Influence of advanced glycation end-products in the development of atherosclerosis

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Glycation is a part of a wider non-enzymatic reaction including oxidative reaction. On the basis of our present knowledge, in my opinion, it is possible to identify three pathways in non-enzymatic modification of biological molecules: glycation, in which the oxidative component is absent or very low; glycoxidation, which has to go through several oxidative steps to turn into the final stable products; and the oxidative cascade, in which the oxidative prevails (Fig. 1). Interestingly, the three ways may be strictly related one another by multipling their own damaging potential.

The precursors of the non-enzymatic cascade are reduced sugars, lipids and free amino group of proteins that interact spontaneously giving rise to a series of reactive intermediate molecules that, through several and mostly unknown steps, develop the end-products. The end-products of glycation and glycoxidation are a heterogeneous group of stable and often fluorescent molecules, which develop over a period of weeks[1-3].

An increasing body of evidence states that advanced glycation end-products (AGE) and advanced glycoxidation end-products (AGOE), stemmed from the non-enzymatic condensation reactions, accumulate in long-lived proteins during aging and at an increased rate in diabetic patients. The best characterized products are pyrraline, pentosidine, and carboxy-methyl-lysine.

The implications in diabetes are almost clearly defined and recently the participation of AGE-AGOE in the development of vascular disease, aging-related or atherosclerosis-dependent, has also been suggested[4].

Several epitopes of glycation (AGE), glycoxidation (AGOE) and lipoxidation end-products have been found in atherosclerotic lesions, not only in collagen fibers, but also in fatty streaks in the extracellular space or in more advanced lesions and in the cytoplasm of macrophages or foam cells found in the lesion[5].

It is noteworthy that the tissue AGE-AGOE concentration correlates with the severity of atherosclerotic lesions and with the accumulation, in the vascular wall, of plasma proteins, lipoproteins and lipids. This last observation suggests that the increase of substrate concentration in the tissue affects its metabolic homeostasis facilitating the chemical modification of proteins and the further accumulation of stable glycoxidated products over time.

The chemical modification of proteins can fulfil its negative effect against the vascular wall through lipoprotein glycation; low density lipoproteins, no more recognized by their specific receptors, are recruited by scavenger receptors and accumulate within the macrophages, accelerating the formation of foam cells and the origin of fatty streaks; the glycated high density lipoproteins are deteriorated in their physiological protective function, indirectly accelerating tissue injury[6].

Furthermore, the end-products within the vascular wall might become a true trap for several circulating molecules: complement, immunoglobulins, lipoproteins, etc., are stuck in the matrix contributing to the wall load[3].

Together with the augmentation of end-products in the vessel there is also an evident increase in the expression of receptors for AGE (RAGE) in the membrane of endothelial cells, smooth muscle cells and macrophages: AGE interact with their receptors eliciting important cellular responses, most of them mediated by the activation of nuclear factor-κB[7]. The RAGE

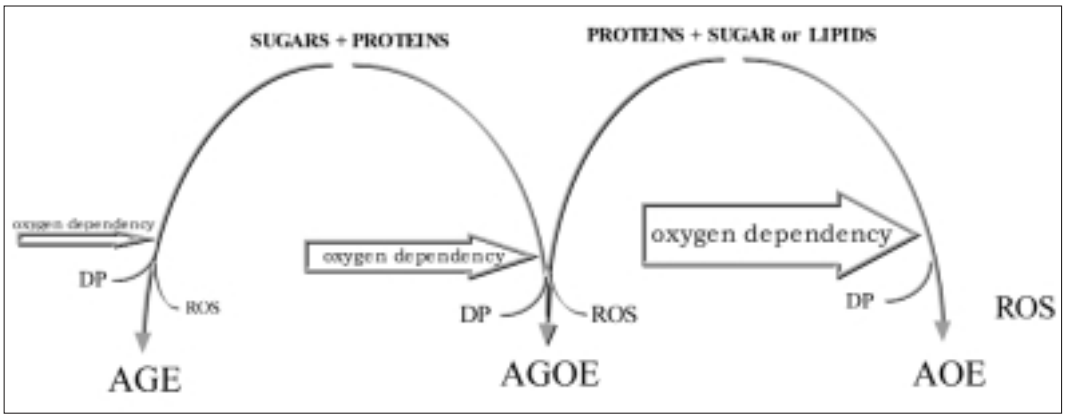

Figure 1. *Pathways in non-enzymatic modification of biological molecules. AGE = advanced glycation end-products; AGOE = advanced glycoxidation end-products; AOE = advanced oxidation end-products; DP = degradation products; ROS = reactive oxygen species.*

Table I. Advanced glycation end-product effect at cellular and tissue level.

Stimulation of lipid peroxidation (increase of reactive oxygen species, decrease of superoxide dismutase)
Modification of vascular tone (increase of endothelin-1, inhibition or reduction of nitric oxide)
Thickening of basal membrane (crosslinking and advanced glycation end-product deposits)
Secretion of cytokines (interleukin-1, tumor necrosis factor-α, insulin-like growth factor-1A and other cellular active molecules such as vascular cell adhesion molecule-1)
Chemotaxis of monocytes-macrophages
Stimulation of T lymphocytes (release of interferon-γ)
Structural modification of collagen (crosslink, etc.)
Interference in cell-matrix connection
Stimulus to thrombosis (increase of tissue factor, plasminogen activator inhibitor-1, platelet aggregation and stabilization of fibrin, decrease of prostaglandin I_2, thrombomodulin, sensitivity of fibrin to the action of plasmin and activity of antithrombin III, alteration of glycoprotein receptor of platelets - IIb and IIIa)

family is a clear defence of the vessel wall against the excess of chemical modification of proteins; the saturation of this mechanism of protection promotes the atherogenic process. Moreover, it is conceivable that this cluster of reactions may be limited to regions in the vascular wall, where the glycoxidative stress is higher. Several cytokines are also released following the glycoxidative stress, leading tissue reactivity to an inflammatory reaction.

Furthermore, the interaction of AGE-AGOE with their specific receptors stimulates an oxidative answer within the cells cooperating to the endothelial damage. The release of reactive oxygen species influences the molecules nearby entrapped maintaining a very noxious vicious cycle[8].

AGE and AGOE are modulators of the vascular tone interacting with nitric oxide or quenching its action, suggesting that AGE may impair also the vasomotor response of the vascular wall[9].

Finally, an unfavorable balance of thrombohemostasis rises from the effects of the glycation and glycoxidation on plasma proteins and platelets[10].

These detrimental effects of AGOE are more evident in diabetes, particularly if the metabolic balance is impaired, and in uremia, where these molecules achieve the highest level. In both syndromes the prevalence of vascular pathology is definitely higher and the progression accelerated[11-13].

These observations support the concept that AGE are a new and essential factor in the development and maintenance of the atherosclerotic plaque.

The discovery of substances able to remove or inhibit the formation and accumulation of AGE might open new therapeutic options in atherosclerosis, but, *in vivo* reported studies are still in the experimental stage.

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