# Pathophysiology and Medical Treatment of Carotid Artery Stenosis

Kailash Prasad, MBBS (Hons.), MD, PhD, DSc, FRCPC, FACC, FIACS, FICA[1]

[1] Department of Physiology, College of Medicine, University of Saskatchewan, Saskatoon, Saskatchewan, Canada

Int J Angiol 2015;24:158–172.

Address for correspondence  Kailash Prasad, MBBS (Hons.), MD, PhD, Department of Physiology, College of Medicine, University of Saskatchewan, 107 Wiggins Road, Saskatoon, S7N 5E5, Canada, SK (e-mail: k.prasad@usask.ca).

## Abstract

### Keywords
► carotid artery stenosis
► epidemiology
► pathogenesis
► risk factors
► treatment
► oxyradicals
► AGE–RAGE axis

Stroke is the third leading cause of mortality. Approximately 80 to 85% strokes are ischemic due to carotid artery stenosis (CAS). The prevalence of significant CAS is 7% in women and 9% in men. Severe asymptomatic CAS varies from 0 to 3.1%. Prevalence of symptomatic CAS is high in patients with peripheral arterial disease. CAS is due to atherosclerosis, the major risk factors for which include dyslipidemia, hypertension, diabetes, obesity, cigarette smoking, advanced glycation end products (AGEs) and its receptors (RAGE, soluble RAGE [sRAGE]), lack of exercise and C-reactive protein (CRP). This article discusses the basic mechanism of atherosclerosis and the mechanisms by which these risk factors induce atherosclerosis. The role of AGEs and its receptors in the development and progression of CAS has been discussed in detail. Lifestyle changes and medical treatment of CAS such as lifestyle changes, lipid-lowering agents, antihypertensive agents, antidiabetic drugs, anti-AGE therapy, measures to elevate soluble receptors of AGE (sRAGE, esRAGE). CRP-lowering agents have been discussed in detail. The drugs especially lipid-lowering agents, and antihypertensive and antidiabetic drugs suppress, regress, and slow the progression of CAS. The possible role of lowering the levels of AGEs and raising the levels of sRAGE in the treatment of CAS has been proposed. Lifestyle changes besides medical treatment have been stressed. Lifestyle changes and medical treatment not only would slow the progression of CAS but would also regress the CAS.

Stroke is the third cause of disability in the world and third leading cause of mortality.[1] Approximately 80 to 85% of strokes are ischemic due to stenosis, clot, and embolism. Approximately 20 to 30% of all strokes are caused by extracranial carotid artery stenosis (CAS),[2] while intracranial CAS accounts for 5 to 10% of strokes.[3] CAS is due to atherosclerosis. As the atherosclerosis progresses the atherosclerotic plaques rupture resulting in the formation of thrombus and arterial occlusion or dislodged materials from the plaques blocking the smaller branches of the carotid artery. Transient ischemic attacks (TIA) are a brief period of symptoms similar to stroke due to temporary blockage of blood supply to a section of the brain and often lasts less than 24 hours. Carotid artery disease is responsible for nearly 50% of all TIAs.[4] Risk of developing stroke after TIAs is as high as 20% within the 1st month.[2] If untreated, TIAs result in development of stroke within 2 years. Risk of stroke events remains high for 10 to 15 years after TIAs.[5]

CAS manifests into clinical syndromes, that is, asymptomatic, TIAs, and ischemic stroke. CAS is considered symptomatic when ipsilateral retinal or cerebral ischemia occurs and asymptomatic when these symptoms are absent. Around 5 to 10% of the general population over 65 years of age has an asymptomatic CAS of 50% or greater.[6,7] Prevalence of asymptomatic CAS of 50% or greater is highest in patients with peripheral arterial disease (15%) and abdominal aortic aneurysm (12%).[8] Risk of stroke increases with increasing CAS.[9] There is less than 1% stroke per year for a CAS less than 80%

but increases to 4.8% per year for a CAS greater than 90%.[8] A stenosis of the carotid artery greater than 50% is considered significant carotid artery disease. Differentiation between asymptomatic and symptomatic CAS is important for treatment of CAS. In general, medical treatment is provided for asymptomatic patients while invasive treatment is considered for symptomatic patients with CAS greater than 50%[10] and for asymptomatic patients with CAS greater than 60%.[11] For invasive or medical treatments, the risk factors for CAS have to be considered.

This article discusses the epidemiology and risk factor for CAS, and medical treatment of carotid stenosis.

## Epidemiology

Carotid artery atherosclerosis is mostly present at the carotid bifurcation into external and internal carotid artery. The ostium of the internal carotid artery is mostly affected. Intracranial internal carotid artery and its branches are less affected with atherosclerosis. The prevalence of CAS varies with the study population, use of equipment, and the criteria employed. The prevalence of significant CAS was 7% in women and 9% men when carotid ultrasound was used for measurement of stenosis and when stenosis was less than 50%.[12] Prevalence is high in individuals with high risk of atherosclerosis (11%), cardiac disease (18%), and acute stroke (60%).[13] The prevalence of moderate asymptomatic CAS in general population is between 0.2% in men aged less than 50 years and 7.5% in men aged greater than or equal to 80 years.[9] For women, this prevalence ranged from 0 to 5%. de Weerd et al[9] also reported that prevalence of severe asymptomatic CAS varies from 0.1% in men aged less than 50 years to 3.1% in men aged greater than or equal to 80 years. For women, this prevalence increased from 0 to 0.9%. They concluded that the prevalence of severe asymptomatic CAS varies from 0 to 3.1%. Around 15% of the patients with extracranial CAS had intracranial CAS.[14] Mild intracranial CAS was observed in 33% of the patients with extracranial CAS.[15] O'Leary et al[16] reported that 25% of the 4,476 elderly patients without clinical evidence of cardiovascular disease in the 5th quartile intimal–medical thickness had myocardial infarction or stroke at 6.2 year follow-up compared with less than 5% in the 1st quantile.

It has been reported that the prevalence of asymptomatic CAS is high in patients with peripheral arterial disease.[17–19] Bavil et al[20] reported that the prevalence of significant internal CAS in Iranian patients with peripheral arterial disease was low (4.2%). Tanimoto et al[21] reported the prevalence of CAS (less than 50%) was 14% with one-vessel disease, 21% with two-vessel disease, and 36% with three-vessel disease in Japanese patients with coronary artery disease (CAD). Kallikazaros et al[22] showed that the prevalence of CAS of less than 50% was present in 5% with one-vessel disease, 13% with two-vessel disease, 25% with three-vessel disease, and 40% with left main disease. In a recent large study, Steinvil et al[23] reported the prevalence of CAS (greater than 50%) as 5.9% with normal or nonobstructive CAD, 6.6% with one-vessel disease, 13% with two-vessel disease, 17.8% with three-

vessel disease, and 31.3% with left main disease. Prevalence of severe CAS (greater than 70%) was 2.1% with normal or nonobstructive CAD, 3.1% with one-vessel disease, 3.6% with two-vessel disease, 7% with three-vessel disease, and 10.8% with left main disease in the same study. The prevalence of significant CAS has been reported to be 30% in patients with CAD.[24] Mathiesen et al[25] reported that prevalence of CAS was higher in men than women (3.8 vs. 2.7%). CAS was associated with history of cerebrovascular disease, CAD, and peripheral arterial disease. They also reported that with each 10% increase in the extent of CAS, the risk of cerebrovascular event increased by 26%. These data suggest that prevalence of CAS is high and is associated with peripheral vascular disease. Association of prevalence with CAD is dependent upon the number of affected coronary artery.

## Pathogenesis of Carotid Artery Stenosis

CAS is a progressive narrowing of the carotid artery due to development of atherosclerosis, characterized by local thickening of the interior arterial wall. Pathogenesis of atherosclerosis has been reviewed early by Prasad.[26] Classical types of lesion are fatty streaks, fibrous cap, and complicated lesion, based on the progression of atherosclerosis. Carotid plaques consist of lipid core with infiltration of inflammatory cells covered with a fibrous cap. A typical fibrous cap consists of the following: (1) fibrous cap composed of smooth muscle cells, few leukocytes, dense connective tissue that contains elastin, collagen fibrils, proteoglycans, and a basement membrane; (2) a cellular area beneath that consists of a mixture of macrophages, smooth muscle cells, and T lymphocytes; and (3) a deeper necrotic core that contains cellular debris, lipids, cholesterol crystals, and calcium deposit. With time the plaque can become large and produce narrowing in the carotid artery. A plaque can be stable and asymptomatic or it may be a source of embolization. Rupture-prone carotid plaques are called vulnerable or unstable plaques which are characterized by active inflammation, extensive accumulation of macrophages, thin cap with a large lipid core, endothelial denudation with superficial platelet aggregation, fissures, and severe stenosis.[27] Vulnerable plaques are more susceptible to rupture when the fibrous cap becomes thin with remodeling of extracellular matrix by matrix metalloproteinase secreted by leukocytes within the intima.[28] The vulnerable plaques are more likely to rupture resulting in thromboembolic events.[29] Inflammation of the fibrous cap occurs most likely in noncalcified plaque as compared with calcified plaque suggesting that calcification of plaque is a marker of stability of plaque.[30] Asymptomatic plaques are more calcified and less inflamed than symptomatic plaques.[31]

Atherosclerotic plaques generally develop at branch ostia and bifurcation of the common carotid artery into the external and internal carotid artery. The ostium of the internal carotid artery is mostly affected, involving posterior wall of carotid sinus. It also extends into the distal common carotid artery. Intracranial internal carotid artery and its branches are affected by atherosclerosis. Besides the general risk factor for atherosclerosis, the fluid dynamics and vessel geometry

also play a role in the development of atherosclerosis.[32,33] Hemodynamic forces at the carotid bifurcation have a role in localization of intimal thickening. Both in vivo and in vitro studies it has been reported that disturbed flow and low-shear conditions produces endothelial dysfunction.[32–34]

Mauriello et al[35] reported that the thrombotic plaques are more frequently detected in patients with stroke (66.9%) than with TIA (36.1%) and asymptomatic patients (26.8%). They also reported that out of 45 carotid plaques removed during carotid endarterectomy 39.6% were thrombotic plaques, 15.8% were vulnerable plaques, and 44.6% were stable plaques.

## Mechanism of Atherosclerosis

The mechanism of atherosclerosis in carotid artery is similar to the atherosclerosis in other arterial locations. Reactive oxygen species (ROS) have been implicated in the initiation and progression of atherosclerosis.[36–40] This hypothesis is universally accepted and it has been described in detail elsewhere by Prasad.[26] ROS increases the expression of cell adhesion molecules including intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial leukocyte adhesion molecule on endothelial cells (ELAMs).[41–44] Monocyte adherence to endothelial cells is mediated through adhesion molecules. Low-density lipoprotein cholesterol (LDL-C) is mildly oxidized to minimally modified LDL (MM-LDL) which stimulates endothelial and smooth muscle cells to produce chemoattractant proten-1 (MCP-1).[45] MM-LDL is further oxidized to fully oxidized LDL (OX-LDL).[46] MCP-1 and OX-LDL accelerate migration of monocytes to subendothelial area.[47–49] Monocyte macrophages express the LDL receptor, but the rate of uptake of native LDL is insufficient to produce foam cells.[50] OX-LDL is a ligand for the scavenger receptor expressed in monocyte differentiated into tissue macrophage.[51,52] This monocyte/macrophage differentiation is facilitated by release of monocyte colony stimulating factor (MCSF) from endothelial cells under the influence of MM-LDL.[45] The differentiated macrophage develops receptor for OX-LDL which is taken up by receptors to produce foam cells. The production of foam cells is the early stage of atherosclerosis. Foam cells also generate ROS.[53]

Macrophages generate a host on growth-regulating molecules (platelet-derived growth factor [PDGF], basic fibroblast growth factor [bFGF],[54] heparin-binding epidermal growth factor [HB-EGF], and transforming growth factors [TGF-α and TGF-β]), and cytokines (IL-1, TNF-α) that affect neighboring cells. Gene expression and transcription in smooth muscle cells could result in the formation of collagen, elastic fiber proteins, and growth-regulating molecules (bFGF, insulin-like growth factor I [IGF-I], HB-EGF, TGF-β) and cytokines (IL-1, TNF-α). Endothelial cells produce growth-promoting molecules (PDGF, bFGF, TGF, IGF-I) and cytokines. T lymphocytes produce TGF-β and cytokines. Smooth muscle cells also produce colony-stimulating factor (macrophage colony-stimulating factor [M-CSF] and granulocyte-monocyte colony-stimulating factor [GM-CSF]). PDGF, bFGF, and IGF-I are critical to the proliferation of smooth muscle cells and possi-

bly of endothelium. Colony-stimulating factor plays a role in macrophage stability and replication. TGF-β is a potent stimulator of synthesis of connective tissue and matrix including collagens, proteoglycans, and elastic fiber proteins. It inhibits the replication of many cells including smooth muscle cells. Cytokines promote smooth muscle cell proliferation. Both PDGF and IGF-I are chemoattractants for smooth muscle cells. Fibroblast growth factors and M-CSF are chemoattractants for endothelium and for monocyte-derived macrophages, respectively.

Smooth muscle cell proliferation and migration, synthesis of connective tissue and matrix, migration of monocytes and formation of foam cells results in the development and progression of atherosclerosis.

## Risk Factors

Risk factors for development of CAS are similar to those for CAD and other peripheral vascular disease. These risk factors include: dyslipidemia, hypertension, diabetes, advanced glycation end products (AGEs) and its receptors, obesity, cigarette smoking, lack of exercise, age, and C-reactive protein. The following section will provide the mechanism of development of atherosclerosis/CAS related to risk factors. Mathiesen et al[25] have reported that total cholesterol (TC), LDL-C, systolic blood pressure, and current smoking were independently associated with CAS both in men and women. In multivariate models adjusted for age and sex. Raitakari et al[55] have shown that carotid artery intima-media thickness (IMT) in adulthood was significantly associated with levels of LDL-C, systolic blood pressure, and smoking in childhood, and with systolic blood pressure and smoking in adulthood.

### Dyslipidemia

#### Total Cholesterol
High levels of serum TC and LDL-C are risk factors for development of atherosclerosis. Hypercholesterolemia increases the generation of ROS through various mechanisms.[26,56] Hypercholesterolemia also increases the activity of nicotinamide adenine dinucleotide phosphate-oxidase (NADPH-oxidase), xanthine oxidase,[57] and myeloperoxidase,[58] resulting in the generation of ROS. Cholesterol also increases the secretion of proinflammatory cytokines.[59] It has been reported that TNF-α, IL-β, and IFN-y increase the mitochondrial and NAPDH-oxidase-generated ROS.[60] The facts that hypercholesterolemia produces atherosclerosis in animal model,[36–38] and antioxidants suppress hypercholesterolemic atherosclerosis,[36–38,61,62] suggest that ROS plays a role in the development of atherosclerosis.

#### Low-Density Lipoprotein Cholesterol
LDL-C takes a major part in the development of atherosclerosis. LDL[63] and OX-LDL[64] activate endothelial NADPH-oxidase resulting in ROS generation. The other effects of MM-LDL and OX-LDL have been described in the section on mechanism of atherosclerosis. Native LDL increases the expression of ICAM-1,[65] VCAM-1, and p-selectin.[66]

OX-LDL also increases the expression of ICAM-1 and E-selectin.[67]

## High-Density Lipoprotein Cholesterol

High-density lipoprotein cholesterol (HDL-C) is protective against atherosclerosis. Classical function of HDL-C is reverse cholesterol transport, that is, removing cholesterol from peripheral tissue and delivering in the liver for metabolism. This way it reduces the serum levels of TC and its consequences. Besides its function as reverse cholesterol transport, it has numerous other functions which may reduce the development of atherosclerosis. Protective effect of HDL-C could be due to its effect on generation of ROS and vascular cell adhesion molecules. Reconstituted HDL-C inhibits leukocyte NADPH-oxidase.[68] This effect of HDL-C may protect vascular injury and development of atherosclerosis. HDL-C suppresses the expression of cell adhesion molecules on the endothelial cells activated by cytokines and inhibits adhesion of monocyte to endothelium.[69,70] Paraoxonase-containing HDLs significantly protects LDL-C oxidation and inhibits expression of MCP-1.[71] LDL-C in a coculture of endothelial and smooth muscle cells in human serum increased the MCP-1 expression and sevenfold increase in monocyte migration into subendothelial space while purified HDL in this culture reduced the monocyte migration by approximately 90%.[48] HDL-C is positively correlated with plasminogen inhibitor-1 in humans.[72] This would reduce the formation of blood clot and reduce the stroke. Tolle et al[73] have reported that HDL-associated lysosphingolipids inhibit NAPDH-oxidase-dependent ROS generation and MCP-1 generation.

## Triglycerides

Triglyceride (TG) is a critical and a well-documented risk factor for atherosclerosis.[74] TGs in the presence of high concentration of very low-density lipoprotein generates small dense LDL,[75] which exhibits atherogenic property. High TG also reduces the levels of HDL. Triglyceride-rich lipoprotein (TGRL) increases the generation of ROS.[76] TGRL increases secretion of TNF-α, expression of cell adhesion molecules, and increases oxidative stress.[77] It increases the expression of VCAM-1.[78] This effect of TG on VCAM-1 would produce atherosclerosis. High TG levels produce a procoagulant state by increasing factor VII, and activated factor VII phospholipid complexes,[79,80] factor X,[81] tissue plasminogen activator inhibitor,[82] and thrombin generation.[83]

These data, on serum lipids, suggest that high levels of TC, LDL-C, and TG increase the risk factors which are responsible for the genesis and progression of atherosclerosis. HDL-C protects the development of atherosclerosis by affecting the factors responsible for development of atherosclerosis adversely.

## Hypertension

Hypertension may induce atherosclerosis by increasing oxidative stress, levels of cytokines, cell adhesion molecules, and chemokines.

There is evidence that oxidative stress is involved in the development and progression of atherosclerosis. In spontaneously hypertensive rats (SHR), the increased levels of ROS precedes the development of hypertension.[84] Superoxide ($O_2^-$) generation is increased in the vasculature of SHR[85] and SHR and deoxycorticosterone acetate (DOCA) salt-sensitive hypertension.[86] There are increased levels of thiobarbituric acid reactive substances (TBARs) and F2α-isoprostane the markers of oxidative stress, tissue concentrations of hydrogen peroxide ($H_2O_2$) and $O^-_2$, and decreased levels of antioxidant enzymes in experimental hypertension.[87–89] Manning et al[90] reported an increased $O_2^-$ production in aortic and mesenteric microvascular of DOCA-salt sensitive rats. Hypertension is attenuated and prevented with antioxidant.[91] $H_2O_2$ levels are elevated in hypertensive patients also.[92] Polymorphonuclear leukocytes of hypertensive patients generate increased amounts of ROS.[93,94] Patients with essential, salt-sensitive, and renovascular hypertension have higher levels of TBARs and 8-isoprostane in the plasma.[95–97] There is an increased levels of ROS and decreased levels of antioxidants or both in experimental models of hypertension.[98–100] These data suggest that ROS levels are elevated in hypertension.

The studies have shown that the plasma levels of proinflammatory cytokines (IL-1β, IL-6, and TNF-α)[101–103] are higher in hypertensive patients compared with normotensive patients. Inflammation contributes to atherosclerosis.[104] Vascular cell adhesion molecules are affected by hypertension. Shalia et al[105] have reported that circulating levels of soluble (s) ICAM-1, sE-selectin, and sP-selectin were significantly elevated in hypertensive patients and the levels of ICAM-1, VCAM-1, and E-selectin are elevated in hypertensive patients with increased IMT and left-ventricular hypertrophy.[106] MCP-1 levels in plasma are elevated in idiopathic pulmonary hypertension,[107] and systematic hypertension.[108,109] MCSF levels in plasma are elevated in hypertensive patients.[110]

These data suggest that the levels of ROS, inflammatory cytokines, cell adhesion molecules, MCP-1, and MCSF which are relevant to development of atherosclerosis are elevated in hypertensive patients.

### Cigarette Smoking

Cigarette smoking contributes to CAS. Tell et al[111] have reported that increasing cigarette smoke increases the thickening of internal and common carotid artery, and internal CAS. The prevalence of clinically significant internal CAS increased from 4.4% in never-smokers to 7.3% in former smokers and to 9.5% in current smokers. It has been reported that smoking was independently associated with severe CAS.[112] They also found that there was a significant association with smoking 20 pack-years, however no significant effect was observed with lower amounts of cigarette smoke. This association was significant with white smokers, less strong for black smokers, and no association for Hispanics. The development of CAS in cigarette smokers could be due to increased levels of ROS, increased expression of vascular cell adhesion molecules, cytokines, MCP-1 and MCSF.

Cigarette smokers have elevated levels of ROS in the serum.[113] Cigarette smoking could generate ROS through gas/tar, activation of macrophage, and polymorphonuclear

leukocytes (PMNLs), xanthine oxidase, and AGEs.[113–117] It has been reported that tobacco smoke is a source of toxic reactive substances that are involved in the generation of ROS. Kalra and Prasad[113] have shown that cigarette smoke increases the generation of ROS by PMNLs and also increase the serum levels of malondialdehyde, a measure of levels of ROS. Cigarette smoke can generate ROS through activation of xanthine oxidase.[115] The levels of serum xanthine oxidase are elevated in cigarette smokers.[118] Nicotine in cigarette smoke enhances PMNL responsiveness to complement C5a,[119] and hence increases the generation of ROS. Cigarette smoke contains peroxyl radicals and can damage the endothelium. Cigarette smoke decreases the levels of vitamin C and E which are antioxidants and hence increases the levels of ROS. Cigarette smoke decreases the serum levels of HDL-C[120] and increases the levels of non-HDL-C.[121] HDL is known to inhibit leukocyte NADPH-oxidase,[68] so reduction in HDL-C levels would increase the activity of NADPH-oxidase resulting in generation of ROS. Increases in non-HDL cholesterol would increase generation of ROS through mechanisms already discussed in dyslipidemia section of risk factors.

Serum levels of AGEs are elevated in cigarette smokers.[116,122,123] Interaction of AGEs with its full length receptor (RAGE) increases the generation of ROS, activates NF-kB and increases the expression of vascular cell adhesion molecules and cytokines.[124–126] Cytokines are also known to stimulate granulocytes to generate ROS.[127,128]

Other factors involved in the genesis of atherosclerosis are also affected in cigarette smokers. The serum levels of MCP-1[129] and MCSF[130] are elevated in cigarette smokers. The serum levels of cytokines (IL-1 β, IL-8, IL-17) are elevated in smokers.[131]

The serum levels of cell adhesion molecules are also elevated in cigarette smokers.[132,133] The levels of sICAM-1[125] and VCAM-1[126] are elevated in cigarette smokers.

These data suggest that cigarette smoke increases all the factors involved in the mechanism of atherosclerosis.

## Diabetes

Diabetes, both type-1 and type-2, are strong and independent risk factors for CAD, stroke, and peripheral vascular disease.[134] Chronic hyperglycemia is considered as a primary causal factor in diabetic complications.[135,136] Glucose can induce atherosclerosis through various mechanisms including oxidative stress, AGEs, and protein kinase C (PKC).

### Oxidative Stress

The sources of oxidative stress include: mitochondria, NADPH-oxidase, insulin, autoxidation of glucose, and uric acid.

Increase in the glucose metabolism in the mitochondria-generate reduced NADPH and reduced flavin adenine dinucleotide (FADH), resulting in the generation of $O_2^-$ which is converted into $H_2O_2$ and $\cdot OH$[137] NADPH-oxidase is a membrane-associated enzyme complex that lies dormant and is present in the vascular endothelium and smooth muscle cells, cardiomyocytes, macrophages, and neutrophils. High glucose levels activate NADPH-oxidase.[138–140]

Activated NADPH-oxidase catalyzes the reduction of $O_2$ to $O_2^-$.

The other mechanism of hyperglycemia-induced ROS involves transition metal catalyzed autoxidation of free glucose in which glucose initiates autoxidation reaction and production of $O_2^-$ and $H_2O_2$.[141] Glucose intake increases the secretion of insulin,[142] which activates plasma membrane enzyme system with the properties of NADPH-oxidase resulting in the generation of $H_2O_2$.[143] Insulin-induced generation of $H_2O_2$ is through activation of $NOX_4$, a homologous family of NADPH-oxidase.[144] Fructose in sugar increases uric acid in humans.[145] Uric acid is pro-oxidant in lipid membrane through interacting with peroxynitrite[146] and oxidized lipids.[147]

### Advanced Glycation End Products

AGEs are heterogeneous group of molecules formed from nonenzymatic reaction of reducing sugars with amino group of proteins, lipids, and nucleic acids.[124,148] Initially, glycation occurs through binding of aldehyde or ketone groups of reducing sugars to free amino groups of proteins, resulting in formation of Schiff base which undergoes rearrangements that form more stable Amadori products. Schiff base and Amadori products (hemoglobin $AI_C$) react at equilibrium state in hours and weeks, respectively. These initial and intermediate glycation products undergo a complex series of further chemical rearrangements to yield a stable and irreversible AGEs.[149] AGEs comprise of chemical structures such as N-€-carboxy-methyl-lysine (CML), N-€-carboxy-ethyl-lysine, pyrraline, pentosidine, and argpyramidine.[150] CML modifications of proteins are predominant AGEs.[151]

AGEs can induce atherosclerosis through a nonreceptor dependent and receptor-mediated mechanism.

### Nonreceptor-Mediated Mechanism

AGEs affect functional properties of extracellular matrix molecules. It enhances the synthesis of extracellular matrix components,[149] traps subendothelial LDL,[152] and crossbinds with collagen.[153]

AGEs affects the lipids. Glycation process affect apoprotein B and phospholipid component of LDL, resulting in functional alteration in LDL clearance, and an increased susceptibility to oxidative modification.[154,155] These nonreceptor-mediated mechanisms would induce the initiation and progression of atherosclerosis.

### Receptor-Mediated Mechanism

The cellular interactions of AGEs are mediated through specific receptors on the cell membrane. There are three receptors of AGEs (RAGE): Full length RAGE, N-truncated RAGE, and C-truncated RAGE. Full length RAGE is a member of immunoglobulin superfamily of receptors.[156] It has a single transmembrane domain and a highly charged cytosolic tail, which is vital for RAGE ligands. N-truncated RAGE is present in the plasma membrane and its functions are not clearly understood. C-truncated RAGE lacks cytosolic tail and transmembrane domain, circulates in the blood, and binds with AGEs but does not activate intracellular signaling.[157] There

are two isoforms of C-truncated RAGE; cleaved RAGE (cRAGE) and endogenous secretory RAGE (esRAGE). cRAGE is proteolytically cleavage of full length RAGE from cell surface[158] and esRAGE formed from alternative splicing of full length RAGE mRNA.[159] Both cRAGE and sRAGE are extracellular soluble receptors. Measurement of total sRAGE includes both cRAGE and esRAGE (measured by sRAGE enzyme-linked immunosorbent assay [ELISA] kits) while esRAGE is measured by esRAGE ELISA kits. Serum sRAGE levels are five times higher than esRAGE in healthy humans.[160] AGEs interact with sRAGE before they interact with full length RAGE.[161,162] sRAGE acts as a decoy for RAGE ligands by sequestering/competing with full length RAGE for ligand binding and hence has a cytoprotective effects.

RAGE has been shown to be expressed in variety of tissues including cells associated with atherosclerotic process such as vascular endothelial and smooth muscle cells, and monocyte-derived macrophages.[163,164] The expression of RAGE is upregulated in various diseases including atherosclerosis and diabetes.[126,161] The interaction of AGEs with RAGE results in generation of ROS and activation of NF-kB. Interaction of AGE with vascular endothelial surface RAGE in vasculature generates ROS through activation of NADPH-oxidase[165] The generated ROS then activates NF-kB. NF-kB leads to transcriptional activation of many genes including TNF-α, IL-1, IL-6, IL-8, interferon-γ and VCAM-1, and ICAM-1.[166–168] Also, interaction of AGE with its receptor leads to reduced endothelial barrier function, increasing the permeability of endothelial cell layer.[169,170] Increased permeability would increase the transmigration of lipids into the subendothelial space.

Interaction of AGEs with RAGE of monocyte induces chemotaxis, which accelerates the monocyte infiltration into subendothelial space.[171,172] This interaction of AGEs with monocyte-macrophage results in the expression and production of IL-β, TNF-α, platelet-derived growth factor, and insulin-like growth factor-1,[173–175] and increases uptake of AGE–LDL by macrophage.[176] Interaction of AGEs with RAGE in vascular smooth muscle cells increases cell proliferation and production of fibronectin.[177,178]

The following data support the involvement of AGE–RAGE axis in the development of atherosclerosis and vascular hyperplasia. Zhou et al[179] have reported that the levels of AGEs and RAGE in carotid arterial wall are elevated in Zucker diabetic rats as compared with euglycemic control rats. They also showed that the balloon injury in the carotid artery of these rats further increases the levels of AGEs and RAGE and produced neointimal hyperplasia. Treatment with sRAGE before and for up to 21 days after balloon injury reduced the neointimal growth significantly. sRAGE also reduced the vascular smooth muscle cell growth in vitro and vascular smooth cell proliferation in vivo. Sakaguchi et al[178] reported that arterial de-endothelialization in wild type mice upregulated RAGE in the injured vessels, particularly smooth muscle, and increased AGE deposition in expanding neointima. sRAGE administration decreased the neointimal expansion, and decreased smooth muscle proliferation, migration, and expression of extracellular matrix proteins. In another study, Wendt el al[180] reported that strepotozotocin-induced diabe-

tes accelerated atherosclerosis in apoE-deficient mice and this was associated with an increased expression of VCAM-1 in aorta, compared with nondiabetic mice. Treatment of diabetic mice with sRAGE significantly decreased VCAM-1 and reduced atherosclerotic lesion in a glycemia—and lipid-independent manner. Treatment of diabetic apoE-deficient mice with sRAGE completely suppressed atherosclerosis in a glycemia- and lipid- independent manner.[162] It has been reported that aorta of diabetic apoE-deficient mice showed an increased expression of RAGE, and VCAM-1 compared with nondiabetic aorta.[181] Treatment with sRAGE suppressed the levels of VCAM-1 and RAGE in aorta of diabetic rats in this study.

Author's laboratory has reported that serum levels of sRAGE were low in patients with non-ST elevation myocardial infarction.[182] Also, it has been reported that low levels of serum sRAGE is predictor for restenosis following percutaneous coronary intervention.[183]

These data suggest that AGE–RAGE axis is involved in the pathogenesis of atherosclerosis.

### Hyperglycemia and Protein Kinase C
Hyperglycemia in diabetes increases intracellular glucose which increases the concentration of intracellular diacylglycerol (DAG). DAG activates PKC in the vascular system.[184] PKC activation in vascular smooth muscle cells modulates vascular growth and DNA synthesis.[185] It increases the platelet-derived growth factor-β receptor expression in a smooth muscle cells.[186] PKC activation increases the expression of transforming growth factor-β which is involved in the regulation of extracellular matrix and collagen synthesis, and decreases the synthesis of matrix metalloproteinase.[187] These data suggest that hyperglycemia accelerates the development of atherosclerosis by activating PKC.

### Obesity
Obesity increases the risk of diabetes,[188] hypertension,[189] and insulin resistance[190] which are involved in the development of atherosclerosis/CAS.

### Age
Age is a risk factor for CAS. The prevalence of CAS (50% stenosis) below the age of 60 years is 0.5% and increases to 10% above 80 years of age. In general men under age 75 have a greater chance of developing CAS than women, but women have greater chance of developing CAS than men after age 75 years.

### C-Reactive Protein
Elevated levels of serum C-reactive proteins (CRP) predict the risk of future ischemic stroke and TIAs irrespective of other risk factors.[191] CRP is moderate but statistically significant marker for CAS.[192] Xiao-Jun et al[193] have reported that high sensitivity CRP (hs-CRP) levels in serum of hypertensive patients with carotid atherosclerosis were higher than those without carotid artery atherosclerosis, suggesting that hs-CRP plays a role in CAS. Preprocedural CRP predicts the stroke and death in patients undergoing carotid stenting.[194]

CRP increases the generation of ROS through activation of neutrophils.[195] CRP induces the development of atherosclerosis through various mechanisms including release of ROS, increased expression of vascular cell adhesion molecule, and foam cell formation.[196]

# Medical Treatments of Carotid Artery Stenosis

The treatment of CAS is directed toward the risk factors for CAS. Some risk factors for CAS such as smoking, diabetes, obesity, hypertension, CRP, and dyslipidemia can be controlled while others such as age and heredity cannot be controlled. Certainly aging process can be delayed.

The treatment of asymptomatic patients with CAS includes lifestyle changes and use of pharmacological agents.

### Lifestyle Changes

Lifestyle changes that could slow the progression of CAS include the following:

1. Cessation of smoking and use of tobacco products.
2. Use of foods low in saturated fats, cholesterol, and sodium.
3. Control of body weight.
4. Daily physical exercise.
5. Reduction of dietary calories intake.
6. Limitation of alcohol use.

### Pharmacological Agents

Asymptomatic patients with low-grade CAS (less than 50%) should receive intensive medical treatment.[197] Medical treatment is targeted at risk factors of CAS and includes: lipid lowering agents, antihypertensive agents, AGE-lowering agents, agents that increase the levels of sRAGE, and CRP-lowering agents. Only the guidelines will be described in this section. Details of the medical treatment are not feasible for this article.

### Lipid-Lowering Agents

The objectives of this treatment is to reduce the serum levels of LDL-C to $< 100$ mg/dL but should be reduced to $< 70$ mg/dL in patients with diabetes and CAD. Statins are used to lower the serum lipids. Statins are known to slow the progression of carotid atherosclerosis.[198] Statins have pleotropic effects and this has been discussed in details by Prasad.[199] They affect all the risk parameters involved in the development of atherosclerosis. Pleotropic effects include, anti-inflammatory, inhibition of expression and secretion of matrix-metalloproteinase, antioxidant, CRP-lowering effects, antithrombotic, anticell proliferation, and antimitotic.[200]

### Antihypertensive Agents

There are numerous articles which show that antihypertensive agents slow the progression[201] and regression[202] of CAS.

The blood pressure should be reduced to below 140/90 mm Hg,[203] but 130/80 mm Hg in patients with diabetes and renal disease. The general guidelines recommended for management of hypertension by the Seventh Joint National Committee on Prevention, Detection, Evaluation and Treat-

ment of High blood pressure (JNC-7),[203] the American Diabetic Association, the National Kidney Foundation and Canadian guideline[204] should be followed for the treatment of hypertension.

The initial therapy for stage I hypertension are monotherapy with thiazide diuretics, angiotensin converting enzyme inhibitor (ACEI), β receptor blockers (BBs), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs) or combination. For stage II without compelling indications the choices are combinations of thiazide diuretics and ACEI, or ARBs, or BBs or CCBs.

For additional hypotensive effects in dual therapy a drug combination from thiazide or ACEI, and CCBs, or ACEIs should be considered. Initial therapy with more than one drug increases the chances of achieving the blood pressure goal. Combination therapy produces greater reduction in blood pressure at lower doses, resulting in lower side effects.

Hypertension with compelling indications require following regimens:

1. Hypertension with heart failure: diuretics, ACEI, ARBs, CCBs, BBs.
2. Hypertension with CAD risk: diuretics, ACEI, CCBs, BBs.
3. Hypertension with diabetes: diuretics, ACEI, ARBs, CCBs, BBs.
4. Hypertension with chronic renal disease: ACEI, ARBs.
5. Hypertension and recurrent stroke prevention: diuretics, ACEI.

### Antidiabetic Agents

Antidiabetic drugs are used for the treatment of diabetes. The main objective is to keep the blood sugar levels closer to normal and prevent complications of diabetes. Other objective is to prevent, slows the progression, and regress the CAS. Hypoglycemic agents prevent,[205] slows the progression,[206,207] and regress[208,209] CAS. Depending upon the stages and type of diabetes the following antidiabetic agents should be used: Metformin, glipizide, prandin, piaglitazone, DPP-4 inhibitors (Januvia, Merck), GLP-1 receptor antagonist (sulfonylurea), $SGLT_2$ inhibitors and insulin.

### Agents that Reduce the Levels of AGEs and Increase the Levels of sRAGE: Anti-AGEs Therapy

#### Diet and Cooking

Food should be cooked at low temperature. Cooking at high heat increases the formation of AGEs.[210] Cooking in oil produces more AGEs than cooking in dry heat. Avoid eating diet with high content of AGEs. It has been reported that bread, cookies, meat, and fish are main contributors of AGEs in the standard diet.[211] Avoid fat consumption. Certain diet has high AGEs content than others, for example, fat and oil.[212]

#### Prevention of AGE Formation

The drugs that prevent the formation of AGEs include: aminoguanidine, pyrido-xanthine (natural vitamin 6), benfotiamine (a lipid-soluble derivative of thiamine), aspirin, metformin, candesartan, and orlistat.

### AGE Crosslink Breaker

The drugs that break AGE crosslink are capable of breaking α-carbonyl compounds by cleaving the carbon–carbon bond between carbonyls. This drug include alagebrium[157,212] and reduces the levels of AGE.

### Exercise

Regular moderate exercise reduces the serum levels of AGEs than irregular severe one.[213]

## Agents that Increase the Levels of sRAGE/esRAGE

### Exercise

Aerobic exercise increases the serum levels of sRAGE in patients with type 2 diabetes.[214]

### Pharmacological Agents

1. Antidiabetic agents: Insulin[215] and rosiglitazone[216] increase the serum levels of sRAGE and esRAGE.
2. Vitamins: Vitamin D increases the serum levels of sRAGE in women with polycystic ovary syndrome.[216]
3. Statins: Statins increase the serum levels of sRAGE.[217,218]
4. Angiotensin converting enzyme inhibitors (ACE-I): ACE-I (ramipril) increases the plasma levels of sRAGE and decreases the levels AGEs in diabetic rats.[219]

## Anti-C-Reactive Protein

CRP-lowering agents have been described in details by Prasad.[196,220] The following agents reduce the serum levels of CRP: Celecoxib, clopidogrel. Statins, rosiglitazone, carvedilol, antioxidants (α-tocopherol, vitamin C), ramipril, quinapril, valsartan, candesartan, calcium channel blockers (amlodipine), and combination of hydrochlorothiazide and amlodipine.

## Antiplatelet Therapy

Antiplatelet therapy with aspirin, clopidogrel, or ticlopidine should be instituted in the patients with CAS.

## Antioxidant Therapy

The antioxidant therapy in patients with CAS has been tried to a limited extent and with variable results. Azen et al[221] in a controlled clinical trial have shown that supplementation of vitamin E ($\geq 100$ IU/d) appears to be effective in reducing the progression of common carotid artery wall IMT in subjects not treated with lipid-lowering drugs. Vitamin C had no effect on the IMT of patients within the drug or placebo group. Kritchevsky et al[222] in the Atherosclerosis Risk in Community Study, measured carotid artery wall thickness in 6,318 female and 4,989 male participants and made a correlation study between carotid artery IMT and intake of dietary and supplemental vitamin C, α-tocopherol, and provitamin A carotenoid. They concluded that there is a limited support for hypothesis that antioxidants protect carotid artery disease, especially in individuals greater than 55 years of age. Devaraj et al[223] in a randomized controlled double-blind trial, showed that high dose of RRR-α-tocopherol (1,200 IU/d, for 2 years) had no significant effect on the carotid IMT. However, it significantly

reduced the biomarkers of oxidative stress. McQuillan et al[224] reported that there was an inverse association between carotid artery IMT and plasma lycopene (an antioxidant) in women, but not in men. They also showed that other antioxidant vitamins A, C, and E, and α- and β- carotene were not associated with carotid artery IMT or focal carotid artery plaques.

However, there are reports that suggest a beneficial effect of antioxidants in carotid artery disease. Karppi et al[225] reported that there was an inverse association between carotid artery IMT and lycopene or α-carotene and β-carotene. This was a population-based study in Finland. Gale et al[226] in a study comprising of 468 men and women aged between 66 and 75 years reported that antioxidants (vitamin E, C, and β-carotene) prevented the progression of CAS. In another study, bilateral duplex ultrasonography revealed carotid artery atherosclerotic regression in 7 and progression in 2 of the 25 tocotrienol (antioxidant) group of patients while none of the control group of patients showed regression, and 10 of 25 patients showed progression.[227] Aviram et al[228] reported that consumption of pomegranate juice resulted in a significant reduction in carotid artery IMT. These data suggest that the antioxidants have variable and limited effects on the slowing of progression and regression of CAS. It is to note that statins that have antioxidant activity, also regress and slow the progression of CAS.[198,199]

The variable data could be due to small doses used in these studies. Also, the ineffectiveness of vitamin E in slowing the progression of CAS could be due to conversion of α-tocopherol to α-tocopheroxyl radical, which is prooxidant.[229,230] Vitamin C rapidly reduces α-tocopheroxyl radical to α-tocopherol.[231] Considering this vitamin E should be used in combination with vitamin C to have maximum effect and avoid the adverse effects of vitamin E.

## Medical Treatment for Asymptomatic Patients with Severe CAS

Carotid endarterectomy (CEA) is generally recommended in asymptomatic patients with CAS of 50 to 60%.[220] Abbott[232] reported that ipsilateral stroke was 1.5% per year in patients treated with CEA in patients with asymptomatic severe CAS and 2.3% for patients with medical treatment. He also reported that medical treatment is three to eight times more cost-effective than surgical treatment. Current data suggest that only 50% of patients with asymptomatic CAS benefit from CEA in this period of advanced medical treatment.[233]

## Perspectives

In the section of medical treatment there are not enough clinical trial based data for lowering of AGEs and CRP and elevation of sRAGE. However the drugs, which are used in hypertension, diabetes, and dyslipidemia, lower the serum levels of AGEs and CRP, and raises the levels of sRAGE. Little attention has been focused on the effects of exercise and diet in the management of CAS. As mention earlier exercise raises levels of sRAGE and HDL-C, and lowers the levels of CRP and

TC. Exercise regimen should be included in the treatment of CAS. Also, diet with low AGEs and cooking at low temperature should be considered along with the drug treatment for CAS.

## References

1 Feigin VL, Lawes CM, Bennett DA, Anderson CS. Stroke epidemiology: a review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. Lancet Neurol 2003;2(1):43–53

2 The Intercollegiate Working Party for Stroke. National Clinical Guidelines for Stroke. 2nd ed. London: Royal College of Physicians; 2004

3 Sacco RL. Clinical practice. Extracranial carotid stenosis. N Engl J Med 2001;345(15):1113–1118

4 Alpert JN. Extracranial carotid artery. Current concepts of diagnosis and management. Tex Heart Inst J 1991;18(2): 93–97

5 Clark TG, Murphy MF, Rothwell PM. Long term risks of stroke, myocardial infarction, and vascular death in "low risk" patients with a non-recent transient ischaemic attack. J Neurol Neurosurg Psychiatry 2003;74(5):577–580

6 The European Carotid Surgery Trialists Collaborative Group. Risk of stroke in the distribution of an asymptomatic carotid artery. Lancet 1995;345(8944):209–212

7 Mineva PP, Manchev IC, Hadjiev DI. Prevalence and outcome of asymptomatic carotid stenosis: a population-based ultrasonographic study. Eur J Neurol 2002;9(4):383–388

8 Goessens BM, Visseren FL, Algra A, Banga JD, van der Graaf Y; SMART Study Group. Screening for asymptomatic cardiovascular disease with noninvasive imaging in patients at high-risk and low-risk according to the European Guidelines on Cardiovascular Disease Prevention: the SMART study. J Vasc Surg 2006;43(3): 525–532

9 de Weerd M, Greving JP, Hedblad B, et al. Prevalence of asymptomatic carotid artery stenosis in the general population: an individual participant data meta-analysis. Stroke 2010;41(6): 1294–1297

10 Barnett HJ, Taylor DW, Eliasziw M, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med 1998;339(20): 1415–1425

11 Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. JAMA 1995;273(18):1421–1428

12 Fine-Edelstein JS, Wolf PA, O'Leary DH, et al. Precursors of extracranial carotid atherosclerosis in the Framingham Study. Neurology 1994;44(6):1046–1050

13 Rockman CB, Jacobowitz GR, Gagne PJ, et al. Focused screening for occult carotid artery disease: patients with known heart disease are at high risk. J Vasc Surg 2004;39(1):44–51

14 Griffiths PD, Worthy S, Gholkar A. Incidental intracranial vascular pathology in patients investigated for carotid stenosis. Neuroradiology 1996;38(1):25–30

15 Kappelle LJ, Eliasziw M, Fox AJ, Sharpe BL, Barnett HJ. Importance of intracranial atherosclerotic disease in patients with symptomatic stenosis of the internal carotid artery. The North American Symptomatic Carotid Endarterectomy Trail. Stroke 1999;30(2): 282–286

16 O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr; Cardiovascular Health Study Collaborative Research Group. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. N Engl J Med 1999;340(1):14–22

17 Klop RB, Eikelboom BC, Taks AC. Screening of the internal carotid arteries in patients with peripheral vascular disease by colour-flow duplex scanning. Eur J Vasc Surg 1991;5(1):41–45

18 Alexandrova NA, Gibson WC, Norris JW, Maggisano R. Carotid artery stenosis in peripheral vascular disease. J Vasc Surg 1996; 23(4):645–649

19 Ahmed B, Al-Khaffaf H. Prevalence of significant asymptomatic carotid artery disease in patients with peripheral vascular disease: a meta-analysis. Eur J Vasc Endovasc Surg 2009;37(3): 262–271

20 Bavil AS, Ghabili K, Daneshmand SE, et al. Prevalence of significant carotid artery stenosis in Iranian patients with peripheral arterial disease. Vasc Health Risk Manag 2011;7:629–632

21 Tanimoto S, Ikari Y, Tanabe K, et al. Prevalence of carotid artery stenosis in patients with coronary artery disease in Japanese population. Stroke 2005;36(10):2094–2098

22 Kallikazaros I, Tsioufis C, Sideris S, Stefanadis C, Toutouzas P. Carotid artery disease as a marker for the presence of severe coronary artery disease in patients evaluated for chest pain. Stroke 1999;30(5):1002–1007

23 Steinvil A, Sadeh B, Arbel Y, et al. Prevalence and predictors of concomitant carotid and coronary artery atherosclerotic disease. J Am Coll Cardiol 2011;57(7):779–783

24 Qureshi AI, Alexandrov AV, Tegeler CH, Hobson RW II, Dennis Baker J, Hopkins LN; American Society of Neuroimaging; Society of Vascular and Interventional Neurology. Guidelines for screening of extracranial carotid artery disease: a statement for healthcare professionals from the multidisciplinary practice guidelines committee of the American Society of Neuroimaging; cosponsored by the Society of Vascular and Interventional Neurology. J Neuroimaging 2007;17(1):19–47

25 Mathiesen EB, Joakimsen O, Bønaa KH. Prevalence of and risk factors associated with carotid artery stenosis: the Tromsø Study. Cerebrovasc Dis 2001;12(1):44–51

26 Prasad K. Pathophysiology of atherosclerosis. In: Chang JB, Olsen ER, Prasad K, Sumpio BE, eds. Textbook of Angiology. New York, NY: Springer Verlag; 2000:85–105

27 Yamazaki M, Uchiyama S. Pathophysiology of carotid stenosis [in Japanese]. Brain Nerve 2010;62(12):1269–1275

28 Galis ZS, Sukhova GK, Lark MW, Libby P. Increased expression of matrix metalloproteinases and matrix degrading activity in vulnerable regions of human atherosclerotic plaques. J Clin Invest 1994;94(6):2493–2503

29 Naghavi M, Libby P, Falk E, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I. Circulation 2003;108(14):1664–1672

30 Wahlgren CM, Zheng W, Shaalan W, Tang J, Bassiouny HS. Human carotid plaque calcification and vulnerability. Relationship between degree of plaque calcification, fibrous cap inflammatory gene expression and symptomatology. Cerebrovasc Dis 2009; 27(2):193–200

31 Shaalan WE, Cheng H, Gewertz B, et al. Degree of carotid plaque calcification in relation to symptomatic outcome and plaque inflammation. J Vasc Surg 2004;40(2):262–269

32 Ku DN, Giddens DP, Zarins CK, Glagov S. Pulsatile flow and atherosclerosis in the human carotid bifurcation. Positive correlation between plaque location and low oscillating shear stress. Arteriosclerosis 1985;5(3):293–302

33 Zarins CK, Giddens DP, Bharadvaj BK, Sottiurai VS, Mabon RF, Glagov S. Carotid bifurcation atherosclerosis. Quantitative correlation of plaque localization with flow velocity profiles and wall shear stress. Circ Res 1983;53(4):502–514

34 Lind L, Andersson J, Larsson A, Sandhagen B. Shear stress in the common carotid artery is related to both intima-media thickness and echogenicity. The Prospective Investigation of the Vasculature in Uppsala Seniors study. Clin Hemorheol Microcirc 2009; 43(4):299–308

35 Mauriello A, Sangiorgi GM, Virmani R, et al. A pathobiologic link between risk factors profile and morphological markers of carotid instability. Atherosclerosis 2010;208(2):572–580

36 Prasad K, Kalra J. Oxygen free radicals and hypercholesterolemic atherosclerosis: effect of vitamin E. Am Heart J 1993;125(4): 958–973

37 Prasad K. Reduction of serum cholesterol and hypercholesterolemic atherosclerosis in rabbits by secoisolariciresinol diglucoside isolated from flaxseed. Circulation 1999;99(10): 1355–1362

38 Prasad K, Kalra J, Lee P. Oxygen free radicals as a mechanism of hypercholesterolemic atherosclerosis: effect of probucol. Int J Angiol 1994;3:100–112

39 Steinberg D. Antioxidants and atherosclerosis. A current assessment. Circulation 1991;84(3):1420–1425

40 Steinberg D. Antioxidants in the prevention of human atherosclerosis. Summary of the proceedings of a National Heart, Lung, and Blood Institute Workshop: September 5–6, 1991, Bethesda, Maryland. Circulation 1992;85(6):2337–2344

41 Willam C, Schindler R, Frei U, Eckardt KU. Increases in oxygen tension stimulate expression of ICAM-1 and VCAM-1 on human endothelial cells. Am J Physiol 1999;276(6 Pt 2):H2044–H2052

42 Chiu JJ, Wung BS, Shyy JY-J, Hsieh HJ, Wang DL. Reactive oxygen species are involved in shear stress-induced intercellular adhesion molecule-1 expression in endothelial cells. Arterioscler Thromb Vasc Biol 1997;17(12):3570–3577

43 Fraticelli A, Serrano CV Jr, Bochner BS, Capogrossi MC, Zweier JL. Hydrogen peroxide and superoxide modulate leukocyte adhesion molecule expression and leukocyte endothelial adhesion. Biochim Biophys Acta 1996;1310(3):251–259

44 Martin A, Foxall T, Blumberg JB, Meydani M. Vitamin E inhibits low-density lipoprotein-induced adhesion of monocytes to human aortic endothelial cells in vitro. Arterioscler Thromb Vasc Biol 1997;17(3):429–436

45 Cushing SD, Berliner JA, Valente AJ, et al. Minimally modified low density lipoprotein induces monocyte chemotactic protein 1 in human endothelial cells and smooth muscle cells. Proc Natl Acad Sci U S A 1990;87(13):5134–5138

46 Steinberg D. Oxidized low density lipoprotein—an extreme example of lipoprotein heterogeneity. Isr J Med Sci 1996;32(6): 469–472

47 Wang GP, Deng ZD, Ni J, Qu ZL. Oxidized low density lipoprotein and very low density lipoprotein enhance expression of monocyte chemoattractant protein-1 in rabbit peritoneal exudate macrophages. Atherosclerosis 1997;133(1):31–36

48 Navab M, Imes SS, Hama SY, et al. Monocyte transmigration induced by modification of low density lipoprotein in cocultures of human aortic wall cells is due to induction of monocyte chemotactic protein 1 synthesis and is abolished by high density lipoprotein. J Clin Invest 1991;88(6):2039–2046

49 Hashimoto K, Kataoka N, Nakamura E, Tsujioka K, Kajiya F. Oxidized LDL specifically promotes the initiation of monocyte invasion during transendothelial migration with upregulated PECAM-1 and downregulated VE-cadherin on endothelial junctions. Atherosclerosis 2007;194(2):e9–e17

50 Goldstein JL, Ho YK, Basu SK, Brown MS. Binding site on macrophages that mediates uptake and degradation of acetylated low density lipoprotein, producing massive cholesterol deposition. Proc Natl Acad Sci U S A 1979;76(1):333–337

51 Nagy L, Tontonoz P, Alvarez JG, Chen H, Evans RM. Oxidized LDL regulates macrophage gene expression through ligand activation of PPARgamma. Cell 1998;93(2):229–240

52 Henriksen T, Mahoney EM, Steinberg D. Enhanced macrophage degradation of biological modified low density lipoprotein. Atherosclerosis 1983;3(2):149–159

53 Rajagopalan S, Meng XP, Ramasamy S, Harrison DG, Galis ZS. Reactive oxygen species produced by macrophage-derived foam cells regulate the activity of vascular matrix metalloproteinases

54 Phan SH, McGarry BM, Loeffler KM, Kunkel SL. Regulation of macrophage-derived fibroblast growth factor release by arachidonate metabolites. J Leukoc Biol 1987;42(2):106–113

55 Raitakari OT, Juonala M, Kähönen M, et al. Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. JAMA 2003;290(17):2277–2283

56 Warnholtz A, Wendt M, August M, Münzel T. Clinical aspects of reactive oxygen and nitrogen species. Biochem Soc Symp 2004; 71(71):121–133

57 White CR, Darley-Usmar V, Berrington WR, et al. Circulating plasma xanthine oxidase contributes to vascular dysfunction in hypercholesterolemic rabbits. Proc Natl Acad Sci U S A 1996; 93(16):8745–8749

58 Liu H-R, Tao L, Gao E, et al. Rosiglitazone inhibits hypercholesterolaemia-induced myeloperoxidase upregulation—a novel mechanism for the cardioprotective effects of PPAR agonists. Cardiovasc Res 2009;81(2):344–352

59 Zhu X, Lee JY, Timmins JM, et al. Increased cellular free cholesterol in macrophage specific Abca 1 knock-out mice enhances proinflammatory response of macrophage. J Biol Chem 2008; 283:2930–2294

60 Yang D, Elner SG, Bian ZM, Till GO, Petty HR, Elner VM. Proinflammatory cytokines increase reactive oxygen species through mitochondria and NADPH oxidase in cultured RPE cells. Exp Eye Res 2007;85(4):462–472

61 Prasad K, Mantha SV, Kalra J, Lee P. Prevention of hypercholesterolemic atherosclerosis by garlic, an antioxidant. J Cardiovasc Pharmacol Therapeut 1997;2(4):309–319

62 Prasad K. Hypocholesterolemic and antiatherosclerotic effect of flax lignan complex isolated from flaxseed. Atherosclerosis 2005; 179(2):269–275

63 O'Donnell RW, Johnson DK, Ziegler LM, DiMattina AJ, Stone RI, Holland JA. Endothelial NADPH oxidase: mechanism of activation by low-density lipoprotein. Endothelium 2003;10(6):291–297

64 Heinloth A, Heermeier K, Raff U, Wanner C, Galle J. Stimulation of NADPH oxidase by oxidized low-density lipoprotein induces proliferation of human vascular endothelial cells. J Am Soc Nephrol 2000;11(10):1819–1825

65 Smalley DM, Lin JH, Curtis ML, Kobari Y, Stemerman MB, Pritchard KA Jr. Native LDL increases endothelial cell adhesiveness by inducing intercellular adhesion molecule-1. Arterioscler Thromb Vasc Biol 1996;16(4):585–590

66 Allen S, Khan S, Al-Mohanna F, Batten P, Yacoub M. Native low density lipoprotein-induced calcium transients trigger VCAM-1 and E-selectin expression in cultured human vascular endothelial cells. J Clin Invest 1998;101(5):1064–1075

67 Zhu HL, Xia M, Hou MJ, Tang ZH, Zheng PY, Ling WH. Effects of LOX-1 on expression of adhesion molecules induced by ox-LDL in HUVECs [in Chinese]. Zhonghua Xin Xue Guan Bing Za Zhi 2005; 33(8):743–747

68 Peshavariya H, Dusting GJ, Di Bartolo B, Rye KA, Barter PJ, Jiang F. Reconstituted high-density lipoprotein suppresses leukocyte NADPH oxidase activation by disrupting lipid rafts. Free Radic Res 2009;43(8):772–782

69 Cockerill GW, Rye KA, Gamble JR, Vadas MA, Barter PJ. High-density lipoproteins inhibit cytokine-induced expression of endothelial cell adhesion molecules. Arterioscler Thromb Vasc Biol 1995;15(11):1987–1994

70 Calabresi L, Franceschini G, Sirtori CR, et al. Inhibition of VCAM-1 expression in endothelial cells by reconstituted high density lipoproteins. Biochem Biophys Res Commun 1997;238(1):61–65

71 Mackness B, Hine D, Liu Y, Mastorikou M, Mackness M. Paraoxonase-1 inhibits oxidised LDL-induced MCP-1 production by endothelial cells. Biochem Biophys Res Commun 2004;318(3): 680–683

72  Eggesbø JB, Hjermann I, Høstmark AT, Joø GB, Kierulf P. Lipopolysaccharide-induced monocyte procoagulant activity, fibrinopeptide A, and PAI-I levels in persons with high or low levels of HDL-lipoprotein. Thromb Res 1993;70(2): 161–171

73  Tölle M, Pawlak A, Schuchardt M, et al. HDL-associated lysosphingolipids inhibit NAD(P)H oxidase-dependent monocyte chemoattractant protein-1 production. Arterioscler Thromb Vasc Biol 2008;28(8):1542–1548

74  Kim YS, Sung HJ, Son SJ, et al. Triglyceride (TG) down-regulates expression of MCP-1 and CCR2 in PMA-derived THP-1 macrophages. Genes and Genomics 2013;35(1):125–130

75  Packard CJ. Triacylglycerol-rich lipoproteins and the generation of small, dense low-density lipoprotein. Biochem Soc Trans 2003; 31(Pt 5):1066–1069

76  Wang L, Gill R, Pedersen TL, Higgins LJ, Newman JW, Rutledge JC. Triglyceride-rich lipoprotein lipolysis releases neutral and oxidized FFAs that induce endothelial cell inflammation. J Lipid Res 2009;50(2):204–213

77  Eiselein L, Wilson DW, Lamé MW, Rutledge JC. Lipolysis products from triglyceride-rich lipoproteins increase endothelial permeability, perturb zonula occludens-1 and F-actin, and induce apoptosis. Am J Physiol Heart Circ Physiol 2007;292(6): H2745–H2753

78  Wang YI, Bettaieb A, Sun C, et al. Triglyceride-rich lipoprotein modulates endothelial vascular cell adhesion molecule (VCAM)-1 expression via differential regulation of endoplasmic reticulum stress. PLoS ONE 2013;8(10):e78322

79  Skartlien AH, Lyberg-Beckmann S, Holme I, Hjermann I, Prydz H. Effect of alteration in triglyceride levels on factor VII-phospholipid complexes in plasma. Arteriosclerosis 1989; 9(6):798–801

80  Negri M, Arigliano PL, Talamini G, Carlini S, Manzato F, Bonadonna G. Levels of plasma factor VII and factor VII activated forms as a function of plasma triglyceride levels. Atherosclerosis 1993; 99(1):55–61

81  Simpson HCR, Mann JI, Meade TW, Chakrabarti R, Stirling Y, Woolf L. Hypertriglyceridaemia and hypercoagulability. Lancet 1983;1(8328):786–790

82  Hamsten A, Wiman B, de Faire U, Blombäck M. Increased plasma levels of a rapid inhibitor of tissue plasminogen activator in young survivors of myocardial infarction. N Engl J Med 1985;313(25): 1557–1563

83  Vanschoonbeek K, Feijge MA, Saris WH, de Maat MP, Heemskerk JW. Plasma triacylglycerol and coagulation factor concentrations predict the anticoagulant effect of dietary fish oil in overweight subjects. J Nutr 2007;137(1):7–13

84  Kitiyakara C, Wilcox CS. Antioxidants for hypertension. Curr Opin Nephrol Hypertens 1998;7(5):531–538

85  Zalba G, Beaumont FJ, San José G, et al. Vascular NADH/NADPH oxidase is involved in enhanced superoxide production in spontaneously hypertensive rats. Hypertension 2000;35(5): 1055–1061

86  Wu R, Millette E, Wu L, de Champlain J. Enhanced superoxide anion formation in vascular tissues from spontaneously hypertensive and desoxycorticosterone acetate-salt hypertensive rats. J Hypertens 2001;19(4):741–748

87  Touyz RM, Schiffrin EL. Reactive oxygen species in vascular biology: implications in hypertension. Histochem Cell Biol 2004;122(4):339–352

88  Welch WJ. Intrarenal oxygen and hypertension. Clin Exp Pharmacol Physiol 2006;33(10):1002–1005

89  Redón J, Oliva MR, Tormos C, et al. Antioxidant activities and oxidative stress byproducts in human hypertension. Hypertension 2003;41(5):1096–1101

90  Manning RD Jr, Meng S, Tian N. Renal and vascular oxidative stress and salt-sensitivity of arterial pressure. Acta Physiol Scand 2003;179(3):243–250

91  Houston MC. Nutraceuticals, vitamins, antioxidants, and minerals in the prevention and treatment of hypertension. Prog Cardiovasc Dis 2005;47(6):396–449

92  Lacy F, Kailasam MT, O'Connor DT, Schmid-Schönbein GW, Parmer RJ. Plasma hydrogen peroxide production in human essential hypertension: role of heredity, gender, and ethnicity. Hypertension 2000;36(5):878–884

93  Sagar S, Kallo IJ, Kaul N, Ganguly NK, Sharma BK. Oxygen free radicals in essential hypertension. Mol Cell Biochem 1992;111(1–2):103–108

94  Yasunari K, Maeda K, Nakamura M, Yoshikawa J. Oxidative stress in leukocytes is a possible link between blood pressure, blood glucose, and C-reacting protein. Hypertension 2002;39(3): 777–780

95  Fortuño A, Oliván S, Beloqui O, et al. Association of increased phagocytic NADPH oxidase-dependent superoxide production with diminished nitric oxide generation in essential hypertension. J Hypertens 2004;22(11):2169–2175

96  Higashi Y, Sasaki S, Nakagawa K, Matsuura H, Oshima T, Chayama K. Endothelial function and oxidative stress in renovascular hypertension. N Engl J Med 2002;346(25):1954–1962

97  Lip GY, Edmunds E, Nuttall SL, Landray MJ, Blann AD, Beevers DG. Oxidative stress in malignant and non-malignant phase hypertension. J Hum Hypertens 2002;16(5):333–336

98  Harrison DG, Gongora MC. Oxidative stress and hypertension. Med Clin North Am 2009;93(3):621–635

99  Vaziri ND. Roles of oxidative stress and antioxidant therapy in chronic kidney disease and hypertension. Curr Opin Nephrol Hypertens 2004;13(1):93–99

100 Addabbo F, Montagnani M, Goligorsky MS. Mitochondria and reactive oxygen species. Hypertension 2009;53(6):885–892

101 Bautista LE, Vera LM, Arenas IA, Gamarra G. Independent association between inflammatory markers (C-reactive protein, interleukin-6, and TNF-α) and essential hypertension. J Hum Hypertens 2005;19(2):149–154

102 Chae CU, Lee RT, Rifai N, Ridker PM. Blood pressure and inflammation in apparently healthy men. Hypertension 2001;38(3): 399–403

103 Dalekos GN, Elisaf M, Bairaktari E, Tsolas O, Siamopoulos KC. Increased serum levels of interleukin-1β in the systemic circulation of patients with essential hypertension: additional risk factor for atherogenesis in hypertensive patients? J Lab Clin Med 1997;129(3):300–308

104 Lusis AJ. Atherosclerosis. Nature 2000;407(6801):233–241

105 Shalia KK, Mashru MR, Vasvani JB, Mokal RA, Mithbawkar SM, Thakur PK. Circulating levels of cell adhesion molecules in hypertension. Indian J Clin Biochem 2009;24(4):388–397

106 Malmqvist K, Wallén HN, Held C, Kahan T. Soluble cell adhesion molecules in hypertensive concentric left ventricular hypertrophy. J Hypertens 2002;20(8):1563–1569

107 Itoh T, Nagaya N, Ishibashi-Ueda H, et al. Increased plasma monocyte chemoattractant protein-1 level in idiopathic pulmonary arterial hypertension. Respirology 2006;11(2):158–163

108 Koh KK, Ahn JY, Han SH, et al. Pleiotropic effects of angiotensin II receptor blocker in hypertensive patients. J Am Coll Cardiol 2003; 42(5):905–910

109 Deo R, Khera A, McGuire DK, et al. Association among plasma levels of monocyte chemoattractant protein-1, traditional cardiovascular risk factors, and subclinical atherosclerosis. J Am Coll Cardiol 2004;44(9):1812–1818

110 Parissis JT, Venetsanou KF, Kalantzi MV, Mentzikof DD, Karas SM. Serum profiles of granulocyte-macrophage colony-stimulating factor and C-C chemokines in hypertensive patients with or without significant hyperlipidemia. Am J Cardiol 2000;85(6): 777–779, A9

111 Tell GS, Polak JF, Ward BJ, Kittner SJ, Savage PJ, Robbins J; The Cardiovascular Health Study (CHS) Collaborative Research Group. Relation of smoking with carotid artery wall thickness and

stenosis in older adults. The Cardiovascular Health Study. Circulation 1994;90(6):2905–2908

112 Mast H, Thompson JLP, Lin I-F, et al. Cigarette smoking as a determinant of high-grade carotid artery stenosis in Hispanic, black, and white patients with stroke or transient ischemic attack. Stroke 1998;29(5):908–912

113 Kalra J, Chaudhary AK, Prasad K. Increased production of oxygen free radicals in cigarette smokers. Int J Exp Pathol 1991;72(1):1–7

114 Pryor WA, Stone K. Oxidants in cigarette smoke. Radicals, hydrogen peroxide, peroxynitrate, and peroxynitrite. Ann N Y Acad Sci 1993;686:12–27, discussion 27–28

115 Kayyali US, Budhiraja R, Pennella CM, et al. Upregulation of xanthine oxidase by tobacco smoke condensate in pulmonary endothelial cells. Toxicol Appl Pharmacol 2003;188(1):59–68

116 Nicholl ID, Bucala R. Advanced glycation endproducts and cigarette smoking. Cell Mol Biol (Noisy-le-grand) 1998;44(7):1025–1033

117 Cerami C, Founds H, Nicholl I, et al. Tobacco smoke is a source of toxic reactive glycation products. Proc Natl Acad Sci U S A 1997;94(25):13915–13920

118 Shah AA, Khand F, Khand TU. Effect of smoking on serum xanthine oxidase, malondialdehyde, ascorbic acid and α-tocopherol levels in healthy male subjects. Pak J Med Sci 2015;31(1):146–149

119 Totti N III, McCusker KT, Campbell EJ, Griffin GL, Senior RM. Nicotine is chemotactic for neutrophils and enhances neutrophil responsiveness to chemotactic peptides. Science 1984;223(4632):169–171

120 Assmann G, Schulte H, Schriewer H. The effects of cigarette smoking on serum levels of HDL cholesterol and HDL apolipoprotein A-I. Findings of a prospective epidemiological study on employees of several companies in Westphalia, West Germany. J Clin Chem Clin Biochem 1984;22(6):397–402

121 Kokaze A, Ishikawa M, Matsunaga N, et al. Difference in effects of cigarette smoking or alcohol consumption on serum non-high-density lipoprotein cholesterol levels is related to mitochondrial DNA 5178 C/A polymorphism in middle-aged Japanese men: a cross-sectional study. J Physiol Anthropol 2014;33:1

122 McDermott DH, Yang Q, Kathiresan S, et al. CCL2 polymorphisms are associated with serum monocyte chemoattractant protein-1 levels and myocardial infarction in the Framingham Heart Study. Circulation 2005;112(8):1113–1120

123 Prasad K, Dhar I. Role of advanced glycation end products and its receptors in the pathogenesis of cigarette smoke-induced cardiovascular disease. Int J Angiol 2015;24(2):75–80

124 Prasad K. Soluble receptor for advanced glycation end products (sRAGE) and cardiovascular disease. Int J Angiol 2006;15:57–68

125 Schmidt AM, Yan SD, Yan SF, Stern DM. The biology of the receptor for advanced glycation end products and its ligands. Biochim Biophys Acta 2000;1498(2–3):99–111

126 Schmidt AM, Yan SD, Wautier JL, Stern D. Activation of receptor for advanced glycation end products: a mechanism for chronic vascular dysfunction in diabetic vasculopathy and atherosclerosis. Circ Res 1999;84(5):489–497

127 Braquet P, Hosford D, Braquet M, Bourgain R, Bussolino F. Role of cytokines and platelet-activating factor in microvascular immune injury. Int Arch Allergy Appl Immunol 1989;88(1–2):88–100

128 Yuo A, Kitagawa S, Kasahara T, Matsushima K, Saito M, Takaku F. Stimulation and priming of human neutrophils by interleukin-8: cooperation with tumor necrosis factor and colony-stimulating factors. Blood 1991;78(10):2708–2714

129 Anil S, Preethanath RS, Alasqah M, Mokeem SA, Anand PS. Increased levels of serum and gingival crevicular fluid monocyte chemoattractant protein-1 in smokers with periodontitis. J Periodontol 2013;84(9):e23–e28

130 Köttstorfer J, Kaiser G, Thomas A, et al. The influence of non-osteogenic factors on the expression of M-CSF and VEGF during fracture healing. Injury 2013;44(7):930–934

131 Al-Ghurabi BH. Impact of smoking on the IL-β, IL-8, IL-10, IL-17 and TNF-α production in chronic periodontitis patients. J Asian Sci Res. 2013;3(5):462–470

132 Scott DA, Palmer RM. The influence of tobacco smoking on adhesion molecule profiles. Tob Induc Dis 2002;1(1):7–25

133 Cavusoglu Y, Timuralp B, Us T, et al. Cigarette smoking increases plasma concentrations of vascular cell adhesion molecule-1 in patients with coronary artery disease. Angiology 2004;55(4):397–402

134 Schwartz CJ, Valente AJ, Sprague EA, Kelley JL, Cayatte AJ, Rozek MM. Pathogenesis of the atherosclerotic lesion. Implications for diabetes mellitus. Diabetes Care 1992;15(9):1156–1167

135 Laakso M. Hyperglycemia and cardiovascular disease in type 2 diabetes. Diabetes 1999;48(5):937–942

136 The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329(14):977–986

137 Turrens JF. Mitochondrial formation of reactive oxygen species. J Physiol 2003;552(Pt 2):335–344

138 Bonnefont-Rousselot D. Glucose and reactive oxygen species. Curr Opin Clin Nutr Metab Care 2002;5(5):561–568

139 Inoguchi T, Li P, Umeda F, et al. High glucose level and free fatty acid stimulate reactive oxygen species production through protein kinase C–dependent activation of NAD(P)H oxidase in cultured vascular cells. Diabetes 2000;49(11):1939–1945

140 Banerjee D, Sharma P. Dual effects of glucose on macrophage NADPH-oxidase activity: a possible link between diabetes and tuberculosis. Oxid Antioxid Med Sci 2012;1(2):91–96

141 Wolff SP. Diabetes mellitus and free radicals. Free radicals, transition metals and oxidative stress in the aetiology of diabetes mellitus and complications. Br Med Bull 1993;49(3):642–652

142 Elrick H, Stimmler L, Hlad CJ Jr, Arai Y. Plasma insulin response to oral and intravenous glucose administration. J Clin Endocrinol Metab 1964;24:1076–1082

143 May JM, de Haën C. Insulin-stimulated intracellular hydrogen peroxide production in rat epididymal fat cells. J Biol Chem 1979;254(7):2214–2220

144 Goldstein BJ, Mahadev K, Wu X, Zhu L, Motoshima H. Role of insulin-induced reactive oxygen species in the insulin signaling pathway. Antioxid Redox Signal 2005;7(7–8):1021–1031

145 Maples KR, Mason RP. Free radical metabolite of uric acid. J Biol Chem 1988;263(4):1709–1712

146 Vásquez-Vivar J, Santos AM, Junqueira VB, Augusto O. Peroxynitrite-mediated formation of free radicals in human plasma: EPR detection of ascorbyl, albumin-thiyl and uric acid-derived free radicals. Biochem J 1996;314(Pt 3):869–876

147 Bagnati M, Perugini C, Cau C, Bordone R, Albano E, Bellomo G. When and why a water-soluble antioxidant becomes pro-oxidant during copper-induced low-density lipoprotein oxidation: a study using uric acid. Biochem J 1999;340(Pt 1):143–152

148 Bucala R, Cerami A. Advanced glycosylation: chemistry, biology, and implications for diabetes and aging. Adv Pharmacol 1992;23:1–34

149 Brownlee M, Cerami A, Vlassara H. Advanced glycosylation end products in tissue and the biochemical basis of diabetic complications. N Engl J Med 1988;318(20):1315–1321

150 Vlassara H, Bucala R, Striker L. Pathogenic effects of advanced glycosylation: biochemical, biologic, and clinical implications for diabetes and aging. Lab Invest 1994;70(2):138–151

151 Reddy S, Bichler J, Wells-Knecht KJ, Thorpe SR, Baynes JW. N epsilon-(carboxymethyl)lysine is a dominant advanced glycation end product (AGE) antigen in tissue proteins. Biochemistry 1995;34(34):10872–10878

152 Brownlee M, Vlassara H, Cerami A. Nonenzymatic glycosylation products on collagen covalently trap low-density lipoprotein. Diabetes 1985;34(9):938–941

153  Brownlee M, Vlassara H, Kooney A, Ulrich P, Cerami A. Amino-guanidine prevents diabetes-induced arterial wall protein cross-linking. Science 1986;232(4758):1629–1632

154  Bucala R, Makita Z, Koschinsky T, Cerami A, Vlassara H. Lipid advanced glycosylation: pathway for lipid oxidation in vivo. Proc Natl Acad Sci U S A 1993;90(14):6434–6438

155  Steinbrecher UP, Witztum JL. Glucosylation of low-density lip-oproteins to an extent comparable to that seen in diabetes slows their catabolism. Diabetes 1984;33(2):130–134

156  Neeper M, Schmidt AM, Brett J, et al. Cloning and expression of a cell surface receptor for advanced glycosylation end products of proteins. J Biol Chem 1992;267(21):14998–15004

157  Schmidt AM, Yan SD, Yan SF, Stern DM. The multiligand receptor RAGE as a progression factor amplifying immune and inflamma-tory responses. J Clin Invest 2001;108(7):949–955

158  Tam XHL, Shiu SWM, Leng L, Bucala R, Betteridge DJ, Tan KCB. Enhanced expression of receptor for advanced glycation end-products is associated with low circulating soluble isoforms of the receptor in Type 2 diabetes. Clin Sci (Lond) 2011;120(2): 81–89

159  Yonekura H, Yamamoto Y, Sakurai S, et al. Novel splice variants of the receptor for advanced glycation end-products expressed in human vascular endothelial cells and pericytes, and their puta-tive roles in diabetes-induced vascular injury. Biochem J 2003; 370(Pt 3):1097–1109

160  Koyama H, Shoji T, Yokoyama H, et al. Plasma level of endogenous secretory RAGE is associated with components of the metabolic syndrome and atherosclerosis. Arterioscler Thromb Vasc Biol 2005;25(12):2587–2593

161  Koyama H, Yamamoto H, Nishizawa Y. RAGE and soluble RAGE: potential therapeutic targets for cardiovascular diseases. Mol Med 2007;13(11–12):625–635

162  Park L, Raman KG, Lee KJ, et al. Suppression of accelerated diabetic atherosclerosis by the soluble receptor for advanced glycation endproducts. Nat Med 1998;4(9):1025–1031

163  Tanji N, Markowitz GS, Fu C, et al. Expression of advanced glycation end products and their cellular receptor RAGE in diabetic nephropathy and nondiabetic renal disease. J Am Soc Nephrol 2000;11(9):1656–1666

164  Brett J, Schmidt AM, Yan SD, et al. Survey of the distribution of a newly characterized receptor for advanced glycation end prod-ucts in tissues. Am J Pathol 1993;143(6):1699–1712

165  Wautier MP, Chappey O, Corda S, Stern DM, Schmidt AM, Wautier JL. Activation of NADPH oxidase by AGE links oxidant stress to altered gene expression via RAGE. Am J Physiol Endocrinol Metab 2001;280(5):E685–E694

166  Hofmann MA, Drury S, Fu C, et al. RAGE mediates a novel proinflammatory axis: a central cell surface receptor for S100/calgranulin polypeptides. Cell 1999;97(7):889–901

167  Reznikov LL, Waksman J, Azam T, et al. Effect of advanced glycation end products on endotoxin-induced TNF-alpha, IL-1beta and IL-8 in human peripheral blood mononuclear cells. Clin Nephrol 2004;61(5):324–336

168  Schmidt AM, Hori O, Chen JX, et al. Advanced glycation end-products interacting with their endothelial receptor induce expression of vascular cell adhesion molecule-1 (VCAM-1) in cultured human endothelial cells and in mice. A potential mech-anism for the accelerated vasculopathy of diabetes. J Clin Invest 1995;96(3):1395–1403

169  Wautier JL, Zoukourian C, Chappey O, et al. Receptor-mediated endothelial cell dysfunction in diabetic vasculopathy. Soluble receptor for advanced glycation end products blocks hyperper-meability in diabetic rats. J Clin Invest 1996;97(1):238–243

170  Esposito C, Gerlach H, Brett J, Stern D, Vlassara H. Endothelial receptor-mediated binding of glucose-modified albumin is asso-ciated with increased monolayer permeability and modulation of cell surface coagulant properties. J Exp Med 1989;170(4): 1387–1407

171  Schmidt AM, Yan SD, Brett J, Mora R, Nowygrod R, Stern D. Regulation of human mononuclear phagocyte migration by cell surface-binding proteins for advanced glycation end products. J Clin Invest 1993;91(5):2155–2168

172  Vlassara H, Fuh H, Makita Z, Krungkrai S, Cerami A, Bucala R. Exogenous advanced glycosylation end products induce complex vascular dysfunction in normal animals: a model for diabetic and aging complications. Proc Natl Acad Sci U S A 1992;89(24): 12043–12047

173  Vlassara H, Brownlee M, Manogue KR, Dinarello CA, Pasagian A. Cachectin/TNF and IL-1 induced by glucose-modified proteins: role in normal tissue remodeling. Science 1988;240(4858): 1546–1548

174  Kirstein M, Brett J, Radoff S, Ogawa S, Stern D, Vlassara H. Advanced protein glycosylation induces transendothelial human monocyte chemotaxis and secretion of platelet-derived growth factor: role in vascular disease of diabetes and aging. Proc Natl Acad Sci U S A 1990;87(22):9010–9014

175  Kirstein M, Aston C, Hintz R, Vlassara H. Receptor-specific induc-tion of insulin-like growth factor I in human monocytes by advanced glycosylation end product-modified proteins. J Clin Invest 1992;90(2):439–446

176  Klein RL, Laimins M, Lopes-Virella MF. Isolation, characterization, and metabolism of the glycated and nonglycated subfractions of low-density lipoproteins isolated from type I diabetic patients and nondiabetic subjects. Diabetes 1995;44(9):1093–1098

177  Sakata N, Meng J, Takebayashi S. Effects of advanced glycation end products on the proliferation and fibronectin production of smooth muscle cells. J Atheroscler Thromb 2000;7(3):169–176

178  Sakaguchi T, Yan SF, Yan SD, et al. Central role of RAGE-dependent neointimal expansion in arterial restenosis. J Clin Invest 2003; 111(7):959–972

179  Zhou Z, Wang K, Penn MS, et al. Receptor for AGE (RAGE) mediates neointimal formation in response to arterial injury. Circulation 2003;107(17):2238–2243

180  Wendt TM, Bucciarelli LG, Lu X, et al. Accelerated atherosclerosis and vascular inflammation develop in apo-E null mice with type 2 diabetes. Circulation 2000;102(Suppl):II-231 [abstract]

181  Kislinger T, Tanji N, Wendt T, et al. Receptor for advanced glycation end products mediates inflammation and enhanced expression of tissue factor in vasculature of diabetic apolipopro-tein E-null mice. Arterioscler Thromb Vasc Biol 2001;21(6): 905–910

182  McNair ED, Wells CR, Qureshi AM, et al. Low levels of soluble receptor for advanced glycation end products in non-ST elevation myocardial infarction patients. Int J Angiol 2009;18(4):187–192

183  McNair ED, Wells CR, Mabood Qureshi A, et al. Soluble receptors for advanced glycation end products (sRAGE) as a predictor of restenosis following percutaneous coronary intervention. Clin Cardiol 2010;33(11):678–685

184  Xia P, Inoguchi T, Kern TS, Engerman RL, Oates PJ, King GL. Characterization of the mechanism for the chronic activation of diacylglycerol-protein kinase C pathway in diabetes and hyper-galactosemia. Diabetes 1994;43(9):1122–1129

185  Koya D, King GL. Protein kinase C activation and the development of diabetic complications. Diabetes 1998;47(6):859–866

186  Kawano M, Koshikawa T, Kanzaki T, Morisaki N, Saito Y, Yoshida S. Diabetes mellitus induces accelerated growth of aortic smooth muscle cells: association with overexpression of PDGF β-recep-tors. Eur J Clin Invest 1993;23(2):84–90

187  Nabel EG, Shum L, Pompili VJ, et al. Direct transfer of transforming growth factor beta 1 gene into arteries stimulates fibrocellular hyperplasia. Proc Natl Acad Sci U S A 1993;90(22):10759–10763

188  Bloomgarden ZT. Obesity and diabetes. Diabetes Care 2000; 23(10):1584–1590

189  Kotsis V, Stabouli S, Papakatsika S, Rizos Z, Parati G. Mechanisms of obesity-induced hypertension. Hypertens Res 2010;33(5): 386–393

190  Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature 2006;444(7121): 840–846

191  Rost NS, Wolf PA, Kase CS, et al. Plasma concentration of C-reactive protein and risk of ischemic stroke and transient ischemic attack: the Framingham study. Stroke 2001;32(11): 2575–2579

192  Mullenix PS, Steele SR, Martin MJ, Starnes BW, Andersen CA. C-reactive protein level and traditional vascular risk factors in the prediction of carotid stenosis. Arch Surg 2007;142(11): 1066–1071

193  Xiao-Jun W, Wei L, Dong-Yang X, Yi-ming Z, Dang-Ming X, Xiao-Jun W. Correlation study of carotid atherosclerosis and serum high sensitivity C- reactive protein levels in elderly hypertensive patients. Heart 2012;98(Suppl 2):E1–E319

194  Gröschel K, Ernemann U, Larsen J, et al. Preprocedural C-reactive protein levels predict stroke and death in patients undergoing carotid stenting. AJNR Am J Neuroradiol 2007;28(9):1743–1746

195  Prasad K. C-reactive protein increases oxygen radical generation by neutrophils. J Cardiovasc Pharmacol Ther 2004;9(3):203–209

196  Prasad K. C-reactive protein (CRP)-lowering agents. Cardiovasc Drug Rev 2006;24(1):33–50

197  Hobson RW II, Mackey WC, Ascher E, et al; Society for Vascular Surgery. Management of atherosclerotic carotid artery disease: clinical practice guidelines of the Society for Vascular Surgery. J Vasc Surg 2008;48(2):480–486

198  Herder M, Arntzen KA, Johnsen SH, Eggen AE, Mathiesen EB. Long-term use of lipid-lowering drugs slows progression of carotid atherosclerosis: the Tromso study 1994 to 2008. Arterioscler Thromb Vasc Biol 2013;33(4):858–862

199  Prasad K. Do statins have a role in reduction/prevention of post-PCI restenosis? Cardiovasc Ther 2013;31(1):12–26

200  Liao JK, Laufs U. Pleiotropic effects of statins. Annu Rev Pharmacol Toxicol 2005;45:89–118

201  Cuspidi C, Negri F, Giudici V, Capra A, Sala C. Effects of antihypertensive drugs on carotid intima-media thickness: Focus on angiotensin II receptor blockers. A review of randomized, controlled trials. Integr Blood Press Control 2009;2:1–8

202  Johnson CT, Brewster LP. Carotid artery intima-media thickness and the renin-angiotensin system. Hosp Pract (1995) 2013;41(2): 54–61

203  The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. U.S. Department of Health and Human Services. National Heart, Lung, and Blood Institute; 2004

204  Khan NA, McAlister FA, Lewanczuk RZ, et al. The 2005 Canadian Hypertention Education Program recommendation for the management of hypertension: part II-Therapy. Can J Cardiol 2006; 22(7):583–593

205  Mazzone T. Prevention of macrovascular disease in patients with diabetes mellitus: opportunities for intervention. Am J Med 2007;120(9, Suppl 2):S26–S32

206  Mazzone T, Meyer PM, Feinstein SB, et al. Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in type 2 diabetes: a randomized trial. JAMA 2006;296(21): 2572–2581

207  Schindler TH, Cadenas J, Facta AD, et al. Improvement in coronary endothelial function is independently associated with a slowed progression of coronary artery calcification in type 2 diabetes mellitus. Eur Heart J 2009;30(24):3064–3073

208  Bianchi C, Miccoli R, Daniele G, Penno G, Del Prato S. Is there evidence that oral hypoglycemic agents reduce cardiovascular morbidity/mortality? Yes. Diabetes Care 2009;32(Suppl 2): S342–S348

209  Esposito K, Giugliano D, Nappo F, Marfella R; Campanian Postprandial Hyperglycemia Study Group. Regression of carotid atherosclerosis by control of postprandial hyperglycemia in type 2 diabetes mellitus. Circulation 2004;110(2):214–219

210  Vlassara H, Cai W, Crandall J, et al. Inflammatory mediators are induced by dietary glycotoxins, a major risk factor for diabetic angiopathy. Proc Natl Acad Sci U S A 2002;99(24):15596–15601

211  Birlouez-Aragon I, Saavedra G, Tessier FJ, et al. A diet based on high-heat-treated foods promotes risk factors for diabetes mellitus and cardiovascular diseases. Am J Clin Nutr 2010;91(5): 1220–1226

212  Kass DA, Shapiro EP, Kawaguchi M, et al. Improved arterial compliance by a novel advanced glycation end-product crosslink breaker. Circulation 2001;104(13):1464–1470

213  Salama ME, EL-Damarawi MA, Salama AF. A comparison between the impact of two different exercise protocols on advanced glycation end products in type 2 diabetic rats. Life Sci J 2013; 10(3):860–869

214  Choi KM, Han KA, Ahn HJ, et al. Effects of exercise on sRAGE levels and cardiometabolic risk factors in patients with type 2 diabetes: a randomized controlled trial. J Clin Endocrinol Metab 2012; 97(10):3751–3758

215  Lam JK, Wang Y, Shiu SW, Wong Y, Betteridge DJ, Tan KC. Effect of insulin on the soluble receptor for advanced glycation end products (RAGE). Diabet Med 2013;30(6):702–709

216  Irani M, Minkoff H, Seifer DB, Merhi Z. Vitamin D increases serum levels of the soluble receptor for advanced glycation end products in women with PCOS. J Clin Endocrinol Metab 2014;99(5): E886–E890

217  Tam HL, Shiu SW, Wong Y, Chow WS, Betteridge DJ, Tan KC. Effects of atorvastatin on serum soluble receptors for advanced glycation end-products in type 2 diabetes. Atherosclerosis 2010; 209(1):173–177

218  Nozue T, Yamagishi S-I, Takeuchi M, et al. Effects of statins on the serum soluble receptor forms of advanced glycation end products and the association with coronary atherosclerosis in patients with angina pectoris. Int J Clin Metab Endocrin. 2014;4:47–62

219  Forbes JM, Thorpe SR, Thallas-Bonke V, et al. Modulation of soluble receptor for advanced glycation end products by angiotensin-converting enzyme-1 inhibition in diabetic nephropathy. J Am Soc Nephrol 2005;16(8):2363–2372

220  Plenge JK, Hernandez TL, Weil KM, et al, Simvastatin lowers C-reactive protein within 14 days: An effect independent of low density lipoprotein cholesterol reduction. Circulation 2002; 106:1447–1452

221  Azen SP, Qian D, Mack WJ, et al. Effect of supplementary antioxidant vitamin intake on carotid arterial wall intima-media thickness in a controlled clinical trial of cholesterol lowering. Circulation 1996;94(10):2369–2372

222  Kritchevsky SB, Shimakawa T, Tell GS, et al. Dietary antioxidants and carotid artery wall thickness. The ARIC Study. Atherosclerosis Risk in Communities Study. Circulation 1995;92(8):2142–2150

223  Devaraj S, Tang R, Adams-Huet B, et al. Effect of high-dose α-tocopherol supplementation on biomarkers of oxidative stress and inflammation and carotid atherosclerosis in patients with coronary artery disease. Am J Clin Nutr 2007;86(5): 1392–1398

224  McQuillan BM, Hung J, Beilby JP, Nidorf M, Thompson PL; The Perth Carotid Ultrasound Disease Assessment Study (CUDAS). Antioxidant vitamins and the risk of carotid atherosclerosis. The Perth Carotid Ultrasound Disease Assessment study (CUDAS). J Am Coll Cardiol 2001;38(7):1788–1794

225  Karppi J, Kurl S, Ronkainen K, Kauhanen J, Laukkanen JA. Serum carotenoids reduce progression of early atherosclerosis in the carotid artery wall among Eastern Finnish men. PLoS ONE 2013; 8(5):e64107

226  Gale CR, Ashurst HE, Powers HJ, Martyn CN. Antioxidant vitamin status and carotid atherosclerosis in the elderly. Am J Clin Nutr 2001;74(3):402–408

227  Tomeo AC, Geller M, Watkins TR, Gapor A, Bierenbaum ML. Antioxidant effects of tocotrienols in patients with hyperlipidemia and carotid stenosis. Lipids 1995;30(12):1179–1183

228 Aviram M, Rosenblat M, Gaitini D, et al. Pomegranate juice consumption for 3 years by patients with carotid artery stenosis reduces common carotid intima-media thickness, blood pressure and LDL oxidation. Clin Nutr 2004;23(3):423–433

229 Burton GW, Ingold KU. Vitamin E: application of the principles of physical organic chemistry to the exploration of its structure and function. Acc Chem Res 1986;19:194–201

230 Bowry VW, Ingold KU, Stocker R. Vitamin E in human low-density lipoprotein. When and how this antioxidant becomes a pro-oxidant. Biochem J 1992;288(Pt 2):341–344

231 Doba T, Burton GW, Ingold KU. Antioxidant and co-antioxidant activity of vitamin C. The effect of vitamin C, either alone or in the presence of vitamin E or a water-soluble vitamin E analogue, upon the peroxidation of aqueous multilamellar phospholipid liposomes. Biochim Biophys Acta 1985;835(2): 298–303

232 Abbott AL. Medical (nonsurgical) intervention alone is now best for prevention of stroke associated with asymptomatic severe carotid stenosis: results of a systematic review and analysis. Stroke 2009;40(10):e573–e583

233 Selim MH, Molina CA. Medical versus surgical treatment of asymptomatic carotid stenosis: the ever-changing nature of evidence-based medicine. Stroke 2011;42(4): 1156–1157