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Soluble receptor for advanced glycation end products and liver stiffness in postoperative biliary atresia

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ABSTRACT

Objectives: Soluble receptor for advanced glycation end products (sRAGE) has emerged as a possible biomarker of several disease conditions, including liver injury. This study was aimed to assess serum sRAGE and liver stiffness in biliary atresia (BA).

Design and methods: Forty postoperative BA patients and 20 controls were enrolled. Serum sRAGE levels were analyzed by enzyme-linked immunosorbent assay. Liver stiffness scores were measured by transient elastography.

Results: BA patients had higher serum sRAGE and liver stiffness values than controls ($P<0.001$). Serum sRAGE and liver stiffness values were significantly elevated in BA patients with jaundice compared to those without jaundice ($P<0.001$). Additionally, serum sRAGE was correlated with liver stiffness and serum total bilirubin ($r=0.65$, $P<0.001$ and $r=0.71$, $P<0.001$, respectively).

Conclusion: Serum sRAGE was associated with the severity of BA. Accordingly, serum sRAGE and liver stiffness may serve as indicators reflecting the severity and the development of hepatic fibrosis in postoperative BA.

Introduction

Biliary atresia (BA), a severe neonatal liver disorder, is defined as progressive fibrosclerotic cholangiopathy leading to obliteration of bile ducts. Even after effective bile flow has been established by Kasai portoenterostomy, the majority of BA patients will develop severe cholestasis, liver fibrosis, and virtually die within a few years [1]. The progression of BA results in end-stage liver disease with severe complications, including portal hypertension, splenomegaly, and progressive ascites [2,3]. To date, etiologies of biliary atresia have not been well established; however, many theories have been proposed for the pathogenesis of BA, including genetic insults, neonatal viral infections, congenital malformations, and autoimmune defects [4].

The receptor for advanced glycation end products (RAGE) is a multiligand receptor classified as an immunoglobulin superfamily cell surface molecule and interacts with a number of different proinflammatory ligands, including advanced glycation end products (AGEs) [5]. In addition to cell-surface RAGE, soluble RAGE (total sRAGE) comprises both the extracellular domain of wild-type, full-length RAGE, which results from proteolytic cleavage at the cell surface, and an endogenous secretory isoform lacking a transmembrane domain (esRAGE) [6]. The assessment of soluble RAGE in human circulation is accomplished by two different immunoassay systems. The most commonly used total sRAGE immunoassay determines the total pool of soluble RAGE using antibodies that recognize both the spliced and cleaved forms of sRAGE [6]. Another assay definitely measures esRAGE in serum by distinct immunoassay due to its unique C-terminus sequence [7]. In addition, emerging evidence suggests that circulating total sRAGE may serve as a reliable biomarker of various RAGE-mediated disorders [8].

Previously, Zeng et al. have shown that the blockade of RAGE through the administration of sRAGE provided protection against hepatocellular necrosis, attenuated hepatic ischemia/reperfusion injury, and enhanced the expression of proregenerative cytokine TNF-α in a mouse model [9]. Furthermore, Ekong and colleagues have documented that treatment with sRAGE increased survival, attenuated the extent of liver injury, and decreased hepatic necrosis in an acetaminophen-induced hepatotoxicity mouse model [10]. In rats in which liver fibrosis was induced by bile duct ligation or a thioacetamide treatment, RAGE expression was upregulated in activated hepatic stellate cells [11]. More recent study has suggested a potential role of the RAGE–ligand axis in the development of liver injury and fibrosis [12].

In recent years, circulating sRAGE has been reported to be involved in several pathological conditions, including diabetes, multiple sclerosis, ulcerative colitis, and nonalcoholic fatty liver diseases [13–16]. To our

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knowledge, serum sRAGE from different clinical stages of BA and its possible role in BA patients have not been studied. We have postulated that serum sRAGE and liver stiffness might be higher in BA patients than in healthy controls. Therefore, the aim of this study was to investigate serum sRAGE levels and liver stiffness values using transient elastography and to determine the possible association of serum sRAGE, liver stiffness, and clinical parameters in BA patients post Kasia operation.

Methods

The present study was approved by the Institutional Review Board on Human Research of the Faculty of Medicine, Chulalongkorn University, and was conducted in agreement with the ethical guidelines of the Declaration of Helsinki. All parents of children were informed of the study's purpose and of any interventions involved in this study. Written informed consent was obtained from the parents prior to the children entering the study.

Study population

Forty BA patients (22 girls and 18 boys with mean age of 9.5 ± 0.8 years) and 20 healthy children (10 girls and 10 boys with mean age of 9.5 ± 0.6 years) were recruited in this study. None of them had undergone liver transplantation. Healthy controls attending the Well Baby Clinic at King Chulalongkorn Memorial hospital for vaccination had normal physical findings and no underlying disease. BA patients were classified into two groups according to their serum total bilirubin (TB). Based on their jaundice status, BA children were divided into a non-jaundice group (TB<2 mg/dL, $n = 22$) and a persistent jaundice group (TB≥2 mg/dL, $n = 18$). Portal hypertension (PH) was validated by the presence of ascites and/or esophageal varices as diagnosed by endoscopy. Sixteen patients had no PH whereas the rest of the 24 patients suffered from PH.

Laboratory methods

Samples of peripheral venous blood were collected from every participant, and were stored at −80 °C for further analysis. Double-blind quantitative assessment of serum sRAGE was performed using commercially available enzyme-linked immunosorbent essay (ELISA) (Quantikine, R&D Systems, Minneapolis, MN, USA). According to the manufacturer's protocol, recombinant human sRAGE standards and serum samples were added into each well, which has been pre-coated with specific antibody to sRAGE. After incubating for 2 h at room temperature, every well was washed thoroughly with wash buffer. Then, sRAGE conjugate was pipetted into each well and incubated for 2 h at room temperature. After 4 washes, substrate solution was added into the wells and the microplate was incubated for 30 min at room temperature with protection from light. Lastly, the reaction was stopped by the stop solution and the optical density was determined using an automated microplate reader at 450 nm. A standard optical density–concentration curve was drawn for the determination of sRAGE concentration. The liver function tests including serum albumin, total bilirubin (TB), direct bilirubin (DB), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) were measured using a Hitachi 912 (Roche Diagnostics, Basel, Switzerland) automated machine at the central laboratory of our hospital.

Liver stiffness measurement

Transient elastography (Fibroscan, Echosens, Paris, France) measured the liver stiffness between 25 and 65 mm from the skin surface, which is approximately equivalent to the volume of a cylinder of 1 cm diameter and 4 cm length. The measurements were performed by placing a transducer probe of Fibroscan on the intercostal space at the area of the right lobe of the liver with patients lying in a dorsal decubitus position with maximum abduction of the right arm. The target location for measurement was a liver portion that was at least 6 cm thick, and devoid of major vascular structures. The measurements were performed until 10 validated results had been obtained with a success rate of at least 80%. The median value of 10 validated scores was considered the elastic modulus of the liver, and it was expressed in kilopascals (kPa).

Statistical analysis

Statistical analysis was performed using the SPSS version 16.0 statistical software package (SPSS Inc., Chicago, IL, USA). Comparisons of demographic and clinical parameters between groups were performed using Chi-square and Student's unpaired *t*-test when appropriate. Correlation between numerical data was acquired using Pearson's correlation coefficient (r). Multiple linear regression analysis was performed to determine the independence of the association between serum sRAGE levels and liver stiffness in BA patients. Data were expressed as mean ± standard error of the mean (SEM). All the P-values<0.05 based on a two-tailed test were considered statistically significant. *Post-hoc* power analysis was conducted to ensure that the study was adequately powered.

Results

Forty BA patients and 20 healthy controls were registered in the present study. The baseline characteristics of the BA children and healthy controls are given in Table 1. Mean age and gender ratio in controls and BA patients were not different, whereas serum sRAGE levels were significantly higher in BA patients compared with healthy controls (1464.8 ± 93.4 vs. 1190.0 ± 52.9 pg/mL, $P = 0.03$) (Fig. 1). In addition, liver stiffness scores in BA patients were markedly greater than those in controls (29.7 ± 3.7 vs. 5.0 ± 0.5 kPa, $P<0.001$).

We further categorized BA patients into a persistent jaundice ($n = 18$) and non-jaundice group ($n = 22$). The demographic data and biochemical parameters, including liver function tests, serum sRAGE, and liver stiffness values based on jaundice status are illustrated in Table 2. BA patients with jaundice had significantly higher serum sRAGE levels than those without jaundice (1758.9 ± 143.4 vs. 1224.1 ± 98.5 pg/mL, $P<0.001$) (Fig. 2). In BA patients, liver stiffness values of patients with persistent jaundice were remarkably higher than those of patients without jaundice (47.3 ± 4.3 vs. 15.2 ± 3.4 kPa, $P<0.001$).

Subsequent analysis revealed that serum sRAGE levels were significantly elevated in the BA patients with PH compared to those without PH (1700.8 ± 111.8 vs. 1110.8 ± 118.4 pg/mL, $P<0.001$) (Fig. 3). In addition, serum sRAGE levels were directly correlated with liver stiffness values ($r = 0.65$, $P<0.001$) and serum total bilirubin ($r = 0.71$, $P<0.001$) (Figs. 4A and B). Furthermore, liver stiffness

Table 1
Demographic data, biochemical characteristics, and liver stiffness scores of controls and biliary atresia patients. The data are expressed as mean ± SEM.

Variables	Controls	BA Patients	*P*-value
N	20	40	
Age (years)	9.5 ± 0.6	9.5 ± 0.8	0.6
Gender (female:male)	10:10	22:18	0.5
Total bilirubin (mg/dL)	–	2.6 ± 0.7	NA
Direct bilirubin (mg/dL)	–	2.1 ± 0.6	NA
AST (IU/L)	–	124.8 ± 14.3	NA
ALT (IU/L)	–	110.3 ± 14.6	NA
ALP (IU/L)	–	415.5 ± 32.5	NA
sRAGE (pg/mL)	1190.0 ± 52.9	1464.8 ± 93.4	0.03
Liver stiffness (kPa)	5.0 ± 0.5	29.7 ± 3.7	<0.001

BA, biliary atresia; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; sRAGE, soluble receptor advance glycation end products; NA, not applicable.

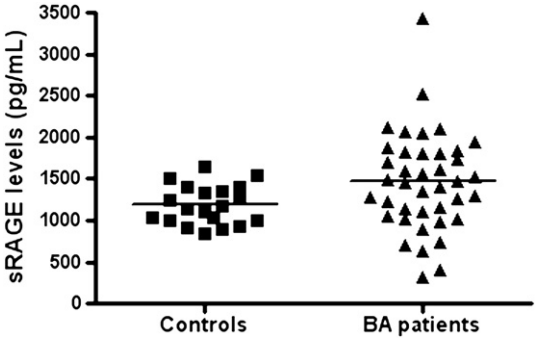

Fig. 1. Comparison of serum sRAGE levels in biliary atresia patients and healthy controls. Horizontal lines across the scatter diagram represent mean values.

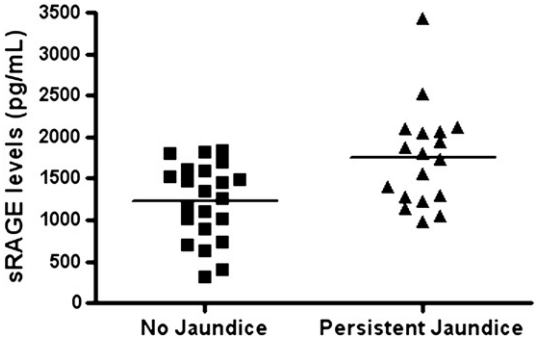

Fig. 2. Comparison of serum sRAGE levels in biliary atresia patients without jaundice and with jaundice. Horizontal lines across the scatter diagram represent mean values.

values were positively correlated with serum total bilirubin ($r = 0.48$, $P = 0.002$) and alanine aminotransferase ($r = 0.61$, $P < 0.001$) (Figs. 4C and D).

To investigate the extent of confounding by other factors on the association between sRAGE levels and liver stiffness values, we performed multiple linear regression analysis with a model adjusting for age, gender, and total bilirubin. When these predictors were entered into the multivariate model, the association between sRAGE and liver stiffness was not affected by other predictors or confounders ($\beta = 0.365$, $P < 0.01$).

Discussion

Biliary atresia is one of the most serious liver diseases of unknown cause in neonates. The etiopathogenic mechanisms of BA are still not entirely clear, and therapeutic options are unsatisfactory. Irrespective of the initiating disorder, all children with BA share a unique progressive inflammatory and fibrosis obstruction of the biliary system [1–3]. The progression of BA leads to liver fibrosis, biliary cirrhosis, and portal hypertension. It has been documented that a number of cytokines and growth factors play essential roles in the pathophysiology of BA [17–20]; however, the measurements on serum sRAGE and liver stiffness of BA have never been investigated. The purpose of this study was to evaluate serum sRAGE, liver stiffness, and clinical parameters in BA patients post Kasai operation.

The current study showed that serum sRAGE and liver stiffness in BA patients were significantly higher than those in healthy controls. In the BA patients, serum sRAGE levels were markedly elevated in BA patients with persistent jaundice compared to those without jaundice. High serum sRAGE was positively correlated with serum TB in postoperative BA patients. These findings indicate that serum sRAGE is associated with jaundice status in BA patients. Moreover, jaundice status in BA is likely to be a parameter for intrahepatic biliary obstruction. Serum alanine aminotransferase is widely utilized as a biochemical indicator of liver dysfunction reflecting hepatocellular damage. Therefore, these results suggest that sRAGE may play a possible role in the pathogenesis of hepatocellular damage in BA, and that it seems to be correlated with the degree of biliary obstruction.

Bile duct inflammation, cytokine response, and bile acid toxicity are the three potential contributors to liver parenchyma destruction and hepatic fibrosis in BA patients [1]. Upon activation, hepatic stellate cells (HSC), the major effecter cells in hepatic fibrogenesis, are transformed into extracellular matrix-producing myofibroblasts. This process leads to the production of collagen and the accumulation of extracellular matrices in the liver parenchyma, thus contributing to liver fibrosis and high liver stiffness in BA.

According to our knowledge, the present study is the first to show that serum sRAGE is elevated in BA patients compared with healthy controls. Previously, receptor for advanced glycation end product has been shown to play a major role in various liver diseases, including chronic hepatitis, liver steatosis and hepatocellular carcinoma [16,21–23]. In line with our findings, Hyogo et al. showed that sRAGE levels were elevated in patients with non-alcoholic steatohepatitis [21]. Furthermore, hepatic expression of RAGE has been demonstrated in patients with hepatitis and hepatocellular carcinoma as described by Hiwatashi et al. [22]. In contrast, Yilmaz et al. demonstrated that serum sRAGE levels were significantly lower in patients with non-alcoholic steatohepatitis and simple fatty liver compared with healthy controls, suggesting that sRAGE were negatively associated with the most severe forms of nonalcoholic fatty liver disease [16].

In view of these considerations, several mechanisms may be responsible for the increased serum sRAGE in BA children, particularly in those with jaundice and/or PH. First, the production of sRAGE in the damaged liver may contribute to the elevation of serum sRAGE.

Table 2
Comparison of biliary atresia patients without and with jaundice. The data are expressed as mean ± SEM.

Variable	Total	Persistent jaundice	No jaundice	*P*-value
N	40	18	22	
Age (years)	9.5 ± 0.8	9.9 ± 1.3	9.1 ± 1.0	NS
Gender (female:male)	22:18	9:9	13:9	NS
Total bilirubin (mg/dL)	2.6 ± 0.7	5.2 ± 1.2	0.4 ± 0.1	<0.001
Direct bilirubin (mg/dL)	2.1 ± 0.6	4.3 ± 1.2	0.2 ± 0.1	<0.001
AST (IU/L)	124.8 ± 14.3	185.2 ± 20.4	75.4 ± 12.4	<0.001
ALT (IU/L)	110.3 ± 14.6	155.0 ± 25.9	73.7 ± 11.5	0.01
ALP (IU/L)	415.5 ± 32.5	550.4 ± 40.1	305.0 ± 34.8	<0.001
sRAGE (pg/mL)	1464.8 ± 93.4	1758.9 ± 143.4	1224.1 ± 98.5	<0.001
Liver stiffness (kPa)	29.7 ± 3.7	47.3 ± 4.3	15.2 ± 3.4	<0.001

BA, biliary atresia; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; sRAGE, soluble receptor advance glycation end products.

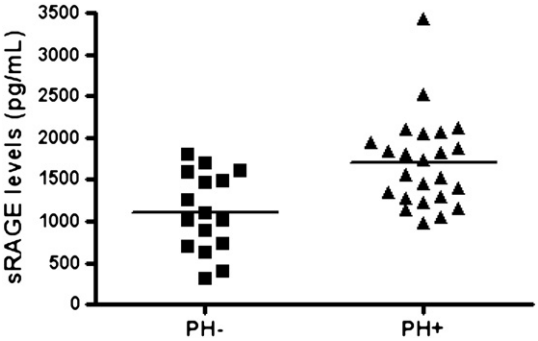

Fig. 3. Comparison of serum sRAGE levels in biliary atresia patients without portal hypertension and with portal hypertension. Horizontal lines across the scatter diagram represent mean values.

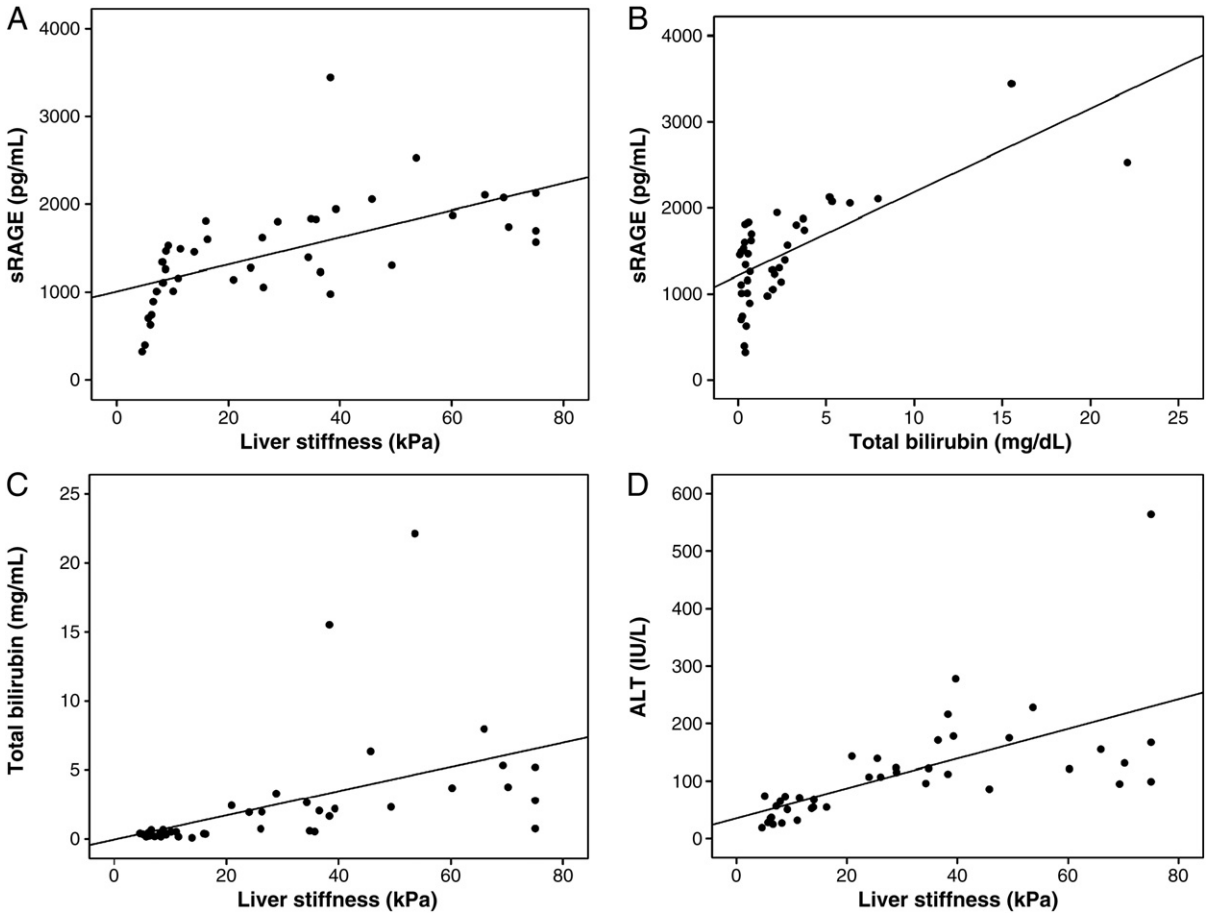

Fig. 4. Scatter diagram and regression analysis in biliary atresia patients. Serum sRAGE levels are correlated with liver stiffness (A) and serum total bilirubin (B). Liver stiffness values are correlated with serum total bilirubin (C) and serum alanine aminotransferase (D).

Secondly, the increased sRAGE levels could be attributed to the imbalance between sRAGE production and sRAGE clearance. In the advanced stage, reduced sRAGE clearance may result in high serum sRAGE. Moreover, extrahepatic organs can produce and secrete sRAGE in systemic circulation. We hypothesize that sRAGE elevation could be due to the consequence of hepatic damage and subsequent catabolic failure. More prospective studies could render more valuable information on the mechanisms of sRAGE in BA.

It is interesting to point out that the more elevated sRAGE was evident in BA patients with PH. Portal hypertension is characterized by the decrease of portal blood flow passing through the liver, secondary to the development of multiple varices. Hence, portal-systemic shunting may alter the clearance of sRAGE. A reduced first-pass effect in the liver could account for the higher sRAGE levels observed in the patients with PH. Whether increased sRAGE levels in BA patients represent decreased clearance, increased synthesis, or both is unclear. The exact mechanisms resulting in high serum sRAGE will require future investigation.

However, the present study has some limitations. The ELISA assay for sRAGE in this study assesses all soluble forms, including soluble RAGE cleaved from cell surface RAGE, endogenous secretory RAGE, and new splice variants of RAGE [24]. Furthermore, the system developed for sRAGE assessment may not distinguish among diverse sRAGE splice variants. Owing to this limitation, we could not identify the precise source of sRAGE detected by the assay we used. sRAGE may derive from alternative splicing of RAGE mRNAs and/or from proteolytic release of the RAGE proteins from the cell surface [24,25]. Since the proportion of various isoforms of sRAGE could be distinct among individuals, the development of novel specific methods will help improve the measurement of sRAGE concentrations. In this regard, we speculate that each soluble variant plays a specific role within the RAGE pathway, being expressed in a highly regulated pattern [26]. In addition, our findings are limited by a relatively small number of enrolled subjects and by cross-sectional design and, therefore, no conclusions regarding cause and effect relationships can be drawn. Finally, it is impossible to differentiate whether high levels of sRAGE reflected high levels of circulating AGEs and hepatic RAGE expression, or resulted from the sRAGE capture of low circulating AGEs levels while functioning as a decoy receptor for RAGE. Further studies of circulating AGEs and hepatic RAGE expression are warranted to shed more light on the pathogenic role of RAGE in BA.

In conclusion, the present study showed that BA patients had significantly higher serum sRAGE and liver stiffness values than healthy controls. Serum sRAGE was more elevated in the BA patients with persistent jaundice compared to those without jaundice. Moreover, patients with PH had significantly higher serum sRAGE compared to those without PH. In addition, serum sRAGE was positively correlated with liver stiffness. Serum sRAGE and liver stiffness measurements could be utilized as possible parameters to determine the disease severity and the development of hepatic fibrosis in the postoperative BA patients. Prospective longitudinal studies are required to determine the disease progression and define the precise role of sRAGE in the pathogenesis of hepatic fibrosis in BA.

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