



## Do Advanced Glycation End Products Predict the Outcome of Coronary Heart Disease? Current Insight and Future Perspectives

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**Received:** May 28, 2018 ; **Published:** June 18, 2018

Despite the advancement in the therapy and diagnosis of ischemic heart disease, its rate is alarmingly increasing during the last decade both in developing and developed countries. According to the recent survey, World Health Organization has estimated ~17.7 million mortality (31% of total global death) due to cardiovascular diseases (CVDs) in 2015. Among this, ~7.4 million deaths were due to coronary heart disease (CHD) [1]. There are multiple etiological factors that favor the pathophysiology of atherosclerosis and its outcome CHD. Among them, diabetes mellitus (DM) have long been proposed as the major contributing factor for the incidence of CHD. Patients with DM, the risk for CVD was found to be elevated many folds. Advanced glycation end products (AGEs) have been demonstrated as factors which involved in the formation and progression of atherosclerosis. They are heterogeneous group of compounds formed during the glycation and oxidation reactions on amino group of proteins. They formed endogenously and exogenously by a reaction referred as "Maillard reaction" in which a labile Schiff base is formed first between carbonyl group of sugar and amino group of arginine or lysine residue of proteins. The Schiff base further rearranges to form a stable Amadori-product. Both Schiff base and Amadori-product slowly converted to stable AGEs through dicarbonyl intermediate. Lipid oxidation or protein degradation products can also slowly convert to AGE. Exogenously, they found in tobacco smoke and, hence, elevated in cigarette smokers when compared to nonsmokers [2]. Furthermore, various cooking methods like broiling at 225°C or frying at 177°C can favor the formation of AGEs [3]. Butter, margarine, cheese and mayonnaise are some high-fat spreads which contain high level of AGEs [4]. Protein rich diet can enhance the formation of AGE endogenously [5]. N-ε-carboxy-methyl-lysine (CML), N-ε-carboxy-ethyl-lysine (CEL), imidazolone, glyoxal-lysine dimer (GOLD), methyl-glyoxal-lysine dimer (MOLD), pentosidine and pyrraline are the major oxygen and nitrogen containing AGEs. Presence of CML, CEL and argpyrimidine were demonstrated in human. The serum AGEs level was found to be increased with age. The mean level of serum CML in adult (above the age of 50 years) is 8.6 U/mL while that of pentosidine is 22.8 µg/L.

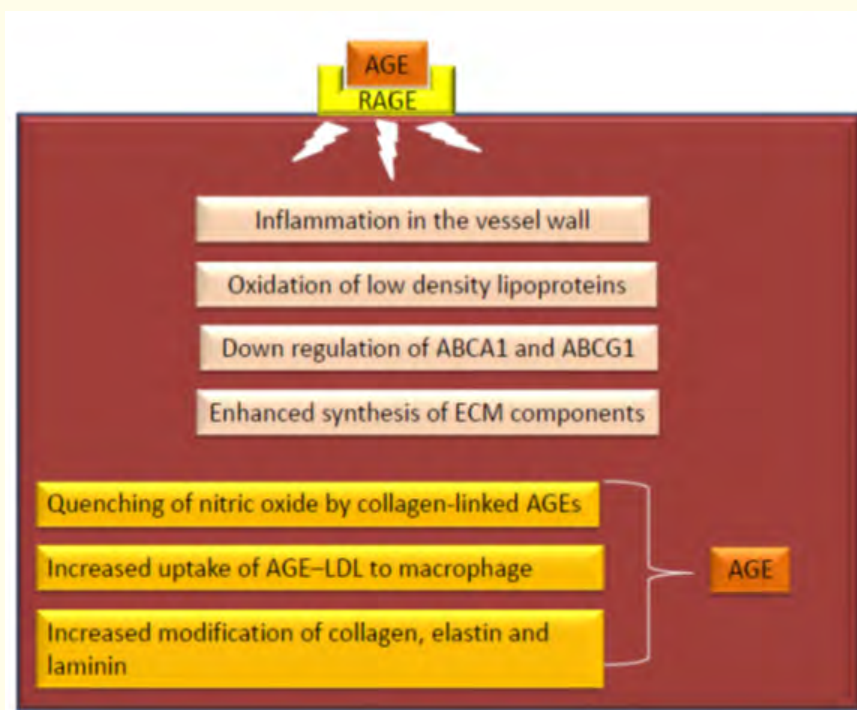
The AGEs interact with the cell surface receptor (RAGE) which eventually results in the release of proinflammatory cytokines and free radicals in the cytosol. Among the AGEs described above, CML has dominant AGE epitope for binding to the RAGE and, thus, is the most abundant form of AGEs in human [6]. RAGE has distributed on a wide variety of cells in the human body including immune cells, cardiomyocytes and nerve cells. The mechanism of cytokine release is mediated through mitogen-activated protein kinase pathway which results in the up regulation of transcription factor nuclear factor kappa B. Inflammation can produce oxidative stress in cell. Other receptors, macrophage scavenger receptor-1 and AGE receptor-1, 2 and 3 are involved in the detoxification and clearance of AGEs. Inside the cell, AGEs process in the endo-lysosomal system and finally excreted in urine. Role of liver and kidneys in the elimination of AGEs was demonstrated as well [7].

The role of AGEs in the initiation and progression of atherosclerosis has been demonstrated in various studies. The major role of AGEs in atheroma formation was mediated through oxidative stress which enhances the formation of oxidized low density lipoproteins (LDL) and increases the uptake of AGE-LDL into macrophage [8,9]. AGEs can interact with RAGE on the endothelial cells, mononuclear phagocytes of the fibro fatty plaque and smooth muscle cells result in the vascular dysfunction. This along with the quenching of nitric oxide and enhanced synthesis of extracellular matrix components further augment the vascular dysfunction [10]. RAGE can suppress the cholesterol efflux from macrophage by down regulating the ATP-binding cassette transporter G1 and A1 [11]. Interaction of AGE with RAGE can activate enzymes such as NADPH oxidase, and xanthine oxidase and, thus, generate the reactive oxygen species [12]. Increase in serum AGEs level has correlated to the stiffness of heart muscle in type 1 diabetic patients which can be ascribed to the increased modification of myocardial collagen probably through the cross-linking [10]. Overall, the generated free radicals and inflammation can mediate vascular injury which can progress to atherosclerosis. Hence, the serum level of AGEs can be considered as marker for CHD and its outcome.

AGE and its receptor have attracted interest in the clinical field as targeted therapy and novel biomarkers for the diagnosis and prognosis of diseases. Analyzing the role of AGEs in the molecular pathophysiology of CHD, mainly their correlation with the level of inflammation, aging and oxidative stress, there is a great chance for developing novel biomarker to predict the outcome of CHD. An elevated serum level of soluble RAGE and pentosidine are considered as independent prognostic factor for heart failure [13,14]. AGEs level in the fasting serum, measured using polyclonal anti-AGE antibody in a competitive immune assay, found that level > 9.0 U/mL is an independent risk factor for total (hazards ratio 1.90; 95% CI, 1.16 to 3.11) and CHD (hazards ratio, 6.51; 95% CI, 1.78 to 23.79) mortality in non-diabetic women living in Kuopio, Turku, East and West Finland, even after adjusting the confounding factors and highly sensitive C-reactive protein level [15]. A similar study in the same population revealed an increased mortality from CVD among women with type 2 diabetes aged 45 - 64 years [16]. Serum pentosidine level in diabetic patients with CVD was significantly higher and found to be correlated with increased arterial wall stiffness [17]. However, later study conducted in patients with type 2 dia-

betes and nephropathy, the serum CML level (Mean 599.9 ± 276.0 ng/mL) did not correlate significantly with the renal or cardiovascular outcome [18]. Hence, studies are limited to conclude the importance of serum AGE level as novel biomarker of CVD.

High-performance liquid chromatography, fluorescence spectroscopy, mass spectrometry, immunohistochemistry and competitive enzyme-linked immunosorbent assays are used to measure the level of cellular and extracellular level of AGE. However, none of the methods or standard units is universally accepted for the AGEs measurement which limits their availability as a useful biomarker. Antagonist to block the RAGE, breaker and inhibitor of AGE cross-linking, inhibitor to block the AGEs-induced proliferation and synthesis of collagen in the vascular smooth muscle cells, scavenging the dicarbonyl precursor of AGEs are the main the drug development area to alleviate the AGE toxicity and related pathogenesis [19,20]. Despite the various natural and synthetic agents that target the AGEs or their pathway, no clinical trials have so far been conducted to explore their clinical utility. Hence, well designed future studies in these areas are warranted.



**Figure:** Effects of AGEs on cell (endothelial cells, mononuclear phagocytes of the fibro fatty plaque and smooth muscle cells) which result in the initiation and progression of atherosclerosis. ROS: Reactive Oxygen Species.

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**Volume 2 Issue 4 July 2018**

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