World Journal of Hepatology

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DOI: 10.4254/wjh.v6.i12.880

World J Hepatol 2014 December 27; 6(12): 880-893
ISSN 1948-5182 (online)

TOPIC HIGHLIGHT

WJH 6th Anniversary Special Issues (7): Non-alcoholic fatty liver disease

Involvement of the TAGE-RAGE system in non-alcoholic steatohepatitis: Novel treatment strategies

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Supported by The Japan Society for the Promotion of Science (JSPS) KAKENHI Grant, No. 19300254, 22300264 and 25282029 (Takeuchi M); Kanazawa Medical University, No. SR2012-04 (Tsutsumi M); the Ministry of Education, Culture, Sports, Science, and Technology (MEXT), Regional Innovation Strategy Support Program (Takeuchi M)
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Received: August 12, 2014 Revised: October 22, 2014
Accepted: October 28, 2014
Published online: December 27, 2014

Abstract

Non-alcoholic fatty liver disease (NAFLD) is a major cause of liver disease around the world. It includes a spectrum of conditions from simple steatosis to non-alcoholic steatohepatitis (NASH) and can lead to fibrosis, cirrhosis, liver failure, and/or hepatocellular carcinoma. NAFLD is also associated with other medical conditions such as obesity, diabetes mellitus (DM), metabolic syndrome, hypertension, insulin resistance, hyperlipidemia, and cardiovascular disease (CVD). In diabetes, chronic hyperglycemia contributes to the development of both macro- and microvascular conditions through a variety of metabolic pathways. Thus, it can cause a variety of metabolic and hemodynamic conditions, including upregulated advanced glycation end-products (AGEs) synthesis. In our previous study, the most abundant type of toxic AGEs (TAGE); *i.e.*, glyceraldehyde-derived AGEs, were found to make a significant contribution to the pathogenesis of DM-induced angiopathy. Furthermore, accumulating evidence suggests that the binding of TAGE with their receptor (RAGE) induces oxidative damage, promotes inflammation, and causes changes in intracellular signaling and the expression levels of certain genes in various cell populations including hepatocytes and hepatic stellate cells. All of these effects could facilitate the pathogenesis of hypertension, cancer, diabetic vascular complications, CVD, dementia, and NASH. Thus, inhibiting TAGE synthesis, preventing TAGE from binding to RAGE, and downregulating RAGE expression and/or the expression of associated effector molecules all have potential as therapeutic strategies against NASH. Here, we examine the contributions of RAGE and TAGE to various conditions and novel treatments that target them in order to prevent the development and/or progression of NASH.

Key words: Non-alcoholic fatty liver disease; Non-alcoholic steatohepatitis; Advanced glycation end-products; Toxic advanced glycation end-products; Receptor for advanced glycation end-products; Toxic advanced glycation end-products-receptor for advanced glycation end-products system; Diabetes mellitus; Cardiovascular disease; Dietary fructose; Dietary advanced glycation end-products

Core tip: Toxic advanced glycation end-products (TAGE) synthesis is increased by non-alcoholic steatohepatitis (NASH), and patients with NASH exhibit significantly increased serum and hepatic TAGE concentrations. Interactions between TAGE and the receptor for advanced glycation end-products (RAGE) have been suggested to cause oxidative stress and increase the fibrogenic potential of cultured human hepatic stellate cells. Therefore, TAGE signaling *via* RAGE and the resultant synthesis of reactive oxygen species might play a role in the worsening of hepatic pathology seen in NASH. These observations led us to suggest that extracellular and intracellular TAGE are involved in the pathogenesis of NASH.

Takeuchi M, Takino J, Sakasai-Sakai A, Takata T, Ueda T, Tsutsumi M, Hyogo H, Yamagishi S. Involvement of the TAGE-RAGE system in non-alcoholic steatohepatitis: Novel treatment strategies. *World J Hepatol* 2014; 6(12): 880-893 Available from: URL: http://www.wjgnet.com/1948-5182/full/v6/i12/880.htm DOI: http://dx.doi.org/10.4254/wjh.v6.i12.880

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a major cause of chronic liver disease in developed countries, and hence, is becoming a global public health issue[1]. NAFLD includes a range of conditions, from simple steatosis to non-alcoholic steatohepatitis (NASH)[2-4]. NASH has the potential to progress, which can result in cirrhosis, liver failure, and/or hepatocellular carcinoma[2-4]. NAFLD is regarded as a hepatic symptom of metabolic syndrome (MetS) and is associated with visceral obesity, abnormalities in glucose and lipid metabolism, insulin resistance (IR), and hypertension[5-7]. In NAFLD patients, underlying metabolic conditions such as those described above result in worsening liver dysfunction and a higher incidence of liver fibrosis and are also involved in the development of cardiovascular disease (CVD)[8,9].

Advanced glycation end-products (AGEs) might be involved in the mechanism that links NASH and diabetes mellitus (DM). Accumulating evidence indicates that in diabetic patients chronic hyperglycemia upregulates the production of AGEs (senescent macroprotein derivatives) *via* non-enzymatic glycation (the Maillard reaction). It has been demonstrated that the binding of AGEs to their receptor (RAGE) induces oxidative stress followed by inflammatory and/or thrombogenic responses in a variety of cell types. Furthermore, in diabetes such binding is considered to be involved in the pathogenesis and worsening of angiopathic conditions[10-16]. In our previous study, the most abundant type of toxic AGEs (TAGE); *i.e.*, glyceraldehyde-derived AGEs (Glycer-AGEs), were found to make a significant contribution to the development of angiopathic conditions in DM[17-20]. In addition, there is a growing consensus that TAGE-RAGE interactions affect gene expression, intracellular signaling, and the secretion of pro-inflammatory factors and induce reactive oxygen species (ROS) production in various cell types including hepatic stellate cells (HSC) and hepatocytes[21,22]. Thus, TAGE-RAGE interactions might play a role in the pathological changes associated with lifestyle-related diseases, particularly NASH. TAGE synthesis is increased in NASH, and NASH patients were found to exhibit significantly higher hepatic and serum TAGE concentrations than individuals with simple steatosis or healthy controls[23]. TAGE-RAGE interactions have also been found to be associated with the induction of oxidative stress and increases in the fibrogenic potential of cultured human HSC[22]. Therefore, it is suggested that TAGE signaling through RAGE and the subsequent ROS production play a role in the worsening of hepatic pathology observed in NASH.

Accordingly, inhibiting the binding of TAGE to RAGE and TAGE synthesis and downregulating RAGE expression and/or the expression of its effectors have potential as treatment strategies for NASH. Here, we examine the contributions of RAGE and TAGE to various conditions and novel treatments that target these molecules in order to prevent the development and/or progression of NASH.

AGEs

The Maillard reaction, in which the N-terminal α-amino or ε-amino regions of protein lysine residues react non-enzymatically with the ketone or aldehyde moieties of reducing sugars, *e.g.*, fructose, glucose, *etc.*, is responsible for synthesizing AGEs. AGEs are known to be involved in protein aging and the pathological complications associated with DM[10-13,17-20,24-27]. In hyperglycemic DM patients, the first step in this process involves the conversion of reversible Schiff base adducts to more stable covalently bound Amadori rearrangement products, which subsequently undergo further rearrangement to produce irreversibly bound moieties (AGEs), and this process can range in duration from days to weeks.

Initially, AGEs were identified based on their fluorescent yellow-brown appearance and their ability to produce cross-links with and between amino groups. However, the term AGEs now refers to numerous products associated with the advanced stages of the glycation process, including *N*-(carboxyethyl)lysine, *N*-(carboxymethyl)lysine (CML), and pyrraline, which are colorless and can not form cross-links with proteins[24-29]. *In vivo* AGE production is affected by the sugar concentration, the rate of turnover of the chemically modified target, and the time available. Increases in the glucose concentration were previously considered to have a major influence on the Maillard reaction; however, glucose is one of the least reactive sugars found in biological organisms[24,30]. As well as extracellular AGE synthesis, the rapid intracellular production of AGEs from intracellular precursors such as trioses, dicarbonyl compounds, and

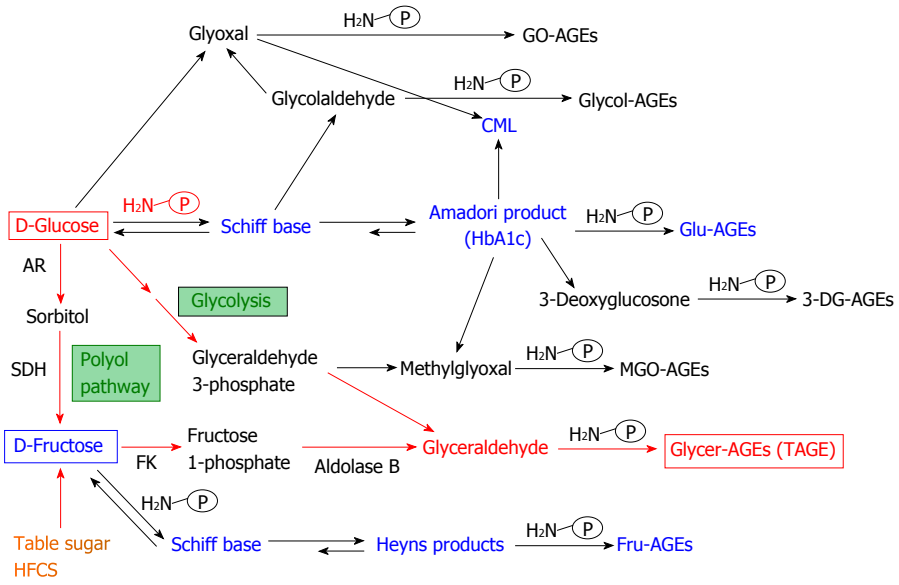

Figure 1 Alternative *in vivo* advanced glycation end-product synthesis routes. Reducing sugars, such as glucose, fructose and glyceraldehyde, are known to react non-enzymatically with the amino groups of proteins to form reversible Schiff bases and Amadori product/Heyns products. These early glycation products undergo further complex reactions such as rearrangement, dehydration, and condensation to become irreversibly cross-linked, heterogeneous fluorescent derivatives termed advanced glycation end-products (AGEs). Glu-AGEs: Glucose-derived AGEs; Fru-AGEs: Fructose-derived AGEs; Glycer-AGEs: Glyceraldehyde-derived AGEs; Glycol-AGEs: Glycolaldehyde-derived AGEs; MGO-AGEs: Methylglyoxal-derived AGEs; GO-AGEs: Glyoxal-derived AGEs; 3-DG-AGEs: 3-deoxyglucosone-derived AGEs; CML: N-(carboxymethyl)lysine; P-NH_2: A free amino residue; HbA1c: Hemoglobin A1c; TAGE: Toxic AGEs; HFCS: High-fructose corn syrup; AR: Aldose reductase; SDH: Sorbitol dehydrogenase; FK: Fructokinase.

fructose has been gaining attention[31,32]. Due to the great degree of variation in the structures of the AGEs found *in vivo* and the complex nature of the reactions required for their synthesis, only some AGEs have had their structures identified[33]. Furthermore, even the structures of cytotoxic AGEs are yet to be elucidated.

In a previous study, we found that α-hydroxyaldehydes (glycolaldehyde and glyceraldehyde), fructose, glucose, and dicarbonyl compounds (glyoxal and methylglyoxal, 3-deoxyglucosone) all contribute to protein glycation[27,34-37]. A total of 7 immunochemically distinct AGEs classes [methylglyoxal-derived AGEs; Glycer-AGEs; fructose-derived AGEs; glucose-derived AGEs (Glu-AGEs); 3-deoxyglucosone-derived AGEs; glyoxal-derived AGEs; and glycolaldehyde-derived AGEs] were found in serum samples collected from hemodialysis patients with type 2 DM (T2DM)[27,34-37]. Accordingly, we suggested that the *in vivo* formation of AGEs occurs *via* a process involving the Maillard reaction, sugar autoxidation, and sugar metabolism pathways (Figure 1).

PATHWAY FOR THE *IN VIVO* SYNTHESIS OF GLYCER-AGEs

In vivo, two different pathways are responsible for glyceraldehyde (GLA) production, (1) the fructose metabolic pathway (fructolysis) and (2) the glycolytic pathway (glycolysis)[18-20,38]. In pathway (1) under hyperglycemic conditions a rise in the intracellular glucose concentration stimulates the production of fructose *via* the polyol pathway in insulin-independent tissues, such as nerve tissue, the kidneys, the lens of the eye, red blood cells, and the brain[39-42]. In addition, fructose is a constituent of sucrose and high-fructose corn syrup (HFCS), and hence, is included in many people's diets[43,44]. Fructokinase phosphorylates fructose to fructose 1-phosphate, which is then broken down into dihydroxyacetone phosphate and GLA by aldolase B[45,46]. Next, the resultant GLA is transported (or leaks passively) across the cell membrane. GLA induces TAGE synthesis in the both intracellular and extracellular compartments; as for pathway (2) the enzyme glyceraldehyde 3-phosphate (G3P) dehydrogenase (GAPDH) usually breaks down the glycolytic intermediate G3P. However, reductions in GAPDH activity lead to the intracellular accumulation of G3P. As a result, G3P metabolism starts to occur *via* an alternative pathway, leading to a rise in the concentration of GLA, which promotes the synthesis of Glycer-AGEs, a major form of TAGE. This indicates that a positive feedback mechanism is in operation; namely, that the inhibition of GAPDH activity by TAGE promotes TAGE synthesis (Figure 2).

DIETARY FRUCTOSE

It is suspected that fructose is at least partially responsible for the obesity epidemic affecting developed countries. The greater prevalence of fructose in people's diets results in greater glucose flux and elevated fructose metabolism in hepatocytes. Fructose used to be considered to be a beneficial dietary substance due to the fact it does not stimulate insulin secretion; however, as insulin signaling plays a key role in the development of NAFLD, this property of fructose might be undesir-

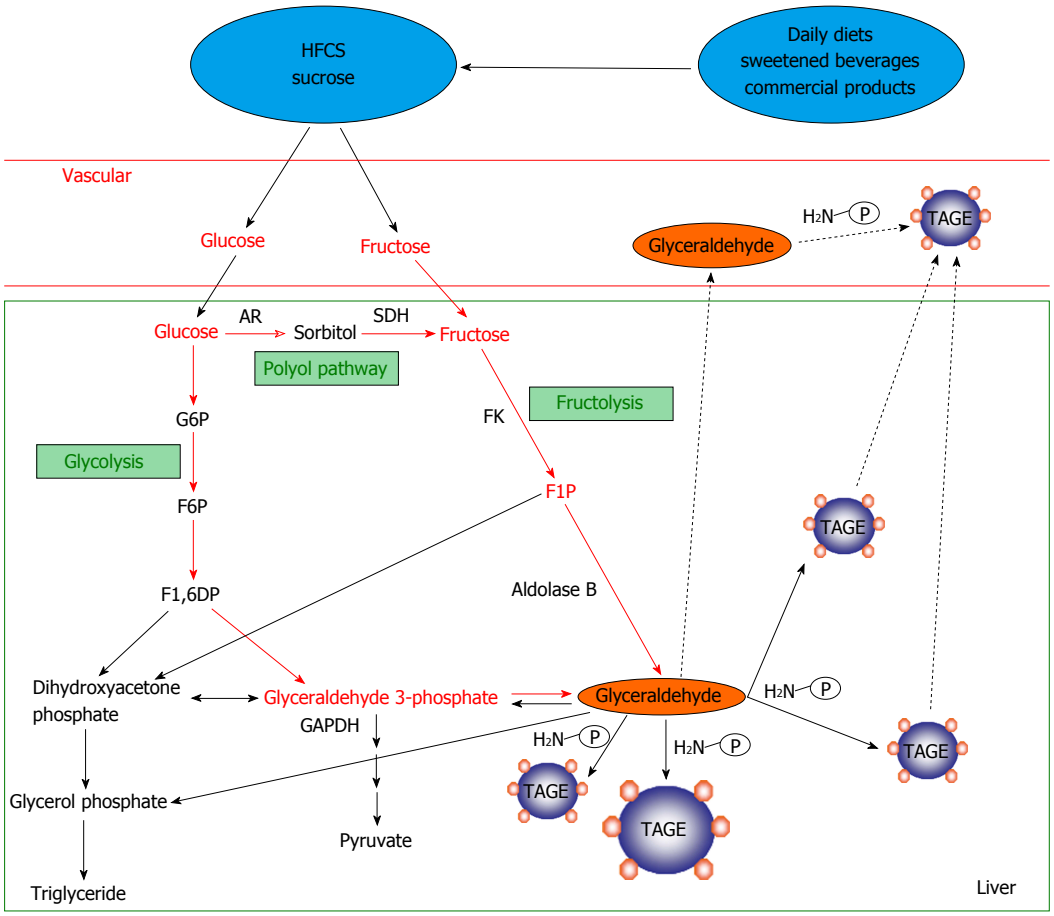

Figure 2 Routes for *in vivo* glyceraldehyde-derived advanced glycation end-products synthesis. The glycolytic intermediate glyceraldehyde 3-phosphate (G3P) is usually catabolized (glycolysis) by the enzyme glyceraldehyde 3-phosphate dehydrogenase (GAPDH). However, reductions in GAPDH activity lead to the intracellular accumulation of G3P. As a result, G3P metabolism starts to occur *via* an alternative pathway, leading to a rise in the concentration of glyceraldehyde, which promotes the synthesis of TAGE. Fructokinase phosphorylates fructose to fructose 1-phosphate, which is then broken down into dihydroxyacetone phosphate and glyceraldehyde by aldolase B (fructolysis). The resultant glyceraldehyde is transported (or leaks passively) across the cell membrane. Glyceraldehyde promotes the formation of TAGE both intracellularly and extracellularly. AGEs: Advanced glycation end-products; TAGE: Toxic AGEs (glyceraldehyde-derived AGEs); HFCS: High-fructose corn syrup; AR: Aldose reductase; SDH: Sorbitol dehydrogenase; FK: Fructokinase; G6P: Glucose 6-phosphate; F6P: Fructose 6-phosphate; F1,6DP: Fructose 1,6-diphosphate; F1P: Fructose 1-phosphate; P-NH2: Free amino residue.

able[47-49]. In adolescents, increased fructose consumption is linked with various CVD risk factors. However, visceral obesity might be responsible for these associations. In the United States, fructose consumption is considered to be associated with the recent rise in the prevalence rates of obesity, fatty liver, and T2DM. The liver is extremely sensitive to variations in dietary content and plays the primary role in the metabolism of simple sugars, such as fructose and glucose[47,48].

The number of calories an individual consumes each day can have a significant influence on their risk of developing NAFLD because excessive energy intake results in obesity, leading to a greater risk of NAFLD. However, the development and progression of NAFLD are also affected by dietary composition. Of all carbohydrates, fructose plays an especially important role in NAFLD progression[50-53]. For example, it has been suggested that fructose consumption is associated with hepatic fat accumulation, fibrosis, and inflammation[54]. The accumulation of visceral adipose tissue and higher plasma triglyceride concentrations have also been linked with fructose consumption[55,56]. Thus, fructose has an important influence on the development of fatty liver disease[57].

Particular dietary sugars (especially fructose) are considered to play a role in the development and progression of NAFLD. The sugar additives (usually HFCS or sucrose) found in beverages and processed foods are widely viewed as the main source of the increased amounts of fructose consumed in developed countries. Dyslipidemia, obesity, and IR have all demonstrated strong associations with greater fructose consumption, and evidence indicating that fructose is involved in the development and progression of NAFLD is accumulating. Human studies have linked fructose consumption to hepatic fat accumulation, fibrosis, and inflammation. At present, it is unclear whether fructose can cause NAFLD on its own or whether it only promotes the condition when consumed in excessive amounts by individuals with a sedentary lifestyle, IR, and/or a positive energy balance. However, there is enough evidence to support a recommendation that the consumption of foods and drinks that are high in added fructose-containing sugars should

be limited[54,58].

Although we need to increase our knowledge regarding the influence of fructose on NAFLD, the links between excessive fructose consumption and hypertriglyceridemia, IR, and the accumulation of visceral adipose tissue are sufficiently clear to support a clinical recommendation that NAFLD patients decrease the amount of fructose in their diets.

AGE RECEPTORS

A variety of signaling pathways are activated by AGE synthesis *via* a series of cell surface receptors. Among AGE receptors, the multi-ligand receptor RAGE has been studied most extensively[59-63]. In addition, various other AGE receptors such as AGE-receptor complexes (AGE-R1/OST-48, AGE-R2/80K-H, and AGE-R3/galectin-3)[64,65] and certain members of the scavenger receptor family (SR-A[66], SR-B:CD36[67,68], SR-BI[69], SR-E: LOX-1[70], FEEL-1, and FEEL-2[71]) have been reported. It was reported that the expression of these AGE receptors varies between different types of cells or tissues and is influenced by metabolic changes, *e.g.*, changes associated with hyperlipidemia, DM, or aging[72]. *In vivo* and *in vitro* experiments examining the mechanisms responsible for the effects of AGEs and the factors that regulate their actions, *e.g.*, soluble RAGE (sRAGE), it was suggested that these molecules have significant pathobiological effects[63,73]. A variety of different cell types, such as neurons, hepatocytes, endothelial cells (EC), HSC, microglia, and pericytes, express RAGE[59-61].

In recent *in vitro* and *in vivo* studies, we found that protein amino moieties readily react with GLA to produce TAGE[18-20]. Furthermore, TAGE induce vascular inflammation and ROS production, and hence, promote the development of atherosclerosis in DM[74,75]. As TAGE display the greatest affinity for RAGE[74,75] and the binding of TAGE to RAGE adversely affects the vasculature of diabetic patients[18-20], TAGE might contribute to the greater CVD incidence rates seen in DM patients and impaired glucose tolerance (IGT) patients that display postprandial hyperglycemia. Furthermore, we have recently reported that in DM patients TAGE make significant contributions to the pathogenesis of angiopathy[19,20]. Accumulating evidence indicates that TAGE-RAGE interactions induce oxidative stress in various cell types, such as HSC and hepatocytes.

THE TAGE-RAGE SYSTEM IS INVOLVED IN LIVER DISEASE

As for the effects of TAGE on hepatocytes, we demonstrated that in Hep3B cells, a human hepatocellular carcinoma cell line, TAGE-RAGE interactions upregulated the hepatic production of C-reactive protein (CRP) by activating Rac-1[76]. The latter study indicated that at least two CRP expression-inducing signaling pathways are in operation in TAGE-treated Hep3B cells: the nuclear factor kappa B (NF-κB)-Rac-1-induced signal transducer and activator of transcription 3-dependent pathway, which is not directly affected by ROS, and an NADPH oxidase-mediated ROS-dependent pathway involving Rac-1[76]. During the induction of CRP expression by TAGE, the early stages of the process might be ROS-independent, whereas the latter stages might involve a ROS-mediated pathway. In Hep3B cells, the phosphorylation of insulin receptor substrate-1 (IRS-1) at its serine-307 residue and of c-Jun N-terminal kinase (JNK), c-JUN, and IκB kinase were promoted by TAGE. The increased phosphorylation of IκB kinase was associated with reductions in the concentration of IκB[77]. These effects of TAGE on Hep3B cells were abrogated by the overexpression of the dominant negative form of Rac-1. Treatment with curcumin, an inhibitor of NF-κB, or a JNK inhibitor decreased the phosphorylation of IRS-1 at its serine-307 residue in Hep3B cells. In addition, TAGE downregulated the tyrosine phosphorylation of IRS-1, weakened the affinity of the p85 subunit of phosphatidylinositol 3-kinase for IRS-1, and decreased glycogen synthesis in insulin-treated Hep3B cells. All of these effects were abrogated by treatment with NF-κB or JNK inhibitors[77]. Taken together, these results suggest that TAGE activate Rac-1, leading to the induction of the JNK- and IκB kinase-dependent serine phosphorylation of IRS-1, which in turn contributes to hepatic IR.

As the main producers of extracellular matrix molecules in the liver, HSC are important contributors to liver fibrogenesis[78]. In a previous study, we found that TAGE promoted the expression of genes and proteins associated with fibrogenesis or inflammation, *e.g.*, collagen type Iα2, monocyte chemoattractant protein-1 (MCP-1), and transforming growth factor-β1, in cultured HSC *via* NADPH oxidase-dependent ROS generation[22]. These results increase our knowledge of the role played by TAGE in the pathogenesis of NASH.

INTRACELLULAR TAGE ARE INVOLVED IN LIVER DAMAGE

GLA is a precursor of TAGE. Two GLA-forming pathways are considered to be in operation in the liver: (1) the glycolytic pathway and (2) the fructose metabolic pathway[18-20,38]. As a result, the liver tends to accumulate GLA to a greater extent than other organs.

Abnormalities in fructose and glucose metabolism can result in elevated intracellular GLA levels, which in turn can lead to upregulated intracellular TAGE synthesis, and such processes might play a role in the development of NASH. We found that in Hep3B cells GLA caused the intracellular TAGE concentration to rise and induced apoptosis in a concentration- and time-dependent manner[79]. Conversely, intracellular TAGE production was downregulated and GLA-induced apoptotic cell death was prevented by the addition of aminoguanidine, which inhibits AGE synthesis. Hepatocyte apoptosis was reported to be a characteristic of NASH in previous studies[80,81].

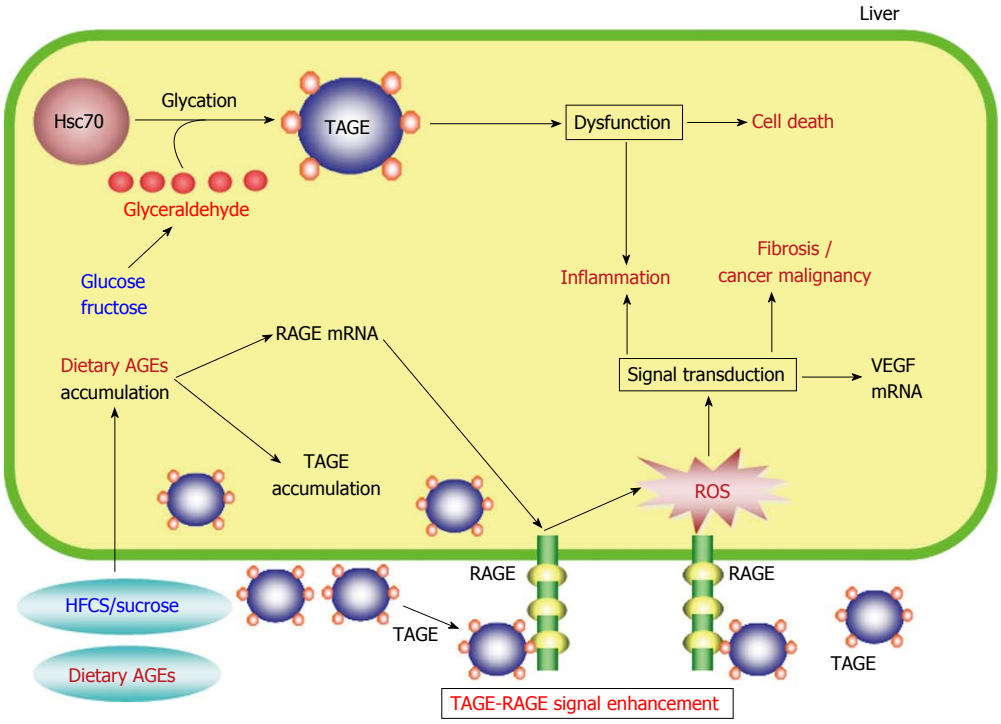

Figure 3 Proposed model for toxic advanced glycation end-products-mediated responses in the liver. HFCS/sucrose and dietary AGEs, which are normally found in sweetened beverages and commercial food products, are taken into the body, where they enhance the production/accumulation of TAGE, upregulate RAGE mRNA expression, and increase serum TAGE concentrations, leading to TAGE-RAGE interactions. The interaction between TAGE and RAGE alters intracellular signaling, gene expression, and the release of pro-inflammatory molecules and also induces oxidative stress in hepatocytes and hepatic stellate cells, which might contribute to the pathological changes observed in NAFLD/NASH. The formation of intracellular TAGE is associated with protein dysfunction followed by inflammation and cell death. Extracellular TAGE induce inflammation and fibrosis/cancer malignancy *via* RAGE signaling. AGEs: Advanced glycation end-products; TAGE: Toxic AGEs; RAGE: Receptor for AGEs; Hsc70: Heat shock cognate 70; ROS: Reactive oxygen species; VEGF: Vascular endothelial growth factor; HFCS: High-fructose corn syrup; NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis.

We identified a TAGE-modified protein (approximately 70 kDa) that was initially observed and tended to accumulate in GLA-treated hepatocytes as heat shock cognate 70 (Hsc70)[79]. Hsc70 might be important for GLA-induced cytotoxicity, as TAGE modifications have been demonstrated to have deleterious effects on protein function[82,83]. Furthermore, we found that the mRNA expression level of the acute phase reactant CRP was upregulated by intracellular TAGE[79]. Recently, it was demonstrated that NASH patients have higher plasma high-sensitivity CRP (hs-CRP) concentrations than healthy subjects or patients with simple steatosis[84,85]. Interestingly, in NASH patients a strong correlation was detected between the plasma hs-CRP concentration and the severity of liver damage[84,85]. In addition, intracellular TAGE were reported to induce inflammation, which is a characteristic of NASH. Taken together, these results indicate that intracellular TAGE make a significant contribution to the pathogenesis of NASH and might have potential as targets of treatments for NASH (Figure 3).

SERUM TAGE CONCENTRATIONS AND LIVER DISEASE

We measured the serum concentrations of three AGEs (Glu-AGEs, CML, and TAGE) in 66 patients with histologically defined-NASH who were free from liver cirrhosis, 10 patients with simple steatosis, and 30 control subjects to examine whether evaluating circulating AGE concentrations is useful for differentiating between NASH and simple steatosis[23]. The results of the latter study suggested that serum TAGE concentrations are involved in the pathogenesis of NASH and might be useful as biomarkers for differentiating between NASH and simple steatosis as: (1) The NASH patients exhibited significantly increased serum TAGE concentrations compared with the patients with simple steatosis and the healthy controls. According to receiver operating characteristic curves of the subjects' circulating TAGE concentrations, the optimal cut-off value for predicting NASH was 8.53 units/mL, which resulted in sensitivity and specificity values of 66.7% and 88.9%, respectively; (2) The subjects' homeostatic model assessment of insulin resistance (HOMA-IR) values and serum adiponectin concentrations (adiponectin is synthesized by adipose tissue and is an anti-inflammatory adipokine that can increase insulin sensitivity) exhibited positive and inverse correlations with their serum TAGE concentrations, respectively; (3) The subjects' serum TAGE concentrations were not correlated with the severity of their hepatic steatosis or fibrosis, nor were they influenced by the subjects' glucose tolerance status. The serum TAGE concentrations of the normal and IGT patients did not differ; (4) The NASH patients' hepatocytes contained TAGE,

whereas those belonging to the patients with simple steatosis exhibited negligible TAGE concentrations; and (5) The subjects' Glu-AGE and CML concentrations did not differ among the groups[23]. The above results indicate that serum TAGE concentrations are useful biomarkers for assessing residual liver function.

PUTATIVE MOLECULAR MECHANISMS RESPONSIBLE FOR THE ASSOCIATION BETWEEN NAFLD AND CARDIOVASCULAR DISEASE

Endothelial progenitor cells (EPC) help to maintain the structure and function of the endothelium, and hence, facilitate angiogenesis and vascular repair. In addition, the number of circulating EPC and their activity levels were found to be inversely correlated with atherosclerotic risk factors. Thus, the number and activity levels of EPC might be useful biomarkers for predicting cardiovascular events. In a recent study, Chiang *et al*[86] demonstrated that compared with the controls NAFLD patients had significantly fewer circulating EPC and the function of their EPC was impaired. Thus, in NAFLD patients reductions in the number of EPC or their activity might increase the likelihood of cardiovascular events.

In recent studies, we found that: (1) the serum concentration of TAGE, but not CML, was independently associated with HOMA-IR in non-diabetic subjects[87]; (2) in T2DM patients, the serum TAGE concentration, but not those of Glu-AGEs or hemoglobin A1c (HbA1c), can be used as a biomarker of cumulative postprandial hyperglycemia[88]; (3) the serum concentration of TAGE, but not those of HbA1c or CML, was demonstrated to be an independent predictor of vascular inflammation (as evaluated by [^{18}F] fluorodeoxyglucose-positron emission tomography in outpatients who visited Kurume University Hospital)[89]; (4) in healthy subjects, the serum TAGE concentration was found to be independently associated with a reduction in the number of circulating EPC and the impairment of the migratory activity of EPC[90]; and (5) a Japanese trial assessing the utility of pitavastatin and atorvastatin as treatments for acute coronary syndrome reported that high baseline TAGE concentrations were associated with plaque progression[91]. These results suggested that the serum TAGE concentration, but not those of HbA1c, CML, or Glu-AGEs, might be a useful biomarker for predicting atherosclerosis progression and future cardiovascular events. Thus, TAGE-RAGE system activation is considered to lead to a greater risk of cardiovascular events and contribute to the progression of liver damage, which would provide a mechanism link between CVD and NAFLD/NASH.

NOVEL TREATMENT STRATEGIES

The majority of studies about NASH have attempted to assess the relationships between NAFLD/NASH and T2DM, CVD, or chronic kidney disease (CKD)[92]. The results outlined above strongly suggest that the TAGE-RAGE system is involved in the development and progression of NASH. As a result, several therapeutic strategies that target this system, *e.g.*, inhibiting TAGE synthesis, downregulating the expression of RAGE or molecules involved in its downstream pathways, and blocking TAGE-RAGE interactions, have been developed as potential treatments for NASH.

The inhibition of TAGE synthesis: Acarbose

Whilst there are many drugs that are able to improve glycemic control, including patients' postprandial plasma glucose concentrations, some drugs specifically target postprandial hyperglycemia.

The absorption of carbohydrates from the small intestine can be delayed by treatment with the α-glucosidase inhibitor acarbose, and T2DM patients that were administered acarbose displayed less severe postprandial hyperglycemia[93]. A recent study found that in patients with T2DM or IGT acarbose treatment reduced the rate at which the intimal media of the carotid arteries thickened and led to a lower incidence of CVD[93], indicating that acarbose ameliorates postprandial hyperglycemia, and hence, inhibits the development and progression of CVD. In an *in vivo* study, we found that protein amino moieties readily react with GLA to produce TAGE, leading to oxidative stress and vascular inflammation. These observations suggested that in DM GLA plays a role in promoting the development of atherosclerosis[18-20]. In a study involving T2DM rats, we demonstrated that the serum concentration of TAGE, but not HbA1c, is a marker of cumulative postprandial hyperglycemia[94]. Based on the abovementioned results, we suggest that acarbose reduces serum TAGE concentrations, which could at least partially explain its cardioprotective effects *in vivo*. In a previous study, 50 mg acarbose (dosing schedule: thrice a day for a 12-wk period) were administered to 13 Japanese T2DM patients who were free from inflammatory conditions, atherosclerotic heart disease, and microangiopathy and had never taken oral hypoglycemic agents. The patients' serum TAGE concentrations as well as their serum levels of other biological molecules were assessed before and after the administration of acarbose[88]. The DM patients' serum free fatty acid and TAGE concentrations had fallen significantly after 12 wk' acarbose treatment. Acarbose also reduced their postprandial plasma glucose concentrations. These results indicate that HbA1c concentrations might not accurately reflect the ameliorative effects of acarbose on postprandial hyperglycemia. Furthermore, they suggest that serum TAGE concentrations might be useful biomarkers for assessing cumulative postprandial hyperglycemia in T2DM patients. As TAGE have adverse effects on CVD[20], acarbose might be useful for preventing CVD in NASH patients with T2DM or postprandial hyperglycemia.

Inhibiting the binding of TAGE to RAGE using sRAGE

RAGE was found to contribute to acute liver damage in

numerous studies, and the blockade of RAGE was demonstrated to reduce cholestatic, toxic, and ischemic liver damage[95-98].

Patients with chronic liver injuries were found to exhibit significantly higher hepatic RAGE expression levels[99], and in NAFLD patients a correlation was detected between the severity of fibrosis and the patients' serum TAGE concentrations, indicating that RAGE and TAGE make significant contributions to the development of liver disease[23]. In addition, DM, which upregulates AGE synthesis and RAGE expression, has been found to accelerate the progression of fibrosis in a number of human liver conditions, including chronic hepatitis C and NAFLD[100]. Recently, we found that TAGE-RAGE interactions promote inflammation, affect the expression levels of various genes and the activity of intracellular signaling pathways, and induce oxidative stress in various kinds of cells. These effects might be involved in the pathological changes seen in various chronic diseases[17-20].

Endogenous sRAGE has recently been detected in humans[74]. It has been suggested that it is synthesized *via* the cleavage of a splice variant of RAGE (a type of secretory RAGE exhibiting C-terminal truncation) or full-length cell surface RAGE[74]. Patients with T1DM or T2DM display increased total endogenous sRAGE concentrations[101-104]. In addition, we and others have detected positive correlations between the total serum sRAGE concentration and serum TAGE concentrations in both non-DM and DM subjects[104,105]. Furthermore, body mass index-, sex-, and age-adjusted TAGE concentrations were found to increase significantly in proportion to the rise in the serum sRAGE concentration in non-DM subjects[104,105]. These results indicate that *in vivo* circulating sRAGE, which functions as a decoy receptor, is unable to bind to and remove the TAGE present in the blood in an efficient manner. As TAGE promote RAGE expression, the blood sRAGE concentration might be a marker of RAGE production within tissues. Furthermore, it might change in response to variations in the serum concentration of TAGE in order to ameliorate TAGE-induced tissue damage including NASH[106-109].

An angiotensin Ⅱ type 1 receptor blocker: Telmisartan

It has been suggested that the TAGE-RAGE axis interacts with the renin-angiotensin system. In a previous study, we suggested that the angiotensin Ⅱ type 1 receptor blocker telmisartan reduces RAGE expression *via* its ability to modulate the peroxisome proliferator-activated receptor-γ (PPAR-γ)[21,110]. We came to this conclusion due to the following observations, which were obtained in experiments involving Hep3B cells: (1) whilst telmisartan downregulated ROS synthesis, TAGE-induced RAGE expression, and CRP expression, candesartan did not induce any of these processes; (2) the PPAR-γ inhibitor GW9662 abrogated the telmisartan-induced inhibition of the expression of RAGE and its associated effector molecules; (3) the effects of ciglitazone and troglitazone, which are full agonists of PPAR-γ, were similar to those of telmisartan; and (4) the administration of curcumin, an inhibitor of NF-κB, or antioxidants abrogated the upregulation of CRP mRNA expression induced by TAGE. Due to its unique ability to modulate PPAR-γ, telmisartan is increasingly considered to be a useful cardiometabolic sartan[21,110,111]. In addition, it has been demonstrated that thiazolidinediones downregulate endothelial RAGE expression *via* NF-κB suppression[112]. These results suggest that telmisartan has anti-inflammatory effects on TAGE signaling; *i.e.*, it reduces hepatic RAGE expression by activating PPAR-γ, and might also help to protect against NASH.

A hydroxymethyl-glutaryl-CoA reductase inhibitor: Atorvastatin

In a recent study, we found that in Hep3B cells the hydroxymethyl-glutaryl-CoA reductase inhibitor atorvastatin reduced TAGE-induced ROS synthesis in a dose-dependent manner[113]. In addition, atorvastatin and the antioxidant N-acetylcysteine downregulated CRP expression at both the mRNA and protein levels in TAGE-treated Hep3B cells[113]. These results showed that the antioxidative effects of atorvastatin abrogate CRP expression-associated TAGE signaling. Furthermore, they indicate that statins protect blood vessels from damage and abrogate the adverse effects of TAGE by downregulating the activity of their effector molecules.

The consumption of fructose-containing beverages is associated with a greater risk of MetS-related conditions, including NAFLD. Despite the fact that caloric restriction and weight loss is the only effective treatment for NAFLD, it has been demonstrated that atorvastatin is safe for use in NAFLD patients and results in improvements in their hepatic histology. In a previous study, we found that atorvastatin reduced the serum TAGE concentrations of 43 patients with a combination of biopsy-proven NASH and dyslipidemia[114]. After 12 mo atorvastatin treatment (10 mg daily), all of the patients demonstrated significant reductions in their hepatic transaminase (aspartate aminotransferase and alanine aminotransferase (ALT) and γ-glutamyl transpeptidase concentrations. In addition, by end of the treatment their plasma tumor necrosis factor-α (TNF-α) and plasma adiponectin concentrations were reduced by 31% and elevated by 16%, respectively. The patients' HOMA-IR values were slightly reduced. The patients' liver/spleen ratios rose significantly from 0.54 ± 0.26 at the baseline to 0.94 ± 0.24 at the end of the treatment; however, their visceral fat area values were unchanged. During the treatment, the patients' serum TAGE concentrations fell significantly (they were 10.4 ± 3.8, 5.9 ± 3.3, and 2.5 ± 1.1 units/mL before the treatment and after 6 mo and 12 mo treatment, respectively). Correlations were detected between the patients' serum TAGE concentrations and their serum concentrations of thiobarbituric acid reactive substances (TBARS), TNF-α, procollagen type Ⅲ propeptide, ALT, and type Ⅳ collagen 7S[114].

The administration of atorvastatin to Sprague-Dawley

male rats that had consumed a liquid fructose solution (10% w/v) abrogated the inflammatory and metabolic changes induced in the liver by fructose. These beneficial effects were considered to be due to the anti-inflammatory activity of atorvastatin and its downregulation of the hepatic expression of fructokinase, which inhibits fructose metabolism in the liver[115]. Reduced synthesis of GLA (a TAGE precursor and a fructose metabolite) leads to a drop in TAGE synthesis. Atorvastatin is able to reduce the serum TAGE concentration without altering glucose metabolism and does so in a cholesterol-lowering-independent manner. In the abovementioned study, the serum TAGE concentrations of the NASH patients with dyslipidemia fell significantly after the atorvastatin treatment, but their glucose metabolism was unaffected[114]. In conclusion, atorvastatin was demonstrated to be an effective treatment for NASH patients with dyslipidemia who did not respond adequately to diet and exercise therapy. In addition to improving their serum TAGE concentrations, atorvastatin also improved their histological and biochemical data. As atorvastatin decreased the serum TAGE concentrations of NASH patients with dyslipidemia, TAGE might be useful biomarkers for the treatment of NASH[114]. Controlled trials should be performed to further examine the clinical utility of TAGE as biomarkers in NASH.

Dietary AGEs: Kremezin

A study involving mice produced found that AGEs facilitate the progression from simple steatosis to NASH and liver fibrosis[116]. In the methionine choline-deficient rat model of NAFLD, high dietary consumption of AGEs results in elevated hepatic AGE concentrations and increased fibrosis, liver damage, and inflammation. The latter effects are considered to be mediated *via* the RAGE- and oxidative stress-dependent profibrotic effects of AGEs on activated HSC[117]. The above observations indicate that pharmacological and dietary strategies that target the AGE-RAGE system are able to slow the progression of NAFLD.

In a recent study, we detected increased hepatic expression levels of vascular endothelial growth factor (VEGF) and RAGE in rats that had been administered Glu-AGE-rich beverages. This suggested that dietary AGE consumption is associated with the hepatic expression of liver fibrosis-related genes[118]. Moreover, the abovementioned rats' livers were found to contain TAGE- and Glu-AGE-positive cells[118]. These results indicate that the consumption of Glu-AGE-rich beverages leads to upregulated hepatic expression of RAGE and VEGF and encourages the build-up of TAGE and Glu-AGEs, resulting in the binding of TAGE to RAGE. Thus, it is important to consider the amounts of Glu-AGEs present in foods to prevent liver disease, especially in people that are at risk of CKD, CVD, NAFLD/NASH, or DM.

It has been demonstrated that Kremezin, an oral adsorbent that consists of porous spherical carbonic particles, is able to attenuate the progression of chronic renal failure (CRF) by removing uremic toxins, *e.g.*, indoxyl sulfate precursors, from the intestine[119]. In CRF patients without DM, 3 mo Kremezin treatment (6 g/d) resulted in markedly reduced serum TAGE and Glu-AGEs concentrations, while the concentrations of these molecules were unaffected in renal function- and age-matched CRF patients that did not receive the drug[120]. The EC in the post-treatment serum samples collected from the Kremezin-treated patients exhibited markedly lower concentrations of MCP-1, vascular cell adhesion molecule-1, and RAGE mRNA than those found in the serum samples collected before treatment[120]. These findings indicate that the pathogenesis of vascular damage is influenced by dietary Glu-AGEs in TAGE-RAGE-related conditions and that reducing the amount of dietary Glu-AGEs taken into the body might represent a useful strategy against NAFLD/NASH.

Further clinical studies might provide insights into whether restricting the consumption of Glu-AGEs would be beneficial for preventing or slowing the progression of NAFLD/NASH and whether Glu-AGEs represent a novel therapeutic target for treatments that aim to reduce the risk of liver disease.

CONCLUSION

TAGE formation and accumulation are known to increase in various tissues during normal aging and to occur at a markedly accelerated rate in DM patients[18-20]. An increasing body of evidence suggests that TAGE are involved in the pathogeneses of various disorders including hypertension, Alzheimer's disease, diabetic vascular complications, CVD, NAFLD/NASH, and cancer growth and metastasis[7,8,18-23,79,87-91,114,121-126]. We found evidence that TAGE are involved in the pathogenesis of NASH in humans[7,23,114]. TAGE stimulated the proliferation and activation of HSC *in vitro via* RAGE, which resulted in hepatic inflammation and fibrosis[22]. In addition, NASH patients exhibited significantly higher serum TAGE concentrations than patients with simple steatosis or healthy controls[7,23]. Atorvastatin reduced the serum TAGE concentrations of NASH patients with dyslipidemia, and correlations were detected between the patients' serum TAGE concentrations and their serum TNF-α, ALT, type Ⅳ collagen 7S, procollagen type Ⅲ propeptide, and TBARS concentrations[114]. In a recent study, we found that non-B or non-C hepatocellular carcinoma (NBNC-HCC) patients had significantly increased circulating TAGE concentrations compared with NASH subjects without HCC and the control subjects[127]. The findings outlined in the present review indicate that TAGE contribute to the pathogenesis of NBNC-HCC and that they might be useful biomarkers for discriminating between NBNC-HCC and NASH.

In conclusion, an increasing amount of evidence indicates that TAGE and RAGE both make important contributions to liver disease. TAGE might play a role in the development and progression of NASH and could be

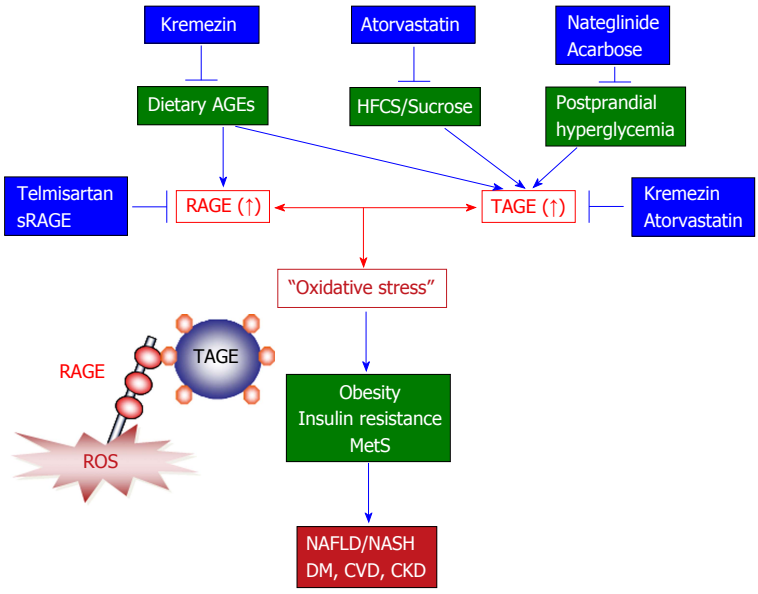

Figure 4 The toxic advanced glycation end-products-receptor for advanced glycation end-products system and novel treatments that target this system to prevent the development and/or progression of non-alcoholic steatohepatitis. Accumulating evidence suggests that TAGE-RAGE interactions affect intracellular signaling, gene expression, and the release of pro-inflammatory molecules and also induce oxidative stress in numerous types of cells, all of which have the potential to contribute to the pathological changes associated with lifestyle-related diseases including NAFLD/NASH. Since TAGE display the strongest binding affinities for RAGE and have adverse effects on diabetic vessels through their interactions with RAGE, TAGE might be partly responsible for the increased risk of cardiovascular disease (CVD) seen in diabetes mellitus (DM) patients and the impaired glucose tolerance observed in patients with postprandial hyperglycemia. NAFLD is considered to be a hepatic symptom of metabolic syndrome (MetS) and is strongly associated with insulin resistance, obesity, and abnormalities in glucose and lipid metabolism. It is important to consider the amounts HFCS/sucrose and AGEs present in foods to prevent liver disease, particularly in individuals that are at high risk of developing NAFLD/NASH, DM, CVD, or chronic kidney disease (CKD). Taken together, the present study suggests that TAGE could be used as novel therapeutic targets for the prevention of lifestyle-related diseases. Therefore, inhibiting the formation of TAGE, blocking TAGE-RAGE interactions, and suppressing the expression of RAGE or its downstream effectors all have potential as therapeutic strategies against lifestyle-related disease including NAFLD/NASH. AGEs: Advanced glycation end-products; TAGE: Toxic AGEs; RAGE: Receptor for AGEs; sRAGE: Soluble form of RAGE; NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; HFCS: High-fructose corn syrup.

useful biomarkers for differentiating between NASH and NAFLD or between NBNC-HCC and NASH. Further clinical and experimental studies are required to elucidate the mechanisms by which the TAGE-RAGE system affects the development and progression of lifestyle-related conditions including NAFLD/NASH (Figure 4).

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P- Reviewer: Basaranoglu M, Czaja MJ, Miyoshi E
S- Editor: Ji FF **L- Editor**: A **E- Editor**: Liu SQ

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