Glycative Stress Research

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Review article

Glycative stress and anti-aging: 1. What is glycative stress?

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Abstract

Glycation is a non-enzymatic chemical reaction between amino acid or protein and reducing sugar and it occurs to various proteins in living organisms. The glycated protein leads to the formation of advanced glycation endproducts (AGEs) through the formation of intermediates dominated by carbonyl compounds. Glycative stress is a concept of comprehensively viewing the stress to living organisms caused by the loads of reducing sugar and aldehyde and its subsequent reactions. Glycative stress in living organisms becomes the factor promoting dysfunction of protein, degeneration of protein (corrected after translation), accumulation of AGEs, impaired TCA cycle, activation of cellular signal, acceleration of tissue damage and degenerative changes associated with aging. Ultraviolet rays and oxidant stress are positioned as the factors accelerating glycative stress. Glycative stress is considered a risk factor for aging in anti-aging medicine.

KEY WORDS: Glycative stress, advanced glycation endproduct (AGEs) and risk factor for aging.

1. Glycation and AGEs

Glycation is a non-enzymatic chemical reaction between amino acid or protein and reducing sugar, discovered by Louis-Camille Maillard, a French scientist, and also called Maillard reaction [1].

Glycation has been attracting attention in the field of food chemistry because it is a chemical reaction associated with food coloring, changes of fragrance and flavor during the heating process and decrease in nutrition during storage [2]. The measurement of hemoglobin A1c (HbAlc), a product of glycation reactions in human blood, is clinically applied as the blood glucose control index in the field of diabetic treatment.

It is known that glycation occurs not only to hemoglobin, but also to various proteins such as albumin, keratin, globulin and collagen, and the glycated proteins lead to the formation of advanced glycation endproducts (AGEs) through the formation of various intermediates dominated by calbonyl compounds such as 3-deoxyglucosone (3DG), glyoxsal (GO), methylglyoxsal (MGO), glyceraldehydes and glycolaldehyde.

AGEs show their characteristics such as dark brown color, fluorescence (excitation wavelength (ex): mainly 370 nm, fluorescence wavelength (em): 440 nm) (***Fig. 1***) and protein cross-link formation. The presence of these characteristics differs by each different material.

AGEs having fluorescence include pentosidine (ex 335 nm/em 385 nm) [3], crossline (ex 379 nm/em 463 nm) [4], pyrropyridine (ex 370 nm/em 455 nm) [5]. Non-fluorescent AGEs includes N^{ε}-(carboxymethyl) lysine (CML) [6], N^{ω}-(carboxymethyl) arginine (CMA) [7]. Pentosidine and crossline are crosslinking AGEs.

2. Glycative stress

Glycative stress is a concept of comprehensively viewing the stress to living organisms caused by the loads of reducing sugar and aldehyde and its subsequent reaction (***Fig. 2***) [8].

Glycation in a narrow sense is a reaction system leading to the formation of AGEs through the formation of Schiff base, glycated protein and other various intermediates by non-enzymatic chemical reactions between reducing sugar and protein. These reactions degenerate tissue proteins and impair their function.

Meanwhile, beta-oxidation and peroxidation of lipids within living organisms also produce aldehyde groups and ketone groups. Carbonyl groups existing within the molecules of aldehyde and ketone polarize when electrons are pulled to oxygen atoms with high electronegativity and carbon atoms become susceptible to nucleophilic attack. Furthermore, when these functional groups react against lysine and arginine compounding protein in an uncontrollable way, the function of protein is impaired.

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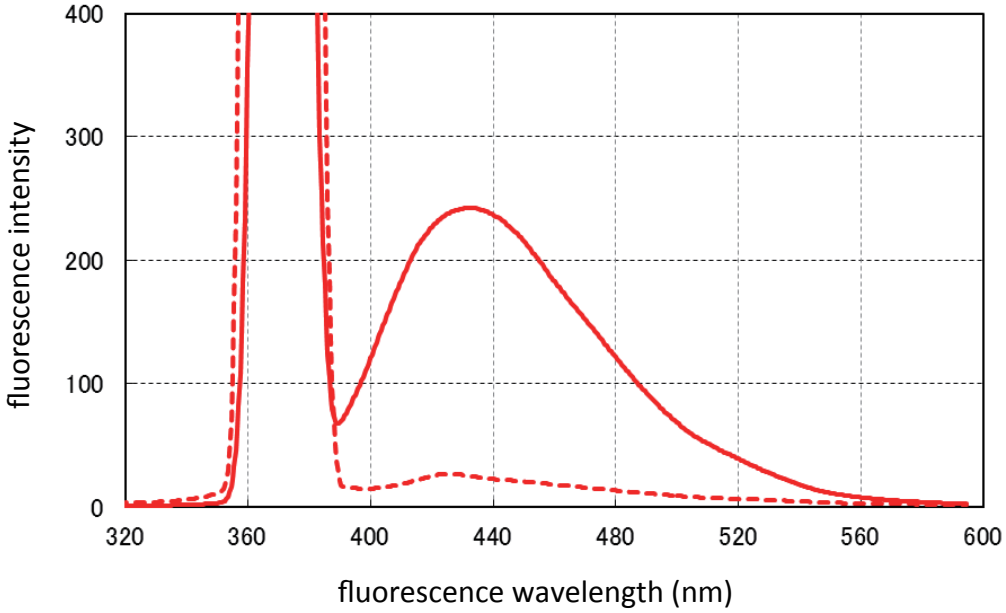


Fig. 1. **Fluorescence spectrum from AGE in glucose-human serum albumin (HSA) model.**
HSA (8 mg/mL) + 0.05 mol/L phosphate buffer (pH 7.4) + glucose (0.2 mol/L) solution (solid line), HSA (8 mg/mL) + 0.05 mol/L phosphate buffer (pH 7.4) solution (broken line). Incubated 60°C, 40 hours. Excitation wavelength at 370 nm.

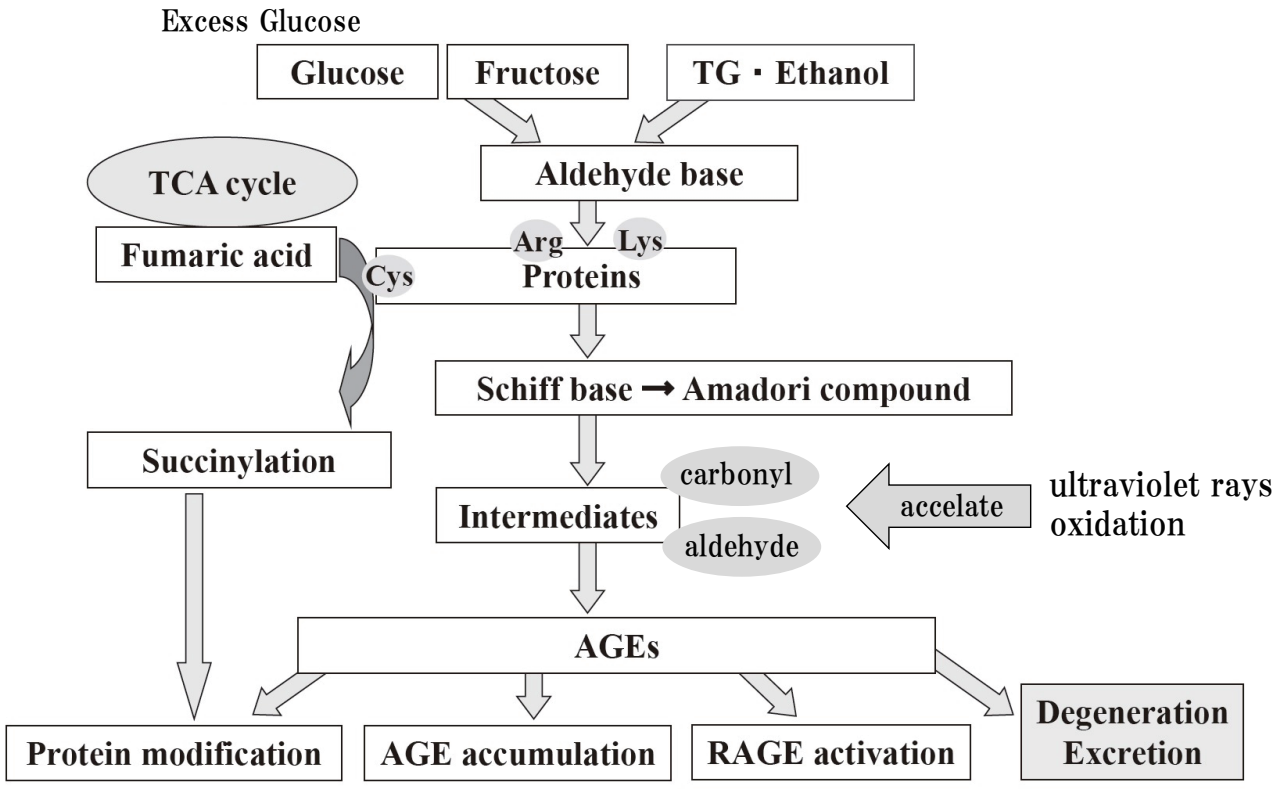


Fig. 2. **Concept of glycative stress.**
Excess Glucose, postprandial hyperglycemia; TG, triglyceride; TCA, tricarboxylic acid; AGEs, advanced glycation endproducts: RAGE, receptor for AGE. Quoted and modified from Ref. 8).

If excessive glucose exists inside the cell, it causes a poor response of the TCA cycle and fumaric acid increases [9-10]. Fumaric acid reacts with cysteine, an amino acid compounding protein and forms S-(2-succinyl) cysteine (2SC). This reaction is called succinylation. Caused by the succinylation of protein, the function of protein declines or is lost, and this causes problems in the living organism. The proteins in the living organization affected by succinylation include cytoskeletal protein, heat-shock protein [9] and adiponectin [10].

AGEs accumulated in organisms combine with RAGE (receptor for AGEs), receptors existing on the surface of cells, activate cell signal and cause the formation of inflammatory cytokine [11]. RAGE induces cell response from intracellular signaling and works for disease state formation as the receptor AGEs [12].

Ligands other than AGEs that connect with RAGE include: 'advanced oxidation protein products (AOPP), that is, oxidative damaged product, an oxidative stress mediator,' 'amyloid beta protein accumulated in the brain with Alzheimer's disease,' 'transthyretin accumulated by familial amyloid polyneuropathy,' 'high mobility group B-1 (HMGB-1)/amphoterin, which relationships with cancer metastasis and inflammation are pointed out,' 'inflammatory mediator S-100 protein' and 'Mac1 on the surface of white cell' [3]. It is said that CML, glyceraldehydes and glycolaldehyde modifiers among AGEs can easily connect with RAGE [13].

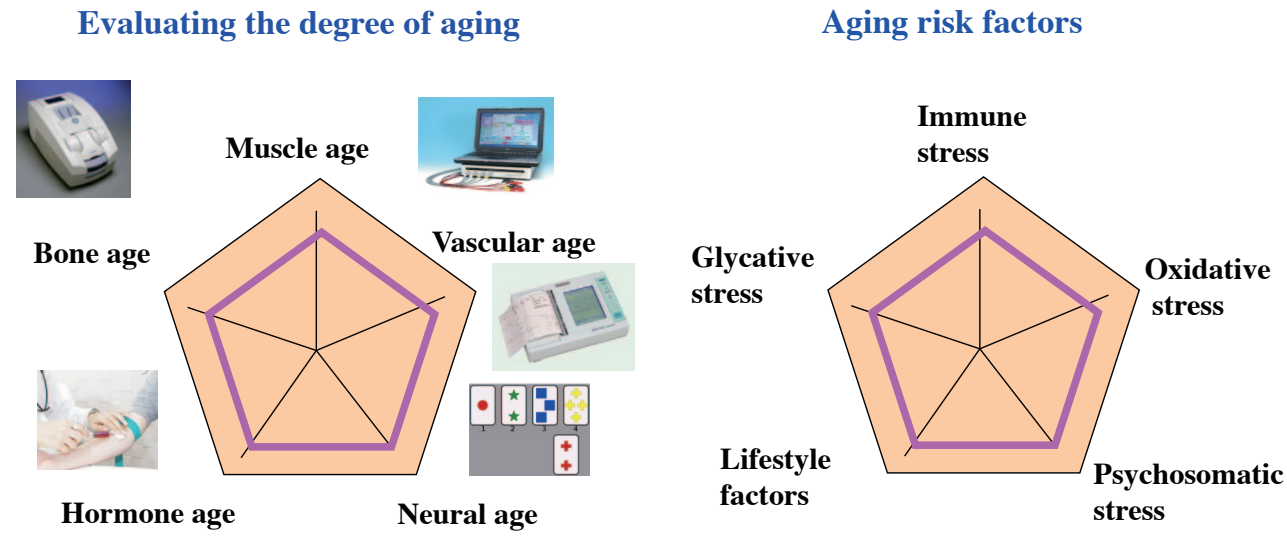
Glycative stress promotes dysfunction of protein, degeneration of protein (corrected after translation), accumulation of AGEs, impaired TCA cycle, activation of cellular signals, acceleration of tissue damage and degenerative change associated with aging. Ultraviolet rays and oxidant stress are positioned as the factors accelerating glycative stress.

3. Glycative stress in anti-aging medicine

Humans intake carbohydrates in food as a major energy source, so it is impossible to avoid the glycation that occurs between glucose and protein in their lifetime [14]. It is obvious from the facts that the accumulation of AGEs in the skin collagen of healthy people increases with aging, that the accumulation of AGEs is larger in diabetic patients than that of healthy people the same age [15], and that the elasticity of the skin of diabetic patients is lower than that of healthy people [16].

The formation and accumulation of AGEs by glycation are involved not only in diabetic complaints but also in skin aging [17], the development of Alzheimer's [18], hypertension [19], arterial sclerosis [20] and osteoporosis [21]. Because the formation of AGEs from collagenous tissues of skin, bone and cartilage is accompanied by browning and decrease of plasticity, it draws attention in the fields of beauty and health.

Anti-aging medicine is a preventative medicine aimed at the improvement of quality of life (QOL), good health and longevity [22]. Human phenotypes of aging include the aging of blood vessels (arterial sclerosis), aging of nerves (dementia and Alzheimer's) and aging of bones (osteoporosis). However, the symptoms of these disorders depend on individuals and



- Bone age : bone mineral density (Ultrasonography)
- Muscle age : muscle mass (PhysionMD)
- Vascular age : fingertip accelerated plethysmography (SPD100)
- Neural age : Wisconsin Card Sorting Test
- Hormone age : blood test (GH, IGF-I, DHEA-s)

- Glycative stress : AGEs, insulin resistance
- Immune stress : DHEA-s, NK cell activity
- Oxidative stress : urinary 8-OHdG, blood isoprostane
- Psychosomatic stress : cortisol, DHEA-s
- Lifestyle factors : exercise, sleep, alcohol consumption, smoking

Fig. 3. **Aging assessment by Anti-Aging Medical Checkup.**

GH, growth hormone; IGF-I, insulin-like growth factor-I; DHEA-s, dehydroepiandrosterone-sulfate; AGEs, advanced glycation end products; NK, natural killer; 8-OHdG, 8-hydroxy-deoxyguanosine

the risk factors of aging differ by individual.

Therefore, in the anti-aging dock, the degree of aging (functional age) is evaluated as muscle age, vascular age, neural age, hormone age and bone age [23]. Furthermore, the factors involved in the decline in functional age are positioned as risk factors for aging and evaluated. They are divided into immune stress, oxidative stress, psychosomatic stress, glycative stress and lifestyle factor (***Fig. 3***).

The evaluation results by anti-aging dock aim at focusing on the items of highest aging degree and those which risk factor is highest and keep a balance of aging degrees as a whole by rectifying especially remarkable items.

Glycative stress is understood in anti-aging medicine as an aging risk factor, as the influence of the stress caused by the loads of reducing sugar and aldehyde and its subsequent reaction grasped as a whole.

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Conflict of interest statement

There are no items deemed to be conflicts of interest in this research.

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