Inflammation and neovascularization in diabetic atherosclerosis

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Diabetes mellitus, the major cardiovascular risk factor, accentuates the inflammation and neovascularization processes leading to enhanced progression of atherosclerotic complications. Inflammation in diabetes mellitus is the key initiator of atherosclerotic process, which results in acute coronary events. Atherosclerosis evolves from the endothelial cell dysfunction and succeeding entry of hemodynamically derived leukocytes by migration, activation and production of lipid gruel leading to atheromatous plaque progression and subsequent regression. Diabetic plaque progression is associated with increased neovascularization, which is a nature’s compliment in the sustenance of plaque growth by its nutrient supply. Neovessels may act as conduit for lipid debridment and alternative channel for inflammatory process. In addition, neovascularization induces intra-plaque hemorrhage due to the fragility of the neovessels and associated inflammation, resulting in plaque instability. The intra-plaque hemorrhage is a detrimental base, which begets the progress of atheroma by inducing oxidative stress and endothelial dysfunction. Intra-plaque hemorrhage is increased in diabetes with an associated increase in hemoglobin-haptoglobin complex (Hb-Hp2-2), which further induces oxidative stress and endothelial cell dysfunction. We conclude that inflammation and neovascularization of the plaque may act as major mechanism augmenting plaque instability in diabetes mellitus.

Keywords: Angiogenesis, Atherosclerosis, Hemorrhage, Neovessels

Diabetes mellitus (DM), the metabolic disorder is manifested by an imbalance in the maintenance of blood glucose level due to sustained resistance to the action of insulin to the excessive glucose load. This results in elevated glucose level of the blood and subsequently increased tissue glucose leads to tissue glycoxylination by advance glycation endproducts (AGE) receptors. The resulting local environment induces reactive oxygen species (ROS) production and nuclear factor-kB (NF-κB) activation that instigates endothelial cell dysfunction and inflammation\(^1\). Neovascularization, the process of angiogenesis evolving from the pre-existing adventitial vasa vasorum is associated with inflammatory process in which the inflammatory macrophages release vascular endothelial growth factor (VEGF) a potent angiogenic factor, in addition to other angiogenic mediators. In diabetes enhanced plaque progression, leads to local hypoxia, which stimulates vasa vasorum to induce neovascularization. In addition, the angiogenic process is upregulated by increased inflammatory cytokines and angiogenic growth factors in diabetes\(^2,3\).

WHO (2002) statistics indicate an increased prevalence of diabetes in India with ≥ 31.7 millions in incidence and expects this may increase to 79.4 millions in 2030 (ranking #1 in the world)\(^4\). According to American Heart Association (AHA), diabetes is the leading cause of cardiovascular and stroke induced deaths in United States accounting to 65% deaths. In adults with diabetes, the incidence of heart disease related death rates was 2 to 4 times higher than in adults without diabetes. The risk for stroke is 2 to 4 times higher among people with diabetes (AHA statistics 2003). Diabetic individual without evidence of prior myocardial infarction is equal in risk to a non-diabetic person who suffered previous myocardial infarct 5 years ago. Hence diabetes is considered as risk equivalent to cardiovascular disease according to the AHA.

Atherosclerotic plaque evolution

The lining endothelium of the artery, when subjected to change in shear stress facilitated by risk factor association such as diabetes, hypertension, smoking and hypercholesterolemia leads to endothelial cell dysfunction. As this is enhanced by the ROS production due to diminished nitric oxide (NO) bioavailability, the dysfunctional endothelium

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favors adhesion molecule expression notably intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1). The E-Selectin and P-Selectin facilitates the circulating low density lipoproteins (LDL) and monocyte adhesion to the dysfunctional endothelium, which is actively or passively transported into the vessel wall. Once internalized, the LDL is oxidized and triggers the production of chemokine, monocyte chemoattractant protein-1 (MCP-1) to attract the migration of the monocytes by diapedesis into the vessel wall. The monocytes are activated to form the macrophage by the monocyte colony-stimulating factor (MCSF), which further incites the monocyte/macrophage scavenger receptor (CD36). The activated macrophages scavenge the oxidized LDL (OxLDL) and become foam cell, which is the hallmark in the initiation of atheroma.

Progression and regression of atherosclerosis

Based on the pathological changes in the intima the plaque progression is divided into six distinct AHA categories (Fig. 1):

Early Atherosclerotic lesions: **Type I:** Intimal thickening with focal accumulation of monocyte/macrophage/ T-lymphocyte aggregates. **Type II:** Intimal foam cell macrophage aggregates in linear streaks commonly noted as fatty streak. **Type III:** Pre-atheroma: Intimal focal or diffuse extra-cellular lipid deposition and intimal smooth muscle cell proliferation with occasional lipid deposition.

Advanced Atherosclerotic lesions: **Type IV:** Atheroma: The initial accumulation of confluent lipid core formation with accompanied smooth muscle cell proliferation and collagenization with distinct fibrocollagenous cap formation. **Type Va:** Fibroatheroma: Formation of a fibro-atheromatous lesion which is a high-risk category featuring distinct lipid gruel separated by either thin or thick fibrocollagenous cap. **Type Vb:** Calcific: The dystrophic calcific specks/dense calcific deposits in the lipid core with collagenized intimal matrix. **Type Vc:** Fibrotic: The intimal lipid core may be partly or completely replaced by the exuberant accumulation of fibrocollagenous stroma with smooth muscle cells.

**Type VIa:** The fibrous cap disruption in places leading to lipid core extrusion with or with out superficial thrombus in the early stage. **Type VIb:** Disruption of fibrous cap, associated with surface hemorrhage along with lipid core extrusion.

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**Fig 1 — American Heart Association classification adopted in human aortic atherosclerotic plaques using Elastic Trichrome stain, depicting AHA type I with intimal thickening and sparse inflammatory cells; Type II with fatty streak by foam cell layering; Type III showing extra-cellular lipid accumulation; Type IV with distinct fibro-collagenous cap and subjacent lipid core formation; Type VA illustrating classical fibro-atheroma with large lipid pool and cholesterol crystals; Type VB showing distinct calcific core in the lipid gruel; Type VC showing extensive fibro-collagenous matrix replacing the lipid core; Type VI with rupture of fibrous cap and intra-plaque hemorrhage.**
VIc: Disruption of fibrous cap with accompanying thrombus on the surface.

Type VI abc: A combinatorial feature, which includes disruption of cap with surface thrombus, hemorrhage and ulceration over the ruptured cap area. These stages are clinically well correlated by Fuster et al.8 with the acute coronary syndrome. Stage 1: Slow progression representing AHA Type I to III. Stage 2: Intermediate progression comprising AHA-Type Vb and Vc and Stage 3: Rapid progression involving Type IV and Va which progresses to type VIa to VIabc. The process of plaque progression may undergo regression into type Vb and Vc and sustain quiescent with no acute coronary features unless plaque burden impedes the coronary flow. In diabetes mellitus these processes will be exacerbated due to the preponderance of pro-inflammatory and pro-thrombotic processes.

Inflammation and cellular reactions in atheroma development

The macrophages, T-lymphocytes and few mast cells are the major inflammatory cellular constituents of atherosclerotic plaque. These are mediated by the pro-inflammatory cytokines and influenced by chemokine secretion in the vessel wall.

Macrophages: In the early stage of atheroma the nascent plaque expresses the adhesion molecules, VCAM-1 and ICAM-1. Once the monocytes are adherent to the monolayer of dysfunctional endothelium, they enter through the tunica intima by endocytosis mediated by the directional migration of the monocytes influenced by chemokine, MCP-1 with its receptor CCR2. Once the monocytes become resident cells in the vessel wall, the M-CSF activates it to become tissue macrophage. Macrophages express scavenger receptor (CD-36), which binds to OxLDL or glycated proteins in diabetes mellitus that leads to foam cell congregations. In the diabetic plaque, activated macrophage upregulates the expression of pro-inflammatory cytokines (IL-6, IL-1β and TNF alpha), and enhance the inflammatory process in diabetes.

T-Lymphocytes: Similar to monocytes the T-lymphocytes also enter the intima through the adhesion of VCAM-1, by the process of endocytosis with the activation of inflammatory process in the endothelium. These cells are directionally migrated by the secretion of interferon gamma (IFN-γ) namely (1) Inducible protein-10, (2) Monokine induced by IFN-γ (MIG), and (3) IFN-γ inducible T-cell alpha chemoattractant (I-TAC). These chemokines bind to chemokine receptors CXCR3 expressed by T-Cell in atheroma and internalized in the vascular wall. T-cells induce oxLDL and heat shock proteins of microbial origin. These T-cells influence activation of macrophages by binding with CD154 and CD40 to induce secretion of tissue factor, MMPs and pro-inflammatory cytokines.

Mast Cells: These cells constitute a small population in atheroma. Mast cells are directed to the vessel wall by transmigration through endothelium, by eotaxin, a chemoattractant that interacts with chemokine receptor, CCR3. Mast cells once deregulated result in the release of TNF-α, heparin, serine proteases-tryptase and chymase. The serine proteases activate the inactive zymogen granule to active MMPs and also activate angiotensin II from angiotensin-1.

Inflammation and endothelial dysfunction in diabetes mellitus

Insulin resistance and increased AGE levels are associated with endothelial dysfunction, which enhances the ability of leukocytes and bacteria to enter the plaque. Evidence indicates chronic inflammation may be involved in the pathogenesis of the insulin resistance and Type 2 diabetes mellitus (T2DM). This has led to the hypothesis by Stern that the inflammatory changes may be considered a common pathogenic step in all of these conditions. The close relationship between T2DM and cardiovascular disease (CVD) has led to the “common soil” hypothesis, postulating that T2DM and CVD share common genetic and environmental antecedents. One of the most important of these possible antecedents is considered insulin resistance. The concept that oxidative stress is the common factor underlying insulin resistance, T2DM, and CVD may explain the presence of inflammation in all these conditions. It is well recognized that inflammation is one of the manifestations of oxidative stress, and the pathways that generate the mediators of inflammation, such as adhesion molecules and interleukins, are all induced by oxidative stress. Interestingly, it has been recently proposed that the sub clinical pro-inflammatory state observable in many conditions including atherosclerosis, cancer, and aging is caused by the mitochondrial overgeneration of free radicals. The hypothesis is further supported by in vivo studies, showing that free fatty acids (FFA) and glucose induced inflammation through oxidative stress was reversed by antioxidants.
In diabetes, the pathogenomonic feature is the increased generation of ROS and induction of oxidative stress to the endothelium. Hyperglycemia induces ROS production by several mechanisms, including nonenzymatic, enzymatic and mitochondrial pathways. The excess superoxides production can activate several damaging pathways including accelerated formation of advanced glycation end products (AGE), increased polyol pathway flux, hexosamine pathway, activation of protein kinase C (PKC) isoforms via \textit{de novo} synthesis of the lipid second messenger diacylglycerol and activation of the proinflammatory transcription factor nuclear factor-κB (NF-κB) which is the initiator for inflammatory events leading to atherosclerotic macrovascular complications.

\textit{Advanced glycation end products:} Advanced glycation end products (AGE) are formed by the nonenzymatic covalent bonding of aldehyde/ketone groups derived from reducing sugar to the free amino groups of protein and other molecules. In DM there is an increase in carbonyl group of sugar substrates (glucose, fructose, ascorbates and triose phosphate), which are the precursors of AGE formation due to excess oxidation and no-oxidation reaction and poor detoxification of these substrates as per “carbonyl stress theory” \textsuperscript{20}. Severity of diabetes increases the production of AGE in atherosclerotic plaques \textsuperscript{21,22}. AGE induces direct and indirect effect in the tissue. Directly, AGE can trap the macromolecules and cross-link irreversibly with inherent tissue constituents. Indirectly, AGE can bind to cell surface receptors, which couples with signaling pathways leading to the activation of transcription factors and modulate gene expression. AGE contributes changes in the extra-cellular matrix and lipoprotein complexes by modification. In addition, they bind to receptors in the vessel wall for AGE termed as receptor for AGE (RAGE). RAGE induces ROS production \textsuperscript{23} through the NAD(P)H oxidase and activation of transcription factors which induce expression of inflammatory mediators evoking inflammation.

\textit{Polyol pathway:} In diabetes, the increased intracellular glucose results in its increased enzymatic conversion to the polyalcohol sorbitol by aldose reductase. This reduction process is enhanced (30-35\%) in presence of the enzyme NAD(P)H oxidase with the concomitant decrease in NADPH\textsuperscript{24}. As NADPH is required to regenerate reduced glutathione (GSH), this could induce or exacerbate intracellular oxidative stress. Sorbitol is oxidized to fructose by sorbitol dehydogenase with the production of NADH, which is utilized by NAD(P)H oxidase to produce superoxide which further induce oxidative stress.

In addition, excess liberation of free fatty acids (FFAs) from adipose tissue in diabetes increase the generation of acetyl-CoA to induce NADH resulting in mitochondrial superoxide production. Leptin, the adipocytokine is increased in DM, which is also associated with increased ROS production by an unknown mechanism \textsuperscript{25,26}.

\textbf{Evolution of endothelial dysfunction in diabetes mellitus}

The activation of the redox-sensitive transcription factor NF-κB, by hyperglycemia inhibits endothelial cell migration by regulating intracellular nitric oxide (NO). The nitric oxide is a vasodilator and inhibitor of platelet aggregation, increases leukocyte adhesion and smooth muscle cell proliferation. The excess production of superoxides during hyperglycemic condition reacts with nitric oxide (NO) to produce toxic peroxynitrite, which uncouples eNOS by oxidizing its cofactor tetrahydrobiopterin (BH4). The uncoupling of eNOS causes further production of superoxides\textsuperscript{16}, resulting in reduced bioavailability of nitric oxide and subsequent impairment of vasodilatation. This forms the basis of endothelial dysfunction in diabetes, which initiates endothelial alteration for the leucocytes adhesion, transmigration and subsequent inflammatory process in the atheroma of the diabetic atherosclerosis.

\textbf{Morphological features of inflammation in human diabetic atherosclerosis}

The observations from the post-mortem analysis in patients dying due to diabetes indicates a stronger predilection for higher inflammation in the coronary arteries, as indicated by immunohistochemistry with increased content of macrophage and T-lymphocyte density and HLA-DR\textsuperscript{27}, in correlation to lipid core increase in plaques of diabetes mellitus type I and II. In concurrence with this, aortic atherosclerosis was studied\textsuperscript{28} to assess the plaque inflammation severity in the rupture prone area of cap and shoulder region. In this study, autopsy derived 231 plaques from both diabetic and non-diabetic fibrous cap and shoulder inflammation, in human aortic atherosclerosis were measured. Predetermined score grade for inflammation in cap and shoulder in the rupture prone area of cap and shoulder was evaluated by measuring inflammatory cells using immunolabeled CD-68 for
macrophages and CD-3 for T-lymphocytes and graded as score 0 = ≤ 5 inflammatory cells; score 1 = 6-25 inflammatory cells; and score 2 = ≥ 26 inflammatory cells and analyzed as depicted (Fig. 2). There was a preponderance of severe grade 2 inflammations in the cap and shoulder regions of diabetics when compared to non-diabetics indicating a highly vulnerable zone for plaque rupture in diabetic atherosclerosis.

This indicates diabetes showing increased incidence of inflammation severity. This score was also associated with increased neovascularization in the same plaques with subsequent study\textsuperscript{29}. In addition an alternative pathway for inflammatory cellular trafficking through the neovascular channels in diabetes was observed\textsuperscript{30}.

**Infections and inflammatory markers**

Chronic low-grade infections are associated with extra-vascular production of increased inflammatory cytokines that accentuate atherosclerotic process. Human atherosclerotic plaque may show signs of Chlamydia pneumonia resulting in endotoxin – lipopolysaccharide (LPS) and heat shock protein production, stimulating pro-inflammatory mediators in endothelium and smooth muscle cells\textsuperscript{31}. Chlamydia pneumonia infection is also evident in the ischemic heart disease indicated by the presence of increased IgA antibodies to C.pneumonia due to an acute or chronic infection associated with myocardial infarction\textsuperscript{32}. In addition, other epidemiological studies indicate associated vascular risk with antibody increase due to *Helicobacter pylori*, herpes simplex virus, or cytomegalovirus and other bacterial infections due to gingivitis, prostatitis and bronchitis. The elevated values of serum CRP, serum Amyloid A, IL-6, IL-1 receptor antagonist are commonly associated inflammatory markers accompanying acute coronary syndrome (ACS). Elevated CRP (≥ 3 mg/L) is a predicted feature of 95% of patients with acute myocardial infarction preceded by unstable angina\textsuperscript{33}.

**Implications of inflammatory process in diabetes mellitus**

The association of chronic low-grade inflammation in diabetes invokes increased cytokines and interleukins, which will degrade the stability of plaque especially induced by activated macrophages. The MMP 2 and MMP 9 induced by macrophage further destabilize the plaque at the shoulder level. In addition inflammation may further induce neoangiogenesis by the growth factors liberated through the macrophages.

**Neovascularization in diabetes mellitus**

Hayden and Tyagi\textsuperscript{34} indicated that the mechanism of vasa vasorum proliferation is due to the injury and response to injury process, which is dynamic and ongoing in the arterial wall of diabetes leading to the phenomenon akin to natural inflammation-healing process inciting angiogenesis. In diabetes, the inherent plaque composition makes this phenomenon of neovascularization, a preponderant incidence. Inflammatory cellular composition mostly macrophages/T-lymphocytes, and few mast cells and lipid core expansion, are more evident in diabetes\textsuperscript{27}. Purushuthaman *et al.*\textsuperscript{35} supplemented this evidence in diabetic atherosclerosis where in neovascularization and association of inflammatory cellular elements at cap and shoulder (macrophages and T-Lymphocytes) correlated with neovessels in the plaque base and lipid
core expansion as independent predictors. Diabetes is known to be associated with a low-grade chronic inflammatory state, with systemic elevated levels of TNF alpha. In addition, AGE formation induces VEGF expression, TNF alpha, IL-1, PDGF and IGF-1 in monocytes/macrophages. VEGF, PDGF, IGF-1 are potent stimuli for angiogenesis inducing neovessels by the process of endothelial cell activation, migration and sprouting of neovessels. DM associated endothelial dysfunction and ROS production increases NF-κB activation leading to TGF-β up-regulation. Hyperglycemia up-regulates E Selectin, ICAM-1 and VCAM-1 in the endothelial cells. Increased cytokines and adhesion molecules lead to enhanced emigration of leucocytes into the vessel wall with resultant influx of macrophage/monocyte proliferation and induction of plaque progression which is associated with neovessel proliferation. In addition, Purushuthaman et al. have provided evidence that neovessels may present an alternative inflammatory pathway in diabetes mellitus which supplements the angiogenic process. Anghelina et al. by in vivo and in vitro matrigel assay using THP-1 cells with monocyte/macrophage cell culture provided evidence of Tie-2 + cells in columns and branches as sprouting, indicating angiogenic differentiation from macrophages. Furthermore, Moulton et al. identified a strong linear correlation between vasa vasorum and macrophages (R2=0.815), but no correlation between vasa and intimal thickness, confirming that vasa is more dependant on inflammation than on plaque size. Again, endostatin and TNP-470 reduced plaque sprouts by 70%. Of note, plaque macrophages were reduced by 55%. Most importantly, the spraying activity of atheroma was reduced by 84%. This study shows that the positive feedback cycle between activated macrophages stimulating angiogenesis by recruiting more inflammatory cells can be interrupted in vivo.

Mediation of neovascularization in diabetes mellitus

In diabetes, the plaque progression is enhanced with lipid core expansion and the positive remodeling of the vessel wall invokes hypoxia of the intimo-media with increasing plaque burden. The hypoxia inducing Factor –1 (HIF-1) alpha is a transcription factor inducing the VEGF stimulation as it is up-regulated in the vessel wall in hypoxic condition. Hypoxia leads to the inactivation of the prolyl hydroxylases allowing HIF-1α protein stabilization and dimerization with HIF-1α subunit, upregulating HIF-1α dependent pathways and multiple target genes, including nitric oxide synthase and the angiogenic vascular endothelial growth factor-A. The hypoxic stabilization of HIF clearly represents a mechanism of plaque angiogenesis. Additionally, ROS generated within atherosclerotic plaques may independently regulate HIF expression through prolyl hydroxylase dependent and independent mechanisms.

Atherosclerotic plaque type and neovessel distribution

Neovascularization is increased in the ruptured plaques (AHA VI) when compared to advanced high-risk, lipid rich plaques (AHA IV-Va) and diminished in the fibro-calcific plaques (AHA Vb and Vc). Neovessels are minimally distributed in the early plaques (AHA II –III). Neovessels are located more in the base of plaque as well as in the inner and outer tunica media. Shoulder region shows increase in the neovessels than the fibrous cap. Purushuthamanan et al. also demonstrated increased neovascularization in the base of the plaque (Fig. 3) as an independent predictor of plaque rupture (p = 0.0001) when comparing the features of plaque vulnerability in the human aortic atherosclerosis with 95% CI: 1.14- 1.36 (odds ratio 1.25). They also compared the differences in neovascularization distribution pattern between diabetes and non-diabetes in human atherosclerotic plaques, which shows increased predominance of plaque neovascularization in the base, inner and outer tunica and in the fibrous cap/shoulder regions in diabetes mellitus.

Diabetic neovessel morphology

Purushuthaman et al. also showed the distinctive morphology in 530 neovessels featuring with (1) tubulo-luminal pattern having circular and oval configuration, (2) branched pattern with out inflammation and (3) Complex branched/ sprouting pattern with peri-neovascular inflammation. (Fig. 4).

The morphological pattern in neovessels of diabetes showed a complex branched or sprouting morphology associated with peri-neovascular inflammation, surfacing the possibility of a microangiopathic process in the diabetic vasculopathy.

Neovessels and inflammatory cell trafficking

Purushuthaman et al. provided first observational evidence macrophages inside the lumen of neovessels
in diabetes mellitus using the bicolor double label immunohistochemistry with CD 34 in blue chromogen staining neovessels and CD 68 in red chromogen staining macrophages, illustrating the intense neovessels in the plaque base of diabetes mellitus in contrast with less intense neovessels in the non-diabetic plaque.

**Intra-plaque hemorrhage in diabetes mellitus**

**Mechanism of intra-plaque hemorrhage inducing endothelial cell dysfunction**

Intra-plaque hemorrhage (IPH) was increased in DM (39%) when compared to non-diabetics (12%) (p = 0.002)\(^9\). Further, peri-hemorrhagic inflammation and erythrophagocytosis subsequent to the IPH also increased in diabetes\(^9\). This induced oxidative stress in the diabetic plaques evolving into further endothelial dysfunctional status resulting in pro-inflammatory state of DM and plaque instability.

**Diabetes and IPH**

Diabetes increases the pro-thrombotic state further by enhancing the risk of thrombosis. There is increased lipid core expansion and raised expression of PAI-1 and tissue factor in diabetic state, indicating a potential thrombogenicity involved in these plaques. Intra-plaque hemorrhage is associated with increased neovascularization and inflammation in diabetes. Plaque hemorrhage liberates
extracorpuscular hemoglobin (Hb), a potent generator of oxidative injury. Haptoglobin (Hp) binds with free hemoglobin (Hb), inhibiting its oxidative potential. However, the effects of Hp may be determined by its genotype Hp1 and Hp2 (ref. 51). Hp genotype plays a critical role after plaque hemorrhage in diabetic atherosclerosis. After plaque hemorrhage in individuals with the Hp 1 genotype, a redox-inactive, Hb-Hp 1 complex is generated that binds to the macrophage CD163 receptor to induce the secretion of anti-inflammatory cytokines such as interleukin-10 (IL-10). Conversely, after plaque hemorrhage in diabetic individuals with the Hp 2 genotype, a redox-active Hb-Hp 2 complex gene is generated that produces reactive oxygen species (ROS) and induces macrophages to secrete pro-inflammatory cytokines by both CD163 dependent and independent pathway. Diabetic patients, predisposed with the Hp 2 genotype had a higher incidence of CVD. Most importantly, the Hp 1 genotype appeared to negate the harmful effects of DM on CVD risk.

**Conclusion**

It can be concluded that diabetes mellitus augments the process of inflammation, neovascularization and intra-plaque hemorrhage in human atherosclerosis. The underlying mechanism for inflammation is enhanced endothelial cell dysfunction and increased leukocyte transmigration by this dysfunctional state. The neovascularization is associated with inflammation by the increased angiogenic factors and the matrix degradation, which favors neoangiogenesis in diabetes. In addition, fragile neovessels induce intra-plaque hemorrhage and the plaque thrombogenicity status is accelerated due to prothrombotic activity by increased tissue factor and plasminogen activator inhibitor (PAI-1) and the increased incidence of Hp-2 redox-active genome expression in diabetes potentiates the risk of plaque instability leading to plaque rupture and atherothrombosis.

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**References**


PURUSHOTHAMAN et al.: INFLAMMATION AND NEOVASCULARIZATION IN DIABETIC ATHEROSCLEROSIS


