Vascular reactivity in diabetes mellitus

PARESH DANDONA

Division of Endocrinology and Metabolism. State University of New York at Buffalo. USA.
Diabetes-Endocrinology Center of Western New York. Kaleida Health/Millard Fillmore Hospital. Buffalo. New York. USA.

INTRODUCTION

A patient with type 2 diabetes carries a cardiovascular risk similar to that of a non-diabetic with a prior history of myocardial infarction. Endothelial dysfunction, an early event in the pathogenesis of atherosclerosis is present in diabetes mellitus in the absence of clinical cardiovascular disease. The assessment of the endothelium dependent vasodilatory effect in response to various stimuli known to increase NO (nitric oxide) production is termed vascular reactivity[1,2].

Vascular reactivity has been assessed in conduit arteries, forearm resistance vessels capillaries and vein in diabetes. The cerebral, myocardial, skeletal muscle, renal, skin and penile blood vessels in type 1 and type 2 diabetes have been shown to have abnormal vascular reactivity. It is possible that impaired vascular reactivity may contribute to the clinical manifestations of cardiovascular disease, the pathogenesis of nephropathy, diastolic dysfunction, foot ulcers and erectile dysfunction in subjects with diabetes mellitus[2,3].

MEDIATORS OF VASODILATION

There are two major vasodilators that are secreted by the endothelium (fig. 1). Endothelial cells express nitric oxide synthase that generates NO in response to a variety of stimuli including acetyl-choline, nor-epinephrine and insulin. Glucose suppresses the expression of e-NOS and NO release while insulin increases it. Therefore in diabetes the combination of hyperglycemia, insulin lack and insulin resistance results in diminished NOS expression and secretion and thus to impaired vasodilation[1,3].

NO exerts its vasodilatory effect through the stimulation of guanylate cyclase, which induces an increase in cGMP (cyclic guanosine monophosphate) which is a vascular smooth muscle relaxant. In diabetes, NOS may undergo alterations due to the binding of N-acetyl glucosamine which prevents the essential serine phosphorylation necessary for its action. Furthermore, there may be a reduction in the availability of tetrahydro-biopterin necessary for NO to be generated by NOS. THB levels are reduced in diabetes

Correspondence: Dr. P. Dandona.
Diabetes-Endocrinology Center of Western NY.
State University of New Jork at Buffalo.
Buffalo. New York 14209. USA.
E-mail: pdandona@KaleidaHealth.org

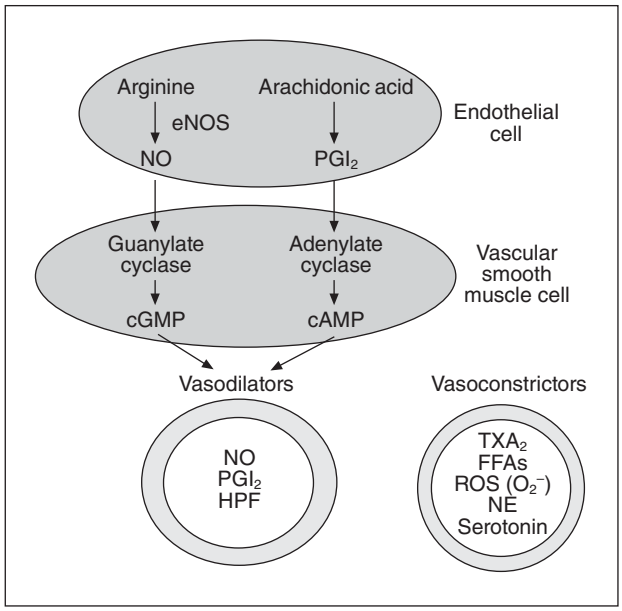

Fig. 1. Nitric oxide (NO) and PGI_2 (prostacyclin 2) mediated vasodilation. The endothelium-dependent NO mediated vasodilation is exerted through the activation of guanylate cyclase and the formation of cGMP (cyclic guanosine monophosphate). PGI_2 exerts its effect through the activation of adenyl cyclase and the formation of cAMP which causes the relaxation of VSMC. Adapted from reference 3.

because it is destroyed by oxidative stress. In oxidative stress states, NOS can also cause nitration of prostacyclin synthase and impair its ability to generate PGI2 (prostacyclin 2)[1,3].

Similarly, there is a diminution in the ability of the endothelium to generate PGI2 in diabetes. This again contributes to an overall pro-constrictor state in diabetes. Glucose inhibits PGI2 production by endothelial cells and arteries obtained from animals rendered diabetic generate less PGI2[3].

MEDIATORS OF VASOCONSTRICTION

The major vasoconstrictors are norepinephrine, angiotensin II, endothelin, thromboxane A2 and 5-hydroxyeicosatetraenoic acid. Endothelin –1 is increased in type 2 diabetes mellitus, however vascular response to endothelin is decreased in this disease. In the obese, angiotensinogen secretion is increased since the adipocyte expresses this protein and secretes it. Thus, the basic substrate for angiotensin generation is in excess. Its conversion to angiotensin I and II would thus lead to a proconstrictor state. Angiotensin II can increase free radical generation; impair NO generation and cause smooth muscle contraction. Moreover angiotensin receptor blockers and ace inhibitors have been associated with improved endothelial function and better cardiovascular outcomes in clinical studies of subjects with type 2 diabetes[3].

VASODILATORY EFFECT OF INSULIN: ARTERIAL, VENOUS AND CAPILLARY

The increase in leg and forearm blood flow by insulin is NO mediated since this is inhibited by L-NAME, an inhibitor of NOS. The flow enhancing effect of insulin is diminished in the obese and in type 2 diabetics[4]. This vascular 'insulin resistance' may contribute to metabolic insulin resistance since the availability of macronutrients and insulin to insulin sensitive end organs post prandially may be dependent upon an enhanced blood flow.

Physiologically relevant concentration of insulin exerts a direct vasodilatory effect in the veins of the dorsum of the hand and the cephalic vein at the wrist in normal subjects[5]. This vasodilatory effect of insulin is mediated by the NO-cGMP pathway and is impaired in the obese and type 2 diabetics.

Insulin increases endothelial cell NO release and the expression of NOS in human endothelial cells at physiologically relevant concentrations. Clearly, the impairment of the vasodilatory effect of insulin in type 2 diabetes and obesity is likely to have significant effect on NO release and vasodilatory reserve particularly in the post prandial period when insulin concentrations increase and macronutrients need to be distributed and taken up at the tissue level[6].

OXIDATIVE AND INFLAMMATORY STRESS

Oxidative stress reduces the bio-availability of NO since NO binds avidly to the superoxide radical to form peroxynitrate. This is likely to have an effect on vascular reactivity. With oxidative stress following a fast food meal, normal post ischemic vasodilation changes to a markedly impaired one. Elevated plasma free fatty acid concentration induces abnormal vascular reactivity within two hours in association with a marked increase in NADPH oxidase dependent ROS generation. Inflammatory stress is also associated with impaired vascular reactivity. Indeed, there is an inverse relationship between plasma CRP concentration and post ischemic brachial vasodilation. Pro-inflammatory cytokines like TNFα are known to reduce the expression of NOS in the endothelium and to lead to a reduction in the generation of NO by the endothelium[1].

RELATIONSHIP OF VASCULAR REACTIVITY WITH ATHEROSCLEROSIS

The positive predictive value of abnormal brachial artery dilation (< 3%) in predicting coronary endothelial dysfunction is 95%. FMD% is also predictive of coronary artery disease. Post-ischemic brachial arterial vasodilation is impaired in diabetes and is therefore predictive of cardiovascular events[2].

Endothelial dysfunction occurs early, can be measured noninvasively and improvement of glycemic control and lowering of cholesterol shown to decrease cardiovascular events in clinical studies have also improved endothelial dysfunction in diabetes and dyslipidemic conditions. This technique could thus be used as an additional marker for assessing the risk of CAD in this population. As endothelial function can be impaired by factors other than hyperglycemia, the choice of antihyperglycemic, antihypertensive, lipid lowering therapy and the goals of these therapy could be determined on this assessment.

EFFECTS OF INSULIN AND THIAZOLIDENEDIONE ON VASCULAR REACTIVITY AND ATHEROSCLEROSIS

While the abnormality of post ischemic brachial vasodilation is well established, it has also been shown that following thiazolidenedione therapy, there is a restoration towards normality. This reversal occurs over a period of only four weeks and hence the abnormality of vascular reactivity in obesity and type 2 diabetes is not due to a structural change. Thiazolidenediones are known to suppress ROS generation and thus to reduce superoxide. In addition, they also exert an anti-inflammatory effect, which suppresses pro-inflammatory cytokines. Both of these effects are likely to induce an enhancing affect on NO bioavailability and thus to potentially contribute to the improvement in vascular reactivity[3].

Since insulin also exerts a profound suppressive effect on NADPH oxidase dependent superoxide generation and NFkB dependent inflammation, it should be expected to improve post ischemic vasodilatory responses in the obese and type 2 diabetics. While insulin is known to exert a definitive vasodilatory effect its ability reverse abnormalities in vascular reactivity in the obese and type 2 diabetics needs to be investigated. The profound ROS suppressive and anti-inflammatory effects of insulin have been demonstrated also in patients with acute myocardial infarction and those undergoing coronary artery bypass grafts[6].

CONCLUSIONS

Impaired vascular reactivity by invasive and non-invasive methods has been shown in different vascular beds in type 1 and type 2 diabetes mellitus. It is probable that impaired vascular reactivity contributes to atherosclerosis and the pathogenesis and prognosis of the clinical manifestations of cardiovascular disease like acute coronary syndrome and stroke. It may also play a role in the pathogenesis of diastolic dysfunction, nephropathy, foot ulcers and erectile dysfunction. Resistance to the beneficial vasodilatory effects of insulin and increased reactive oxygen species generation due to various factors are probably responsible for the decreased bioavailability of NO and impaired vascular reactivity seen in diabetes. Improved glycemic control, insulin sensitizers, HMG CoA reductase inhibitors, fibric acid derivatives, ACE inhibitors and angiotensin receptor blockers, improve endothelial function and have also improved cardiovascular outcomes in clinical studies. Non-invasive assessment of vascular reactivity can thus be used, as a surrogate marker of coronary endothelial dysfunction, is reproducible and could reflect a treatment benefit if an intervention improves brachial dilatation.

Conflict of interest

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