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Review article

Glycative stress and anti-aging: 8. Glycative stress and arteriosclerotic disease.

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Abstract

Arteriosclerotic disease is a generic term for arterial lesions characterized by thickening, hardening and remodeling of the arterial wall. Under this term, three lesions are listed: atherosclerosis, arteriolosclerosis and Mönckeberg's medial calcific sclerosis. Among them, atherosclerosis is the most deeply associated with the onset of life-style diseases. In the processes and histologic changes, cellular debris of necrosis accumulates in the intima of a blood vessel, which is referred to as atheroma and fibrous capsule covers its surface layer. In this lesion, the oxidation and glycation of LDL (low-density lipoprotein) is involved in accumulation in endothelial cells in the formation of atheroma. Glycated-LDL is involved in the enhancement for expression of inflammatory cytokine and cell adhesion factors, which are induced by the production of reactive oxygen and the activation of protein kinase C (PKC) via bonding with receptors for advanced glycation end products (RAGE). Rupture of fibrous capsules covering atheroma, malignant transformation, and hemorrhage are factors that promote the formation of thrombin, which induces acute coronary syndrome and cerebral infarction. Apoptotic death of smooth muscle cells and foam cells around atheroma induces cytolysis and membranous vesicle is discharged into the extracellular matrix. Subsequently, hydroxyapatite is formed. When mineralization occurs, amorphous calcium is deposited in tissues. This vascular calcification induces arterial dysfunction, which is a risk factor of increased pulse pressure, cardiac stress, impaired peripheral circulation, and also the destabilization of atherosclerosis.

***KEY WORDS*:** advanced glycation end products (AGEs), atheroma, calcification

1. Introduction: Definition of arteriosclerosis

Arteriosclerotic disease designates mainly cardiovascular disease and cerebrovascular disease but is recognized as multiple vessel diseases including peripheral arterial disease. Therefore, arteriosclerosis involves a variety of risk factors, hence comprehensive countermeasures are required for the prevention of atherosclerotic cardiovascular disease [1, 2].

Arteriosclerosis is a generic term for arterial lesions characterized by thickening, hardening and remodeling of the arterial wall. Under this term, three lesions are listed: atherosclerosis, arteriolosclerosis and Mönckeberg's sclerosis with calcification. Among them, atherosclerosis is the most deeply associated with the onset of lifestyle-related diseases and occurs in a relatively large elastic type artery. From the viewpoint of histology, atherosclerosis is a lesion where fatty decay products of necrosis, which is referred to as atheroma, accumulates in the intima of a blood vessel and fibrous capsule covers its surface layer (*Fig. 1*) [3]. According to a guideline of World Health Organization (WHO), atherosclerosis is defined as "a lesion of the accumulation of lipid, acid mucopolysaccharide, blood-derived materials, fiber and calcium deposition due to changes mainly in the intima."

2. Atherosclerosis and AGEs

Multiple mechanisms are involved in the formation of atheroma along with the progression of atherosclerosis. The early stage in arteriosclerotic lesion is referred to as a fatty streak. A fatty streak is characterized by the deposition of blood-derived lipid in the intima of a blood vessel, which underwent fibrocellular thickening, the accumulation of macrophage-derived foam cells, and the infiltration of T lymphocyte [4]. This lesion is induced as follows: Low-density lipoprotein (LDL) comprises of lipoprotein, especially one molecule of apolipoprotein B (ApoB), which passes through an endothelial cell from a blood vessel, and lipoids such as cholesterol, phospholipid and triglyceride. LDL binds with

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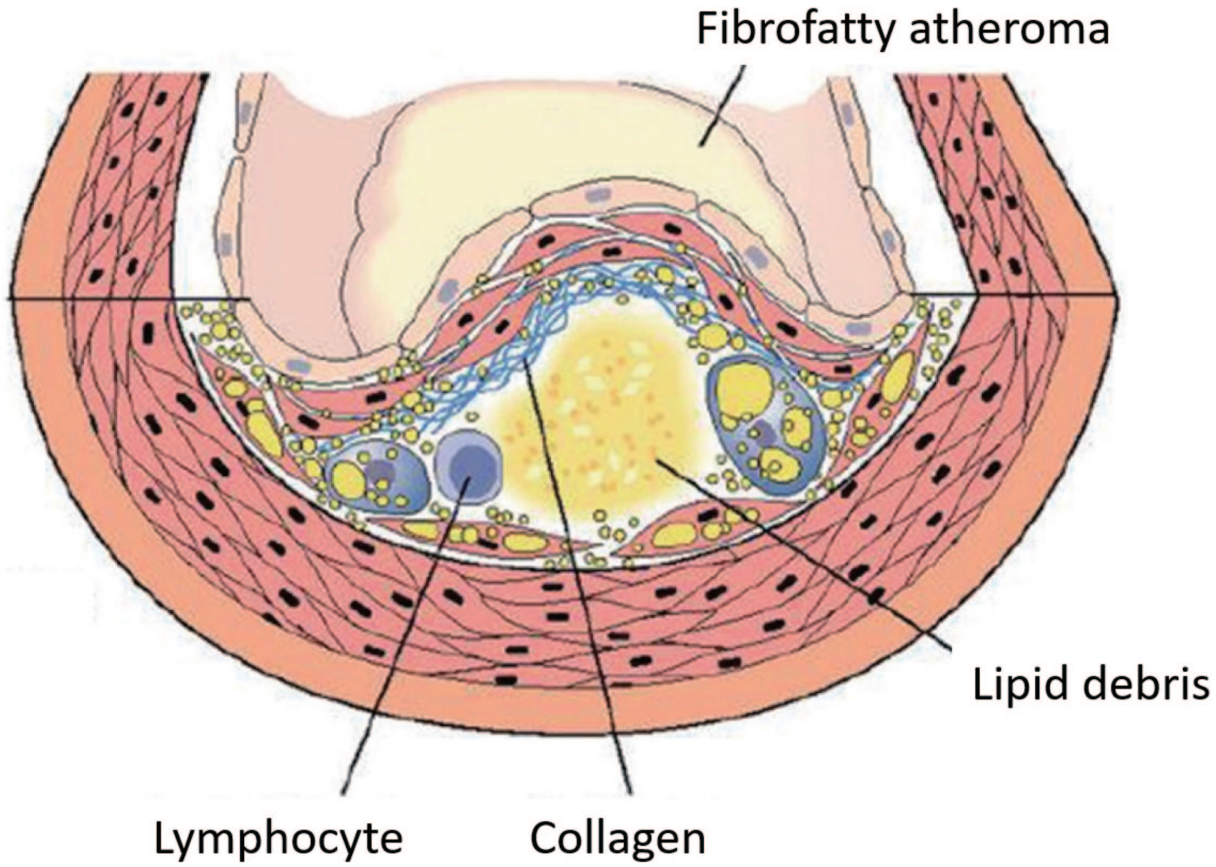

Fig. 1. **Structures of the atherosclerosis.**
The figure is adapted and modified from Reference 3.

an extracellular matrix or proteoglycan and accumulates in the intima. When LDL is glycated, the glycated LDL is not recognized by low density lipoprotein receptor (LDL-R) and accumulates in endothelial cell. AGE-LDL is produced from Gly-LDL. AGE-LDL binds with receptors for advanced glycation end products (RAGE), which are expressed in vascular cells such as endothelial cells and smooth muscle cells. The enhancement of inflammatory cytokine and cell adhesion factor expression are induced via the production of reactive oxygen species (ROS), the activation of protein kinase C (PKC) and the activation of mitogen-activated protein kinase (MAPK). Consequently, in the endothelial cells, the migration and proliferation of smooth muscle cells, the abnormality of cells and the acceleration of oxidative stress are induced. ROS produced by oxidative stress oxidizes not only vascular wall cells but also glycated LDL. When Gly-LDL is oxidized, lipid hydroperoxide is produced. Furthermore, malondialdehyde (MDA) is produced as a secondary product. Glycation of LDL induces the production of hexitollysine (HL). Meanwhile, under the existence of ROS, N^{ε}-(carboxymethyl) lysine (CML) is formed from LDL. Subsequently, LDL is oxidized, glycated and oxidatively modified, and accumulates in the intima (***Fig. 2***)[5]. The binding activities of oxidized LDL with collagen is greater than those of intact LDL, thus the oxidized LDL is retained longer in the arterial wall[6]. Glycated and oxidized LDL accumulated in the intima, along with formed CML and oxidized phosphatidylcholine (OxPC) of lipoperoxide, is uptaken in macrophage, which infiltrates the intima. Subsequently, foam cells are formed from macrophages. Contrarily, ApoB and pyrraline, which are types of AGEs, are not uptaken in macrophage and are distributed in the extracellular matrix of the intima[7]. Further, macrophage secretes inflammatory cytokine such as tumor necrosis factors of (TNF)-α, TNF-β and interleukin (IL) and growth factors. Consequently, smooth muscle cells are transformed, and the migration, proliferation and collagen production are promoted. As proteolytic enzymes such as matrix metalloproteinase (MMP) are secreted, deconstruction and repair is repeated. As a consequence of these processes, atheroma is formed in the intima of blood vessels.

Rupture of fibrous capsules covering atheroma are, malignant transformation and hemorrhage, promote the formation of thrombin, which induces acute coronary syndrome and cerebral infarction.

3. Arterial calcification and AGEs

Atheroma with progressive atherosclerosis has calcification. This is regarded as a final stage of the condition in arterial wall degeneration and necrobiosis. Apoptotic death of smooth muscle cells and foam cells around atheroma induces cytolysis and membranous vesicle is discharged into the extracellular matrix. Subsequently, hydroxyapatite is

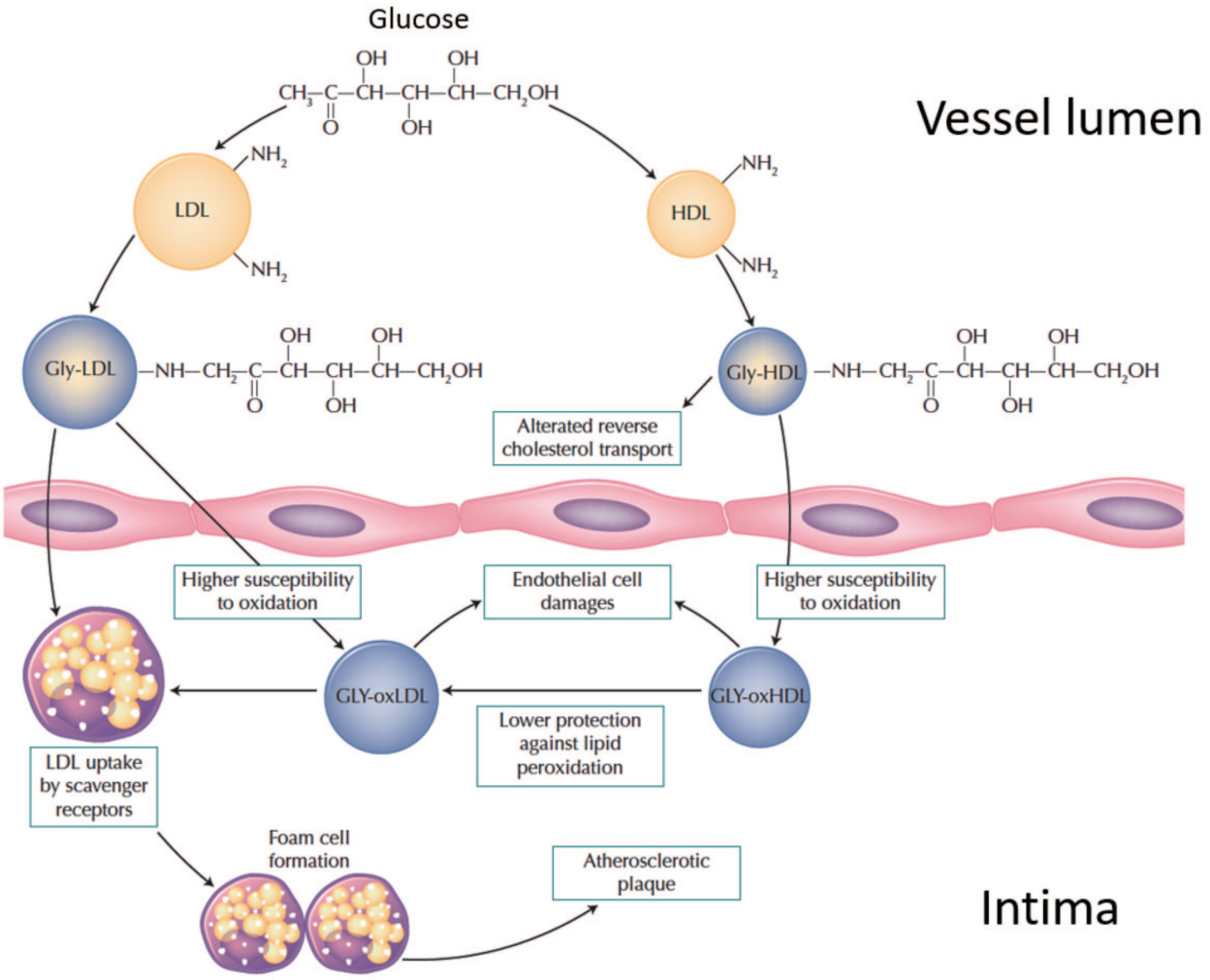

Fig. 2. **Atherogenic effects of glycation of LDL and HDL.**

LDL; low density lipoprotein; HDL, high density lipoprotein; Gly-LDL, glycated LDL; Gly-HDL, glycated HDL; Gly-ox-LDL, oxidized glycated LDL; Gly-ox-HDL, oxidized glycated HDL. The figure is adapted from Reference 5.

formed. When mineralization occurs, amorphous calcium is deposited in tissues.

Diabetes mellitus includes the acceleration of glycation, and the accumulation of AGEs in collagen of arterial walls. Changes in molecular structure of AGE-collagen easily induce calcification [3]. For this reason, granular calcification as an early stage lesion of Mönckeberg's arteriosclerosis is found in tunica media of arteries in patients with diabetes. CML localizes in calcified tunica media. CML is also formed in arterial collagen, as was previously shown [8].

Patients with renal failure exclusively have calcification along elastic fibers of an elastic type artery of the aorta. The elevation of AGE-protein in serum, pentosidine, and also intermediate products of glycation of dicarbonyl compounds, such as CML, along with the dysbolism of calcium and phosphorus, are involved in arterial calcification in patients with renal failure [9, 10]. Renal failure induces the accumulation of AGEs and intermediates of AGEs and accelerates AGEs formation, which is a vicious circle. Therefore, as sclerosis, including atherosclerosis develops, calcification develops.

This vascular calcification induces arterial dysfunction, which includes risk factors of increased pulse pressure, cardiac stress, impaired peripheral circulation, and also atherosclerotic plaque destabilization. From theses viewpoints, the inhibition of glycation can lead to the reduction of arterial calcification. There is a possibility that the inhibition of glycation can contribute to the prevention and improvement of cardio vascular complications in diabetes and renal failure.

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Conflict of Interest Statement

The authors claim no conflict of interest in this study.

Reference

1) Teramoto T. Dietary management in Japan atherosclerosis society (JAS) guidelines for the prevention of atherosclerotic cardiovascular diseases in Japanese 2012 version. Jpn J Nutr Diet 2013; 71: 3-13. (in Japanese)
2) Japan Atherosclerosis Society (ed). Japan Atherosclerosis Society (JAS) guidelines for prevention of atherosclerotic cardiovascular diseases 2017 version, Kuwatani-shoten, Tokyo, 2017. (in Japanese)
3) Mahmoud R-K, Mahbubeh S, Monir D, et al. Atherosclerosis: Process, indicators, risk factors and new hopes. Int J Prev Med. 2014; 5: 927-946.
4) Nakashima Y, Fujii H, Sumiyoshi S, et al. Early human atherosclerosis: accumulation of lipid and proteoglycans in intimal thickenings followed by macrophage infiltration. Arterioscler Thromb Vasc Biol. 2007; 27: 1159-1165.
5) Ansell BJ, Fonarow GC, Navab M, et al. Modifying the anti-inflammatory effects of high-density lipoprotein. Curr Atheroscler Rep. 2007; 9: 57-63.
6) Jimi S, Sakata N, Matunaga A, et al. Low density lipoproteins bind more to type I and III collagens by negative charge-dependent mechanisms than to type IV and V collagens. Atherosclerosis. 1994; 107: 109-116.
7) Sakata N, Uesugi N, Takebayashi S, et al. Glycoxidation and lipid peroxidation of low-density lipoprotein can synergistically enhance atherogenesis. Cardiovasc Res. 2001; 49: 466-475.
8) Sakata N, Takeuchi K, Noda K, et al. Calcification of the medial layer of the internal thoracic artery in diabetic patients: relevance of glycoxidation. J Vasc Res. 2003; 40: 567-574.
9) Sakata N, Noma A, Yamamoto Y, et al. Modification of elastin by pentosidine is associated with the calcification of aortic media in patients with end-stage renal disease. Nephrol Dial Transplant. 2003; 18: 1601-1609.
10) Miyata T, Ueda Y, Yamada Y, et al. Accumulation of carbonyls accelerates the formation of pentosidine, an advanced glycation end product: carbonyl stress in uremia. J Am Soc Nephrol. 1998; 9: 2349-2356.