). Furthermore, lack of cardiomyocyte insulin signalling in this model results in a shift of substrate utilization, with decreases in fatty acid oxidation and increases in glucose oxidation (41). This is paradoxically the opposite change from that observed in diabetes, in which the myocardium primarily utilizes fatty acids rather than glucose as an energy substrate (42). Insulin stimulated cellular glucose uptake is partly mediated by translocation of glucose transport proteins from intracellular pools to the cell membrane. During myocardial ischaemia, insulinstimulated translocation of glucose transporter-1 and -4 in cardiomyocytes is particularly increased in ischaemic regions of the myocardium (43). From the discussion above, it is apparent that many mechanisms believed to play a role in diabetic cardiovascular complications are insulin sensitive, and that several have been shown be deficient during insulin stimulation. Therefore, improving insulin sensitivity of cardiovascular mechanisms is an obvious target for preventing diabetic complications.

HEART FAILURE IN DIABETES MELLITUS

Diabetic cardiomyopathy has been recognized for many decades. Early studies in experimental animals treated with streptozotocin or alloxan to induce insulin insufficiency demonstrated changes in calcium cycling and in myocardial contractility. We, and others, found that myocardial infarction of a given magnitude in patients with diabetes was associated with more severe congestive heart failure and that, despite the preserved systolic function, myocardial ultrasonic backscatter was altered in people with diabetes, which is indicative of structural alterations within the heart. It is now known that diabetes is a potent, independent risk factor for mortality in patients hospitalized with heart failure, and that the excess risk associated with diabetes is particularly prominent in women.

Heart failure associated with diabetes can be manifested by diastolic dysfunction, systolic dysfunction or both, attributable to abnormal calcium cycling, impaired energetic and deposition

of AGEs. The AGEs can alter ventricular compliance by the cross-linking of collagen, through receptor-mediated release of proinflammatory cytokines by macrophages or through non-receptormediated inactivation of nitric oxide and augmentation of oxidative stress. They have also been thought to increase renal sodium reabsorption, activate the sympathetic nervous system, alter peripheral arterial compliance, increase deposition of lipids within cardiomyocytes, induce small vessel coronary artery disease and incite oxidative damage to matrix proteins. As a consequence of impaired arterial compliance and endothelial function, myocardial oxygen demands are increased, predisposing to subendocardial ischemia that can exacerbate diastolic dysfunction. Left ventricular mass increases in proportion to the severity of impairment of glucose tolerance, particularly in women. An elevated concentration of fasting glucose is a risk factor for congestive heart failure with or without concomitant coronary artery disease. The presence of diabetes is a powerful predictor that heart failure and death will occur in long-term survivors of acute myocardial infarction. Patients with ST segment elevation acute myocardial infarction who are diabetic exhibit increased long-term mortality as a concequence of heart failure, whether or not they have been treated with revascularization procedures. Diabetes profoundly increases the development of heart failure following acute coronary syndromes. In patients that are hospitalized for heart failure with preserved systolic function, conditions such as hypertension, diabetes and obesity are common. Systolic hypertension (also known as wide pulse pressure hypertension) reflects increased central arterial stiffness. The strong association between diastolic heart failure and systolic hypertension appears to mirror deleterious cardiac responses to back reflected central arterial pressure waves with consequent increases in left ventricular chamber stiffness. Because coronary artery disease has such a prominent association with type 2 diabetes, it is somewhat surprising that factors other than coronary flow limitation, particularly congestive heart failure, are prominent determinants of risk for death and recurrent myocardial infarction in patients with unstable coronary artery disease. Thus, despite the use of bare metal and drug-eluting stents in diabetic patients undergoing revascularization procedures, mortality in the subsequent three years is 63% greater in those with diabetes than controls that are not diabetic (44). Even after adjustments for differences in baseline characteristics, the hazard ratio remains elevated at 1.462 (44).

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