GLYCATION: IMPLICATION IN PERCEIVED AGE AND DERMATOLOGY

Perceived age comprises different facial features and it is associated with multiple external factors, one of which is high levels of serum glucose. Modern Western diet is associated with systemic elevated sugar levels. Excess sugars react with proteins, forming protein-bounded sugars involved in the process named glycation and resulting in the formation of advanced glycation end products or AGEs. This article reviews the pathophysiological mechanisms involved in glycation and AGEs’ impact on tissues and organs of both healthy and diabetic individuals. Dietary advice must be an important part of medical consultation, emphasizing the benefits of a hypoglycemic diet. Future research aimed at discovering universal molecules that could interfere with AGEs will be a major breakthrough in the management of diabetes and aging related conditions.

1. INTRODUCTION

Aging is a complex process, influenced by genetic, endogenous and environmental factors (1).

Perceived age is a specific term referring to facial appearance and comprising multiple facial features such as the nasolabial fold, skin wrinkling, the presence of pigmented spots or lip height (2, 3).

Research revealed the fact that an older looking facial appearance or higher perceived age is associated with increased risk of morbidity and mortality (4).

Multiple external factors, such as smoking, high sunlight exposure, low body mass index and low social class are associated with higher perceived age (5).

In addition, higher perceived age is also associated with high levels of serum glucose (6). Serum glucose is a major determinant factor of the aging process, while also inducing many age-related diseases at younger ages, as observed in diabetic patients when compared to healthy controls (7, 8).

One of the most important features of facial aging, with a strong association with perceived age, is aging of the skin (2).

Collagen is the main structural protein of all connective and interstitial tissues and parenchymal
organs, providing integrity and stability of these structures (9). In addition, collagen is a major component of the extracellular matrix and basal membranes, since it is involved in the formation of fibrillar networks (10).

Up to date, 20 different collagens have been identified; the most abundant amongst them is type I collagen, found predominantly in connective tissues, skin, tendons, ligaments and cornea (11).

Sugar consumption induces the cross-linking of collagen fibers, and these changes in collagen and elastic fibers in the skin are strongly related with the appearance of rhytides, sagging skin and loss of elasticity (12).

In the beginning of 1942, warning signs have been issued regarding the elevated amounts of sugar contained in North American diet (13). Soon after that, in 1945, Urbach and Lentz revealed the fact that a high sugar diet was associated with elevated serum and skin sugar levels and that a hypoglycemic diet lowered the skin's sugar level (14).

Moreover, some of the excess sugars are bound to proteins and this form of protein-bounded sugars are involved in the process named glycation, which results in the formation of a complex named advanced glycation end products or AGE (13).

It is now current knowledge that modern food is a source of preformed AGEs and monosaccharides, which also catalyze AGE's production (13).

The most well known AGE amongst this heterogeneous group of molecules is glycated hemoglobin (HbA1C), a widely used parameter for the evaluation of glycemic control in patients suffering from diabetes (15).

Since it is clear now that AGEs are associated with both pathological conditions and skin ageing, researchers hypothesized that this group of molecules might be a strong connector between perceived age and morbidities (4).

2. WHAT IS GLYCATION?

Glycation is a complex non-enzymatic reaction between proteins, lipids or nucleic acids and sugar molecules (glucose or fructose) (16), resulting in the formation of the so called advanced glycation end-products (AGEs). During this process, intra- and inter- molecular cross-links are being formed between adjacent proteins, impairing their properties and normal function (17-19).

This process seems to appear randomly on the target molecule and its major effect is the inhibition of the molecule's function (15).

Unlike glycation, glycosylation is an enzymatic reaction, vital for the target molecule's function and occurring in specific sites on the target molecule (15).

The glycation process has been first described by Maillard in 1912. Fifty years later, Hodge highlighted that glycation could be promoted by food thermal processing during cooking methods that involved browning (frying, grilling, and pan-ning). Since then, its involvement in aging, diabetes and other pathologies has been intensely studied (20, 21).

The classic glycation reaction described by Mail-lard involved electrophilic carbonyl groups of glucose or other sugars and the free amino groups of amino acids of proteins, lipids or nucleic acids (15), which eventually formed a non-stable Schiff base (22); the latter undergoes rapid changes in order to become a more stable ketoamine, named Amadori product. Both Schiff bases and Amadori products are products of reversible reactions. Once this point has been reached, the Amadori products and Schiff bases can undergo the next possible steps: a) reverse reaction; b) irreversible reaction with lysine or arginine, forming protein cross-links and stable AGEs; c) oxidation, dehydration or polymerization, all of which end up forming more AGEs (16, 22, 23).

Besides their formation from the classical molecules, glucose and protein, AGEs can be produced by lipid intermediates, resulting in advanced lipoxidation products (23), but also through other routes such as reactive carbonyl compounds like (methyl)glyoxal (so-called carbonyl stress), produced during oxidative stress (24).

The major mechanism of defense against this pathway is represented by the glyoxalase system (25).

To summarize, the formation of advanced glycation end-products (AGEs) can be realized either by cross-linking between two neighboring molecules such as lysine to lysine or lysine to arginine, or by side-chain modifications, affecting the cell-colla-gen interaction (26). The cross-linking process is believed to take place between triple helical do-mains of adjacent molecules, producing physical changes, such as stiffness and enzyme resistance, all of which are age dependent but considerably accelerated in diabetic patients because of their hyperglycemic status (26).

The side chain modifications alter the molecule's charging profile, affecting cell-collagen interactions, which ultimately interfere with major repair mechanisms, such as vascular damage control and wound healing (26).

The main in vivo AGE, carboxymethyl-lysine (CML), has been first described by Ahmed (27, 28). CML is a non-fluorescent protein, formed through oxidative degradation of Amadori products or after direct reaction between glyoxal and lysine and it is currently the major epitope of polyclonal anti-AGE antibodies. CML can also be found in the normal epidermis, aged and diabetic dermis, photodamaged skin or in actinic elastosis lesions (29-31).
Different other AGEs, such as pentosidine, glyoxal, methylglyoxal, glucosepane, fructoselysine, carboxymethyl-lysine, glyoxal-lysine dimer and methylglyoxal-lysine dimer have been identified in the skin (32).

Glucosepane, carboxymethyl-hydroxy-lysine, carboxyethyl-lysine (CEL), fructose-lysine, methylglyoxal-lysine-derived hydromimidazolones and pyrraline, which form non-fluorescent protein adducts are other in vivo AGEs. Unlike the last ones, glyoxal-lysine dimer (GOLD) and methylglyoxal-lysine dimer (MOLD) form non-fluorescent protein cross-links (16, 23).

Sell and Monier isolated a fluorescent glycoxidation product, named pentosidine, composed of an arginine and a lysine residue cross-linked to a pentose (33), which forms protein-protein cross-links (22).

Other very reactive molecules resulted from oxidative degradation or oxidation of the Amadori products (16, 34), which also produce cross-links (16), are the so called dicarbonyl compounds (3-deoxyglucosome, methylglyoxal and glyoxal).

In conclusion, glycation has the ability to induce structural and functional protein alterations and it is a fundamental process involved in the etiology of diabetic complications (35).

### 3. FACTORS INVOLVED IN GLYCATION

Researchers revealed the fact that glycation process begins early in life and it is established by 20 years of age. Glycated collagen has been shown to accumulate at a rate of 3.7% per year (36), percentage highly influenced by environmental factors such as diet and smoking (37). Moreover, studies conducted on healthy twins, both monozygotic and heterozygotic, concluded that circulating AGEs level's are genetically determined (38).

Ages formation is accelerated by hyperglycemia, cooking temperatures above 120°C (248°F), the presence of active transition metals or reactive oxygen species, accelerated protein turn-over, etc (23).

Dietary fructose impacts profoundly on the carbohydrate metabolism, therefore contributing to diabetic complications, inducing glycation through collagen cross-linking (39).

Diet is the main source of both sugars (glucose and fructose) and also pre-formed AGEs produced by cooking at high temperatures (40).

Moreover, besides the exogenous ingestion through food consumption, AGEs can be produced endogenously at lower rates during normal metabolic processes and at increased rates in diabetes (41).

Preformed AGEs resulted from dietary sources are absorbed and introduced in the circulating stream, increasing the ageing burden, by inducing protein cross-linking, inflammation and oxidative stress (13). As mentioned above, sugar is not the only source of AGEs, therefore avoiding cooking at high temperatures, in the oven or pan, browning, grilling, frying, roasting of proteins and lipids (15), not only sugars, is equally important in the process of preventing AGEs accumulation.

Dietary consumption of such products may be just as detrimental as a hyperglycemic diet (42). In contrast, water-based food preparation such as boiling or steaming produce significantly lower amounts of AGEs (43, 44).

10-30% of ingested AGEs are absorbed in the circulation (45) and their serum levels correlate directly with inflammatory markers in healthy individuals.

UV exposure seems to promote the accumulation of AGEs in extrinsically aged skin, besides inducing oxidative damage, mutagenesis, MMPs, apoptosis or proinflammatory changes (46, 49). The sun-exposed skin of young individuals has been shown to display increased levels of AGEs, in contrast with sun-protected areas (31, 48). In addition, lesions of solar elastosis contain large amounts of AGEs (49), which sustains the theory that AGEs formation in sun-exposed skin is another deleterious factor contributing to the various structural and functional alterations induced by photo-ageing.

UV exposure also induces the cross-linking of the skin's proteins (48, 50) which further decreases the natural defense mechanisms against free radicals. Another factor sustaining that UV can mediate AGE formation is the presence of CML-modified elastin in sites of solar elastosis and it's nearly absence in sun-protected areas (15, 51).

UV radiation induces oxidative stress through the formation of hydrogen peroxide, hydroxyl radicals, superoxide anion radicals (52), reactive oxygen species (ROS) and redox active transition metals, accelerating the formation of AGEs (23, 16).

Smoking also accelerates AGEs' formation and their deposition in various tissues, including the skin, contributing to skin ageing (53, 54).

AGEs are considered to accumulate in various tissues, abundant in proteins with slow turnover rate (55), such as collagen, making AGEs a marker of chronological age (56). To be more specific, the collagen in the skin has a half-life of approximately 15 years and can undergo 50% increase in glycation during an individual's lifetime (57).

Another long-lived dermal protein, fibronectin, is deeply affected by glycation and it is a marker of intrinsic chronological ageing (30, 31).

Collagen is a strong candidate for glycation because it is abundantly present in many tissues, it can be influenced on many levels and, as mentioned before, it is a protein with slow turnover rate (58). Glycated collagen has been identified in the skin by the age of 20, it seems to accumulate at a
rate of 3.7% per year reaching a 30-50% increase by the age of 80 (31, 57).

The kidney is the main organ implicated in the excretion of AGE free adducts and peptides (59), on a rate dependant on the glomerular filtration rate (60).

Besides that, many cells have developed detoxifying mechanisms to fight against AGEs accumulation (34), such as the glutathione-dependent glyoxalase system (61), fructosyl-amine oxidases (FAOXs) and fructosamine kinases (67). FAOXs, which are only present in bacteria, fungi and yeast and not on mammals, exert their action by breaking the Amadori products (63).

One of the most important enzymes expressed in almost every human tissue, including the skin, fructosamine-3-kinase (FN3K), also has the ability to breakdown Amadori products.

Diabetic patients display higher levels of cross-linked collagen, presumably caused by advanced glycation end products (AGEs) resulted from chronic exposure to high glucose levels (22).

A team from Netherlands outlined the fact that diabetic patients present dangerous amounts of AGEs not only in the skin, but also in other organs, which induces the appearance of complications such as polyneuropathy, renal failure, atherosclerotic heart disease, macular degeneration of the retina, and lupus erythematosus (13).

Patients with chronic kidney disease (CKD) also have increased amounts of AGEs in their bodies, not only due to increased production but also because of impaired excretion mechanisms (64).

4. AGE’s NEGATIVE EFFECTS

Glycation influences many physiological functions of the organism, such as DNA regulation, enzyme functions and protein-DNA interactions by modifying the structure and function of proteins, lipids and nucleic acids (32).

Moreover, AGEs are directly implicated in the function of the immune response, gene expression, inflammation processes and cell proliferation, because they have the ability to interact with specific receptors and to consequently activate different molecular pathways in vivo (32).

To synthesize, AGEs exert their negative effects on the following levels:

1. Extracellular matrix proteins
2. Intracellular proteins
3. Receptors for AGEs: RAGE
4. Resident skin cells
5. Oxidative stress

The main pathophysiological factor responsible for diabetic complications and age-related diseases is the cross-linking of proteins (19, 65).

The changes in collagen function and structure observed in diabetic patients have been documented to be an important link between chronic high glucose serum levels and microvascular disease (66).

Diabetic status is characterized by AGEs accumulation and protein cross linking, both due to high levels of glucose (67). In vitro studies revealed the impairment of glycated skin samples’ biochemical properties (68). Decreased skin elasticity is the main in vivo feature of diabetic subjects in comparison with healthy controls (32, 69).

Chronic kidney disease comprises a wide spectrum of abnormalities, including progressive loss of renal function, but also an important increase in cardiovascular disease (CVD) and premature death (59).

The uremic toxins accumulating in the body in CKD include advanced glycation end-products (AGE) (70), which accumulate themselves in other organs, including the skin, where they induce increased stiffness and reduced elasticity, important features of skin ageing (13, 32).

4.1. Extracellular matrix proteins

Extracellular matrix (ECM) proteins are a major target for glycation. One of the strongest proteins in the human body is collagen, present in large amounts in the skin, predominantly type I and type IV. Collagen acts as a mechanical support framework but it is also actively involved in different cellular functions, such as migration, differentiation and proliferation. Therefore, intermolecular cross links of collagen fibers induced by glycation changes its flexibility, impairing its functions (26), increasing its vulnerability to mechanical stimuli (26) and affecting the protein’s ability to proper interact with neighboring cells (71). In addition, important cofactors involved in the cross-linking of collagen fibers, such as the conversion of L-arginine to nitric oxide, are also affected by glycation (72).

Finally but not least, glycated collagen becomes resistant to degradation by matrix metalloproteinases (MMPs), making collagen turnover difficult and inhibiting its replacement with functional proteins (73). As a direct result, tissue permeability and renewal are affected (22, 74).

Elastin and fibronectin are also affected by glycation, further augmenting dermal dysfunction (32, 75), because the body does not have the resources to repair glycation cross-linked molecules, like with their normal counterparts. Glycation modified elastin has decreased elasticity as well as resistance to proteolytic degradation (51).

4.2. Intracellular proteins

Glycation also affects intermediate filaments such as vimentin in fibroblasts and cytokeratin 10 (CK10) in keratinocytes (29, 76).

The intermediate filaments maintain the cytoskeletal stability while also coordinating cellular functions, such as migration and division (32).
Non-enzymatic sugar reactions also target different enzymes and growth factors, such as basic fibroblast growth factor (bFGF), which loses its mitogenic activity in endothelial cells once glycated (32, 77).

In addition, enzymes with protective and antioxidant properties such as Cu-Zn-SOD can be inactivated in tissues affected by glycation (78). DNA and lipids can also be affected by AGEs with negative effects on their structure and function (16, 79).

In vitro studies on human skin revealed that glycated fibroblasts display premature senescence and apoptosis (80, 81), while keratinocytes suffer from decreased mobility, premature senescence and increased levels of proinflammatory mediators (82).

4.3. Receptors for AGEs: RAGE
AGEs are capable of binding and interacting with specific cell surface receptors, called “Receptors for AGEs” (RAGE), immunoglobulins encoded by a gene located on chromosome 6, near the major histocompatibility complex III (32).

RAGE is present at low levels in all healthy tissues, with increased expression under various pathological conditions (83, 84). RAGEs are also present in the epidermis and dermis, especially in solar elastosis affected regions. RAGEs are expressed on fibroblasts, keratinocytes, dendritic and endothelial cells.

AGEs bond to their receptors, RAGEs, affecting gene expression, cell cycle and proliferation, extracellular matrix synthesis and inducing inflammation (reviewed in Bierhaus et al.) (83). Once activated, RAGEs stimulate different signaling pathways known to mediate various pathogenic mechanisms, such as nuclear factor-kappa beta (NFkB), mitogen-activated protein kinases (MAPKs), phosphatidylinositol-3-kinase (PI3K), extracellular signal-regulated kinases (ERK) (83).

The NFkB signaling pathway is involved in the induction of apoptosis, increased MMPs production and decreased cell proliferation in skin cells (81).

RAGE also induces oxidative stress, either directly by activating nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase (NOX) or decreasing superoxide dismutase’s (SOD) activity, or indirectly by reducing the activity of cellular antioxidant defenses, such as ascorbic acid (32, 83, 85, 86).

4.4. Effects of AGEs on resident skin cells
AGEs have been shown to affect various functions of skin cells in vitro, by decreasing cell proliferation rates, activating fibroblasts’ apoptosis in a RAGE-dependent manner and in conjunction with NFkB and caspases activation (80).

In vitro AGEs affect both keratinocytes and fibroblasts by reducing their migration and viability, while also inducing the expression of proinflammatory mediators and premature senescence (32, 50, 87, 88).

Regarding extrinsic ageing, AGEs decrease cell viability, while also rendering them more susceptible to external stimuli, like UV-irradiation (32, 52, 89).

Chronic exposure to hyperglycemic status induces premature cell senescence in the dermis and the linking of collagen fibers (22, 90, 91).

4.5. The role of oxidative stress
It is well known that oxidative stress is the central piece of photo aging (32), but in vitro studies revealed the fact that the exposure of AGEs to UVA leads to the formation of ROS (reactive oxygen species) such as Hydrogen peroxide, hydroxyl radicals and superoxide anion (52). Moreover, AGEs are themselves very reactive molecules, because they can act as electron donors during cross-linking reactions, producing superoxide anions (92).

Glycation of proteins generates ROS with or without the presence of oxygen or metals like iron or copper (92-94).

Petosidine, an auto fluorescent AGE, acts as an endogenous photosensitizer after UVA irradiation, leading to increased ROS formation (89).

In addition, AGEs also influence the normal gut flora (95), reducing the amounts of “good bacteria” (96) and compromising nutrient’s and phytochemicals’ absorption.

Moreover, AGEs also contribute to cardiovascular disease (97), reduced kidney function (98), and vascular complications in diabetes (99) and premature cellular senescence (90, 91, 100).

5. AGE EVALUATION METHODS
Several studies support the theory that serum AGEs may not be a good indicator of AGE dependent tissue damage (101-103).

Better methods for assessing the link between glucose levels and perceived age via AGEs levels seem to be skin fluorescence (the cross-linked collagen is fluorescent) and circulating pentosidine (marker of circulating AGES) (6).

The first glycated protein identified is glycated hemoglobin (HbA1), used to assess glycemic control in diabetic patients. Since its discovery, many other AGEs have also been detected and, due to some of their auto-fluorescent properties, they are easier to be identified both in situ and in vivo (16).

Because of AGEs auto-fluorescent properties and the skin’s accessibility, the epidermis is a very good platform for minimal invasive or non-invasive investigation on glycation (32).

Therefore, skin AGEs have been thoroughly studied in the assessment of diabetes and skin ageing (31, 104, 105).
Studies on a large number of healthy subjects revealed the fact that auto-fluorescence of the skin is directly associated with chronological ageing (36).

Cross-linking of proteins induces their polymerization (106), an important marker of AGE-related cross-linking.

The structural and functional changes produced in the skin as a result of glycation are known as “sugar sag” (15).

Recently, a non-invasive method to measure the skin’s content of AGEs using their autofluorescent characteristic, the AGE-Reader (DiagnOptics B.V., Groningen, The Netherlands), has been developed (107-109). The in vivo measurements of fluorescent AGEs correlated strongly with those taken from skin biopsies specimens, as well as with the non-fluorescent forms of AGEs (110-112).

Up to date it has been proven that skin auto-fluorescence (SAF) is a reliable predictor of other systemic complications such as chronic renal disease, macular degeneration, vascular abnormalities, diabetic complications and general mortality (108, 113-115).

In addition, skin auto-fluorescence positively correlates with perceived age and chronological aging (116), while also estimating the relative risk of future adverse events (117).

The DCCT-EDIC (The Diabetes Control and Complications Trial-Epidemiology of Diabetes Interventions and Complications) highlighted the fact that AGEs are an independent predictor of worse renal and cardiovascular disease (59, 115).

McIntyre et al. reported that a large number of cardiovascular and renal risk factors, such as hemoglobin, age, smoking, total cholesterol, diastolic blood pressure, C-Reactive Protein, waist to hip ratio, albuminemia, pulse wave velocity, diabetes and uremic acid are associated with SAF (118).

6. ANTI-AGE STRATEGIES

Once produced, glycated collagen is impossible to be repaired; therefore, the best defense against this process is prevention, begun as early as possible (13).

Since the identification of AGEs as major factors implicated in diabetes and aging pathogenesis, different substances capable to prevent AGEs formation or to destroy those already formed, have been identified and are currently tested in clinical trials (119, 120).

The main therapeutic approaches include better control of blood sugar in order to prevent AGE formation and the use of specific molecules with AGE inhibiting or breaking properties (19).

Dietary modifications are an adjuvant tool for preventing the formation of AGEs and also to reduce systemic oxidative stress and inflammation (13, 121, 122).

As already mentioned, cross-links are irreversible, therefore the dietary intervention has a major preventive benefit, but it must be remembered that although sugars are important contributors to glycation, other foods and the cooking method may contain or induce preformed AGEs (40).

Up to date, no dietary sources have been identified as being capable to extract or eliminate AGE-induced adducts (13, 123). However, some foods and natural substances such as cinnamon, oregano, cloves, ginger, garlic, spices, taurine, carnosine, some flavonoids, benfotiamine, niacinamide, sodium selenite, selenium, riboflavin, zinc, manganese can inhibit AGEs’ production, therefore protecting against sugar-induced AGE formation (9, 123). Moreover, some of these culinary compounds, specifically cloves, cinnamon, oregano and all spice are believed to be able to inhibit endogenous produced AGEs, based on in vitro and preliminary animal models (9, 123, 124).

Based on the above described data, topical products with anti-AGE formation properties have already been released, most of them containing carnosine and α-lipoic acid (42).

It has been hypothesized that a 25% reduction of glycated collagen may be achieved through tight glycemic control over a 4-months period (13, 42).

So far, a hypoglycemic diet and cooking using water-based methods seem to be the easiest way to prevent the ingestion of exogenous AGEs but also their endogenous production through glycation. Also, the most effective strategy for slowing down the aging process or “sugar sag” is the strict avoidance of AGE-rich foods, such as golden-crusted pastry, barbecued and roasted meats and dark-colored soft drinks (43).

In addition, antioxidants should be used as adjuvants, since studies suggest that they can reduce AGE-related tissue damage (125).

In vivo and in vitro studies identified many molecules capable to inhibit the production of AGEs (126), resulting in a reduction of glycated proteins with medium or fast turn-over. However this inhibition seems to be less effective on proteins with a slow turn-over rate, such as collagen (19).

Some of the molecules implicated in glycation protein crosslinks are glucosamine, pentosidine, methylglyoxal-lysine dimer (MOLD) and others (127).

One of the first crosslink breaker, Alagebrium or ALT-711 (Alteon Inc., Montvale, NJ, USA), has been described in 1996, but without any mention regarding the type of crosslink being broken (128). Later on, in 2013, it has been shown that the molecule is able to influence the function of Amadori products before the cross-link formation, by breaking their alpha-dicarboxyl groups (129).
Classification

6.1. Substances preventing or inhibiting AGE formation

Aminoguanidine, a nucleophilic hydrazine, is one of the first molecules identified to be capable of limiting AGEs' formation (130). Its anti-AGE mechanisms involve blocking early glycation products but it is inefficient on more advanced stages of glycation (32). Because of its adverse effects, aminoguanidine's use in clinical practice is limited (32, 131).

Another molecule used in the fight against AGEs is pyridoxamine, a vitamin B6 natural isoform, able to inhibit post-Amadori stages of AGE formation; it can also trap reactive carbonyl intermediates, while also scavenging ROS (132). Pyridoxamine is being currently studied in a phase II clinical trial regarding its use against diabetic nephropathy (128).

6.2. “AGE breakers”

“AGE breakers” are chemical substances and enzymes, such as dimethyl-3-phenacyl-thiazolium chloride (ALT-711), N-phenacylthiazolium and N-phenacyl-4,5-dimethylthiazolium, which are capable to recognize and chemically destroy glycation induced cross links through a thiazolium structure (128).

Other viable strategies to remove intrinsic AGEs with fewer side effects are the enzymes with detoxifying activity, such as the enzymatic system of Glo, FAOXs and FN3K (32, 61, 62, 133).

6.3. Nutriceuticals

Since AGEs formation is crucially linked to oxidation, antioxidants and metal chelators may be useful for their antiglycating effect (134). Therefore, vitamins and nutrients, also named “nutriceuticals”, have been intensely studied for their anti-AGE properties (120, 135). Ascorbic acid, niacinamide, pyridoxal, α-tocopherol, trolox, riboflavin, zinc and manganese are only some natural antioxidants that are able to inhibit glycation in vitro (124).

Polyphenols and avonoid epigallocatechin-3-gallate also revealed anti AGE effects in vitro by antagonizing their proinflammatory activity (136).

Vinson et al. suggest that supplementing vitamin C significantly decreases the protein’s glycation rate (137).

In addition, some spices and herbs, such as cinnamon, ginger, rosemary, cloves, tarragon, marjoram, blueberries and natural flavonoids, like luteolin, quercetin and rutin have been shown to inhibit AGEs formation (19, 123, 138, 139).

6.4. Caloric restriction and dietary measures

In conclusion, advising patients to restrain from a hyperglycemic diet and high AGE preformed foods, as well as to embrace the use of broad spectrum sunscreens are truly effective methods to obtain long-term results after cosmetic procedures.

CONCLUSIONS

Cardiometabolic syndrome X, comprising diabetes, obesity, acne, hidradenitis suppurativa and other cutaneous abnormalities has been shown to be related with sugar intake, insulin-resistance, systemic inflammation and oxidative stress.

Tissue-bound AGEs should be carefully monitored, since they are both a marker of patients’ outcome in CKD and also an important factor of the underlying condition (59).

Dietary advice must therefore be an important part of medical, surgical or cosmetic consultation, emphasizing the benefits of a hypoglycemic diet by reducing oxidative stress and inflammation (13). Other important aspects that should be addressed during regular interactions with patients are UV-protection measures and smoke avoidance.

Future research aimed at discovering universal molecules that could interfere with AGE-protein cross-links will be a major breakthrough in the management of diabetes and aging related conditions (19).

The most effective strategy of slowing the general aging process, the dietary caloric restriction, has been proven effective in reducing the levels of AGEs in rat and mice, resulting in increased lifespan in the study models (140, 141).

Therefore, since youthful and flexible collagen fibers are the mainstay of youthful appearance, its preservation by preventing degradation through cross-linking should be avoided as much as possible (13).

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