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Serum levels of toxic AGEs (TAGE) may be a promising novel biomarker in development and progression of NASH

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ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) ranges from simple steatosis to nonalcoholic steatohepatitis (NASH), leads to fibrosis and potentially cirrhosis, liver failure, and hepatocellular carcinoma, and is one of the most common causes of liver disease worldwide. NAFLD has also been implicated in other medical conditions such as insulin resistance, obesity, metabolic syndrome, hyperlipemia, hypertension, cardiovascular disease, and diabetes. Continuous hyperglycemia has been implicated in the pathogenesis of diabetic micro- and macro-vascular complications *via* various metabolic pathways, and numerous hyperglycemia-induced metabolic and hemodynamic conditions exist, including the increased generation of various types of advanced glycation end-products (AGEs). We recently demonstrated that glyceraldehyde-derived AGEs (Glycer-AGEs), the predominant components of toxic AGEs (TAGE), played an important role in the pathogenesis of angiopathy in diabetic patients. Moreover, a growing body of evidence suggests that the interaction between TAGE and the receptor for AGEs may alter intracellular signaling, gene expression, and the release of pro-inflammatory molecules and also elicits the generation of oxidative stress in numerous types of cells including hepatocytes and hepatic stellate cells. Serum levels of TAGE were significantly higher in NASH patients than in those with simple steatosis and healthy controls. Moreover, serum levels of TAGE inversely correlated with adiponectin (adiponectin is produced by adipose tissue and is an anti-inflammatory adipokine that can increase insulin sensitivity). Furthermore, immunohistochemical staining of TAGE showed intense staining in the livers of patients with NASH. Serum levels of TAGE may be a useful biomarker for discriminating NASH from simple steatosis. The administration of atorvastatin (10 mg daily) for 12 months significantly improved NASH-related metabolic parameters and significantly decreased serum levels of TAGE. The steatosis grade and NAFLD activity score were also significantly improved. These results demonstrated that atorvastatin decreased the serum levels of TAGE in NASH patients with dyslipidemia and suggest the usefulness of TAGE as a biomarker for the attenuation of NASH. Serum levels of TAGE were significantly higher in non-B or non-C hepatocellular carcinoma (NBNC-HCC) patients than in NASH subjects without HCC or control subjects. TAGE may be involved in the pathogenesis of NBNC-HCC, and could, therefore, be a biomarker that could discriminate NBNC-HCC from NASH. We propose that serum levels of TAGE are promising novel targets for the diagnosis of and therapeutic interventions against NASH.

Introduction

Nonalcoholic fatty liver disease (NAFLD) is among the most common causes of chronic liver disease in the westernized world, which now represents a worldwide public health problem [1]. NAFLD encompasses a broad spectrum of conditions, ranging from simple steatosis to nonalcoholic steatohepatitis (NASH) [2–4]. NASH is recognized as a potentially progressive disease that could lead to cirrhosis, liver failure, and hepatocellular carcinoma (HCC) [2–4]. NAFLD is considered to be a hepatic manifestation of metabolic syndrome (MetS) and has been correlated with insulin resistance (IR), obesity, hypertension, and abnormalities in the metabolism of glucose and lipids [5–7]. A high total energy intake has been

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positively associated with the development of NAFLD [8], and specific dietary components have been shown to affect the pathogenesis of this disease. A cross-sectional study reported that a greater intake of soft drinks (SD) was associated with an increased risk of NAFLD [9]. Fructose may contribute to disease development [10] and progression [11]. The increased ingestion of regular SD has recently been linked to NAFLD independent of MetS [12], with NAFLD patients consuming 5 times more carbohydrates from SD than healthy individuals [13]. Fructose is one of the most commonly ingested carbohydrates [14]. The two sources of fructose *in vivo* are its endogenous formation from glucose through the polyol pathway [15,16] and an exogenous supply from the diet (SD and commercial products), either as sucrose or high-fructose corn syrup (HFCS) [17,18].

Glyceraldehyde (GLA), a precursor of glyceraldehyde-derived advanced glycation end-products (Glycer-AGEs), is derived from two distinct pathways in the liver, (i) the glycolytic pathway (glycolysis) and (ii) fructose metabolism pathway (fructolysis) [19–21]. (i) The glycolytic intermediate GLA 3-phosphate (G3P) is normally catabolized by the enzyme G3P dehydrogenase (GAPDH). G3P accumulates intracellularly when GAPDH activity decreases. The metabolism of G3P then shifts to another route, and the amount of GLA is increased, which elevates the formation of Glycer-AGEs, a predominant component of TAGE. (ii) Fructose, a component of HFCS and sucrose, is present in the daily diets of many individuals [17,18]. Fructose is phosphorylated to fructose 1-phosphate by fructokinase and then catabolized to GLA and dihydroxyacetone phosphate by aldolase B [17,18]. Newly synthesized GLA is then transported or leaks passively across the plasma membrane. GLA promotes the formation of TAGE both intracellularly and extracellularly. There is a growing body of evidence to suggest that the interaction between TAGE and the receptor for AGEs (RAGE) may alter intracellular signaling, gene expression, and the release of pro-inflammatory molecules and also elicits the generation of reactive oxygen species (ROS) in numerous types of cells including hepatocytes and hepatic stellate cells (HSCs) [22,23].

The formation of TAGE is enhanced during NASH, and serum and hepatic TAGE levels have been shown to be significantly higher in patients with NASH than in healthy controls or patients with simple steatosis [24]. Therefore, TAGE is considered a useful diagnostic tool with which to differentiate NASH from simple steatosis. The clinical usefulness of TAGE as a marker for the attenuation of NASH has been reported; therefore, we herein investigated whether the treatment of NASH with dyslipidemia by atorvastatin could decrease serum levels of TAGE. Atorvastatin was previously reported to decrease serum levels of TAGE in NASH patients with dyslipidemia [25]. HCC is one of the most common malignancies and causes of cancer-related deaths in the world [26,27]. Although most cases of HCC are attributable to chronic liver disease resulting from chronic hepatitis B virus or C virus infections, a large proportion of HCC patients are negative for the markers of the HBV antigen or HCV antibody, and are diagnosed as non-B or non-C HCC (NBNC-HCC). Serum levels of TAGE were shown to be significantly higher in NBNC-HCC patients than in NASH subjects without HCC or control subjects. TAGE may be involved in the pathogenesis of NBNC-HCC, and, as such, may be used as a biomarker that could discriminate NBNC-HCC from NASH [28].

We proposed that serum levels of TAGE may be a promising novel biomarker for the development and progression of NASH.

Hypothesis-1. TAGE may be a useful biomarker for discriminating patients with NASH from those with simple steatosis

In order to investigate whether the measurement of circulating AGE levels was also a useful tool for discriminating NASH from simple steatosis, we measured serum levels of AGEs (TAGE, glucose-derived AGEs [Glu-AGEs], and N^{ε}-(carboxymethyl)lysine [CML]) in 66 patients with histologically defined-NASH without liver cirrhosis, 10 with simple steatosis, and 30 control subjects [24]. We found that serum levels of TAGE could play a role in the pathogenesis of NASH and be used as a biomarker for discriminating NASH from simple steatosis on the basis of the following findings: (i) serum levels of TAGE were significantly higher in NASH patients (9.78 ± 3.73 U/ml) than in those with simple steatosis (7.17 ± 2.28 U/ml) or healthy controls (6.96 ± 2.36 U/ml). Receiver operating characteristic curves for circulating levels of TAGE revealed that the threshold value for the prediction of NASH was 8.53 U/ml. At this threshold, sensitivity was 66.7% and specificity was 88.9%; (ii) serum levels of TAGE positively correlated with a homeostatic model assessment of insulin resistance (HOMA-IR) and were inversely associated with adiponectin levels; (iii) although serum levels of TAGE did not correlate with the severity of hepatic steatosis or fibrosis, these values were not affected by the status of glucose tolerance. No significant difference was observed in TAGE levels between normal and impaired glucose tolerance patients; (iv) TAGE was detected in the hepatocytes of patients with NASH, but was negligible in those with simple steatosis; and (v) no significant difference was noted in Glu-AGE or CML levels among these groups [24]. These findings suggested that serum TAGE levels may be a useful biomarker for evaluating residual liver function.

The 'two-hit theory' is the simplest and most accurate explanation for the pathological mechanisms of NASH; the first hit is the accumulation of excessive fat in the liver, and the second is the development of oxidative stress [29,30]. Nevertheless, the present study provided the following important information: (i) the overproduction of TAGE was necessary to cause NASH on the basis of simple steatosis as the first hit; and thereafter (ii) continued elevations in the serum level of TAGE were needed to induce fibrogenic changes and progression of the disease; however, further studies are needed to confirm these findings. Liver biopsy currently remains the best diagnostic tool for distinguishing NASH from simple steatosis. NAFLD is now the most frequent liver disorder, and assuming that some cases of NAFLD may progress to NASH, liver biopsy is not an appropriate procedure for all patients. To address this important issue in the clinical management of NAFLD, namely discriminating between NASH and simple steatosis, ROC curves were employed. The measurement of TAGE appeared to be able to discriminate NASH from simple steatosis, as shown by the area under the ROC curve of 78%. A scoring system combining such a non-invasive marker with other clinical features may permit the reliable differentiation of NASH and, accordingly, contribute to a higher probability of NASH diagnoses.

In conclusion, the results of our present study suggest that serum level of TAGE may be a useful diagnostic tool to differentiate NASH from simple steatosis. A limitation to this study was the difference in the numbers of patients to be subjected to this study. Thus, further studies are needed to clarify the underlying mechanism(s) whereby TAGE play a pathophysiological role in NASH.

Hypothesis-2. Clinical usefulness of TAGE as a biomarker for the attenuation of NASH

The consumption of beverages that contain fructose favors the increasing prevalence of MetS alterations in humans, including NAFLD. Although the only effective treatment for NAFLD is caloric restriction and weight loss, existing findings indicate that atorvastatin, an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, can be used safety in patients with NAFLD and improves hepatic histology. We previously demonstrated that atorvastatin decreased serum levels of TAGE in 43 patients with biopsy-proven NASH with dyslipidemia [25]. After a 12-month treatment with

atorvastatin (10 mg daily), significant reductions in liver transaminases (alanine aminotransferase, ALT & aspartate aminotransferase, AST) and γ-glutamyl transferase (GGT) levels were observed in all patients. Plasma adiponectin levels were significantly increased by 16% and plasma tumor necrosis factor-α (TNF-α) levels were significantly decreased by 31% at the end of the treatment. IR as determined by HOMA-IR was slightly decreased. Liver/spleen ratios were significantly increased from 0.54 ± 0.26 at baseline to 0.94 ± 0.24 at the end of treatment, without significant changes in the visceral fat area. Serum levels of TAGE significantly decreased during the treatment (10.4 ± 3.8, 5.9 ± 3.3, and 2.5 ± 1.1 U/ml before, after 6 months, and after 12 months of the treatment, respectively). Serum levels of TAGE correlated with those of ALT, TNF-α, thiobarbituric acid reactive substances (TBARS), type IV collagen 7S, and procollagen type III propeptide, respectively [25].

We recently reported that atorvastatin decreased serum levels of TAGE in patients with type 2 diabetes [31]. In the present study, blood glucose control levels were unchanged by the atorvastatin treatment and changes in TAGE did not correlate with those in the lipid parameters examined. The administration of atorvastatin to Sprague–Dawley male rats ingesting fructose as a liquid solution (10% w/v) prevented the metabolic and inflammatory alterations induced in liver tissue by the ingestion of fructose. These effects have been attributed to the well-known anti-inflammatory properties of atorvastatin and to this drug effectively decreasing the hepatic expression of fructokinase, thereby reducing fructose metabolism in liver tissue [32]. Atorvastatin could decrease serum levels of TAGE without changing glucose metabolism (fasting glucose and hemoglobin A1c), and this effect was shown to occur in a cholesterol-lowering-independent manner. In the present study, serum levels of TAGE were significantly decreased by the atorvastatin treatment in NASH patients with dyslipidemia without changes being observed in glucose metabolism.

In conclusion, atorvastatin was found to be effective for the treatment of NASH patients with dyslipidemia who did not respond adequately to diet and exercise therapy. Biochemical findings, histological findings, and serum levels of TAGE were improved by this treatment. The present results demonstrate that atorvastatin decreased serum levels of TAGE in NASH patients with dyslipidemia and suggest the usefulness of TAGE as a biomarker for the treatment of NASH. Controlled trials are needed to further investigate the clinical usefulness of TAGE as a biomarker in NASH.

Hypothesis-3. TAGE may be a novel biomarker that could discriminate non-B or non-C hepatocellular carcinoma (NBNC-HCC) from NASH

The clinical and laboratory characteristics of 90 patients with treatment-naive NBNC-HCC, 56 biopsy-proven NASH, and 27 healthy controls were examined. Among the NBNC-HCC patients, 10 had NASH-associated HCC, 49 alcoholic liver disease-associated HCC, and the etiology of the remaining patients ($N = 31$) was unknown. Serum levels of TAGE were significantly higher in NBNC-HCC patients than in NASH subjects without HCC or controls (9.1 ± 2.7 vs. 5.2 ± 1.7 or 3.5 ± 1.2 U/ml, respectively) [28]. No significant difference was observed in serum levels of TAGE among NASH-, alcohol-associated, and unknown-etiology HCC (9.1 ± 2.1 vs. 8.6 ± 1.9 vs. 9.8 ± 3.7 U/ml). We performed a multiple stepwise regression analysis in order to determine the independent correlates of serum TAGE levels. Age, GGT, and high-density lipoprotein (HDL)-cholesterol (inversely) remained significant and were independently related to TAGE levels [28].

We previously showed that TAGE could play a role in the pathogenesis of NASH in humans [7,23,24]. TAGE could stimulate the proliferation and activation of HSCs *in vitro*, thereby causing hepatic inflammation and fibrosis [23]. In humans, serum levels of TAGE were significantly higher in NASH patients than in those with simple steatosis [24]. In this study, we found for the first time that serum levels of TAGE were significantly higher in NBNC-HCC patients than in NASH subjects without HCC or controls. The present results have extended our previous findings in which TAGE not only enhanced the angiogenic potential of HCC by up-regulating vascular endothelial growth factor expression, but also stimulated the proliferation of HCC *in vitro* [33]. TAGE may contribute to the development and progression of NBNC-HCC in humans, and, thus, may be a biomarker of NBNC-HCC. In the present study, besides age, GGT and HDL-cholesterol (inversely) were independent correlates of serum TAGE levels in all subjects. GGT levels were previously shown to be a biomarker that could predict outcomes and overall survival in HCC patients treated with or without transarterial chemoembolization or surgery [34–36]. These findings suggest that increased TAGE levels could partly explain the link between high GGT values and shorter survival in HCC patients. Furthermore, since HDL-cholesterol levels were reported to decrease in HCC subjects [37], TAGE may decrease HDL-cholesterol levels, which could lead to a poor prognosis in these patients.

In conclusion, we found that circulating TAGE levels were significantly higher in NBNC-HCC patients than in NASH subjects without HCC or controls. These findings suggest that TAGE could be involved in the pathogenesis of NBNC-HCC and be used as a biomarker to discriminate NBNC-HCC from NASH. Further studies are needed to investigate the clinical usefulness of TAGE as a biomarker to discriminate NBNC-HCC patients from NASH subjects without HCC.

Conclusion

The formation and accumulation of TAGE in various tissues is known to progress during normal aging and at an extremely accelerated rate in diabetes [20,21,38]. There is accumulating evidence to show that TAGE plays a role in the pathogenesis of various disorders such as diabetic vascular complications, hypertension, cardiovascular disease, Alzheimer's disease, NAFLD/NASH, and cancer growth and metastasis [7,19–25,28,33,38–45]. We previously demonstrated that TAGE could play a role in the pathogenesis of NASH in humans [7,24,25]. TAGE *via* RAGE stimulated the proliferation and activation of HSCs *in vitro*, thereby causing hepatic inflammation and fibrosis [23]. In humans, serum levels of TAGE were significantly higher in NASH patients than in those with simple steatosis and healthy controls [7,24]. Atorvastatin decreased serum levels of TAGE in NASH patients with dyslipidemia [25]. Serum levels of TAGE correlated with those of ALT, TNF-α, TBARS, type IV collagen 7S, and procollagen type III propeptide, respectively [25]. We recently reported that circulating TAGE levels were significantly higher in NBNC-HCC patients than in NASH subjects without HCC or control subjects [28]. These findings suggested that TAGE may be involved in the pathogenesis of NBNC-HCC and could be used as a biomarker to discriminate NBNC-HCC from NASH.

In conclusion, there is accumulating evidence to suggest the active involvement of the TAGE-RAGE system in liver disease. TAGE may contribute to the development and progression of NASH, and may be used as a biomarker that can discriminate NASH from NAFLD and NBNC-HCC from NASH. Further clinical and experimental studies are needed to clarify the underlying mechanisms by which the TAGE-RAGE system is involved in the development and progression of lifestyle-related diseases including NAFLD/NASH.

Conflict of interest

None declared.

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