



Review

Endothelial cell dysfunction in hyperglycemia: Phenotypic change, intracellular signaling modification, ultrastructural alteration, and potential clinical outcomes

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ABSTRACT

Hyperglycemia, the hallmark of Diabetes mellitus, is a major risk factor for endothelial dysfunction and vascular complication. In recent years, significant achievements have been made in understanding endothelial cell dysfunction triggered by high glucose concentration. The purpose of this review is to discuss the results of these recent developments. First, the remarkable plasticity of vascular endothelial cell in response to the high glucose insult is emphasized. This is evident through the switch in the cell's normal quiescent profile into new phenotypes, endowed with biosynthetic, inflammatory, adhesive, proliferative, migratory, pro-atherogenic, and pro-coagulant properties, frequently overlapping each other. Then, we underline the imbalanced expression and activity of transcription and signaling pathways, and the intense metabolic activity that accompanies the change in endothelial cell phenotype. As an adaptation to the high glucose-induced biochemical modification, a severe alteration of cell structure is produced. The review concludes with the clinical outcomes of the subject, emphasizing the high glucose-associated endothelial cell dysfunctional molecules of potential for targeting, and for reducing the impact of hyperglycemia on vascular endothelium. Such interventions may lead to a more efficient therapy for the benefit of those diabetic patients who are at increased cardiovascular risk.

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1. Introduction

Endothelial cells (ECs) are flat epithelial cells that form a monolayer that lines the internal lumen of the blood vessels. In normal, physiological condition, ECs are exposed to circulating blood glucose levels in the range of ~3.6–5.8 mmol/L, which are tightly regulated as part of metabolic homeostasis. The cells are metabolically active, and produce mediators that affect vascular tone, cell adhesion, and the homeostasis of clotting, and fibrinolysis. Through its contribution to hemostasis, ECs ensure fluidity of the blood. In normal conditions, the phenotype of EC is characterized as quiescent, with turnover rates of the order of months to years. Latest reports have identified several molecules that control EC quiescence. These are the circulating form of human Bone Morphogenetic Protein-9 (BMP-9) [1], the cytosolic phospholipase A₂-α when sequestered within Golgi apparatus [2], the transcription factor E2-2 (member of the basic helix–loop–helix family) [3], the very low-density lipoprotein receptor [4], and Angiopoietin 1 (Ang1), the ligand for the receptor tyrosine kinase Tie2 [5–7]. Shear stress is also a potent physiological regulator of EC quiescence. As a biomarker of

vascular quiescence stands the anti-angiogenic R-ras gene expression [8].

2. High glucose concentration induces phenotypic switch and modifies the intracellular signaling in vascular endothelial cells

Exposure of vascular ECs to glucose levels over than 10 mmol/L (in vitro or in vivo, as in Diabetes mellitus) is regarded as a high glucose (HG) condition. The over normal glucose concentration perturbs cells homeostasis and biochemistry, triggering modifications both in large vessels (macrovasculature) and in small blood vessels, such as arterioles, venules, and capillaries (microvasculature). As a consequence of HG concentration, EC quiescence is lost, cells acquire new phenotypes, their normal function is impaired, and “endothelial cell dysfunction” is installed. EC dysfunction is characterized by one or more of the following features: deficiency in bioavailable nitric oxide (NO), reduced endothelium-mediated vasorelaxation, hemodynamic deregulation, impaired fibrinolytic ability, enhanced turnover, overproduction of growth factors, increased expression of adhesion molecules and inflammatory genes, excessive generation of reactive oxygen species (ROS), increased oxidant stress, and enhanced permeability of the cell layer [9–12]. In examination of HG effects on vascular EC, one should also take into account that over physiological glucose concentrations lead to the accelerated formation of multiple biochemical

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species unusual in physiological conditions. Among these are the nonenzymatic reactive Amadori products, 3-deoxyglucosone, diacylglycerol, methylglyoxal, advanced glycation end products (AGEs), ROS, and nitrosylated species, which further amplify the imbalance that portrays HG-associated EC dysfunction. ROS production also triggers the peroxidation of plasma membrane polyunsaturated fatty acids like linoleic acid and arachidonic acid, generating endogenous 4-hydroxy nonenal, a highly reactive carbonyl compound. The increased oxidative stress seems to be a common alteration, triggered by a Type 2 diabetes milieu, in which hyperglycemia is adjoined by insulin resistance, hyperinsulinemia, and dyslipidemia [13]. There is a common agreement that endothelial dysfunction precedes the development of micro- and macrovascular complications associated with Type 2 diabetes, such as nephropathy, retinopathy, atherosclerosis, and coronary artery disease; the underlying mechanism includes the accelerated formation of AGEs, activation of protein kinase C, increased pro-inflammatory signaling, and impaired sensitivity of the PI 3-kinase signaling pathways [14]. Recent data show that etiopathogenesis of EC dysfunction differs in Types 1 and 2 diabetes [15]; it is present at the earliest stages of metabolic syndrome and insulin resistance, and may precede the clinical diagnosis of Type 2 diabetes by several years [16].

A first issue examined in this overview is the remarkable plasticity of EC in HG conditions, allowing the transition of the normal quiescent profile into a spectrum of new biosynthetic, pro-inflammatory, pro-adhesive, migratory, pro-atherogenic, pro-coagulant, proliferative, pro-apoptotic, and/or senescent phenotypes; these frequently overlap, e.g. the biosynthetic phenotype is also adhesive, pro-inflammatory, and pro-atherogenic, while the pro-apoptotic phenotype is a senescent one.

As a function of the duration of HG exposure (in vitro) and of circulating glucose level (in vivo) vascular ECs gradually turn into biosynthetic cells, endowed with an over developed rough endoplasmic reticulum (rER); however, in this condition, the protein folding process within rER might be affected, and the endoplasmic reticulum stress is installed [17]. In time, and also as a function of glucose concentration, ECs enlarged and thickened their basal lamina by mechanisms that involve complex biochemical changes [18]. To this modification contribute TGF- β and its receptor ALK1 [19], fibronectin over expression [20], AGEs [21], as well as AGEs cross-linking to collagen molecules; the latter products are less sensitive to degradation, and promote extracellular matrix accumulation [22].

HG concentration also induces pro-inflammatory and pro-adhesive phenotypic changes of vascular ECs [23,24]; in these circumstances, cell surfaces express adhesion molecules (intracellular adhesion molecule-1, vascular cell adhesion molecule-1, and endothelial selectin), interleukin (IL)-1 β expression becomes up-regulated [24], and secretion of VEGF, IL-8, IL-6, and TNF- α attains significantly increased levels [25]. Along with the typical cytokines (TNF- α and IL-1 β), and chemokines (such as the monocyte chemoattractant protein-1), the latest reports emphasize that the pro-inflammatory phenotype of EC is associated with an increased expression of inflammatory genes (e.g. the Neuronatin gene) [26], with the presence of ROS and phosphorylation of ERK1/2, c-Jun NH₂ – terminal kinase (JNK), NF- κ B [23,27,28], and of NF- κ B transcription factor inhibitor I κ B α [29]. Interestingly, the effect of HG on this phenotypic change is dependent on the anatomic position of the vessel, as well as on the duration of diabetes. Thus, regions of arteries exposed to low shear stress are susceptible to inflammation, whereas regions exposed to high shear stress are protected; in the latter areas, the transcription factor NF-E2-related factor 2 inhibits p38 phosphorylation, and suppresses EC dysfunction [30]. Moreover, the duration of diabetes selectively up-regulates the inflammatory genes expression, i.e. in short-term diabetes, the

mRNA transcripts for chemokine ligands CCL2 and CCL5 were up-regulated in the aortic ECs, while at later stages of diabetes these genes were up-regulated in both the aortic and venous ECs [31].

HG significantly enhanced the migration of ECs (within the retina) concomitant with the sustained activation of the downstream prosurvival and promigratory signaling pathways, including Src kinase, phosphatidylinositol 3-kinase/Akt1/endothelial NO synthase, and ERKs [32]. Recent reports demonstrate that EC migration is NO-induced in a process, which implies the inactivation of the transcription factor FOXO3a and subsequent down-regulation of peroxisome proliferator-activated receptor γ coactivator 1 α (PGC-1 α) [33]. Much of the current literature deals with the migratory properties of ECs as manifest in the angiogenesis process, and with endothelial progenitor cells (EPCs) migration during vascular repairs. Although these issues are beyond the subject of this review, an interesting recent report underlines that Type 2 Diabetes mellitus impairs EPC migration, in a process linked to the stimulation of CXCR4 receptor-4 (CXCR4) and activation of PI3K/Akt/eNOS signaling pathway [34].

Interestingly, although hyperglycemia is acknowledged to be an independent risk factor for developing diabetes-associated atherosclerosis, the pro-inflammatory environment in diabetes is the critical factor conditioning the early pro-atherosclerotic actions of HG [35]. Reportedly, the presence of hyperglycemia stimulates expression of thioredoxin-interacting protein (TXNIP) [36] with a possible role in the EC pro-atherosclerotic response to extracellular diabetic-like environment [37].

Another imbalance associated with the effect of HG concentration is the promotion of a pro-coagulant condition of endothelium (by production of pro-coagulant mediators such as plasminogen activator inhibitor-1, fibrinogen, and P-selectin) associated with a reduced fibrinolytic activity [15,38]. Reportedly, Type 2 diabetes patients may be especially vulnerable to prothrombotic events when hyperglycemia is concurrent with systemic inflammation [39]. Not only is the endothelial cell affected by HG, but also the circulating cells. Thus, a recent report emphasizes that a glucose-regulated protein (GRP78) is involved in platelet deposition during interaction with the vascular wall [40].

High glucose concentration may also trigger two opposed phenotypic changes of vascular EC: in some circumstances, EC turns into proliferative, while in others, into apoptotic. An important player in the induction of EC proliferation is nicotinamide phosphoribosyltransferase (Nampt); which enables cells to resist HG concentration, and to use excess glucose to support replicative longevity and angiogenic activity [41]. For the retinal ECs exposed to HG, it was demonstrated that proliferation was accelerated as the number of pericytes gradually decreased [42]. The altered hemodynamic forces generated by changes in blood flow, influence also EC proliferation [43]. Although there is a common agreement on HG concentration as an inductor for EC apoptosis [44,45], the circumstances that favor this process are diabetes duration (via selective up-regulated caspase-1mRNA) [31], the sequential activation of ROS, JNK, and caspase-3 [46,47], the down-regulation of connexins Cx43 [48], Cx37, and Cx40 [49], and the presence of auto-antibodies in patients with macular edema or progression to albuminuria [50]. The intracellular consequences of EC apoptotic changes consist in DNA fragmentation, and mitochondrial dysfunction, manifest by alteration of membrane potential, release of cytochrome-c, and mitochondrial fragmentation, and these changes play a potential pathogenic role in mediating the risk of Type 2 Diabetes mellitus. Thus, defective or insufficient mitochondrial function may lead to the chronic accumulation of lipid oxidative metabolites that can mediate insulin resistance and secretory dysfunction [48,51,52].

Moreover, in HG condition, a senescent phenotype of EC occurs [53]; reportedly, cell turnover and oxidative stress are engaged in

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