Role of Metabolic Factors: Lipids, Glucose/Insulin Intolerance

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8.1 Introduction

The main cause of arterial disease (AD) is hardening of the arteries or atherosclerosis due to a thickening of the artery lining from fatty deposits or plaques. There are several different symptoms, depending on the location of the AD. It most commonly affects the arteries in the heart, brain, and legs [1]. Diabetes is associated with a two- to fourfold increase in the risk of developing coronary artery disease (CAD). Diabetic patients presenting with unstable angina are more likely to develop myocardial infarction. The mortality caused by myocardial infarction in diabetic patients is more than in nondiabetic individuals [2]. Similarly, diabetes increases the risk of stroke and stroke-related mortality [3]. Meanwhile, diabetes is a major risk factor for the development of peripheral arterial disease, which is typically caused by progressive narrowing of the arteries in the lower extremities [4]. Thus, AD is the major cause of mortality and significant morbidity in diabetes and cardiorenal metabolic syndrome (CRS).

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Epidemiologic evidence supports the hypothesis that diabetes adds to the impact of individual risk factors, such as hypertension and hyperlipidemia, for the prediction of excess AD [3]. It was suggested that integrative effects of elevated glucose, insulin, and triglycerides may have a considerable impact on AD and play an important role in the early pathophysiology of AD in patients with type 2 diabetes [5]. In individuals with the CRS and those with clinical diabetes, AD has been observed in all age groups, including children. Indeed, obese children prematurely manifest signs of AD [6]. In individuals 40 years and older, multiple logistic and linear regression analyses from a total of 2,188 individuals demonstrated that AD was independently associated with insulin resistance (IR) in middle-aged adults [7]. In elderly people without diabetes mellitus, the Rotterdam study found that impaired fasting glucose was associated with increased AD [8]. Therefore, glycemic control, low-density cholesterol-lowering therapy, blood pressure lowering, and comprehensive approaches targeting multiple metabolic risk factors to reduce cardiovascular risk may therefore account for the clinical beneficial effects in obese and diabetic patients with AD. In the present review, we will discuss the roles of metabolic factors in the pathogenesis of AD and provide a better understanding of potential therapeutic strategies.

8.2 Risk Factors for AD in CRS

Several metabolic risk factors such as hyperglycemia, IR, dyslipidemia, obesity, fructose, and uric acid may initiate and accelerate artery impairment (Fig. 8.1).

8.2.1 Hyperglycemia and IR

Hyperglycemia, a hallmark of diabetes, has been implicated in the development of vascular cell dysfunction including vascular smooth muscle cells (VSMCs) and endothelial cells (ECs) via mechanisms of protein kinase C (PKC) activation, activation of the hexosamine, and advanced glycation end products (AGEs). These pathways are believed to mediate vascular dysfunction through the unifying mechanism of reactive oxygen species (ROS) overproduction, most notably increases in O_2^- [9]. Studies have also shown that elevated glucose concentration may activate the tissue renin–angiotensin–aldosterone system (RAAS), and this plays an important role in the pathogenesis of vascular complications of diabetes [10, 11]. In vivo exposure of healthy human subjects to an acute glucose load leads to attenuated endothelium-dependent vascular relaxation [12]. This impaired endothelial relaxation is associated with increased oxidative stress, adhesion molecule expression, vascular permeability, and plasma levels of plasminogen activator inhibitor-1 [12]. In vitro, both high glucose and angiotensin II (Ang II) induced a progressive increase in Ang II receptor type 1 receptor 1 (AT-1R) expression on the cultured human ECs. Furthermore, high glucose enhanced Ang II-mediated peroxisome proliferation-activated receptor-γ inactivation and expression of pro-inflammatory adhesion molecules via signaling through the AT-1R [13]. With chronic exposure to elevated

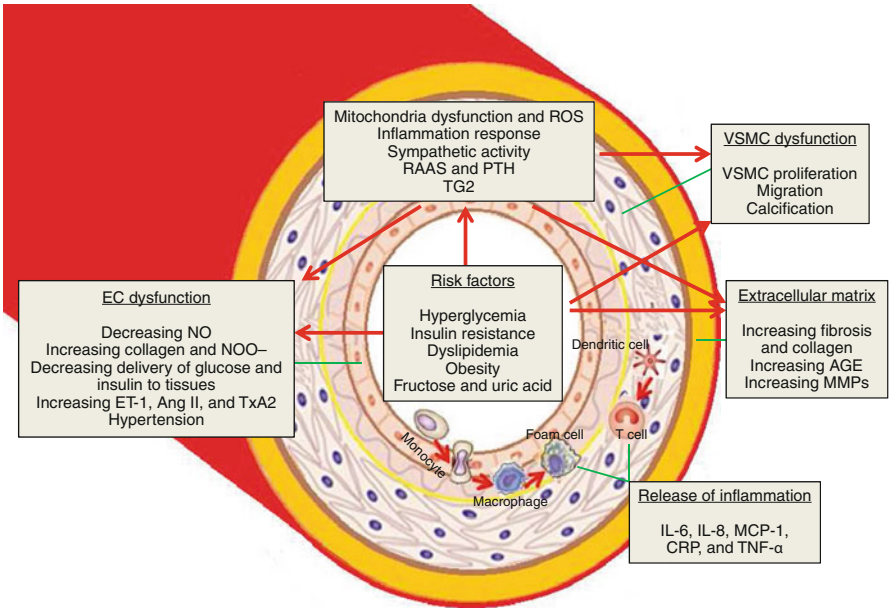

Fig. 8.1 Proposed the interaction of metabolic risk factors, adaptive metabolic response, and AD in CRS. Risk factors for AD such as hyperglycemia, insulin resistance, dyslipidemia, fructose, and uric acid induce the adaptive metabolic responses including mitochondria dysfunction, ROS, inflammation response, sympathetic activity, RAAS, PTH, and TG2, resulting in the pathophysiological abnormalities in ECs, VSMCs, and extracellular matrix on CRS. *Abbreviations*: *AD* arterial disease, *RAAS* renin–angiotensin–aldosterone system, *PTH* Parathyroid hormone, *AGE* advanced glycation end products, *TG2* tissue transglutaminase, *ROS* reactive oxygen species, *IL* interleukin, *TNF* tumor necrosis factor, *NO* nitric oxide, $ONOO^-$ peroxynitrite, *ET-1* endothelin-1, *Ang II* angiotensin II, *TxA2* thromboxane A2, *MCP-1* monocyte chemotactic protein-1, *CRP* C-reactive protein, *MMP* matrix metalloproteinase

plasma glucose, the resulting glucotoxicity may activate mitogen-activated protein kinase (MAPK) thus increasing secretion of inflammatory cytokines and inhibiting phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) signaling leading to reduced nitric oxide (NO) production and endothelial dysfunction [13].

IR, a metabolic risk factor in patients with normal glucose tolerance and even after adjustment for known risk factor such as low-density lipoprotein (LDL), triglycerides (TG), high-density lipoprotein cholesterol (HDL), and systolic blood pressure, is frequently present in obesity, hypertension, dyslipidemia, and AD [14]. In nonobese subjects without diabetes, IR predicted the development of cardiovascular disease (CVD) independently of other known risk factors. In another group of subjects without diabetes or impaired glucose tolerance, patients with IR had a 2.5-fold increase in CVD risk. These data indicate that IR itself promotes atherogenesis [15]. Our study has found that abnormal insulin metabolic signaling is an important contributor to AD. In this regard, IR is typically accompanied by reduced PI3K-NO pathway and heightened MAPK-endothelin-1 (ET-1) pathway [16].

8.2.2 Dyslipidemia and Obesity

Lipid abnormalities play an important part in raising the cardiovascular risk in patients with diabetes. The main components of diabetic dyslipidemia are increased plasma TG, low concentration of HDL, preponderance of small dense LDL, and excessive postprandial lipemia [17]. Small, dense LDL, the elevation in remnant TG-rich lipoprotein particles, and the low HDL are the most powerful atherogenic components. The coexistence of these factors strongly aggravates the lipid accumulation in the arterial wall and the formation of atherosclerotic plaques. Small, dense LDL particles are held to be more atherogenic than their larger, buoyant counterparts because they are more liable to oxidation and may more readily adhere to and subsequently invade the arterial wall. The atherogenicity of LDL may also be enhanced by nonenzymatic glycation [18]. Thus, the benefits of statin therapy in type 2 diabetics can no longer be questioned.

Obesity has a strong association with atherogenic dyslipidemia. In a large series of 26,000 overweight children, concentrations of one or more of the lipids were abnormal in 32 %, total cholesterol in 14.1 %, LDL-C in 15.8 %, HDL-C in 11.1 %, and TG in 14.3 % of those in whom data were available [19]. Indeed, overweight and obesity are associated with development of CRS which is a constellation of risk factors, such as IR, dyslipidemia, and high blood pressure [16]. The development of AD in obese patients can be attributed to a number of factors including pro-inflammatory cytokines, inappropriate activation of RAAS, vasoconstriction from increased sympathetic nervous system (SNS) activation, and dysregulation in adipokine production and secretion [20]. These data suggest that obesity and dyslipidemia are involved in AD in CRS.

8.2.3 Fructose and Uric Acid

The increasing fructose consumption has led to a rise in obesity from 13 to 34 % since 1960 and the subsequent rise in diagnosed type 2 diabetes from 5 to 8 % since 1988 [21]. In children, the intake of artificially sweetened beverages was found to be positively associated with adiposity [22]. A prospective cohort analyses of non-diabetic women in the Nurses' Health Study II concluded that higher consumption of sugar-sweetened beverages is associated with greater magnitude of weight gain and an increased risk for the development of type 2 diabetes [22]. In the Framingham Heart Study, the relationship between soft drink consumption and cardiovascular risk factors was evaluated in 6,039 participants; consumption of more than one can of soft drink per day was significantly associated with the prevalence of CRS [23]. Thus, fructose has been implicated in promoting obesity and CRS by altering appetite, inducing leptin resistance, and resulting in increased food intake. Recently, The Third National Health and Nutrition Examination Survey (NHANES III) report has indicated that consumption of sugar-sweetened beverages is significantly associated with plasma uric acid concentrations [23]. Thus, a novel hypothesis has been proposing to link fructose intake, hyperuricemia, and AD in CRS.

8.3 EC Dysfunction Initiates AD

Forming a vast interface between blood and surrounding tissues, the endothelium forms a monolayer comprising the innermost lining of blood vessels. The arterial endothelium provides a continuous barrier between the elements of blood and the arterial wall and is a critical component to vascular homeostasis, actively responding to biochemical and physical stimuli through the release of a diverse set of vasoactive substances [24]. Endothelial damage and thickening of the intima-media layers induced by risk factors we discussed above are early events in the AD process. For example, LDL particles invade the endothelium and become oxidized, creating risk for a subsequent inflammatory response and ultimately CVD. Monocytes enter the artery wall from the bloodstream with platelets adhering to the area of insult, differentiate into macrophages, and eventually form foam cells. Foam cells die and further propagate the inflammatory process [25] (Fig. 8.1).

NO, a most significant endothelium-derived mediator, plays multiple roles in preventing AD. NO diffuses into neighboring VSMCs, activating guanylyl cyclase and producing cyclic guanosine monophosphate (cGMP) and activating kinases responsible for vascular relaxation [16]. NO also inhibits platelet aggregation, smooth muscle cell proliferation, and nuclear transcription of leukocyte-adhesion molecules including vascular cell adhesion molecule (VCAM) and intercellular adhesion molecule (ICAM) [9]. Indeed, vascular homeostasis is tightly controlled by EC secreting the vasodilatory substances, such as NO, endothelium-derived hyperpolarizing factor (EDHF), prostacyclin (PGI_2), and vasoconstrictory substances, such as ET-1, Ang II, and thromboxane A2 (TxA2) [26]. These EC-secreting vasoactivity substances have been proposed to mediate the AD in CRS, including continued activation of the SNS; increased production and activity of vasoconstrictors, such as ET-1, Ang II, and TxA2; and impaired endothelium-dependent relaxation [27]. Thus, endothelial dysfunction has been suggested as a common underlying mechanism in AD with IR, hyperinsulinemia, and CRS.

8.4 Dysregulation of VSMCs and Vascular Extracellular Matrix Promotes AD

Following the EC dysfunction, the metabolic abnormalities that characterize diabetes, hyperglycemia, free fatty acids, and IR provoke the impairment of the function and structures in blood vessels include VSMC and extracellular vascular matrix (Fig. 8.1).

8.4.1 VSMC Dysfunction

The impact of CRS on vascular function is not only limited to the ECs but also to VSMCs, which are the predominant cell type found in the arterial wall and are essential for the structural and functional integrity of the vessel. Diabetes

increases PKC activity, NF-kappaB (NF-κB) production, and generation of oxygen-derived free radicals in VSMCs and heightens migration of VSMCs into atherosclerotic lesions, where they replicate and produce extracellular matrix—important steps in mature lesion formation [28]. Dysregulation of VSMC function is exacerbated by impairments in SNS function. Studies from the Zucker obese insulin-resistant rat have shown that VSMCs from these rats manifested greater concentrations of ROS and impaired activation of the NO/cGMP/protein kinase G (PKG) pathway when compared to VSMC from the lean, insulin-sensitive Zucker rats [29]. Our recent data also showed excessive serine phosphorylation of insulin receptor substrate (IRS-1) as a key mechanism underlying cellular IR in VSMCs. Furthermore, after treatment with aldosterone or Ang II, VSMCs show increased activation of p70 S6 kinase 1 signaling pathway, increased proteasome degradation of IRS-1, and attenuated insulin-induced Akt phosphorylation and glucose uptake [30]. These observations provide a biochemical basis to the IR in VSMCs in the development of AD.

8.4.2 VSMC Calcification

Studies conducted in the United States have revealed that calcium deposits in arterial walls are reported in nearly 30 % of Americans over 45 years of age [31]. Vascular calcification risk factors are similar to those of atherosclerosis including hypertriglyceridemia, increased LDL, decreased HDL, obesity, and hypertension. It has also been shown that diabetes and renal failure contribute significantly to higher risk of accumulation of calcium depositions in the vessel wall [32]. Calcification of vessels reduces their elasticity, affecting hemodynamic parameters of the cardiovascular system. Vascular calcification is an active and complex process that involves numerous mechanisms responsible for calcium deposits in arterial walls. They lead to an increase in arterial stiffness and in pulse wave velocity, which in turn increases CVD morbidity and mortality. We have known that VSMCs can differentiate from a quiescent, contractile phenotype to a proliferative, synthetic phenotype following arterial injury and in atherosclerotic diseases [33]. Indeed, VSMCs are capable of osteoblast transdifferentiation in calcifying arteries [34]. Epidemiological data have shown that higher insulin levels in diabetes can independently predicate arterial calcification [35]. The mechanisms of insulin involved in arterial calcification in these clinical settings are still controversial. Furthermore, it has been demonstrated that insulin enhances the calcification of VSMCs in vitro [36]. In this regard, insulin promotes alkaline phosphatase activity, osteocalcin expression, and the formation of mineralized nodules in VSMCs by increased receptor expression of NF-κB ligand (RANKL) through extracellular signal-regulated protein kinases 1 and 2 (Erk ½) activation [37]. However, others suggest that insulin attenuated VSMC calcification induced by high phosphate conditions [38]. These contradictory results may be explained by different cell types or different experimental conditions.

8.4.3 Elastin, Collagen, and Advanced Glycation End Products

Elastin is the most abundant protein in the walls of the arteries, which are subjected to pulsatile pressure generated by cardiac contraction. Matrix metalloproteinases (MMPs) have an important role in the degradation of elastin [39]. Recently, it was reported that in the arterial vasculature from chronic kidney disease patients, the presence of diabetes markedly upregulated MMP-2 and -9, and this adaption is strongly associated with elastic fiber degradation and AD. The increase in MMPs in diabetic vessels was also accompanied by pronounced generation of angiostatin, and the reduction of microvascular density was associated with impaired vasorelaxation [40]. In addition, the degradation of elastin also induces the overexpression of transforming growth factor beta (TGF-β). TGF-β1 not only plays an important role in osteoblast differentiation but also accelerates the calcification of VSMCs [39]. Meanwhile, hyperglycemia may cause changes in the type or structure of elastin and/or collagen in the arterial wall through nonenzymatic glycosylation of proteins that generate AGE. AGE may form irreversible cross-links between long-lived proteins such as collagen, leading to accumulation of stiffer molecules that are less susceptible to hydrolytic turnover [41]. These data confirm that the interaction among MMPs, elastin, collagen, and AGE plays a key role in the development of AD with CRS.

8.5 Misregulation of Adaptive Metabolic Responses Aggravate to the Progression of AD

Misregulation of an adaptive metabolic response contributes to the risk factors related CRS and dysfunction of ECs, VSMCs, and extracellular vascular matrix in AD (Fig. 8.1).

8.5.1 Mitochondria Dysfunction and ROS

Mitochondria are essential for intermediary metabolism as well as energy production and normally provide more than 90 % of the cellular energy [42]. It has been established that mitochondrial respiratory chain function is responsible for energy metabolism and adenosine triphosphate (ATP) production through the tricarboxylic acid (TCA) cycle, coupling of oxidative phosphorylation (OXPHOS), and electron transfer [43]. Mitochondria dysfunction is recognized as playing a central role in the development of various abnormalities, including disturbed glucose homeostasis, IR, abdominal fat accumulation, dyslipidemia, hypertension, and associated cardiac and renal pathology. ROS production occurs mainly at complex I and complex III in mitochondria [44]. Under conditions of glucose and fatty acid overnutrition, nutrient overflow into cells prompts electrons transferring to oxygen without ATP production and further favors a state of increased ROS, which potentially leads to oxidative damage within mitochondria [45]. Therefore, ROS generated from

mitochondria damages proteins, DNA, and lipid in membrane components, which result in mitochondrial dysfunction. Although this review is concerned with mitochondrial ROS, it should be recognized that the considerable amount of ROS is derived from outside of mitochondria, such as oxygen radicals from peroxisomal β-oxidation of fatty acids, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, xanthine oxidase, arachidonic acid metabolism, microsomal P-450 enzymes, and prooxidant heme molecule [46].

8.5.2 Adaptive Immunity and Inflammation Response

Atherosclerosis is a chronic inflammatory disease of the arterial wall characterized by an innate and adaptive immune system, which is composed of diverse cellular components including granulocytes, mast cells, monocytes, macrophages, dendritic cells (DCs), and natural killer cells [47]. Upon activation, partly in response to immunological stimuli from the local microenvironment as well as systemic circulation, macrophages polarize into classical (M1) or alternative (M2) phenotypes [48]. M1 macrophages are found in advanced lesions where they accumulate a large amount of lipids, which promotes their differentiation into foam cells. Meanwhile, M1 macrophages secrete tumor necrosis factor alpha (TNF-α), interleukin (IL)-6, and metalloproteinases, which exacerbate and destabilize lesion development. However, M2 macrophages predominate in the early stages of atherosclerosis and are characterized by IL-10 secretion and smaller amounts of accumulated lipids; these events are atheroprotective and can reduce plaque development [49].

DC precursors or monocytes are recruited to lesions where they differentiate into DCs. The DC population is heterogeneous and can be divided into four major categories: conventional DCs (cDCs), plasmacytoid DCs (pDCs), monocyte-derived DCs, and Langerhans cells [50]. DC accumulation in regions prone to AD suggests that their recruitment accounts for an initial inflammatory or immune activation. The exact localization and origin of vascular DCs, however, is still under debate [51]. In general, immature and semimature DCs uptake lipids and other intimal antigens, thus preventing them from eliciting pro-inflammatory signaling in other artery wall cells. Toll-like receptor (TLR) ligation by ligands such as oxLDL induces DC maturation. Under hyperlipidemic conditions, lipid uptake and efferocytosis likely lead to DC-foam cell formation, and mature DCs and foam cells emigrate from the vessel wall in a C-C chemokine receptor type 7 (CCR7)-dependent manner, clearing inflammatory cells, lipids, and apoptotic cell debris from the intimal space and preventing necrosis and persistent inflammation. Mature CD11b+ DCs likely expand regulatory T cells (Tregs) and CD4+ effector T cells within the artery wall [52]. $CD4^{+}CD25^{+}Foxp3^{+}$ Tregs can protect the pro-inflammatory activation of vascular cells. The mechanisms by which Tregs protect against inflammation are thought to be mediated, at least in part, by directing cell-to-cell interactions as well as through the secretion of soluble anti-inflammatory cytokines, including IL-10 TGF-β [53]. Thus, further studies are required to understand the role of adaptive immunity and inflammation response in AD with CRS.

8.5.3 Sympathetic Activity

The role of increased SNS activity in IR with CRS is increasingly recognized. Individuals with central obesity show increased sympathetic nervous activity. Increased sympathetic outflow has been reported in obese nonhypertensive individuals with the determination of circulating catecholamines, urinary norepinephrine (NE), and muscle sympathetic nerve activity (MSNA) [54]. Multiple neurohumoral mechanisms can activate the SNS in patients with CRS including direct activation of the SNS in response to the activation of higher cerebral nuclei and renal afferent nerve activation mediated by perirenal fat accumulation and kidney compression [55]. Sympathetic activation can also be triggered by reflex mechanisms such as arterial baroreceptor impairment, psychological stress, oxidative stress, obstructive sleep apnea, inflammation, and metabolic factors and dysregulated production and secretion of adipokines from visceral fat with a particular important role of leptin [20]. Although enhanced activation of SNS is an important component in IR, it is often related to activation of RAAS since the RAAS system causes sustained sympathetic overactivity by modulating central neurons in the subfornical organ of the forebrain [49]. The link between sympathetic nervous activity and AD offers new clues to identify AD and may allow for development of novel-targeted therapeutic interventions.

8.5.4 Renin–Angiotensin–Aldosterone System and Parathyroid Hormone

There is evidence that RAAS activation plays an important role in the pathogenesis of AD. In the course of RAAS-induced vascular injury, Ang II binds to its type 1 receptor to induce oxidative stress, mainly mediated by NADPH oxidase. Our study has also found that Ang II increased serine phosphorylation of IRS-1 and inhibited the insulin-stimulated phosphorylation of endothelial NO synthase through activation of S6 kinase (S6K) signaling pathway [30]. Recent data also suggests that increased mineralocorticoid receptor (MR) is associated with IR. Studies have demonstrated a relationship between MR activation and decreased insulin sensitivity in animal models and humans. For example, patients with primary hyperaldosteronism were found to have IR suggesting the contribution of MR signaling to IR [56]. Spironolactone, a blocker of the MR, has been shown to decrease local inflammation and vascular stiffness in rodent models of hypertension and IR [57, 58]. These observations suggest that inhibition of MR might be a beneficial therapeutic approach for preventing AD in diet-induced obesity and IR [58]. Thus, enhanced RAAS activation may represent a link between obesity, hypertension, dyslipidemia, and IR, features present in the AD with CRS [59]. Moreover, cross-talk between Ang II and aldosterone signaling underscores the importance of Ang II–aldosterone interactions in the development of IR, vascular dysfunction, and AD.

Parathyroid hormone (PTH) is secreted from parathyroid glands and increases the concentration of calcium in the blood. Recent research suggests that PTH is

implicated in regulating RAAS which is proposed to regulate PTH hormones [60]. Ang II seems to be an acute modulator of PTH, potentially through direct stimulation of PTH release via the AT-1R. In contrast, aldosterone may be involved in the modulation of PTH in the chronic setting via indirect and direct mechanisms [61]. PTH may increase sensitization towards Ang II and directly stimulate aldosterone synthesis by binding to the PTH-related protein receptor, voltage-gated calcium channels, and the adrenocorticotropic hormone receptor [62]. Therefore, the interaction of PTH and RAAS plays a key role in the pathogenesis of AD.

8.5.5 Tissue Transglutaminase

Tissue transglutaminase (TG2) is a multifunctional protein that plays an important role in vascular function, including remodeling of resistance vessels, increased aortic stiffness with age, and arterial calcification [63]. TG2 is a link between IR and AD because of its regulation by NO availability. A study has found that bioavailability of NO impaired by inflammation cytokines and RAAS is associated with decreased TG2 *S*-nitrosylation [63, 64]. Thus, increased secretion of TG2 to the cell surface and extracellular matrix and enhanced cross-linking activity in isolated endothelial, smooth muscle, and fibroblast cells resulted in AD in CRS [65]. In addition, increased vascular TG2 activity was also associated with AD in high fat-fed mice that preceded hypertension [66], thereby suggesting TG2 activation and AD as an early vent in the long-term effects of obesity on the vasculature.

Conclusion

AD increases the risk of developing coronary, cerebrovascular, and peripheral arterial disease and is a major cause of disability and death in patients with diabetes mellitus and CRS. The pathophysiology of AD in diabetes and CRS involves abnormalities in ECs, VSMCs, elastin, collagen, and AGE products, which increase the risk of the adverse cardiovascular events. Elucidation of mechanisms leading to the pathophysiological alterations in vasculature will enable us to specifically target therapeutic interventions since currently available cardiovascular medications fall short at reducing AD. Future therapeutic strategies should emphasize the need to achieve control of hyperglycemia, dyslipidemia, blood pressure, obesity, and cigarette smoking, in addition to exercise therapy. A better understanding of the mechanisms leading to vascular dysfunction may unmask new strategies to reduce disability and death in these patients.

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