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*Atherosclerosis: Pathophysiology of Insulin Resistance, Hyperglycemia,
Hyperlipidemia and Inflammation*

| Running title: Pathophysiology of Atherosclerosis

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Atherosclerotic cardiovascular disease is on course to surpass infectious diseases as the leading cause of morbidity and mortality worldwide.⁶ Multiple risk factors are responsible for this trend, including the increasing average life expectancy, reducing rates of communicable diseases in addition to potentially modifiable risk factors, such as tobacco use, hypertension, hyperlipidemia, and diabetes mellitus.⁶

The development of atherosclerosis is driven by multiple factors including hypertension, dyslipidemia, inflammation, insulin resistance, hyperglycemia. While many techniques are available to accurately measure atherosclerosis (coronary artery calcium scanning, CT angiography, intravascular ultrasound), understanding the pathophysiology of the disease may help drive discovery to ultimately prevent the disease.

Insulin Resistance and Atherosclerosis

An important distinction to draw is the role of insulin resistance versus hyperglycemia in the development of atherosclerosis. Although both likely have a synergistic atherogenic effect in the setting of type 2 diabetes, insulin resistance has been shown to have a strong link to CVD, even in the absence of hyperglycemia.²

Insulin resistance promotes a pro inflammatory state and dyslipidemia in addition to perturbed insulin signaling on important intimal cells (endothelial, vascular smooth muscle cells, and macrophages) resulting with advanced plaque progression in the setting of hyperinsulinemia.² Normal insulin signaling in skeletal muscle starts with insulin binding to its receptor, which causes tyrosine phosphorylation of insulin

receptor substrate (IRS - 1) to exert insulin's effect on glucose metabolism.² Meanwhile in liver, IRS - 1/IRS - 2 activates phosphatidylinositol (PI - 3) kinase which phosphorylates PI, PI - 4, PI - 4,5, and mediates glucose transport and glycogen synthase.⁴ In vivo trials conducted in hyperinsulemic, euglycemic lean type II diabetics and obese non diabetics have shown that the impaired phosphorylation of IRS - 1 and PI - 3 kinase activation caused significant dysfunction in glucose and glycogen synthesis.¹⁰ Nitric oxide synthase is activated through the same PI - 3 kinase pathway, the resultant decrease in nitric oxide production leads to endothelial dysfunction and accelerated atherosclerosis.¹⁰

Hyperglycemia and Atherosclerosis

Chronic hyperglycemia has been shown to interfere with multiple metabolic pathways resulting in microvascular complications (e.g retinopathy, neuropathy, nephropathy).¹¹ However, there is uncertainty in the literature on the degree of impact hyperglycemia exerts on macrovascular outcomes compared to other risk factors.¹² Nevertheless, recent meta analyses have found that elevated blood glucose is an independent risk factor for cardiovascular and all cause mortality in both diabetic and non diabetic patients.³ Three major mechanisms have been described to facilitate these outcomes: 1) non enzymatic glycosylation of proteins and lipids 2) oxidative stress 3) protein kinase C (PKC activation).¹

Advanced glycation end-products (AGEs) occur through the Maillard reaction in which reducing sugars undergo non-enzymatic reactions leading to the formation of reactive carbonyl compounds and the subsequent glycooxidation of proteins, lipids, and nucleic acids.⁵ AGEs accumulate with advancing age, but this process markedly

increases in the setting of hyperglycemia, oxidative stress, and inflammation.⁵ The mechanisms in which AGEs further atherosclerosis can be classified as non-receptor dependent and receptor mediated (Aronson).

The prototypical non receptor mechanism is the alteration in the normal physiology of the low-density lipoprotein (LDL) particle.¹ Glycosylation of the apoprotein B (Apo B) and phospholipid components of LDL result in disturbances in LDL clearance and susceptibility to oxidative modification.¹ Human monocyte - derived macrophages have a higher affinity for glycated LDL via the nonspecific (scavenger) receptor which stimulates foam cell formation and promotes atherosclerosis.¹ Furthermore, glycation of LDL confers increased susceptibility to LDL becoming oxidized, which is a key step in atherogenicity.¹ Aminoguanidine is an inhibitor of AGE formation, but has not been clinically efficacious due to toxicity limitations.¹¹

The receptor mediated mechanism involves the binding of AGE receptor (RAGE).¹ RAGE has been demonstrated in all cells relevant to atherosclerosis including monocyte-derived macrophages, endothelial cells, and smooth muscle cells (SMCs).¹

Oxygen free radicals leading to atherosclerosis and diabetic complications is a long held theory.¹¹ Glucose is metabolized into reductive equivalents which drive the generation of ATP via oxidative phosphorylation with free radicals as byproducts.¹¹ "Increased oxidant stress reduces nitric oxide levels, damages cellular proteins, and promotes leukocyte adhesion to the endothelium while inhibiting its barrier function."¹¹ These effects ultimately result in accelerated atherosclerosis.

Protein Kinase C are chronically elevated in diabetics. The physiologic activation of Protein Kinase C (PKC) occurs from activating phospholipase C, increasing calcium and diacylglycerol (DAG) levels, which in turn activate PKC.¹¹ In diabetes, pathologic activation can occur through elevation of glyceraldehyde-3-phosphate, subsequent elevation of DAG, and ultimately, activation of PKC.¹¹ PKC pathway dysfunction can have many downstream consequences, including increased permeability, nitric oxide dysregulation, increased leukocyte adhesion, and induction of growth factor expression (VEGF, TGF - beta).¹¹

Cholesterol and Atherosclerosis

An undeniable causal relationship exist between plasma cholesterol levels and atherosclerosis.⁶ Atherogenesis is mediated in large part by the endothelium causing inflammation and accumulation of oxidatively modified LDL in the intima of the vessel wall facilitating monocyte recruitment and foam cell formation.⁸ Typically, the endothelium acts as a selective barrier between blood and tissues with increased permeability at arterial branch points/curvatures.⁸ The initial, most atherogenic event is accumulation of LDL in the subendothelial matrix.⁸ Conditions for this event are optimal when circulating amounts of LDL are increased and HDL (a lipid which transports excess cholesterol from peripheral tissues for storage/degradation in the liver) is decreased.⁸ LDL is taken up by macrophages to form foam cells once it is sufficiently oxidized by a multiplicity of factors including reactive oxygen species, myeloperoxidase, sphingomyelinase, and a secretory

phospholipase (group II sPLA2).⁸ Macrophages primarily uptake the LDL by scavenger receptors, SR - A and CD 36.⁸

Inflammation and Atherosclerosis

Historically, the pathogenesis of atherosclerosis was based on the lipid theory with explanations related to excess cholesterol being the sole cause of lipid deposition in the arterial wall. In the past two decades, it has been increasingly recognized that inflammation is involved in every step of the atherosclerotic process.^{7,9} Currently, atherogenesis is characterized by chronic accumulation of monocytes/macrophages, SMCs, and lymphocytes which release pro inflammatory molecules within the arterial wall.^{7,9} As a result, ongoing research is being performed in order to create anti - inflammatory therapies to prevent the development of atherosclerotic plaques.⁷ Both innate and adaptive responses of the immune system are leveraged in atherogenesis.

As mentioned previously, the initial event for atherogenesis is lipid retention in the intima of arteries enabled by endothelial dysfunction from insult-induced damage. Next, the trapped LDL is modified by enzymes and oxygen radicals, which subsequently stimulates endothelial cells to express adhesion molecules (e.g. VCAM-1 and ICAM-1) and vascular SMCs to release chemokines (CCR2, ZCCR5, ZCX3CR1 and their ligands) and chemoattractants, which recruit “inflammatory” monocytes and T cells into the developing plaque.^{7,13} Monocytes differentiate in situ into macrophages and uptake oxidized LDL.

The adaptive immune system begins to facilitate atherogenesis in the early stages as well when lymphocytes transmigrate into the arterial wall.⁷ Helper T (Th) - cells have multiple subtypes, most notably, Th1 cells are clearly atherogenic, whereas Treg is athero-protective, the other subtypes do not yet have clearly defined roles.⁷ The protein component of the LDL particle is presented by macrophages and dendritic cells to T - lymphocytes via the major histocompatibility complex class II (MHC - II) and the T cell produces pro inflammatory cytokines.⁷ Another key component of the adaptive response is B cells. B1 cells predominantly produce IgM antibodies, which are protective of atherosclerosis while B2 cells produce IgG antibodies, which promote atherosclerosis by interacting with CD4 T-cell activation and stimulating effector T-cell proliferation.⁷

Toll like receptors play a central role in innate and adaptive immune responses and appear to be expressed in atherogenic leukocytes, including monocytes/macrophages, dendritic cells, T and B lymphocytes.⁷ As the inflammatory process becomes chronic, SMCs also start to migrate into the intimal layer of the artery in response to chemokines and aided by release of metalloproteinases (MMPs).⁹ With chronicity, plaque vulnerability becomes the primary determinant of thrombus and rupture-mediated complications.¹³ Macrophages become pivotal in plaque destabilization through various enzymes, bioactive mediators, but notably, MMP has been implicated as an important pathogenic molecule contributing to plaque destabilization.¹³ Eventually, continuous apoptosis of macrophages and accumulation of non degradable necrotic debris leads to the formation of the lipid laden necrotic core seen in late lesions.¹³ Fibrous plaques are characterized by a growing mass of extracellular lipid and by

accumulation of SMCs and SMC - derived extracellular matrix.⁸ The most vulnerable plaques to rupture generally have thin fibrous caps and increased numbers of inflammatory cells.⁸

Concluding Remarks

Atherosclerosis is a chronic disease, which only stands to become even more significant as life expectancy continues to increase and risk factors, such as hypertension, diabetes, tobacco use, and hyperlipidemia become more prevalent. We have demonstrated multiple etiologies and accompanying mechanisms contributing to the formation and propagation of atherosclerotic plaques.^{14,15} Going forward, it will be important that our understanding of this complex disease continues to evolve in concert with imaging modalities and novel therapeutic targets to detect and prevent the disease.

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