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HYPOTHESIS

Microvascular Endothelial Cell Susceptibility Patterns as Template for Progressive Ischemia in Diabetes Mellitus

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ABSTRACT. Revolving susceptibility spectra of involvement of endothelial pathobiology would operatively entail a further complex interactivity based on primal template functionality or dysfunctionality. One might view the further realized involvement of tissues and organs within specific redefined concepts of ischemia and reperfusion injury largely as a result of such template pathobiology exhibited by endothelium of the microvasculature. It is in the further reconstructive remodeling of injury to tissues and organs beyond simple flow disturbance of hemodynamic type that there would further evolve a real or parallel representation of injury of ischemic type based on beta islet cell microvascular pathobiology. Insulin action and peripheral insulin resistance would operatively also implicate secretory dysfunctionality within schemes of further injury as exhibited by both microvasculopathy and atherogenesis in diabetes mellitus patients. The added exquisite sensitivity of cardiomyocytes and neurons to ischemia further compounds pathobiology of template dysfunctionality of microvascular endothelium.

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Abbreviations used: VEGF, vascular endothelial growth factor

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1. Clinical Diabetes Mellitus

The clinical diabetic state resolves itself largely in terms of the onset dynamics of impaired or abnormal secretory patterns induced partly by the insulin resistance exhibited by peripheral tissues. One might further recognize the importance of glucose intolerance in view of the development of a diuresis accompanied by hyperglycemia. Diabetes mellitus is as much a vascular disease as it is a metabolic disorder [14]. Endothelial participation in the evolution of injury in diabetes mellitus involves a metabolic impairment in the utilization of glucose as a primary substrate that is inter-related with episodes of ischemia or hypoxia. Endothelial cells produce various factors that regulate vascular tone, vascular permeability, angiogenesis and inflammatory responses [28]. One might further realize a complexity in development of ideal states of involvement as evidenced by consequent lesions of atherosclerosis and diabetic nephropathy. Endothelial dysfunction is an early marker of atherosclerosis [2]. Even the diabetic retinopathy as presenting lesion complex is ideally structured as a representative lesion that bears further towards ongoing injury to endothelial cells in the first instance. Advanced glycation end products modulate vasopermeability factor expression in the diabetic retina and alter inter-endothelial cell tight junction integrity [1].

The complexity in evolution of atherosclerosis in general, but particularly within the context of a diabetic impairment in glucose tolerance, might bespeak of the ongoing development of cell injury. This, traditionally, is viewed as interacting phenomena at the individual cell level, but is more properly representative of the continual impairment of tissue dynamics of cell recovery and reaction.

2. Dynamic Evolution

Dynamics of evolutionary development of ischemic lesions per se are representative of the ongoing evolution of injury as further expressed by the accelerated atherosclerotic lesion in blood vessels and by the diabetic retinopathy. It is particularly significant that evolution of lesions is closely related to the further expansion of the atherosclerotic plaque as this develops in the subintima. Endothelial dysfunction induced by oxidized, modified low-density lipoprotein is a key step in the initiation of atherosclerosis [9]. The dynamics of ischemia resulting from severe atherosclerosis of the diabetic patient are inherently reflected in the initial evolution of injury to the endothelial cells, both in terms of metabolic impairment of glucose utilization and also particularly by the ever-present and evolving dynamics of cellular response to such impairment.

Stress fiber assembly controls endothelial cell reorientation and nitric oxide production, with also reorganization of the cytoskeleton and progression of vascular pathophysiology [3].

One might speak of the inherent tendency and susceptibility of cellular injury in terms of the abnormal insulin secretory cascades affecting the beta cells of the pancreas involving especially diffusion of insulin into the supplying capillary networks. The intricate capillary phenomena of tissue ischemia and of impaired insulin action are participant players towards a cellular injury that evolves initially at the interface between the pancreatic beta cell islets and the supplying capillary units. Poor glycemic control reduces advanced glycation end products receptor levels, in association with enhanced oxidative stress and endothelial dysfunction in diabetes [4].

One might speak of the onset dynamics of an injury and impairment to insulin secretory cycles in terms of the evolving abnormalities of blood supply to the pancreatic islets in the first instance. Multifactorial regulation of endothelial function includes effects due to hyperglycemia, hyperinsulinemia and hyperlipidemia [7].

3. Ischemic Injury

There would be envisaged a problematic impairment of ischemic dimensions in the face of a consequent abnormality in insulin secretory function that further compromises dynamics of recovery and of reactive response of beta cells to both hypoglycemia and hyperglycemia. Many diabetics develop hypertension and this is a major risk factor for cardiovascular and microvascular complications [13].

The acute responsiveness of islet cells to the acute insulin secretory response to hyperglycemia might specifically compromise the islet-capillary unit structure beyond simple dynamics of interface reactivity.

One might speak of a lesion at the endothelial cell layer that specifically evolves as onset dynamics of injury to the capillary endothelial cells. Cardiovascular disease accounts for some 70% of the mortality rate in diabetics [5]. Only in terms of the ensuing injury to various subcomponents that comprise the unit membrane of cells does there further develop the atherosclerotic lesion.

Oscillations in regulatory control of insulin secretion are only partly reflected in the further disturbance in glucose homeostasis and in the ischemic cascades affecting cells in general but particularly the further development of involving injury to cell membranes.

There is implicated an evolving injury that comprises ischemia and hypoxia both in terms of the injury to the cells themselves, but particularly as inadequate supporting recovery systems and as ischemic blood supply to peripheral tissues. Impaired endogenous fibrinolysis might contribute to microvascular ischemia in human diabetic neuropathy [6].

4. Hyperglycemia

Hyperglycemia is inadequately represented by dynamics of involvement of the injury as constituted by the individual atherosclerotic plaque. Accelerated cardiovascular disease is a frequent complication of renal disease [12]. The simplistic proposition of injury to tissues as represented by the evolving hyperglycemia might reflect secondarily an impaired response to the initial injury to cells in general.

The modeling representation of the beta cell-capillary structural unit might involve a realized impairment of responsiveness of cells to the hyperglycemia as reflected within the general context of abnormal recoverability in general. This is further explained in terms of the ischemic injury to cells that are peripherally represented but centrally constituted by beta cell islets of the pancreas.

Microvascular barrier injury in diabetes may result from increased polyol flux promoting oxidative stress, advanced glycation that leads to carbonyl stress, and excessive glucose metabolism resulting in protein kinase C activation [10]. Structural and anatomic remodeling of injury to tissues in the diabetic state might indicate a realistic evolution in terms of onset impairment of receptive and responsive biology borne out by dynamics of the blood glucose levels.

5. Cyclical Control of Blood Glucose

One might speak of injury as contributed to by impaired control in cyclical turnover of blood glucose levels in the first instance, and only secondarily, in the further injury as ischemia and hypoxia of an all-encompassing nature. Interleukin 6 is a mediator between cardiovascular risk factors and several biologic mechanisms for cardiovascular disease [15].

To be stressed are the full conceptual implications of an injury that primarily targets the endothelial cells both at the micro- and macrovascular level, and also the dynamic turnover of such injury in the face of ischemia to heart, kidneys and peripheral tissues in general.

Insulin resistance plays a significant role in the relationship between hypertension, type 2 diabetes mellitus, chronic kidney disease and cardiovascular disease [16].

The myocardial susceptibility to atherosclerosis affecting the coronary arterial system might specifically entail a further progressiveness as diagrammatically represented also by the accelerated atherosclerosis of major blood vessels in general, but particularly by the abdominal aorta. The all-ensuing precipitation of injury to endothelial cells is a component of the injury to the islet cell microcirculation in the pancreas.

Additional factors in susceptibility patterns of injury to the myocardium appear particularly involved in the further development of an injury that, beyond all considerations, is metabolically initiated and hemodynamically propagated. Metallothionein can rescue hypoxia-inducible factor-1 transducible activity in cardiomyocytes under diabetic conditions, and so control vascular endothelial growth factor (VEGF) and angio-

genesis in diabetic hearts [17].

Hemodynamics and involvement of the injury in the onset dynamics of a hyperglycaemic cascade might bespeak of an injury that is primarily constructed as modeled response and repair of tissues.

The inflammatory enzyme inducible nitric oxide synthase plays an important role in the pathogenesis of vascular lesions in diabetic retinopathy [18].

6. Microvascularity

One might speak of the further complications of the diabetic state in terms of a continual recurrence of injury to the endothelial cells both as individual cellular and subcellular units and as networks of microvasculature. Microvascularity is a system mechanism for the further developmental pathways in evolving hyperglycemia and ischemia of heart and peripheral tissues.

Understanding microvascularity might indicate the repeated response to injury to tissues as represented by hemodynamic disturbance and atherogenesis.

A duality involving abnormal secretory function and also peripheral tissue resistance to insulin would resolve itself in terms of an abnormal microvascular blood supply to the beta islet cells of the pancreas leading to progressive intolerance to glucose.

The actual process of inherent progressiveness in insulin resistance might specifically implicate endothelial susceptibility to abnormal insulin activity as denoted by blunted acute insulin response to hyperglycemia. Oxidative stress has been proposed to link insulin resistance with endothelial dysfunction in diabetics [19].

The specificities of the complication rate in diabetic patients resolve themselves largely as complexity of the insensitivity phenomenon to insulin action. Several hyperglycemia-induced mechanisms may induce vascular dysfunctions which include increased polyol pathway flux, altered cellular redox state, increased diacylglycerol and the subsequent activation of protein kinase C isoforms and accelerated non-enzymatic formation of advanced glycated end products. Changes in blood flow occur with basement membrane thickening, extracellular matrix expansion, increased vascular permeability, abnormal angiogenesis and apoptosis [20].

It is in the paradoxical context of impaired insulin action that the inadequacy of insulin secretion tends to promote a progressiveness of the hyperglycaemia as indicated by the susceptibility also in development of acute ketotic acidosis in many such patients. Components of the metabolic syndrome may include effects of hypertension, insulin resistance, hyperglycemia and inflammation [11].

Complex resolution of the contrasting influences of inadequate action in the further progressiveness of impaired insulin secretion would further compound a phenomenon of insulin resistance as evidenced by progression of the hyperglycaemic state in most diabetic patients.

The centrality of glucose tolerance curves and particularly the hyperglycemia develop as a hallmark of endothelial pathology recognizable as accelerated atherosclerosis that selectively targets the coronary arterial system.

The myocardial ischemia would apparently evolve step by step with the effects of a microvascular pathology determined, in large part, by a role of endothelial involvement and as permeability indices of capillary pathobiology. VEGF appears implicated in the development of diabetic nephropathy [8].

The diabetic retinopathy exemplifies a role for vascular endothelial growth factor in an endless series of reactive injuries and responses on the part of an endothelial cell that transforms cellular participation to one of ischemia and vascular proliferation.

7. Ischemic Hypoxia

The whole scope of the ischemic hypoxia inherently arising as a product of the interactions of injury to cells and to endothelium of the microvasculature might specifically incriminate a susceptibility spectrum in the evolution of peripheral resistance to insulin action.

In a real sense it would appear that dynamics of functionality of insulin action in both peripheral tissues and organs such as the myocardial muscle mass would evolve largely parallel

to onset attributes of the microvascularity of the beta cell islet mass in the pancreas.

Simple interchange conditions might specifically give the insulin secretory functionality of beta islet cells of the pancreas a scope of operability that is borne out by the endothelial cell pathology and the microvasculopathy surrounding and integrating the beta cells and the various interchange dynamics of the insulin secretory cascade. Low-grade inflammatory markers may precede elevation of levels of endothelial adhesion molecules [21].

The involvement of neutrophils in bacterial chemotaxis and in the oxidative burst phenomenon might specifically reclassify the oxidative injury to cells that evolves especially with reperfusion injury to ischemic myocardium.

The neuropathy and the metabolic roles of dysfunctional maintenance of individual neurons and axons might specifically implicate the development of an injury that spans endothelial cell and variant microvascular roles. Such roles would operate in enhancing ischemia and oxidative injury to individual parenchymal cells of metabolically active tissues such as myocardium. The exquisite sensitivity of myocardium to ischemia in the diabetic patient goes beyond the cascades of pathologic precipitation of atherogenesis and might parallel further compromised viability of the endothelial cells lining the microvasculature.

The dynamics of involvement of microvessels might specifically involve a dual pathology arising from and enhancing a mutually derived participation of roles contributed by both ischemia and oxidative stress.

8. Vascular Impermeability

A concept of simple impermeability and abnormal interchange of nutrients and cells across the endothelial cell barrier of capillaries might not fully account for a phenomenon of acquired toxic functionality arising as dysfunctional reactivity of the endothelial cell. Endothelial nitric oxide synthase is a key mediator of vascular homeostasis and is reduced early in diabetes [22].

9. Biology of Endothelium

Biology of endothelium might be incriminated in a progressive ischemia of tissues in general that evolves within shifting contexts of extreme susceptibility of myocardium and neurons to the further significant injury to tissues and organs in general. Overproduction of superoxide by the mitochondrial electron transport chain, and subsequent inhibition of the key glycolytic enzyme glyceraldehyde-3 phosphate by increased activity of nuclear poly (ADP-ribose) polymerase, may damage endothelial cells in chronic hyperglycemic states [23]. Organ pathology, as a stratification injury arising beyond involvement of constituent cells and tissues, might indicate particularly a realized involvement of the injury that spreads progressively in a largely mechanistic manner and as also determined, in part only, by hemodynamic flow within the microvasulature.

It would appear that ischemia as a pathobiologic phenomenon set to develop within systems of hemodynamic stress and atherogenesis might specifically comprise an essential endothelial cell participation in further progression of an injury coupled to extreme susceptibility of tissues such as myocardium or neurons.

It would perhaps prove significant that ischemia is not a simple formula constituted by hemodynamic impairment of blood flow, but, in a real sense, constitutes a realization of factors of susceptibility in the further transformation of whole spectra of tissue and organ susceptibility pathology. Chronic inflammation contributes to vascular insulin resistance and endothelial dysfunction, implicating in particular Tumor Necrosis Factor-alpha and the p38 MAPK pathway [27].

10. Susceptibility Patterns

Susceptibility patterns in the evolution of injury as ischemia to the myocardium is well illustrated in the diabetic population and evolves in terms of injury to various other tissues and organs such as brain and kidney, retina and peripheral tissues and nerves. A relationship exists

between oxidative stress, immune dysregulation and vascular injury in type 1 diabetes [24].

The spectrum of pathobiologic involvement of the glomerulus and of the renal tubule further enhances the development of ischemia to tissues and to the myocardium, in particular, within contexts of progressive insulin resistance of action. It might bespeak of injuries that transform reproducible and reactive patterns on the part of injured endothelial cell beds.

The complexity of capillary and microvasculature pathology in creating a persistent injury to endothelial cells, both as individual cell units, but particularly as components of an integral endothelium, might specifically recharacterize the diabetic state as a resistant form of insulin action in maintaining normal or abnormal biologic viability of the endothelium.

Circulating levels of VEGF may predict microvascular complications in type 1 diabetes mellitus and are elevated when metabolic control is poor [25].

In terms beyond injury to tissues as characterized ischemia, one might further recognize the injury to further conform to patterns of occurrence based on systems of susceptibility of endothelium and myocardium in particular.

The intense reactivity that evolves both as injury and as further promotion of the transformed phenotype of the pathobiologic variants of endothelial cells might help reclassify endothelium beyond simple dynamics of transfer of nutrients and cells or oxygen to tissues.

Hyperglycemia can disrupt the physiological endothelial cell barrier of the microcirculation, even in the absence of increased overt leukocyte-endothelial interactions [26].

11. Holistic Approach

A range of considerable complexity seems to implicate the evolution of susceptibility patterns to injury and ischemia in the diabetic patient that further compromises such injury beyond simple cellular attributes, and in terms especially of tissue and organ dysfunctionality. Angiogenesis or neovascularization has been implicated in diabetic retinopathy, impaired wound healing, diabetic neuropathy and diabetic nephropathy [29].

The sequence and relative contribution of metabolic characteristics of the diabetic state involve a progressive deterioration in blood supply to tissues. The fat mass and fat-free mass are critical indices determining insulin action and insulin secretion patterns. A chronic hypersecretion of insulin (fasting hyperinsulinemia) may indicate an impaired acute secretory response.
The acute insulin secretory response is abnormal early in the pathogenesis of the diabetic state, with glucose tolerance that is normal or impaired.

Insulin resistance and insulin secretory dysfunction contribute to a holistic approach to the natural history of diabetes mellitus and would indicate abnormal patterns of endogenous glucose output.

Overall but specific attributes of pathobiology of diabetic progression refer to a dual abnormal representation of insulin secretory patterns and of insulin action targets.

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