Glycative Stress Research
Online edition : ISSN 2188-3610
Print edition : ISSN 2188-3602
Received : September 1, 2015
Accepted : October 10, 2015
Published online : December 31, 2015

Review article

Photoaging and Glycation of Elastin: Effect on Skin

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Abstract

This article provides an overview of the effects of photoaging and glycative stress on elastic fibers in skin. The risk factors for accelerated skin aging include photoaging (oxidative stress) and glycative stress. Reducing sugars and aldehydes bind to amino acid residues in protein, such as lysine and arginine, in an uncontrolled and non-enzymatic fashion to produce intermediates, which form advanced glycation end products (AGEs) through further reactions. Glycation of elastin leads to reduced skin elasticity or skin slackening. Oxidative stress also enhances the glycation reaction. When AGE production from elastin was compared with that from albumin, keratin and proteoglycan using an *in-vitro* protein glycation model, elastin produce a lower amount of carboxymethyl-lysine (CML) and comparable amounts of AGE intermediates, such as 3-deoxyglucoseone, glyoxal and methylglyoxal. Skin AGE fluorescence, as well as its individual variations, increased with increasing age. Skin elasticity decreased with increasing age, and this trend was more prominent in diabetic patients with higher glycative stress. These data demonstrate that the mechanisms of age-related changes in skin AGEs content and skin elasticity involve a variety of proteins, including collagen and elastin, and complicated interactions of glycative as well as oxidative stress (photoaging) factors.

KEY WORDS: skin elasticity, elastic fibers, elastin, collagen, advanced glycation end products

Introduction

At anti-aging medical institutions, clinicians assess the degree of aging by determining functional ages, including muscular, vascular, neural, hormone and bone ages, while identifying risk factors for accelerated aging, such as immune stress, oxidative stress, mental and physiological stress, glycative stress and poor lifestyle [1,2]. Aging is accompanied by various degenerative changes of skin. The degree of skin aging is determined by assessing wrinkle age (increase in wrinkles), freckle age (freckles and discoloration), moisture age (decreased moisture retention), skin elasticity age (decreased skin elasticity) and glycation age (increased accumulation of advanced glycation end products [AGEs]). Photoaging (oxidative stress) has been reported to account for about 70% of the causes of skin aging [3], but it is increasingly overcome by the use of ultraviolet (UV) skin care and anti-oxidative products. Meanwhile, there is an increasing prevalence of lifestyle-related diseases, such as obesity and diabetes. These conditions are associated with high glycative stress [4] (***Fig. 1***). Glycative stress will become increasingly important as a non-photoaging risk factor for skin aging. This article focuses primarily on the roles of elastin, a component protein of skin, in photoaging and glycative stress.

What is elastin?

Elastin is an insoluble protein formed by lysil oxidase-mediated crosslinking of tropoelastin, a precursor protein secreted by fibroblasts with a molecular weight of 60,000-70,000 Da. Tropoelastin contains α-helix and β-sheet structures; the former contains an abundance of lysine residues and contributes to crosslinking while the latter confers the stretching property of elastin (***Fig. 2***) [5]. Elastin contains disproportional amounts of amino acid residues proline (P), alanine (A), valine (V) and glycine (G) in GVGVP and VGVAPG repeats [6-9].

Elastin also binds to microfibrils of 10-12 nm in diameter to form a larger elastic fiber of 1-3 µm in diameter [10]. Elastic fiber formation is mediated by fibulin-4 [11], fibulin-5 [12,13], microfibril-associated glycoprotein-1 (MAGP-1) [14], lysil oxidase subtypes LOX (lysil oxidase) [15] and LOXL-1 (lysil oxidase like-1) [16], and latent TGF-β binding protein 4 (LTBP-4) [10], a binding protein for transforming growth factor-β (TGF-β).

Microfibrils are formed by crosslinking of fibrillin, a glycoprotein secreted by smooth muscle cells, fibroblasts, chondrocytes and other cells, with a molecular weight of approximately 350,000 Da [5]. Microfibrillar-associated

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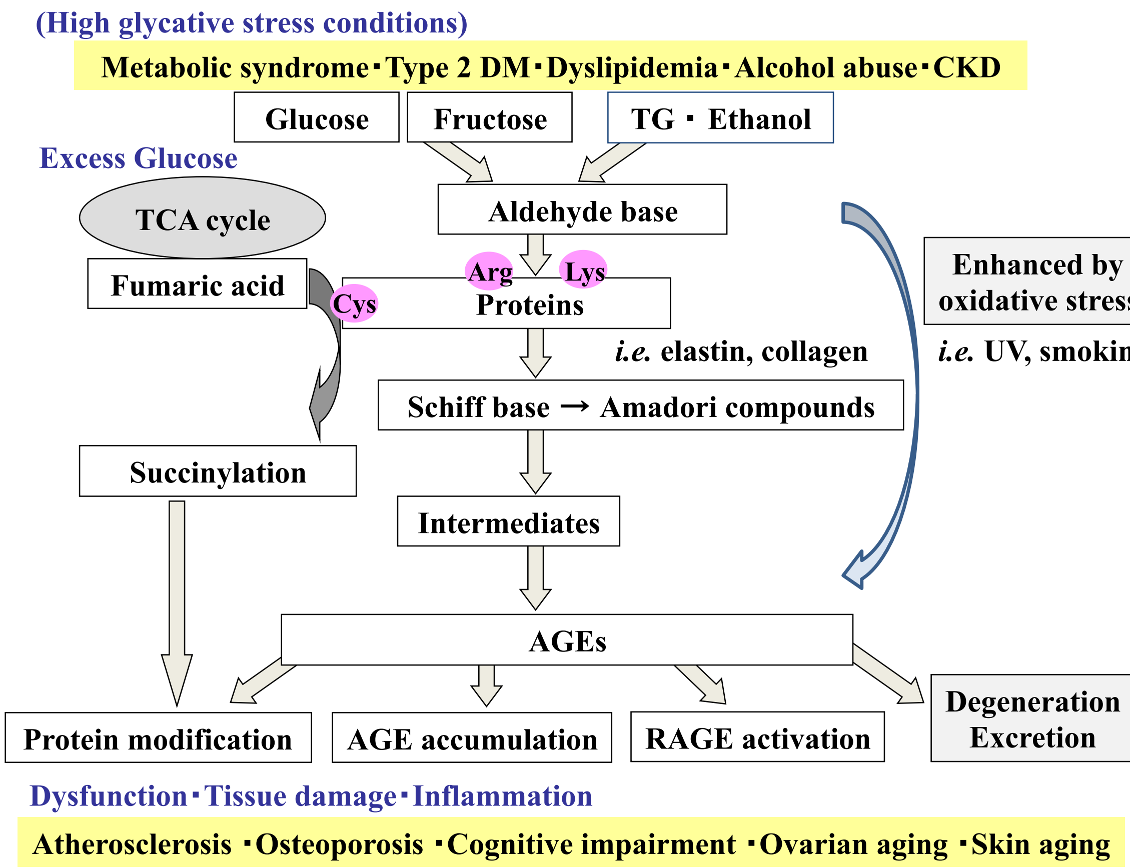

Fig 1. **Concept of glycative stress.**
DM, diabetes mellitus; CKD, chronic kidney disease; TG, triglycerides; TCA, tricarboxylic acid; UV, ultra violet; AGEs, advanced glycation endproducts; RAGE, receptor for AGEs; Cys, cysteine; Arg, arginine; Lys, lysine. Adapted and modified from reference (4).

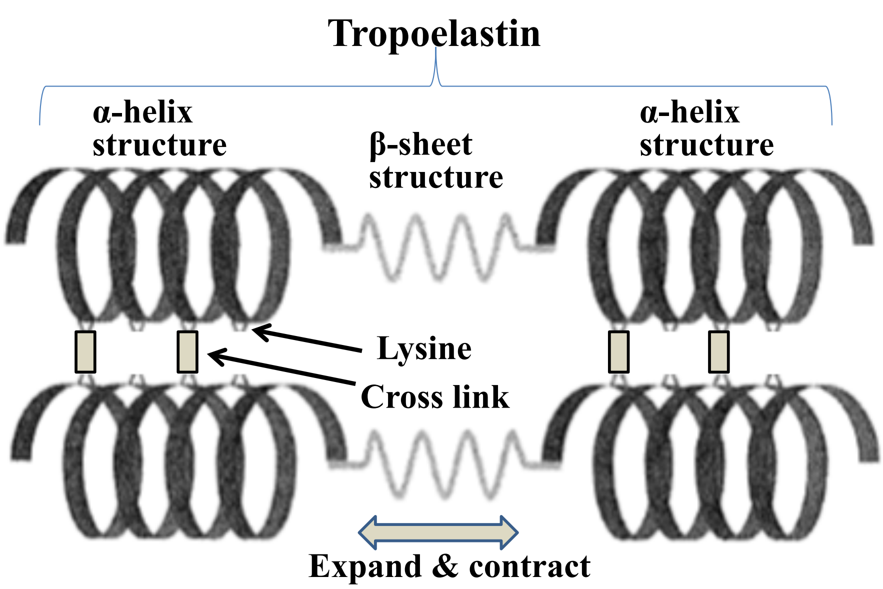

Fig 2. **Structure of elastin**
Adapted and modified from reference (5).

protein 4 (MFAP-4) which coexists with fibrillin-1, plays an essential role in microfibril formation, and has a protective action against photoaging by inhibiting metalloproteinase-12 (MMP-12) activity [17].

Skin content of elastin is about 2%, which is lower than that of collagen (*Table 1*) [18]. Nevertheless, its impairment results in significant skin changes, such as wrinkles and slackening. Fibulin-5 deficient mice, in which the normal formation of elastin fibers is genetically impaired, show a marked decrease in skin elasticity [13]. In patients with mid-dermal elastosis, the skin contains normal collagen fibers while elastic fibers are degraded in the dermis, causing a marked formation of skin wrinkles [19-21]. Cutis laxa is a condition associated with a decreased skin content of elastin fibers and characterized by skin slackening and an elderly-like appearance [22,23].

Table 1. Percentage content of elastin and collagen in the human tissues.

Content (%)	Elastin	Collagen
Skin	0.6 - 2	72
Lung	3 - 7	10
Aorta	28 - 32	12 - 24
Ligament	75	17
Achilles' tendon	4	86

Data are expressed as dry weight percentage. Adapted from reference (18).

Photoaging and elastin

Skin changes associated with photoaging are considered to be due to quantitative and qualitative changes in elastin and collagen proteins produced by fibroblasts in the dermis [24-26]. A brief sun exposure can activate activator protein 1 (AP-1) and nuclear factor-kB (NF-κB) and thereby increase the expression of metalloproteinase (MMP), causing the degeneration of collagen and elastin [24]. It can also lead to a decreased production of type-1 procollagen [25]. Shallow wrinkles can also be formed as a result of altered dermal structure caused by dry skin.

UV-B radiation from sunlight stimulates epidermal keratinocytes to produce and release pro-inflammatory cytokines interleukin-1α (IL-1α), IL-6 and tumor necrosis factor-α (TNF-α). These cytokines stimulate dermal fibroblasts and, through an autocrine mechanism, stimulate keratinocytes to promote the expression of messenger RNAs (mRNAs) for MMP-1, MMP-3 and MMP-9, enzymes that degrade collagen and elastin, and increase their protein levels and activity, resulting in accelerated degradation of these fibers [27]. Photoaging also affects the basal membrane [28,29]. It is likely that these changes collectively lead to wrinkle formation. In animal studies, suppressed activity of elastin-degrading enzyme elastase has been shown to reduce UV-induced wrinkle formation [26]. Like UV, infrared radiation has also been shown to induce collagen degradation by enhancing MMP-1 activity through active oxygen species [30]. Its intracellular activation pathway involves mitogen-activated protein kinase (MAPK) [31]. In a skin photoaging model developed by irradiating UV to human skin grafts in immunodeficient mice [32], a comprehensive genetic analysis revealed a marked decrease in microfibrillar-associated protein-4 (MFAP-4) expression, and the overexpression of MFAP-4 resulted in a reduction in UV-induced wrinkle formation and suppression of decreased skin elasticity [17].

Aging is accompanied by increasing dullness of facial skin color and decreasing skin transparency, partially due to delayed skin turnover. Although it is unclear how UV-A is involved in this delayed turnover, it is probable that UV-A at least induces decreased activity of the enzymes involved in horny layer exfoliation. The histological features of photoaging include atrophy of extracellular matrix, which is characterized by decreased elastin, disintegration of elastin fibers, loss of mature collagen fibers, retention of degraded collagen and degenerated connective tissue.

Elafin, a molecule first discovered in fibroblasts damaged by UV-A exposure or other factors, prevents the binding of elastase to elastin by forming an elafin-elastin complex [33]. Elafin-elastin complexes are prominently found in UV-damaged connective tissues. These complexes interfere with enzymatic degradation of elastin, resulting in the accumulation of unmetabolized elastin in skin connective tissue. These changes are also accompanied by accumulation of glycosaminoglycans. A variety of these factors are considered to be involved in the complicated process of wrinkle formation.

Glycative stress

Glycative stress is as important a risk factor for skin aging as oxidative stress [4]. Reducing sugars, such as fructose and glucose, bind to amino acid residues in protein, such as lysine and arginine, in an uncontrolled and non-enzymatic fashion to produce intermediates, which form into AGEs through further reactions. AGEs deposit in skin tissue and bind to cell surface receptors called RAGE (receptor for AGEs) to induce inflammation [34]. Excessive glucose can also disturb the tricarboxylic acid (TCA) cycle and the resulting fumaric acid reacts with cysteine residues in protein to cause protein degeneration [35]. Lipids and alcohol-derived aldehydes can also cause post-translational modification of protein. High glycative stress conditions include not only conditions associated with excessive glucose levels, such as diabetes, but also excessive levels of reducing sugars, such as fructose, dyslipidemia characterized by excessive triglyceride and/or low-density lipoprotein (LDL) cholesterol, and alcoholism as a predisposing factor for excessive acetaldehyde production. AGE elimination disorder due to chronic kidney disease (CKD) can enhance glycative stress [36]. The Maillard reaction is not the only reaction system involved, but various other pathways are also involved. All of these pathways must be viewed as a collective concept (*Fig. 1*) [4].

Effect of glycative stress on skin

In aging skin, various proteins, including collagen and elastin, undergo glycation-related degenerative changes. In order to maintain young, healthy and beautiful skin, it is important to manage glycative stress as a risk factor for skin aging.

In the outermost layer of the epidermis, glycation of keratin occurs in the horny layer, resulting in altered optical property and loss of transparency of skin [37]. Keratinocyte differentiation proceeds from the basal layer to horny layer, and is accompanied by the production of K10 protein, which can also be a target of glycation [38]. Glycative stress is thus expected to have a negative impact on keratinocyte differentiation.

AGE accumulation in the dermis leads to yellow discoloration (yellowing) of skin [39]. In addition to N^{ε}-(carboxymethyl) lysine (CML), a typical skin accumulating AGE, various other AGEs are present in the dermis. Collagen proteins are abundant in the dermis and can be targets of glycation. A collagen fiber has a triple helical structure and plays a role, together with elastic fibers, in maintaining skin elasticity. Amino acid residues comprising a collagen protein, such as lysine and arginine, are susceptible to glycation. Glycated lysine and arginine residues form crosslinks between fibers, which leads to a loss of collagen mobility [40,41].

There is another pathway for glycation stress involving pentosidine. Pentosidine has a strong NF-κB activation activity and induces inflammatory changes of skin through pro-inflammatory cytokines [42].

These changes induced by AGE accumulation can be enhanced by photoaging and other types of oxidative stress [43,44]. Deep wrinkles are formed in the face and neck, body parts typically exposed to sunlight. Farmers are exposed to a large amount of sunlight almost everyday and thus tend to develop deep, triangle-shape wrinkles especially in the neck, referred to as cutis rhomboidalis nuchae, at around 50 years of age. The skin part surrounded by deep wrinkles is colored slightly yellow and has a coarse and stiff texture. Pathological features of cutis rhomboidalis nuchae include massive deposition of anti-CML antibody-positive substances in the upper to middle layers of the dermis, for which the condition is also referred to as solar elastosis. This massive deposition can also be identified by van Gieson staining [44].

Skin elasticity is increasingly reduced with aging. The reasons for this include reduced fibroblast function and the resulting reduced production of extracellular matrix components, such as fibronectin, [45] and also the reduced production of collagen/elastic fibers [46]. Collagen and elastin are also deteriorated by oxidation and glycation. Collagen and elastin have a long half-life of more than 15 years [47] and their deterioration causes long-term effects. Studies have confirmed that crosslinking as a post-translational modification also occurs in elastin [48,49].

Glycation of elastin

There is limited information on the glycation of elastin. The data presented here are mostly from our laboratory [50]. When assessing the amino acid content of skin-related proteins, elastin is characterized by a lower arginine content compared to other proteins and a slightly higher lysine content compared to type 1 collagen (***Table 2***).

Using an *in vitro* protein glycation model, we compared the production of AGEs and their intermediates from each protein after they were dissolved at a concentration of 3.0 mg/ml and reacted with 2.0 M glucose at 60°C for 10 days (***Figs. 3-7***) [50]. The results showed that fluorescent AGEs can be produced by glycation of elastin (***Fig. 3***). Fluorescent AGEs production from elastin was lower than that from albumin, i.e. bovine serum albumin (BSA) and human serum albumin (HSA), and higher than those from proteoglycan and keratin. We have examined the correlation between fluorescent AGEs in ***Fig.3*** and amino acid contents in ***Table 2***. The correlation coefficients (r^2 values) are as follows: 0.611 ($p = 0.198$) in lysine, 0.450 ($p = 0.370$) in arginine + lysine and -0.277 ($p = 0.594$) in arginine, indicating that proteins with more abundant lysine may produce more fluorescent AGEs.

CML production in the elastin glycation model was extremely low (0.02 μg/mL) and similar to that from type 1 collagen (0.64 μg/mL). CML production is dependent on the lysine content of protein. The elastin glycation model produced 1.7 μg/m of 3-deoxyglucosone (3DG) production, 20.8 μg/mL of glyoxal (GO) and 252.6 μg/mL of methylglyoxal (MGO), demonstrating that elastin produces comparable amounts of AGE intermediates compared to other proteins. Even with a comparable intermediate production, the type of AGEs produced may vary depending on the amino acid composition of each protein.

Table 2. Percentage content of arginine and lysine in the protein tested.

Content (%)	Elastin	Keratin	Proteoglycan	Collagen	HSA	BSA
Arginine	0.89	4.82	5.90	4.78	4.43	4.28
Lysine	5.37	0.00	6.00	3.90	9.85	9.88
Arginine + Lysine	6.26	4.82	11.90	8.68	14.29	14.17

Data is referenced from NCBI, except proteoglycan which is obtained from Biomatec Japan (Kushiro, Hokkaido). NCBI, National Center for Biotechnology Information; BSA, bovine serum albumin; HSA, human serum albumin.

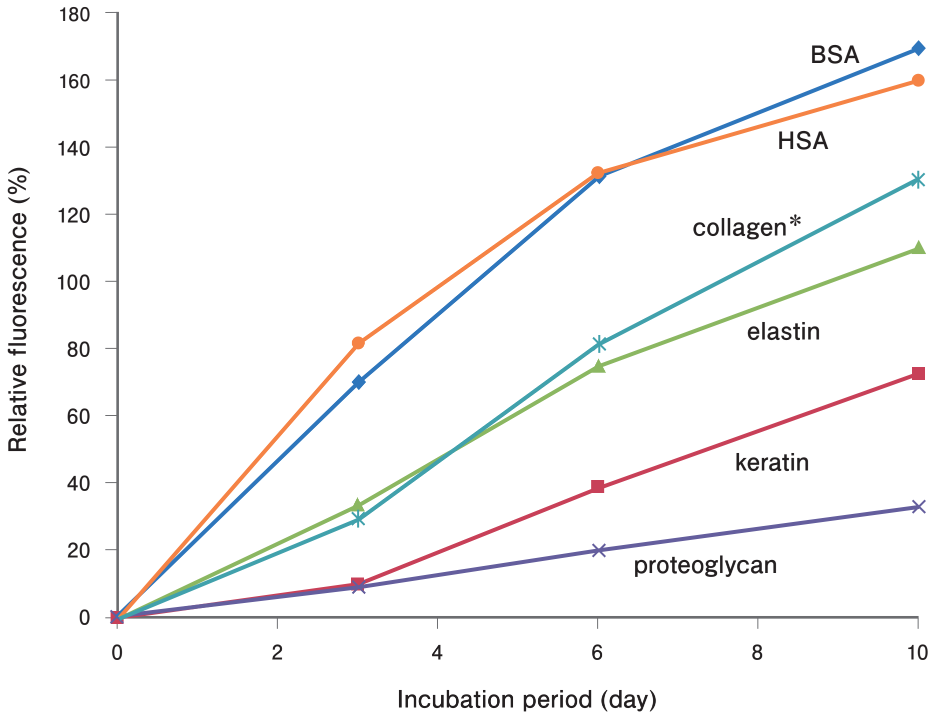

Fig 3. **Fluorescence arising from AGE formation of various proteins and glucose.**
In vitro glycation model; protein concentration 3.0 mg/dL, glucose 2.0 M. Relative fluorescence (370 nm/440 nm) of glucose-protein solutions was measured at 0, 3, 6, 10 days after incubating at 60°C. BSA, bovine serum albumin; HSA, human serum albumin; AGE, advanced glycation end product; * bovine collagen type 1. Adapted from reference (50).

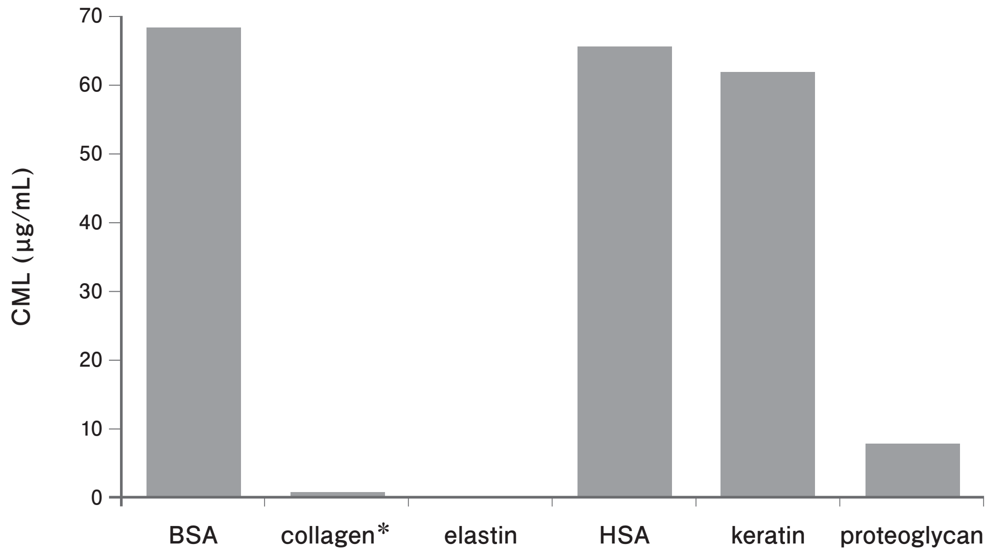

Fig 4. **Level of CML formation from the reaction between various proteins and glucose.**
In vitro glycation model; protein concentration 3.0 mg/dL, glucose 2.0 M. CML levels were measured by ELIZA at 10 days after incubating at 60°C. CML, N^{ε}-(carboxymethyl)lysine; BSA, bovine serum albumin; HSA, human serum albumin; ELIZA, enzyme-linked immunosorbent assay; * bovine collagen type 1. Adapted from reference (50).

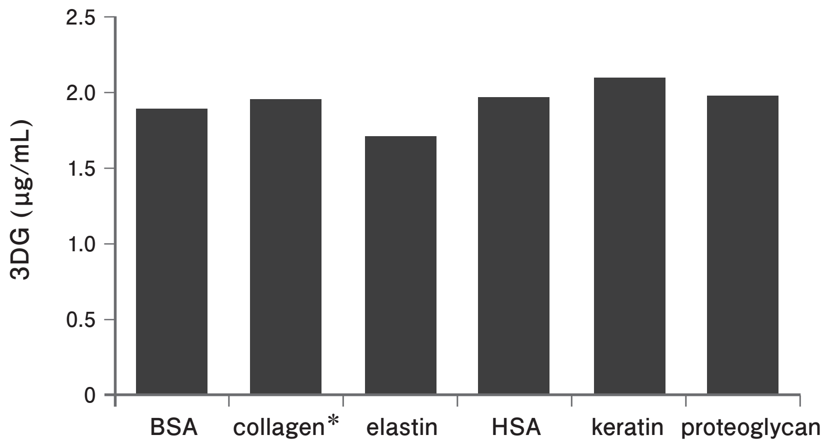

Fig 5. **Level of 3DG formation from the reaction between various proteins and glucose.**

In vitro glycation model; protein concentration 3.0 mg/dL, glucose 2.0 M. 3DG levels were measured by HPLC at 10 days after incubating at 60°C. 3DG, 3-deoxyglucosone; BSA, bovine serum albumin; HSA, human serum albumin; HPLC, high performance liquid chromatography; * bovine collagen type 1. Adapted from reference (50).

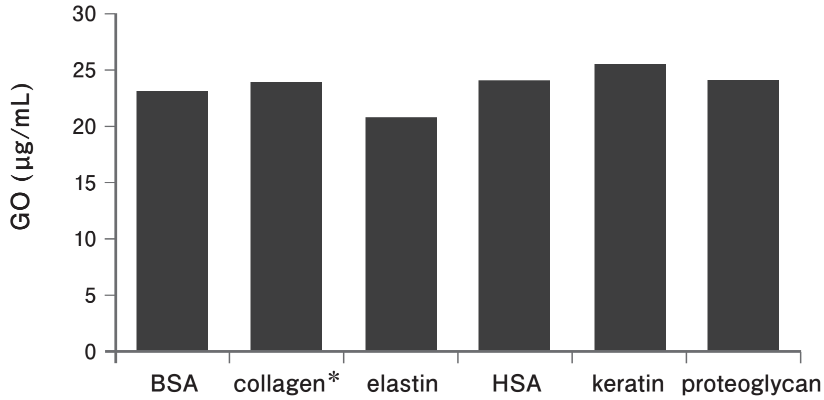

Fig 6. **Level of GO formation from the reaction between various proteins and glucose.**

In vitro glycation model; protein concentration 3.0 mg/dL, glucose 2.0 M. GO levels were measured by HPLC at 10 days after incubating at 60°C. GO, glyoxal; BSA, bovine serum albumin; HSA, human serum albumin; HPLC, high performance liquid chromatography; * bovine collagen type 1. Adapted from reference (50).

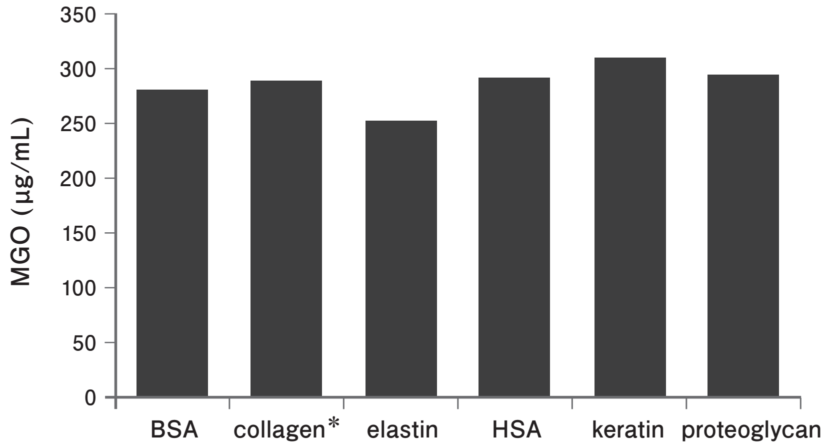

Fig 7. **Level of MGO formation from the reaction between various proteins and glucose.**

In vitro glycation model; protein concentration 3.0 mg/dL, glucose 2.0 M. MGO levels were measured by HPLC at 10 days after incubating at 60°C. MGO, methylglyoxal; BSA, bovine serum albumin; HSA, human serum albumin; collagen, type 1. HPLC, high performance liquid chromatography; * bovine collagen type 1. Adapted from reference (50).

Age-related change in skin AGE accumulation

The age-related changes in skin AGE content are shown in ***Fig. 8***. Fluorescence intensity from AGEs was measured as autofluorescence using an AGE Reader™ (DiagnOptics, Netherland) in the medial aspect of the left upper arm of each healthy volunteer [51]. Skin AGE fluorescence increased with increasing age, and this trend was also accompanied by increased standard deviations, meaning increased individual variations. Among lifestyle-related factors, drinking, smoking and lack of sleep are known to increase skin AGE content [52]. Fluorescent AGEs include pentosidine, crossline and pyrropyridine. Elastin-derived fluorescent AGEs have not been identified and their ratios relative to the total fluorescence remain to be determined.

Age-related changes in skin elasticity

The age-related changes in human skin elasticity are shown in ***Fig. 9***. Skin elasticity was measured with a Cutometer (Courage+Khazaka, Germany) in the medial aspect of the left upper arm of each healthy volunteer or type-2 diabetes patient [53]. Skin elasticity decreased with increasing age. Diabetes patients showed a steeper decline in elasticity index R7, indicating accelerated reduction in skin elasticity. As the medial aspect of the upper arm is less susceptible to photoaging, the reduced elasticity is considered to be primarily due to glycative stress. Glycation is known to cause reduced mobility of skin tissue by forming crosslinks between type 1 collagen fibers [40, 41]. Since elastin is also crosslinked by glycation [48, 49]; it is likely that both collagen and elastic fibers are involved in reduced skin elasticity.

Conclusion

This report provided *in vitro* data on AGEs and their intermediates produced by glycation of elastin, and clinical data on age-related changes in skin AGE-derived fluorescence and skin elasticity. The data presented here demonstrate that the mechanisms of age-related changes in skin AGEs content and skin elasticity involve a variety of proteins, including collagen and elastin, and complicated interactions of glycative as well as oxidative (photoaging) stress factors.

Acknowledgement

A part of this content was presented in the Journal "Bio Industry" in 2015 [54]. This work was supported by Japanese Council for Science, Technology and Innovation (CSTI), Cross-ministerial Strategic Innovation Promotion Program (SIP Project ID 14533567)

Conflict of Interest Statement

The authors state that performance of this study entailed no issues representing a conflict of interest.

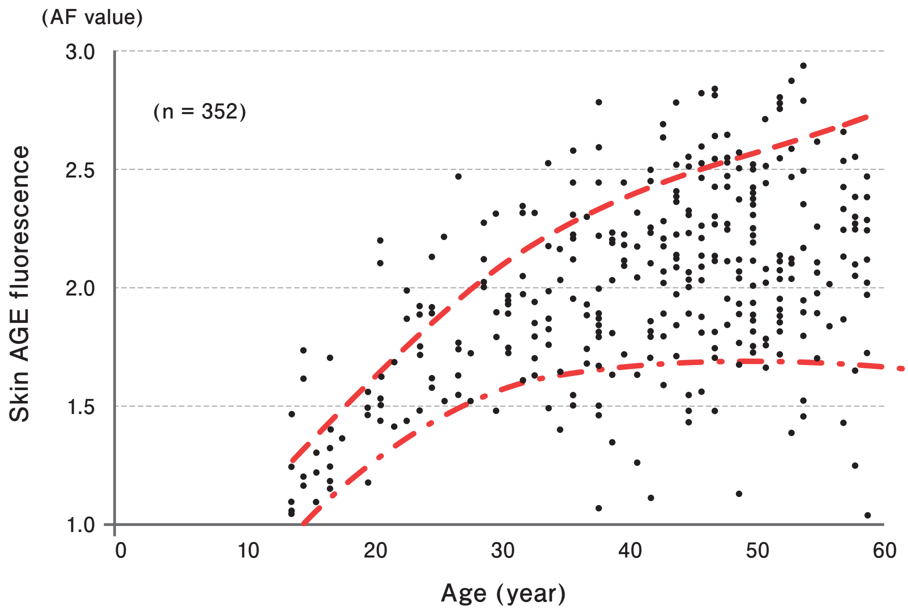

Fig 8. **Skin AGE fluorescence intensity with aging.**

Skin AGE-derived fluorescence was measured at the inside of the upper arm by AGE Reader (DiagnOptics, Netherland). AGEs, advanced glycation endproducts; AF, auto fluorescence. Adapted from reference (51).

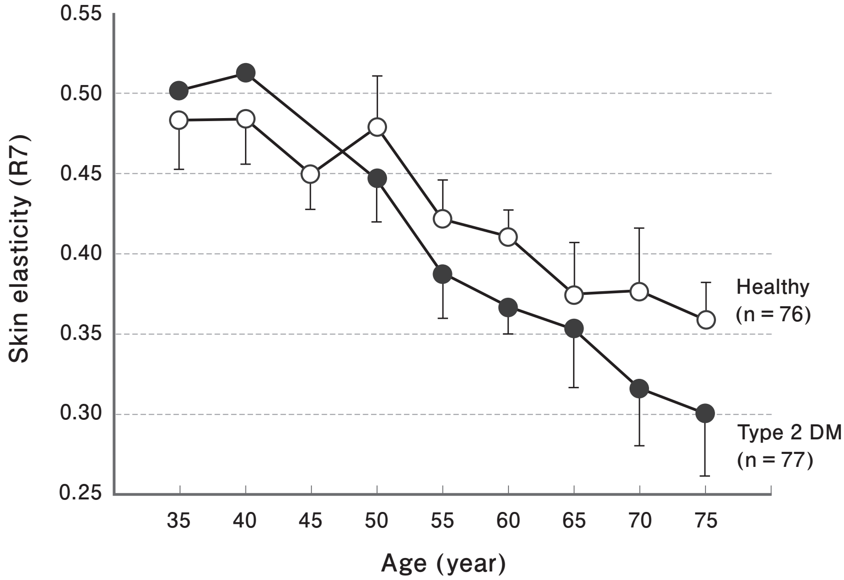

Fig 9. **Comparison of skin elasticity between healthy and DM subjects.**

Skin elasticity index R7 was measured at the inside of the upper arm by Cutometer (Courage+Khazaka, Germany). DM, diabetes mellitus. Adapted from reference (53).

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