Chapter

Advanced Glycation End Products and Oxidative Stress in a Hyperglycaemic Environment

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Abstract

Protein glycation is the random, nonenzymatic reaction of sugar and protein induced by diabetes and ageing; this process is quite different from glycosylation mediated by the enzymatic reactions catalysed by glycosyltransferases. Schiff bases form advanced glycation end products (AGEs) via intermediates, such as Amadori compounds. Although these AGEs form various molecular species, only a few of their structures have been determined. AGEs bind to different AGE receptors on the cell membrane and transmit signals to the cell. Signal transduction via the receptor of AGEs produces reactive oxygen species in cells, and oxidative stress is responsible for the onset of diabetic complications. This chapter introduces the molecular mechanisms of disease onset due to oxidative stress, including reactive oxygen species, caused by AGEs generated by protein glycation in a hyperglycaemic environment.

Keywords: glycation, advanced glycation end products, gestational diabetes, reactive oxygen species, oxidative stress

1. Introduction

Glycosylation is a post-translational modification mediated by an enzymatic reaction catalysed by glycosyltransferases, which add a carbohydrate molecule to a predetermined region of a protein. More than 300 glycosyltransferases have been identified in mammals [1]. In contrast, glycation is a random nonenzymatic reaction that occurs under conditions of hyperglycaemia and ageing. The reactive reducing ends of free sugars (e.g., glucose, fructose, and galactose) covalently attach to the amino acid residue of the protein, thereby creating glycated products.

Glycation has been previously studied. Robert Lynn from the United Kingdom first reported that proteins and reducing sugars react during the beer-making process to form new compounds [2]. Subsequently, the French chemist Louis-Camille Maillard discovered that heating a mixed solution of amino acids and reducing sugars produced a brown compound [3]; this was the first report of the Maillard reaction or aminocarbonyl reaction, which is a nonenzymatic reaction between the amino group of an amino acid and carbonyl group of a reducing sugar (**Figure 1**).

In the early stages of the Maillard reaction, the imine produced by the nucleophilic reaction of the amino group and carboxyl group becomes a stable Amadori compound through Amadori rearrangement. The Amadori compound then undergoes a repeated polycondensation reaction with an amino compound using ozone or

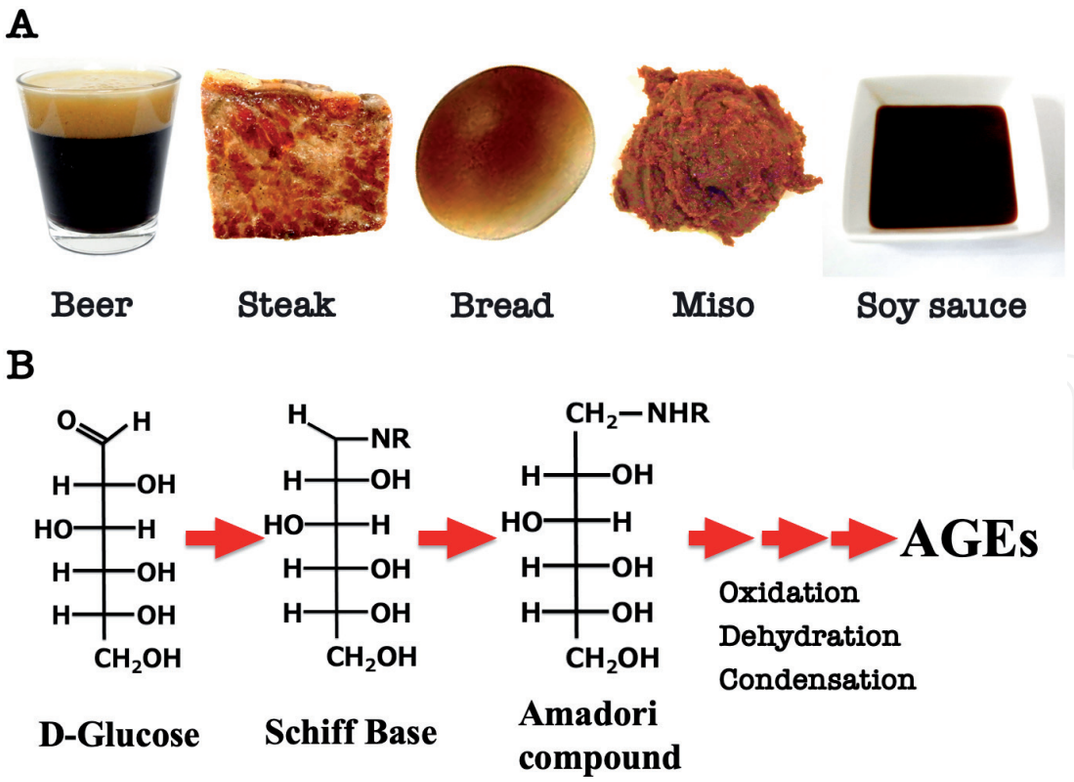

Figure 1.
Maillard reaction in foods and the formation of AGEs. (A) Proteins contained in foods are saccharified during fermentation and processing, and the Maillard reaction is accompanied by browning/denaturation. (B) The amino group of the amino acid of the protein and the carbonyl group of the reducing sugar react nonenzymatically, and AGEs are produced by repeating oxidation, dehydration, and condensation from the Schiff base via the Amadori compound.

furfural as an intermediate to produce a brown product, melainodin, in late stages [4]. Structures formed in the latter stage of the nonenzymatic glycation reaction between reducing sugars and proteins are collectively known as advanced glycation end products (AGEs).

Fermented foods, such as dark beer, miso, and soy sauce, contain large amounts of AGEs, including 3-deoxyglucosone and melanoidin [5]. Additionally, milk, cheese, and butter contain carboxymethyl lysine (CML) [6]. These chemicals are consumed on a daily basis and some AGEs, such as carbonyl compounds and CML, which are closely related to disease states, are known to be glycotoxins. Many studies have evaluated the adverse health effects of ingesting glycotoxins present in such foods in relation to nephropathy [7–9], type 2 diabetes [10, 11], and arteriosclerosis [12]; however, these relationships are not completely understood. Therefore, research on phytochemicals that prevent adverse effects on the living body caused by ingestion of these glycotoxins is being conducted [13–15].

In this chapter, we first introduce the biochemical properties of AGEs and their reaction processes. We then discuss intracellular signal transduction systems related to oxidative stress caused by AGEs in a hyperglycaemic environment and describe the relationships between AGEs and diseases.

2. Biochemical basis of AGEs

Protein glycation can be subdivided into three major stages: early, middle, and late. In the initial reaction, the carbonyl group (C=O) of a reducing sugar, such as glucose, reacts with the amino group (NH_2) of the amino acid residue in the protein

to form a Schiff base (C=N). This Schiff base is relatively unstable and eventually becomes an enol, causing Amadori rearrangement and finally leading to the formation of a stable Amadori compound (C-N).

Kunkel found abnormal haemoglobin levels in the blood of normal people [16], and increased levels of abnormal haemoglobin were observed in patients with diabetes [17]. Currently, haemoglobin A1c (HbA1c), which is used as a diagnostic criterion for diabetes, is formed via Amadori rearrangement of the amino-terminal valine of the haemoglobin β chain and reflects the blood glucose level for 3–4 weeks [18, 19]. In the intermediate stage, α-dicarbonyl compounds, which are derivatives of sugars such as glucosone, 3-deoxyglucosone, glyoxal, and methylglyoxal, are produced from Amadori compounds. After further reacting with the amino compound, these α-dicarbonyl compounds undergo dehydration, condensation, cyclisation, and intermolecular crosslinking to form stable AGEs in the advanced stage (**Figure 2**). The pathway through which AGEs are produced from these series of Schiff bases via Amadori compounds and α-dicarbonyl compounds is known as the Hodge pathway [4]. In addition, the Namiki pathway, which produces glyoxal and glycolaldehyde, generates free radicals from Schiff bases without producing Amadori compounds [20].

Because the Schiff base is in a state in which it easily undergoes a secondary reaction with sugars and amino acids, dehydration, isomerisation, cleavage, cyclisation, and polymerisation can be repeated; the final products produced through these intermediates are extremely diverse. Therefore, the structures of many compounds are complicated, and most have not been identified. The structures of typical AGEs, such as CML, pyrarin, argpyrimidine, and pentosidine, have been reported (**Figure 2**).

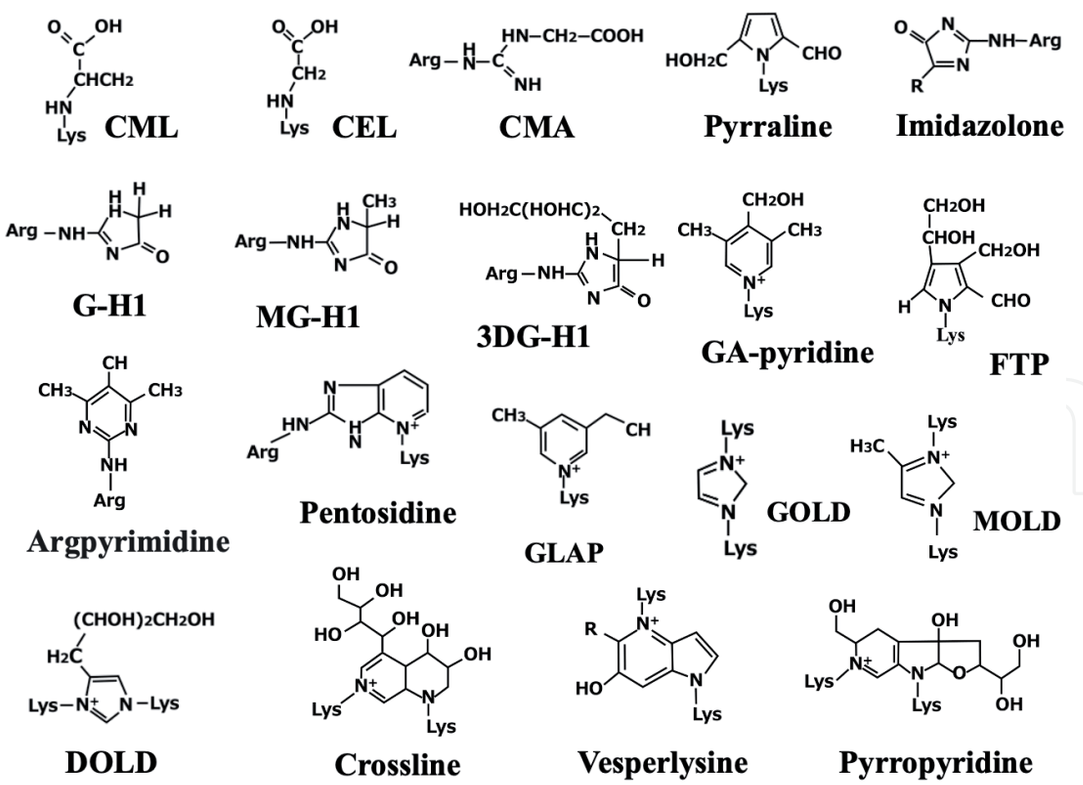

Figure 2.
The main chemical structures of AGEs. Abbreviations used: CML, Nε-carboxymethyl-lysine; CEL, Nε-(1-carboxyethyl)lysine; CML, Nω-(Carboxymethyl)-L-arginine; G-H1, Nδ-(5-hydro-4-imidazolon- 2-yl) ornithine; MG-H1, Nδ-(5-hydro-5-methyl-4-imidazolon-2-yl)-ornithine; 3DG-H1, Nδ-[5-(2,3,4-trihydroxybutyl)-5-hydro-4-imidazolon-2-yl] ornithine; GA- pyridine, Glycolaldehyde-pyridine; FTP, Formyl Threosyl Pyrrole; GLAP, glyceraldehyde-derived pyridinium-type advanced glycation end product; GOLD, glyoxal-derived lysine dimer; MOLD, methylglyoxal-derived lysine dimer; DOLD, 3-deoxyglucosone-derived lysine dimer

3. *In vivo* AGE generation pathways

To date, AGEs have been widely studied because of the close involvement in diabetic complications. HbA1c is currently used as a diagnostic criterion and indicator of mean blood glucose levels over a period of 1–2 months in patients with diabetes. Albumin, another representative protein in the blood, is also related to diabetic complications. In patients with diabetes, albumin has been shown to glycate four lysine residues (K199, K281, K439, and K525) in the molecule [21]. In addition, albumin is more easily saccharified than haemoglobin, and its reaction is rapid; thus, blood GA levels fluctuate more than HbA1c levels. Accordingly, gluco-albumin, which has a short half-life, was recently reported as an index of the average blood glucose level over a period of approximately 2 weeks [22].

At the experimental level, bovine serum albumin (BSA) has been used to evaluate the functions of AGEs *in vivo*. Various specific antibodies have been produced by immunisation with glycated AGE-BSA as antigens. Many commercially available AGEs are produced *in vitro* by incubating BSA and D-glucose at 37°C for 8 weeks in 0.2 M phosphate buffer (pH 7.4) and 5 mM DTPA. Farboud et al. reacted BSA with glycolaldehyde to produce pentosidine-BSA and obtained antibodies that recognise CML and pentosidine from this antigen [23]. Takeuchi named these six types of AGEs as glucose-derived AGE-1 (Glc-AGE), glyceraldehyde-derived AGE-2 (Glycer-AGE), glycol aldehyde-derived AGE-3 (Glycol-AGE), methylglyoxal-derived AGE-4 (MGO-AGE), glyoxal AGE-5 (GO-AGE), and 3-deoxyglucosone-derived AGE-6 (3DG-AGE); they then produced specific antibodies against each of the six types [24–26] (**Figure 3**). Using these antibodies, Takeuchi et al. clarified that AGE-2 derived from glyceraldehyde and AGE-3 derived from glycolaldehyde, produced by Schiff bases and Amadori compounds, were closely related to the onset and progression of diabetic retinopathy and nephropathy compared with AGE-1 [27–30]. The authors also demonstrated that these highly toxic AGE-2 and AGE-3 act via receptors for AGEs (RAGE) and therefore named these molecules toxic AGEs (TAGEs) [31], and identified nontoxic AGEs, including AGEs such as CML, pentocidin, and pyrrolin that are generated from glucose and by active trapping and detoxification of highly chemically reactive aldehyde/carbonyl compounds occurring in the body. TAGEs derived from glyceraldehyde, glycolaldehyde, and acetaldehyde are critical to the development and progression of various diseases and should be considered separately from other AGEs [32].

During the production of TAGEs, unique glucose metabolism pathways have been identified in the hyperglycaemic environment associated with diabetes. For example, in the hyperglycaemic environment observed in patients with type 2 diabetes, intracellular glucose levels are abnormally elevated in cells that take up insulin-independent glucose, such as the liver, brain, and placenta. The liver expresses the glucose transporter (GLUT) named as GLUT2, which has a low affinity for and takes up a large amount of glucose. GLUT3, which has a high affinity for glucose, also functions in glucose transport [33]. In such cells, the extra glucose is shunted into the polyol pathway by saturation of the normal glycolytic pathway [34, 35]. The polyol pathway is a side pathway that is activated when glycolysis is stagnant. First, excess glucose, which is not metabolised by glycolysis, is converted to sorbitol (polyol) by aldose reductase, after which sorbitol is metabolised to fructose by sorbitol dehydrogenase. When aldose reductase is enhanced, excessive consumption of its coenzyme NADPH causes a decrease in reduced glutathione and abnormalities in the active oxygen scavenging system. Such an increase in aldose

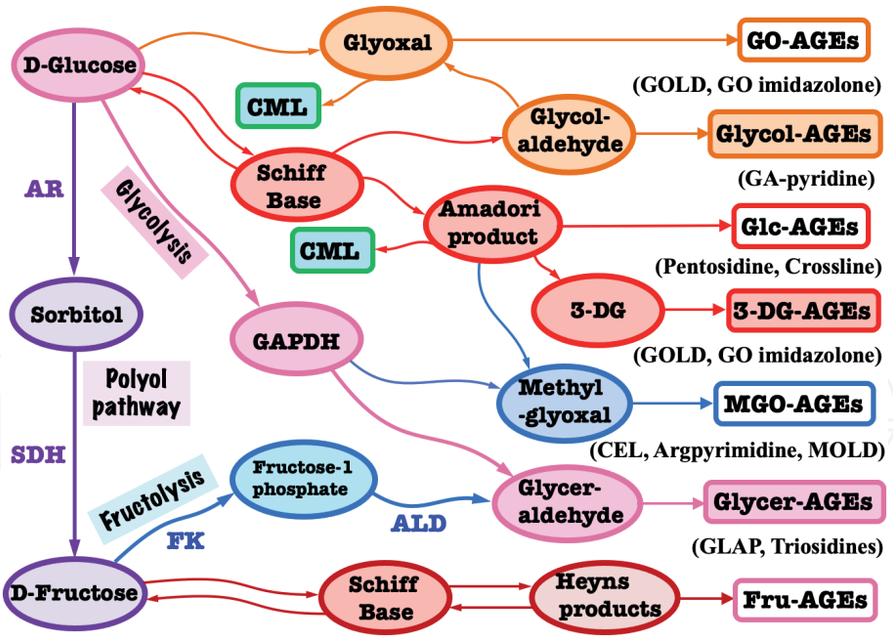

Figure 3.
AGE generation process in vivo. In the living body, AGEs are produced via dicarbonyl compounds generated during glucose metabolism of reducing sugars, such as glucose. In a hyperglycaemic environment, when glycolysis is stopped, the polyol circuit is enhanced, and glyceraldehyde-AGEs are produced. GO-AGEs, glyoxal (GO)-derived AGEs; glycol-AGEs, glycolaldehyde-derived AGEs; Glc-AGEs, glucose-derived AGEs; 3-DG-AGEs, 3-deoxyglucosone (3-DG)-derived AGEs; MGO-AGEs, methylglyoxal (MGO)-derived AGEs; glycer-AGEs, glyceraldehyde-derived AGEs; CML, Nε-(carboxymethyl) lysine. This figure has been modified based on the reference [25, 26].

reductase in type 2 diabetes is thought to worsen haemodynamics and lead to diabetic neuropathy (DN) [36]. Therefore, in patients with diabetes, the concentration of fructose produced from glucose is increased intracellularly because of enhancement of the polyol pathway [37, 38].

Fructose produced by this polyol pathway is thought to have a stronger protein glycation ability than glucose [39]. Therefore, increases in intracellular fructose promote AGE formation [40]. In our research, we attempted to suppress protein saccharification by inhibiting aldose reductase. Administration of the aldose reductase inhibitor Solvinyl to streptozotocin-induced diabetic rats reduced AGEs in skin collagen [41]. Moreover, the pentosidine-like fluorescence (335/385 nm) of the crystalline lens of galactosaemic rats was suppressed by treatment with the aldose reductase inhibitor sorbinin [42]. Administration of an aldose reductase inhibitor to patients with diabetes reduces the amount of N-epsilon-(carboxymethyl)-lysine in erythrocytes [43]. Following the development of many aldose reductase inhibitors, epalrestat was used clinically [44].

Fructose generated from such a polyol pathway is converted to fructose-1-phosphate by fructokinase, and fructose-1-phosphate further produces glyceraldehyde by aldolase. AGEs formed from this glyceraldehyde are highly toxic TAGEs. Increases in intracellular fructose, which trigger glyceraldehyde production, are caused not only by the polyol pathway but also by excessive intake of high-fructose syrup, such as high-fructose corn syrup.

Fructose is a natural ketose that is abundant in fruits and honey. However, in recent years, many soft drinks have been produced using high-fructose corn syrup, which is an isomerised sugar, and a relationship between excessive intake of fructose and metabolic syndrome has been reported [45]. Fructose ingested from soft drinks is taken up into cells by passive transport via GLUT5 in the epithelium of

the small intestine. In contrast, glucose and lactose-derived galactose are taken up into cells by active transport via sodium-glucose cotransporter 1. Excessive fructose is transported from small intestinal epithelial cells through the portal vein to the liver and the whole body, thereby increasing glyceraldehyde-derived TAGEs. As discussed later, glyceraldehyde-derived TAGEs generated from fructose can cause liver diseases.

4. AGE receptors

Accumulation of AGEs *in vivo* causes a decrease in physiological function, leading to the onset and progression of various diseases. Recent studies revealed the existence of receptors involved in degrading and removing AGEs accumulated by glycation of such proteins and the intracellular signal transduction system via receptors [46]. AGEs are categorised into two groups based on their receptors; the first group includes the receptors AGE-R1, AGE-R3, scavenger receptor class A (SR-A) I, SR-AII, scavenger receptor-BI (SR-BI), cluster of differentiation 36 (CD36), FEEL1, FEEL2, and ezrin/radixin/moesin (ERM), which exert scavenger functions to removes AGE, and the second group includes RAGE, which is related to the enhancement of inflammation and oxidative stress (**Figure 4**).

AGE-R1 and AGE-R2 were identified as oligosaccharyltransferase-48 (OST-48) and 80-kDa protein kinase C (PKC) substrate (80 K-H), respectively, in rat livers [47]. Subsequently, AGE-R3 was identified as a protein that binds to AGE-1 and AGE-2 [48] to form a complex. AGE-R1 is also known as OST-48, belongs to the single transmembrane lectin family, and has a molecular weight of 48 kDa. AGE-R1 is expressed in endothelial cells, mesangial cells, macrophages, and mononuclear cells and functions by removing AGEs via endocytosis. AGE-R1, which enhances AGE removal, may also be a distinct receptor, as it suppresses AGE-mediated mesangial cell inflammatory injury by protecting against injury to the kidneys and other tissues due to diabetes [49]. Recent studies reported that AGE-R1 may be involved in lifespan extension [50, 51]. AGE-R2, also known as 80 K-H, is a tyrosine phosphorylated protein with a molecular weight of 80 kDa that was initially identified as a substrate for PKC and is expressed in the cytoplasm [47]. AGE-R2 is expressed

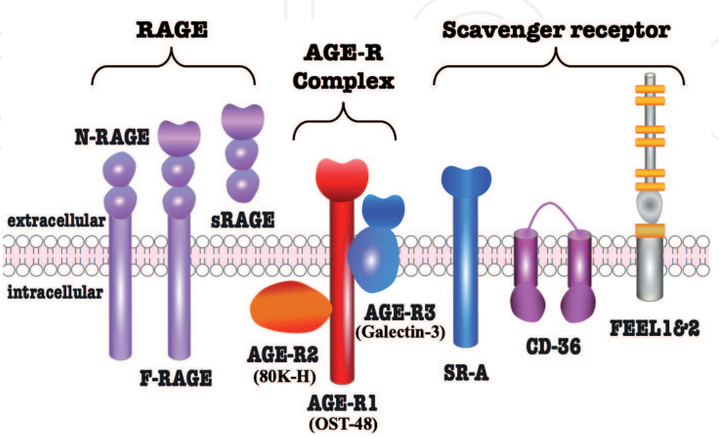

Figure 4.
The receptors for AGEs. A schematic diagram of AGE receptors is shown [46]. The receptor of AGEs (RAGE) includes full-length RAGE (F-RAGE), N-terminally truncated RAGE (N-RAGE), and soluble RAGE (sRAGE), which are cleaved from the cell surface membrane by matrix metalloproteinases. The AGE receptor (AGE-R complex) contains AGE-R1 (OST-48), AGE-R2 (80K-H), and AGE-R3 (Galectin-3). Scavenger receptor class A (SR-A), cluster of differentiation 36 (CD36), fasciclin EGF-like, laminin-type EGF-like, and link domain-containing scavenger receptor 1 and its homolog 2 (FEEL1 and – 2) are indicated as scavenger receptors.

in mononuclear cells and in the kidneys, vascular endothelium, brain, and nerves. Importantly, AGE-R2 is involved in activating intracellular signals via receptors, such as fibroblast growth factor receptor [52, 53]. AGE-R3, also called galectin-3, is a receptor that belongs to the lectin family and has a molecular weight of 32 kDa [48]. AGE-R3 binds directly to AGEs via the carbohydrate recognition domain in cells and is expressed in macrophages, eosinophils, and mast cells as well as in the nerves and kidneys. AGE-R3 has been reported to suppress adhesion between cells and the matrix laminin [54], activate mast cells [55], and degrade AGEs via endocytosis [48]. In addition, when diabetes develops in AGE-R3-knockout mice, the expression of macrophage scavenger receptor A and AGE-R1, which is involved in degrading AGEs, is decreased, and the expression of AGE receptors related to cell damage, such as RAGE and AGE-R2, is increased [56]. Because the expression of AGE-R3 is enhanced in ageing and diabetes, this receptor may have protective effects against ageing [57].

SR-A has been identified as a macrophage scavenger receptor [58, 59] and has a wide range of functions, such as removal of acetylated or oxidised low-density lipoprotein (LDL), removal of apoptotic cells, biological defence from bacteria, and cell adhesion [60]. SR-A is highly expressed in peritoneal macrophages derived from humans and from diabetic mice after culture in high-glucose medium [61]. Furthermore, SR-A promotes macrophage infiltration and foaming by incorporating AGEs into cells from the cell surface of macrophages [62, 63]. SR-BI is expressed in macrophages and in the liver adrenal glands and ovaries, functioning to promote the uptake of the cholesterol ester of high-density lipoprotein (HDL) and subsequent return of HDL to the liver [64, 65]. CD36, also known as scavenger receptor-BII, is a highly expressed receptor for single-stranded glycoprotein of 88 kDa in macrophages, vascular endothelial cells, and adipocytes [66]. CD36 binds to fatty acids, collagen, and oxidised LDL and is responsible for the uptake of oxidised LDL into macrophages and transport of fatty acids to adipocytes. Because CD36 is involved in removing AGEs, this protein may play protective roles in atherosclerotic diseases [67, 68]. The fasciclin, EFG-like, laminin-type EGF-like, and link domain-containing scavenger receptor-1 (FEEL-1) is expressed in the liver, vascular endothelial cells, and monocyte lineage cells, whereas FEEL-2 (a homologue of FEEL-1) is expressed in the spleen and lymph nodes. Despite the different tissue specificity, FEEL-1 and -2 are believed to be involved in the degradation of AGEs [69]. Megalin was identified as a 600-kDa glycoprotein (gp330) antigen expressed in glomerular epithelial cells (podocytes) of Heymann nephritis, a rat model of membranous nephropathy [70]. In recent studies, megalin was shown to bind to AGEs; AGEs that have passed through glomeruli are trapped and taken up by lysosomes to be decomposed [71]. AGEs bind to the N-terminus of the ERM protein family, which is a linker protein that crosslinks actin filaments and cell membrane proteins [72]. AGEs have been shown to promote angiogenesis through the hyperpermeability of human umbilical vein endothelial cells by inducing the phosphorylation of moesin via the RhoA/ROCK pathway [73].

RAGE is a single-pass 45-kDa transmembrane protein belonging to the immunoglobulin superfamily and was first isolated and identified from bovine lungs as a cell surface receptor that binds to AGEs [74]. RAGE is expressed in monocytes, macrophages, nerves, renal tubule cells, and mesangial cells [75]. In addition to AGEs, RAGE also binds to amyloid β protein, S100/calgranulins, and high-mobility group box 1 as ligands and is involved in the enhancement of inflammation and oxidative stress [76, 77]. RAGE is composed of a total of five domains: the extracellular domain of one V domain and two C domains, transmembrane domain, and intracellular domain [78]. When AGEs bind to this full-length RAGE, NADPH oxidase is activated, and the production of intracellular reactive oxygen species

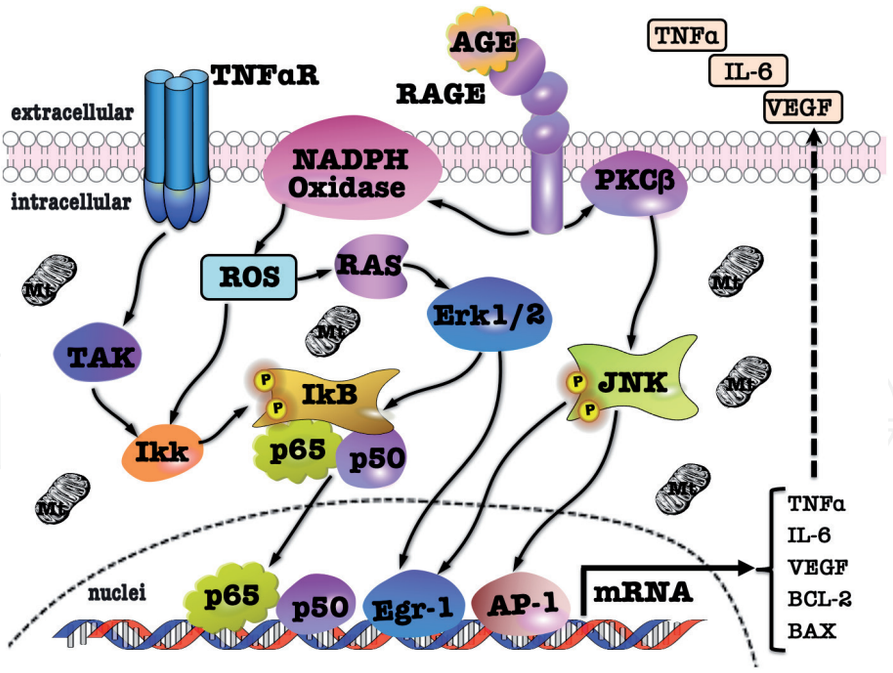

Figure 5.
AGE/RAGE signalling. NADPH oxidase is activated by the binding of AGE to RAGE, and intracellular ROS levels are elevated. Intracellular ROS activates the IκB kinase (IKK) complex and inhibitor of NF-κB (IκB), stimulating the translocation of the NF-κB subunits p65 and p50 and activating transcription. In addition, activation of PKCβ stimulates transcription via activator protein-1 (AP1) in the nucleus by phosphorylation of c-Jun N-terminal kinase (JNK). Enhancement of these inflammatory signals releases inflammatory cytokines, such as TNFα and IL-6, as well as VEGF, which is involved in angiogenesis, and B-cell lymphoma 2 (Bcl-2) and Bcl-2 associated X protein (Bax), which are involved in apoptosis. TNFα, an inflammatory cytokine, is released extracellularly and binds to the TNFα receptor, and activation of TGFβ activated kinase (TAK) reactivates JNK.

(ROS) is promoted [79, 80]. ROS upregulate various inflammatory cytokines, growth factors, and adhesion molecules by activating nuclear factor-kappa B (NF-κB) signalling. In addition, c-Jun N-terminal kinase (JNK), a major subfamily of ROS-activated mitogen-activated protein kinase pathways, has been shown to cause cell apoptosis and dysfunction (**Figure 5**) [81]. In addition to full-length RAGE on the cell surface, RAGE can be expressed as two splice variants, i.e., the intracellular domain-deficient type (C-terminally truncated RAGE) and extracellular V domain-deficient type (N-terminally truncated RAGE) [82]. Of these, the intracellular domain-deficient RAGE is called soluble RAGE (sRAGE). sRAGE can further be divided into endogenous secretory RAGE (esRAGE) and soluble RAGE, which are cleaved by proteases such as matrix metalloproteinases [83]. sRAGE has a binding site for AGEs and is thought to function as a decoy receptor that captures extracellular AGEs and inhibits binding to RAGE on the cell surface, thereby blocking intracellular signals [84]. Blood esRAGE levels are significantly lower in patients with type 2 diabetes than in patients without diabetes, suggesting that this target is involved in the development of type 2 diabetes [85]. Moreover, blood esRAGE levels in patients with type 2 diabetes are inversely correlated with the severity of carotid atherosclerosis and coronary artery disease as complications [86, 87].

5. AGEs and oxidative stress

Intracellular signal transduction of AGEs via RAGE increases intracellular ROS. ROS are oxygen-containing molecular derivatives that are in a more activated state than triplet oxygen, which is a ground-state oxygen molecule necessary for

normal biological activities and is highly reactive, resulting in oxidative damage to various biological components. The main active oxygen species are singlet oxygen, superoxide, hydrogen peroxide, and hydroxyl radicals [88]; these molecules react with biopolymers, such as DNA, lipids, proteins, and enzymes, resulting in lipid peroxidation, DNA mutations, protein denaturation, and enzyme inactivation. Many amino acids are carbonylated and modified by ROS for detection of protein carbonylation using mass spectrometers [89]. Moreover, carbonylation of this protein is caused by addition reaction of aldehydes because of the peroxidation reaction of lipids and saccharification reaction of proteins described above [90, 91]. Highly reactive α-dicarbonyl compounds, such as 3-deoxyglucosone (3-DG), glyceraldehyde, and methylglyoxal, are produced from the Amadori compound generated by saccharification [91]. These AGEs then recombine with RAGE, creating a vicious cycle in which more ROS are generated. Such ROS are considered to have negative effects because overproduction of ROS is closely associated with ageing due to oxidative stress, cancer, and the development of lifestyle-related diseases [91]. However, ROS (e.g., superoxide and hydrogen peroxide) produced by white blood cells play important roles in biological defence and immune function [92]. ROS are also used in a wide range of tissues and cells as bioactive substances for intracellular signal transduction, fertilisation, cell differentiation, and apoptosis [93].

Because glucose is metabolised to obtain energy, the carboxyl group of glucose reacts with the amino group of the protein during the metabolic process to form AGEs in the body nonenzymatically via the Amadori compound. With ageing, these AGEs accumulate in various organs in the body, resulting in oxidative stress, ROS generation, and progression of organ stress. Thus, ageing is related to oxidative stress induced by AGEs. Additionally, AGEs-ised HbA1c levels in the blood have been used as an index for controlling blood glucose levels in clinical practice for patients with diabetes. Kusunoki et al. showed that fasting serum 3-DG levels in patients with diabetes were significantly higher than those in controls. Additionally, serum 3-DG levels tended to be higher in patients with diabetes showing low nerve conduction velocity [94]. In patients with diabetes, AGEs generated from excess glucose circulate throughout the body via the blood and increase oxidative stress in various organs. Therefore, in the hyperglycaemic environment associated with diabetes, oxidative stress due to excess glucose is thought to be significantly involved in the development of diabetic complications.

6. AGEs and diabetic complications

Hyperglycaemia in diabetes mellitus affects many organ systems, including the eyes, kidneys, heart, and peripheral and autonomic nervous systems. They can be broadly divided into microangiopathy, which occurs mainly in the capillaries, and macroangiopathy, which occurs in relatively large blood vessels. Three major complications, i.e., diabetic retinopathy, diabetic nephropathy, and DN, are microangiopathies that occur in patients with diabetes [95]. In contrast, arteriosclerotic diseases, which cause vascular diseases, such as myocardial infarction and cerebral infarction, are considered as macroangiopathies. AGEs are the leading causes of complications caused by microangiopathy and macroangiopathy [96–98].

Diabetic retinopathy causes bleeding and ischaemia in capillaries due to the hyperglycaemic environment, and progression results in bleeding or retinal detachment inside the vitreous body. AGEs are associated with the presence and progression of diabetic retinopathy [99]. Diabetic keratopathy, in which the corneal epithelium is exfoliated due to aggregation of AGEs-ised proteins, is thought to be related to AGE formation via laminin, which is found in the basement membrane

of the corneal epithelium [100]. In human RAGE transgenic mice induced by streptozotocin as an experimental model of diabetes, the blood-retinal barrier was disrupted, and leukostasis was increased [101]. However, systemic administration of sRAGE intraperitoneally suppressed collapse of the blood-retinal barrier and leukostasis [101]. Administration of soluble RAGE, which comprises the extracellular domain of RAGE, enhances AGEs in the blood and blocks the interaction with cell membrane RAGE. As a result, pathological conditions related to diabetic retinopathy, such as increased retinal vascular permeability and adhesion of leukocytes to retinal blood vessels, can be suppressed [101, 102]. Thus, AGE/RAGE signalling plays important roles in the development of diabetic retinopathy.

The kidney is an organ that filters waste products in the blood to produce urine and is formed by the renal glomerulus, which is similar to a mass of capillaries. In patients with diabetes, renal dysfunction can also occur. Chronic kidney disease occurs in approximately 20–40% of patients with diabetes [103]. If renal failure occurs, artificial haemodialysis is required. Diabetic nephropathy is the most common cause of dialysis. In diabetic nephropathy, accumulation of AGEs has been reported in various cells, such as the glomerular basement membrane, mesangium, podocytes, tubular cells, and endothelial cells [104]. In addition, several studies have suggested that RAGE expression is increased in patients with diabetic nephropathy [104, 105]. Administration of AGEs to nondiabetic rats induces proteinuria and degenerative changes in the renal tissue, highlighting the important roles of AGEs in the development of diabetic nephropathy [106]. CML in patients with type 1 diabetes was found to correlate with the severity of nephropathy [107]. Moreover, the levels of CML- and hydroimidazolone-AGEs in the serum of patients with type 2 diabetes are significantly increased [108]. CML-human serum protein levels are higher in patients with proteinuria, and increased levels of circulating AGE peptides are correlated with the severity of renal dysfunction [109]. Studies in RAGE transgenic mice revealed the development of advanced diabetic nephropathy features, such as renal hypertrophy, glomerular hypertrophy, mesangial enlargement, glomerulosclerosis, and proteinuria [110]. In OVE26 mice, a diabetic mouse model that exhibits progressive glomerular sclerosis and decreased renal function, RAGE deficiency alleviates histological and morphological changes and albuminuria associated with diabetic nephropathy and does not result in decreased renal function [111]. Thus, these findings support that RAGE is involved in the development of diabetic nephropathy and as a target molecule in for treating this disease.

DN is a peripheral nerve disorder caused by prolonged hyperglycaemia in diabetes, resulting in numbness, pain, and hypoesthesia of the limbs. In the nervous tissue, hyperglycaemia increases non-insulin-dependent glucose uptake. Excess glucose is thought to cause sorbitol accumulation via the polyol pathway and microangiopathy, which nourishes the nerves. Accumulation of AGEs is observed in perineurial cells, nerve axons, and Schwann cells in the peripheral nerves of patients with diabetes [112]. In Schwann cells, neurofilaments and tubulin, which are important for axonal transport, are converted to AGEs [113]. Overexpression of AGEs and RAGE in the nerves of patients with diabetes activates NF-κB; these changes correlate with hypoesthesia [114]. Therefore, antiglycation agents, such as aminoguanidine, have been promoted as treatments for DN [115]. However, aminoguanidine was shown to have various side effects in a clinical trial of patients with DN, and thus its development was discontinued. Recently, the anti-inflammatory cytokine interleukin-10 has attracted attention because of ability to suppress AGE-induced apoptosis in Schwann cells by reducing oxidative stress through inhibition of NF-κB activation [116]. Thus, the potential use of interleukin-10 for treating DN is also being discussed.

7. AGEs and arteriosclerosis

In addition to the three major complications of diabetes (i.e., diabetic retinopathy, diabetic nephropathy, and DN), if hyperglycaemia continues for a long time, ischaemic heart disease, cerebral infarction, and macroangiopathy (peripheral arterial disease progression) can occur due to arteriosclerosis in large blood vessels, such as the heart and brain. Inflammation in the blood vessel wall is critical for the onset and progression of arteriosclerosis. AGEs produced in a hyperglycaemic environment bind to RAGE in vascular endothelial cells and activate AGE/RAGE signalling. As a result, the expression of inflammatory cytokine genes is enhanced by NF-κB signalling and the phosphorylation of JNK because of the production of ROS by NADPH oxidase, causing inflammation of the blood vessel wall [117]. Recent studies showed that vascular endothelial growth factor is involved in increases in atheroma in atherosclerotic lesions [118]. Moreover, AGEs induce angiogenesis by promoting the production of vascular endothelial growth factor autocrine signalling in endothelial cells, enhancing inflammation in blood vessels, and increasing atheroma [117]. Excess sRAGE has been reported to inhibit AGE/RAGE signalling and suppress the onset and progression of arteriosclerosis [119–121]. Furthermore, AGEs have been detected in cultures of mouse or human aortic endothelial cells in a hypoxic state, suggesting that RAGE signalling is activated by hypoxia in aortic endothelial cells [122]. Early growth response-1 expression under hypoxic conditions, PKC translocation, and JNK phosphorylation are inhibited by sRAGE or anti-AGE antibodies, and *RAGE* is downregulated by aminoguanidine and siRNA.

8. AGEs and intrauterine hyperglycaemia

In pregnant women or those with gestational diabetes during pregnancy, hyperglycaemia can create a hyperglycaemic environment in the uterus through the placenta. However, few studies have evaluated the molecular mechanisms by which the intrauterine hyperglycaemic environment affects foetal development and future illnesses in offspring. One study evaluated the hearts of infants born from diabetic pregnancy model rats with hyperglycaemia during pregnancy [123]. Additionally, a gestational diabetes rat model was created by administration of streptozotocin via the tail vein immediately after pregnancy. Akt-related insulin signalling was abnormal in the hearts of offspring born to mothers of these gestational diabetes model rats [124]. We investigated the expression of the insulin signalling system, ROS, AGEs, and related genes in the hearts of infants and in primary myocardial cultured cells (cardiomyocytes) isolated from the heart [125]. In primary cardiomyocytes isolated from the hearts of infants born to mothers with diabetes, insulin stimulation inhibited the translocation of GLUT4 to the cell membrane, indicating that insulin resistance was induced. Moreover, various proteins were excessively AGE-ised in the hearts and cardiomyocytes of offspring born from diabetic mother rats [125]. Intracellular ROS levels and *NF-κB*, tumour necrosis factor (*TNF*α), and *IL-6* gene expression levels in isolated cardiomyocytes were significantly increased compared with those in offspring of normal mother rats [125]. Thus, in offspring who spent the foetal period in an intrauterine hyperglycaemic environment, maternal hyperglycaemia may have caused abnormal insulin signalling due to the chronic inflammation induced by intracellular ROS and excessive AGE formation, thereby leading to cardiac hypertrophy [125]. Interestingly, daily oral administration of the n-3 unsaturated fatty acid eicosapentaenoic acid by gastric sonde to mother rats ameliorated this abnormal signal transduction in the

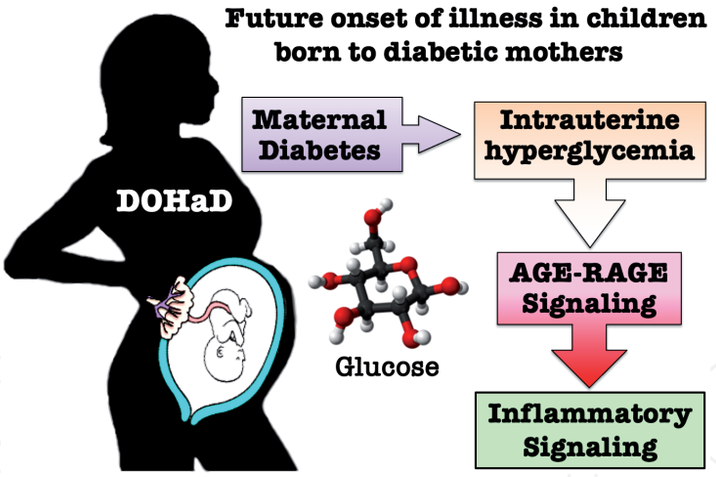

Figure 6.
The risk of future illness in children born to diabetic mothers. In diabetic mothers, maternal hyperglycaemia creates a hyperglycaemic environment in the womb through the placenta. During this time, the foetus is exposed to hyperglycaemia, and excessive hyperglycaemia activates AGE/RAGE signalling. This can cause the foetus to be exposed to an inflammatory cytokine storm. In addition, many proteins and enzymes are denatured by oxidative stress, which can also affect foetal development, and these effects may lead to the onset of disease after birth. Therefore, glycaemic control during pregnancy is critical.

heart. Based on these findings, the intrauterine hyperglycaemic environment of pregnant women may have major effects on various organs other than the heart in children through oxidative stress caused by excessive AGEs, including AGE/RAGE signalling. In addition, the intrauterine hyperglycaemic environment may affect offspring through epigenetics [125, 126].

The concept that malnutrition in the womb may affect the future development of lifestyle-related diseases in children was first proposed by David Barker of Southampton University in the 1980s [127]. Barker and colleagues used birth weight as an indicator of foetal nutrition and examined its association with various causes of death; their results showed that children born with a low birth weight were at high risk of dying from heart disease in the future [128]. Birth cohort studies have reported a series of epidemiological studies supporting the theory of adult disease foetal onset, including the fact that foetuses exposed to malnutrition may develop lifestyle-related diseases in adulthood [129] by inducing an adaptive response that predicts the future environment by regulating gene expression [130]. Peter Gluckman, Mark Hanson, and others further developed this theory of adult disease foetal onset into a generalised theory on the developmental origins of health and disease [131]. However, in modern society, eating habits have changed dramatically, and overnutrition, including obesity and diabetes, has become a challenge. Importantly, oxidative stress caused by exposure to the maternal hyperglycaemic environment may also have major effects on the future onset of illness in offspring (**Figure 6**).

9. Development of therapeutic agents targeting the AGEs-RAGE system

As described above, in a hyperglycaemic environment, oxidative stress induced by AGEs and RAGE can induce the onset and progression of various diabetic complications; hence targeting the AGEs-RAGE system, using AGEs formation inhibitors, AGEs degrading agents, AGEs-RAGE inhibitors and signal transduction inhibitors, may be an effective treatment strategy.

The first reported AGEs formation inhibitors are aminoguanidine and OPB-9195 (2-isopropylidenehydrazono-4-oxo-thiazolidine-5-ylacetanilide) which can capture

reactive carbonyl compounds such as methylglyoxal and 3-DG and inactivate metal ions that catalyse radical formation such as chelating agents [132–134]. OPB-9195 has a stronger AGEs formation inhibitory activity than aminoguanidine [135], however, these compounds are associated with side effects such as vitamin B6 deficiency due to the capture of pyridoxal phosphate, anaemia, and liver damage, therefore, their clinical application has been discontinued. LR-90 (methylene bis [4,4-(2 chlorophenylureido phenoxyisobutyric acid)]) and ALT946 (N-(2-acetamidoethyl) hydrozinecarboximidamide hydrochlolide) are more potent AGEs inhibitors than aminoguanidine and OPB-9195 [136, 137], and are associated with fewer side effects; in particular, ALT946 has no NO synthase inhibitory activity, which is a side effect of aminoguanidine [137].

Pyridoxamine, a vitamin B6, has been reported to have renal damage-suppressing effects as well as carbonyl compound capturing and antioxidant effects [138–140]. Benfophothiamine, a vitamin B1 derivative, has various effects such as inhibiting AGEs formation, suppressing PKC activity and oxidative stress, activating transketolase, and inhibiting the polyol pathway [141]. Furthermore, sorbinin inhibits AGEs formation by blocking the polyol pathway [41, 42]. The renal protective effect of the renin-angiotensin system targeting drugs is attributed to the inhibition of pentosidine production [142]. The oral hypoglycaemic agent metformin inhibits AGEs formation via carbonyl compound capturing, metal chelate formation, and antioxidant activity [143].

N-phenacylthiazolium bromide (PTB) can cleave protein cross-linked by AGEs [144]. PTB water solubility increases when it is in the form of 3-phenacyl-4,5-dimethylthiazorium chloride (ALT-711). ALT-711 has been reported to suppress the accumulation of AGEs and improve vascular hardening and systolic blood pressure [145]. PTB and ALT-711 are therefore referred to as AGEs breaker agents. Certain plant extracts have been reported to exhibit this anti-AGEs effect. For example, terpinen-4-ol of citron (*Citrus junos*) has also been reported to decompose AGEs [146]. In addition, RAGE antagonists that block the interaction between AGEs and RAGE have been extensively studied [147].

Drugs targeting the AGEs-RAGE system primarily include AGEs formation inhibitors, AGEs breakers, and AGEs-RAGE signal inhibitors, which are investigated in non-clinical studies. Presently, the agents used for targeting AGEs-RAGE system in clinical settings include aldose reductase inhibitors, renin-angiotensin-based active drugs, and metformin. The reason behind using such diverse drugs and difficulty in discovering a specific drug is attributed to the structural diversity of AGEs, the multi-ligand receptor characteristics of RAGE, and the limited underdamping of the condition in which oxidative stress is generated in cells. However, oxidative stress induced by AGEs in a hyperglycaemic environment significantly influences the onset and progression of several lifestyle-related diseases. Therefore, advance translational research is essential to tackle challenges that basic research cannot.

10. Conclusions

As discussed in this chapter, glycation is a random, nonenzymatic reaction that differs significantly from enzymatically catalysed glycosylation. AGEs formed by saccharification consist of a wide variety of molecular species, many of which have not been structurally characterised, and these species vary from harmful to harmless. Oxidative stress, including ROS, is induced by AGEs during normal metabolism but is mitigated physiologically by antioxidant enzymes in the body. However, in a hyperglycaemic environment, as is typically observed in patients with diabetes,

oxidative stress that cannot be removed via the antioxidant system of the body causes various diabetic complications such as organ stress. As the population of patients with diabetes continues to increase, the number of pregnant women with diabetes is also increasing due to late marriage and an older age of primigravida. Research results have strongly supported that the maternal hyperglycaemic state creates an intrauterine hyperglycaemic environment through the placenta that is involved in the development of various diseases in the offspring. Further studies are needed to clarify the molecular mechanism involved in oxidative stress and disease caused by glycation and to link these mechanisms with the diagnosis and prevention of lifestyle-related diseases.

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Conflict of interest

The authors declare no conflicts of interest.

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