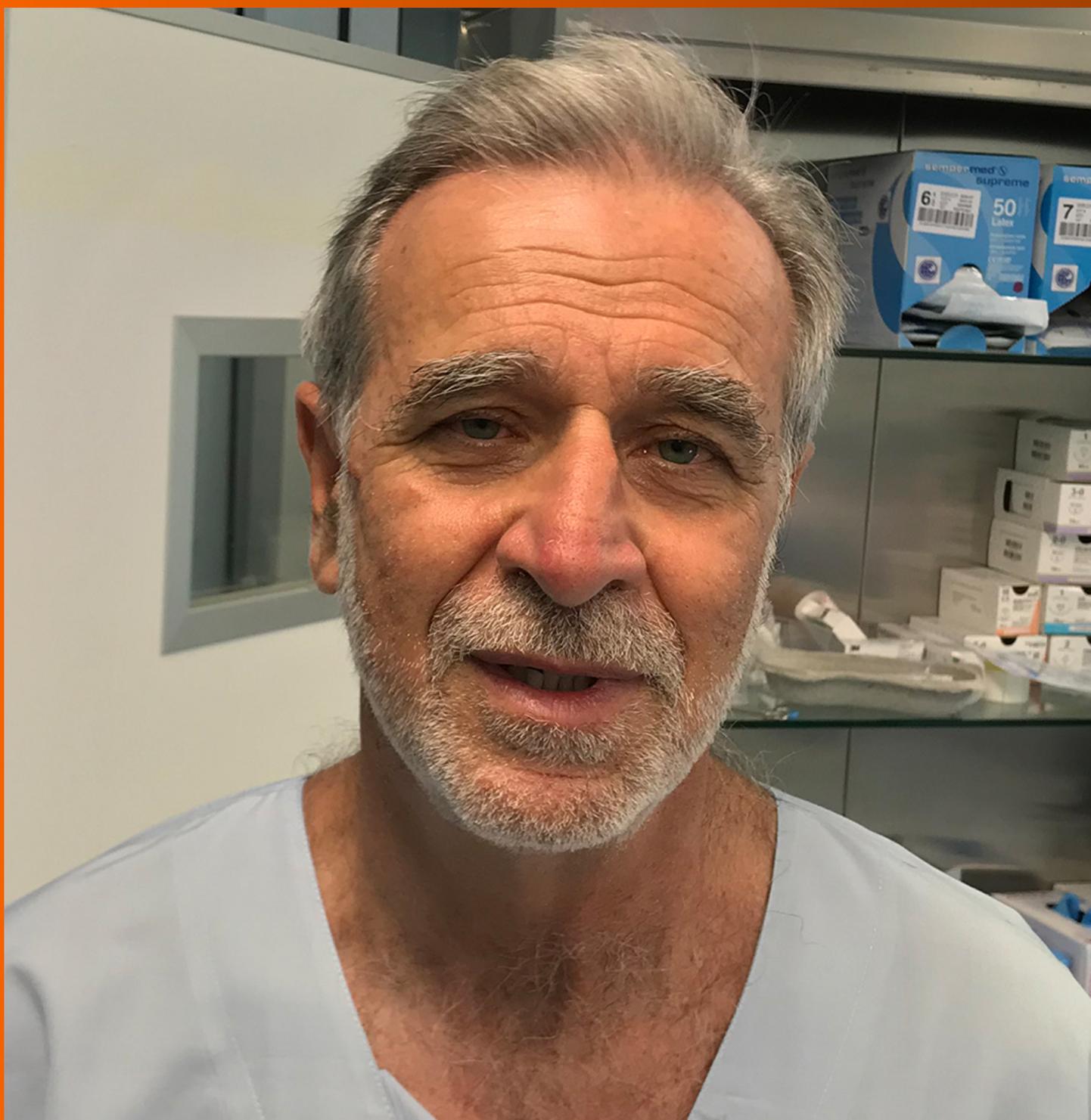


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## Observational Study

**Advanced glycation end product: A potential biomarker for risk stratification of non-alcoholic fatty liver disease in ELSA-Brasil study**

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**Abstract****BACKGROUND**

Liver diseases are associated with the excess formation of advanced glycation end products (AGEs), which induce tissue inflammation and oxidative damage. However, the trend of oxidative marker levels according to the steatosis grade in non-alcoholic fatty liver disease (NAFLD) is unclear.

**AIM**

To compare serum AGE levels between participants with NAFLD accordingly to steatosis severity in the baseline ELSA-Brasil population.

**METHODS**

In 305 individuals at baseline ELSA-Brasil, NAFLD-associated steatosis was classified by ultrasound hepatic attenuation. The participants were grouped according to the severity of steatosis: mild and moderate/severe pooled. The measurement of serum fluorescent AGE concentrations was based on spectrofluorimetric detection. Serum AGE content and clinical and laboratory characteristics of the participants were compared between groups. The correlation between

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serum AGE levels and the grade of steatosis was analyzed. Logistic regression analysis was used to investigate the relationship between serum AGE levels and steatosis severity. A  $P$  value  $< 0.05$  was considered statistically significant.

## RESULTS

According to the steatosis severity spectrum in NAFLD, from mild to moderate/severe, individuals with the most severe steatosis grade had a higher incidence of metabolic syndrome (63% *vs* 34%,  $P \leq 0.001$ ), diabetes mellitus (37% *vs* 14%,  $P \leq 0.001$ ), and high cholesterol levels (51% *vs* 33%,  $P < 0.001$ ). Moreover, individuals with increasing severity of steatosis presented increasing waist circumference, body mass index, systolic and diastolic blood pressure, fasting blood glucose, glycated hemoglobin, insulin, triglycerides, alanine aminotransferase, gamma-glutamyl transferase, C-reactive protein, and uric acid levels and lower high-density lipoprotein. Higher serum AGE content was present in the moderate/severe group of individuals than in the mild group ( $P = 0.008$ ). In addition, the serum AGE levels were correlated with the steatosis grade in the overall sample ( $\rho = 0.146$ ,  $P = 0.010$ ). Logistic regression analysis, after adjusting for confounding variables, showed that subjects with higher serum AGE content had a 4.6-fold increased chance of having moderate or severe steatosis when compared to low levels of serum AGEs. According to the results of the receiver operator characteristic curves analyses (areas under the curve, AUC = 0.83), AGEs could be a good marker of steatosis severity in patients with NAFLD and might be a potential biomarker in predicting NAFLD progression, strengthening the involvement of AGE in NAFLD pathogenesis.

## CONCLUSION

NAFLD-associated steatosis was associated with serum AGE levels; therefore, plasmatic fluorescent AGE quantification by spectroscopy could be a promising alternative method to monitor progression from mild to severe NAFLD accordingly to steatosis grade.

**Key Words:** Advanced glycation end products; Non-alcoholic fatty liver disease; Steatosis; ELSA-Brasil study; Spectroscopy

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**Core Tip:** We evaluated the relationship between fluorescent advanced glycation end product (AGE) levels and the severity of non-alcoholic fatty liver disease (NAFLD)-associated steatosis. We evaluated 305 subjects with NAFLD from Rio de Janeiro in the baseline ELSA-Brasil population grouped according to the steatosis stratification: mild and moderate/severe pooled. Serum AGE levels were correlated with the steatosis grade in the overall sample. The severity of NAFLD-associated steatosis was associated with serum AGE levels; therefore, plasmatic fluorescent AGE quantification by spectroscopy could be a promising alternative method for classifying and grading NAFLD accordingly to hepatic steatosis.

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## INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is characterized by abnormal liver fat accumulation in the absence of significant alcohol consumption or secondary causes of fat accumulation[1,2]. NAFLD includes a large spectrum of clinical phenotypes, from

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non-alcoholic fatty liver to non-alcoholic steatohepatitis (NASH), in which inflammation and hepatocyte injury are present. Individuals with NAFLD can develop progressive fibrosis, liver cirrhosis, hepatocellular carcinoma, and end-stage liver disease[3]. In Western populations, NAFLD is rapidly becoming the top reason for liver transplants[4,5].

The prevalence of NAFLD worldwide is estimated to be 25%, with the highest prevalence in South America (30.45%). This condition is considered the leading cause of chronic liver disease in the United States and Europe[6,7]. Currently, there is a strong bidirectional association between NAFLD and metabolic syndrome (MetS) when components of MetS, such as insulin resistance and hypertriglyceridemia, increase an individual's chance of developing NAFLD[8-10]. Furthermore, metabolic disorders such as diabetes mellitus, dyslipidemia, and obesity have also been associated with NAFLD[1,11,12].

The most common imaging techniques used to diagnose NAFLD are ultrasonography, magnetic resonance, computerized tomography, and controlled attenuation parameter[13,14]. NAFLD can be histologically distinguished from alcoholic steatohepatitis based on histological markers in liver biopsy: Lobular inflammation, hepatocyte ballooning, portal granulocytic inflammation, and Mallory-Denk bodies [15]. Clinical settings and population studies with NAFLD commonly use conventional B-mode ultrasonography because it is non-invasive, easy to use, inexpensive, and widely available[16,17]. Despite the many methods available to assess NAFLD, the pathophysiology of NAFLD is extremely complex and has only been partially elucidated. Although laboratory tests, imaging techniques, and histology play a pivotal role in NAFLD diagnosis, novel alternative methods to diagnose and monitor NAFLD progression are critically needed.

According to the multiple-hit hypothesis, several factors in parallel act synergistically, causing metabolic and molecular alterations that lead to the development and progression of NAFLD[18]. Accumulation of fat in the liver is considered one of the first hits; however, the progression of the disease requires the involvement of other secondary factors, such as insulin resistance, inflammatory mediators, gut microbiome, mitochondrial dysfunction, genetics, nutritional and environmental factors, and/or ER stress[18-20]. Among the "multiple hits", advanced glycation end products (AGEs) have been observed by several studies to play a critical role in the pathogenesis of NAFLD[19,21,22].

AGEs are products of non-enzymatic reactions of reducing sugars or oxidized lipids with amino groups in proteins, lipids, and nucleic acids[23]. In addition to being produced in an endogenous manner, AGEs are also present in foods highly processed or dry heated at high temperatures[24]. Increased AGE levels can trigger loss of normal structure and protein dysfunction due to abnormal cross-linking between intracellular and extracellular proteins. Moreover, the activation of the receptor for AGE (RAGE) by binding AGEs can trigger an increase in inflammation and oxidative stress[25] and participate in insulin resistance, liver injury, and fibrosis[22,26]. AGEs are increased in several pathological conditions such as Alzheimer's disease[27], cardiovascular diseases[28-30] diabetes mellitus[31-33], and liver diseases[34]. We have previously shown that activation of the AGE-RAGE axis, oxidative stress, and inflammation could have a role in microcirculatory alterations in NAFLD[35]. The increased accumulation of AGEs in the serum or liver tissue of NASH patients could induce cell damage and necrotic-type hepatocyte death[36]. AGEs can leak outside of cells and induce inflammatory or fibrotic responses in adjacent cells[36]. To date, there is a lack of clinical studies investigating the role of AGEs in the pathogenesis of NAFLD. Given this, it is of great interest to address the specific pathophysiological mechanisms underlying NAFLD-associated steatosis association with AGEs levels in a large and mixed population cohort. Therefore, in this study, we addressed whether steatosis severity was associated with serum AGE levels in the baseline data from the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) study. We propose plasmatic fluorescent AGE quantification by spectroscopy as a promising alternative method to monitor progression of NAFLD accordingly to steatosis severity.

## MATERIALS AND METHODS

### Study population

This is a cross-sectional study addressing the association between NAFLD and AGEs in the baseline ELSA-Brasil population; a cohort of active or retired employees of both sexes, aged between 35 and 74 years, totaling 15105 civil servants living in six cities in

Brazil (Belo Horizonte, Porto Alegre, Rio de Janeiro, Salvador, São Paulo, and Vitoria) from predefined universities or research institutes[37]. In the present study, subjects from Rio de Janeiro were included ( $n = 305$ ) (Figure 1). Exclusion criteria were as follows: no information on serum AGE content, no information on alcohol consumption, or excessive alcohol consumption ( $> 210$  g/wk for men or 140 g/wk for women). In addition, subjects who had no NAFLD evaluation, poor ultrasound image quality, or normal hepatic deep-beam attenuation (complete viewing) were excluded. This study was approved by all the institutional review boards of the participating institutions, which conforms to the ethical guidelines of the 1975 Declaration of Helsinki, and all participants provided informed consent.

### Data collection

Clinical and anthropometric examination data were collected on-site by questionnaires and clinical exams between August 2008 and December 2010[38]. The questionnaire included information on age at the baseline visit (years), gender, alcohol consumption (never used, ex-user or user), and smoking habit (non-smoker or smoker). Waist circumference (cm), weight (kg), and height (cm) were measured according to standard techniques[39]. Body mass index (BMI) was calculated by dividing body weight by squared height in meters ( $\text{kg}/\text{m}^2$ ). Blood pressure was measured using a validated Omron HEM 705CPINT oscillometer device (Omron Co, Kyoto, Japan) three times with a 1 min interval in the sitting position and the mean of the last two measurements defined the blood pressure value.

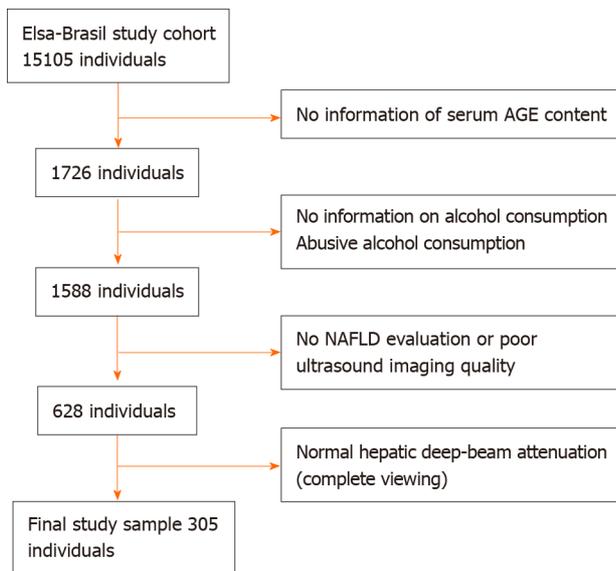
Participants' sera were collected after 12 h of fasting, centrifuged, and stored at  $-70$  °C until analysis. Gamma-glutamyl transferase (GGT) was measured using a kinetic colorimetric assay; aspartate aminotransferase (AST) and alanine aminotransferase (ALT) by enzymatic assay (ADVIA Chemistry, Siemens, Deerfield, United States); uric acid by colorimetric enzyme (uricase) method; total cholesterol, high-density cholesterol, and triglycerides by the enzymatic colorimetric method. Low-density cholesterol was calculated by the Friedewald equation if triglycerides  $\leq 400$  mg/dL or directly measured by enzymatic colorimetric method otherwise; glucose was measured by hexokinase method (ADVIA Chemistry, Siemens, Deerfield, United States), glycated hemoglobin (HbA1c) by high-pressure liquid chromatography (Bio-Rad Laboratories, Hercules, CA, United States), fasting insulin was determined by immunoenzymatic assay (ELISA); and high sensitivity C reactive protein by immunochromatometry (BN II Siemens® nephelometer). Microalbuminuria was measured *via* an immunochemical assay (nephelometry) (Dade Behring). Creatinine levels were measured using an enzymatic colorimetric assay (ADVIA 1200, Siemens, Deerfield, United States). Diabetes was defined by previous medical history of diabetes, antidiabetic drug use, 2 h plasma glucose  $\geq 200$  mg/dL, fasting plasma glucose  $\geq 126$  mg/dL, or glycated hemoglobin  $\geq 6.5\%$ . High cholesterol was defined as the use of medication to treat dyslipidemia or low-density lipoprotein cholesterol  $\geq 130$  mg/dL. The presence of MetS was defined according to the NCEP ATP III definition, which requires three or more of the following five criteria: waist circumference  $\geq 88$  cm for women and  $\geq 102$  cm for men; antihypertensive drug use or systolic blood pressure  $\geq 130$  mmHg or diastolic  $\geq 85$  mmHg; triglycerides  $\geq 150$  mg/dL; high-density lipoprotein (HDL) cholesterol  $< 50$  mg for women and  $< 40$  mg for men; and fasting glucose  $\geq 100$  mg/dL with oral or insulin treatment using hypoglycemic agents.

### Plasma AGEs

Measurement of fluorescent AGE concentrations was based on spectrofluorimetric detection[40]. Serum was diluted 200-fold with phosphate-buffered saline ( $\text{KH}_2\text{PO}_4$  1.06 mmol/L, NaCl 155.10 mmol/L, and  $\text{Na}_2\text{HPO}_4 \cdot 7\text{H}_2\text{O}$  2.97 mmol/L, pH 7.4) and homogenized using a vortex mixer for 10 s, measured at an emission wavelength of 445 nm and at an excitation wavelength of 370 nm (SpectraMax M5 ELISA Microplate Reader, Molecular Devices, Acton, MA, United States). A solution of BSA (1 mg/mL in 0.1 N NaOH) was used as a reference and its fluorescence intensity was defined as one unit of fluorescence. The amount of fluorescence of the patient serum sample was measured at a protein concentration of 1 mg/mL and expressed in arbitrary units after normalization with the native BSA preparation[41].

### Hepatic imaging and NAFLD classification

Ultrasound has been recommended as the first-line method for evaluating hepatic steatosis due to its safety, low cost, and noninvasiveness[42,43]. Among the most common ultrasonography parameters for assessing NAFLD, we have chosen hepatic attenuation of the ultrasound beam because of its better diagnostic performance as



**Figure 1** Flow chart of the selection of the eligible study population in the final analysis. AGE: Advanced glycation end product; NAFLD: Non-alcoholic fatty liver disease.

previously described[44]. A standard B-mode ultrasound evaluation was performed using a visual grading system based on the degree of loss of definition of the diaphragm posterior to the right hepatic lobe. Liver ultrasound examinations were performed by previously trained operators using a high-resolution B-mode scanner (SSA-790A, Aplio XG, Toshiba Medical System, Tokyo, Japan) and a convex array transducer (model PVT-375BT), with a central frequency of ~3.5 MHz and a fundamental frequency of 1.9-5.0 MHz, the same models of equipment used by the participants at enrollment. After the acquisition process, the B-mode hepatic ultrasound images were read, and the quality control protocol was verified by a senior ultrasound radiologist following a standardized protocol[44]. The presence of steatosis was classified as mild (partial, *i.e.*, > 50% visualization of the diaphragm), moderate (partial, *i.e.*, < 50% visualization of the diaphragm), or severe (no visualization of the diaphragm), as previously validated[44].

### Serum biomarkers

Liver steatosis predictive models previously reported in the literature were used to compare the effect of NAFLD classification method on the associations based on fatty liver index (FLI) and hepatic steatosis index (HSI), an algorithm for the prediction of fatty liver in the general population. The FLI is a prevalent biomarker panel consisting of BMI, waist circumference, triglycerides, and gamma-glutamyl transferase for identifying NAFLD, with a total score varying between 0 and 100. The presence of liver steatosis was defined as an FLI  $\geq 60$ , and the absence was defined as FLI < 30[45]. The FLI was calculated according to the following algorithm:  $FLI = \frac{ey}{1 + ey} \times 100$ , where  $y = 0.953 \times \ln(\text{triglycerides, mg/dL}) + 0.139 \times \text{BMI, kg/m}^2 + 0.718 \times \ln(\text{GGT, U/L}) + 0.053 \times \text{waist circumference, cm} - 15.745$ .

The HSI is a biomarker panel consisting of BMI, diabetes, and the ALT/AST ratio. Liver steatosis was defined as HSI  $\geq 36$ [46].  $HSI = 8 \times \text{ALT/AST ratio} + \text{BMI} (+ 2, \text{ if diabetes mellitus; } + 2, \text{ if female})$ .

The atherogenic index (AI), a biomarker used to predict the susceptibility of individuals for developing cardiovascular diseases and atherosclerosis, is strongly associated with NAFLD, which can be used in the auxiliary diagnosis of NAFLD. AI consists of the logarithm of the molar ratio of triglyceride to HDL cholesterol. According to previous studies, AI was stratified into three groups: low (< 0.11), intermediate (0.11-0.21), and high (> 0.21) risk[47].

### Statistical analysis

The participants were grouped according to the severity of NAFLD-associated steatosis: mild, and moderate/severe pooled. Clinical and laboratory characteristics were described by median (interquartile range) for continuous variables and by frequency (percentage) for categorical variables. The serum AGE content of the participants was compared across the steatosis stratification. Given the ordinal nature

of steatosis stratification groups, we ran trend analysis using Jonckheere-Terpstra for continuous variables and Cox-Mantel-Haenszel for categorical variables. The Spearman correlation coefficient was used to analyze correlations between serum AGE levels and the grade of steatosis. A *P* value < 0.05 was considered statistically significant. A logistic regression analysis was used to investigate the relationship between hepatic steatosis severity (moderate/severe pooled) and high levels of serum AGEs (AGEs  $\geq$  0.85, according to the median of AGE values in the study population). Odds ratios (ORs) were obtained from logistic regression analysis, and the results were presented as ORs with a 95% confidence interval (CI). NAFLD-associated steatosis severity was the dependent variable. In the first model, AGEs were the independent variables; in the second model, the first model plus gender; in the third model, the second model plus gamma-glutamyl transferase levels; in the fourth model, the third model plus altered fasting blood glucose ( $110 \leq 125$  mg/dL or  $\geq 126$  mg/dL); in the fifth model, the fourth model plus high cholesterol. This study achieved this model's performance by three folder cross-validations, including sensitivity, specificity, and accuracy. The receiver operator characteristic curves (ROCs) were drawn, which can assess the logistic regression model's prediction performance. Data analysis was performed using R version 3.6.2 (R Project for Statistical Computing) and run in RStudio version 1.2.5033 (R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

Of the 305 individuals from the overall sample, 56% were male, and the median age was 51 (45-55) years. The median (interquartile) serum AGE content was 0.85 (0.76-0.96). Mild steatosis was present in 182 (60%), moderate in 111 (36%), and severe in 12 (4%) individuals. The AGE levels based on NAFLD-associated steatosis stratification were 0.82 (0.75-0.92), 0.86 (0.79-0.98), and 0.98 (0.82-1.10) for mild, moderate, and severe steatosis, respectively. For the subsequent analyses, due to the low frequency of severe steatosis, the moderate and severe individuals were pooled into a single group with 123 (40%) individuals.

**Table 1** displays the characteristics of the participants. According to NAFLD-associated steatosis grade, from mild to moderate/severe, individuals were older, but no difference was found between genders. No difference was observed in smoking habits or use of alcohol. According to the NCEP ATP III definition, individuals with the most severe forms of steatosis had a higher prevalence of MetS (63% *vs* 34%,  $P \leq 0.001$ ), diabetes mellitus (37% *vs* 14%,  $P \leq 0.001$ ), and high cholesterol (51% *vs* 33%,  $P \leq 0.001$ ). Similarly, individuals with increasing severity of steatosis presented increasing waist circumference, BMI, systolic and diastolic blood pressure, fasting blood glucose, glycated hemoglobin, insulin, triglycerides, ALT, GGT, C-reactive protein, and uric acid levels and lower HDL. There were no significant differences in total cholesterol, AST, microalbuminuria, creatinine, sodium, and potassium levels among groups (**Table 1**).

**Table 2** shows the association between the FLLI, HIS, and AI with the severity of NAFLD-associated steatosis. Notably, increased degrees of steatosis resulted in increased values of the evaluated indexes (**Table 2**).

Higher serum AGE content was present in the moderate/severe group of individuals than in the mild steatosis group ( $P = 0.008$ ) (**Figure 2**). In addition, the serum AGE levels were correlated with the steatosis grade in the overall sample ( $\rho = 0.146$ ,  $P = 0.010$ ).

Logistic regression analysis was performed to verify if subjects with higher serum AGE content were more likely to have severe forms of NAFLD accordingly to steatosis levels (**Table 3**). The results showed that only high AGE serum levels (OR: 2.65, 95%CI: 1.05-6.92) was an independent risk factor for severe NAFLD-associated steatosis, and all four models showed a consistent relationship with the severity of steatosis in NAFLD (**Table 3**). The risk of moderate or severe NAFLD-associated steatosis in the highest serum AGE content was 239% (OR: 3.39; 95%CI: 1.24-9.98) after adjustment for sex. A similar association was also observed in model 2 after additional adjustment for GGT levels. Model 3 was also associated with an increased risk of severe forms of NAFLD-associated steatosis after additional adjustment for hyperglycemia (OR: 4.53, 95%CI: 1.44-16.28). In model 4, the risk was 4.6-fold higher after adjusting for hypercholesterolemia (OR: 4.67, 95%CI: 1.46-17.17).

To further confirm the predictive power of high AGE levels for NAFLD-stratification accordingly to hepatic steatosis, ROC analysis for the diagnostic value for steatosis was done (**Figure 3**). The areas under the curve (AUC) for AGEs in model 4 of

**Table 1 Clinical characteristics according to non-alcoholic fatty liver disease-associated steatosis severity**

	Mild (n = 182)	Moderate/severe (n = 123)	P value <sup>1</sup>
Age (yr)	50 (44-54)	52 (45-57)	0.002
Gender			
Male	99 (54)	72 (59)	0.503
Female	83 (46)	51 (41)	
Race			
Black	17 (9)	15 (12)	0.383
Brown	52 (29)	41 (34)	
White	109 (61)	61 (50)	
Asian	2 (1)	3 (2)	
Indigenous	0 (0)	2 (2)	
Use of alcohol			
Never used	15 (8)	10 (8)	0.144
Ex-user	46 (25)	22 (18)	
User	121 (67)	91 (74)	
Smoking habit			
Non smoker	102 (56)	62 (50)	0.261
Smoker	80 (44)	61 (50)	
Metabolic syndrome (NCEP ATP III)			
Presence	62 (34)	78 (63)	< 0.001
Absence	120 (66)	45 (37)	
Diabetes mellitus			
Presence	25 (14)	45 (37)	< 0.001
Absence	157 (86)	78 (63)	
High cholesterol			
Presence	59 (33)	62 (51)	< 0.001
Absence	122 (67)	61 (49)	
Body mass index (kg/m <sup>2</sup> )	26.6 (24.6-29.6)	29.2 (27.2-32.3)	< 0.001
Waist circumference (cm)	94.1 (87.5-100.0)	101.5 (94.1-107.5)	< 0.001
Systolic blood pressure (mmHg)	117 (108-127.5)	121.5 (113.5-131.2)	0.001
Diastolic blood pressure (mmHg)	75.5 (69.6-81.5)	79.5 (74.0-86.0)	< 0.001
Laboratory			
Fasting glucose (mg/dL)	99.28 (93.33-105.84)	104.24 (97.79-116.14)	< 0.001
HbA1c (mg/dL)	5.40 (5.1-5.8)	5.76 (5.3-6.2)	< 0.001
Insulin (mcUI/mL)	9.91 (7.1-13.9)	13.71 (10.5-19.32)	< 0.001
Total cholesterol (mg/dL)	199.6 (176.8-227.6)	196.2 (175.3-222.8)	0.636
Triglycerides (mg/dL)	107.8 (79.0-152.4)	137.15 (99.6-225.0)	< 0.001
HDL (mg/dL)	50.1 (42.9-60.1)	47.45 (42.0-54.2)	0.007
ALT (mg/dL)	25 (19-33)	30 (22.5-40)	0.001
AST (mg/dL)	24 (21-28)	24 (21-29.5)	0.276
GGT (mg/dL)	24 (18-35)	33 (23-51)	< 0.001
hs-CRP (mg/dL)	1.6 (0.8-3.5)	2.2 (1.4-4.7)	< 0.001

Uric acid (mg/dL)	5.4 (4.5-6.6)	6 (5.2-6.9)	< 0.001
Microalbuminuria (mg/dL)	0.50 (0.33-0.82)	0.51 (0.31-1.05)	0.265
Creatinine (mg/dL)	0.87 (0.77-0.97)	0.87 (0.77-0.97)	0.324
Sodium (mg/dL)	143 (141-144)	143 (141-144)	0.200
Potassium (mg/dL)	4.5 (4.2-4.7)	4.4 (4.2-4.7)	0.820

Data were presented as median (interquartile range) or count (percentage).

<sup>1</sup>Jonckheere-Terpstra for continuous variables and Cox-Mantel-Haenszel for categorical ones for trend between categories.

HbA1c: Hemoglobin A1c; HDL: High-density lipoprotein; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: Gamma-glutamyl transferase; hs-CRP: High sensitivity C-reactive protein.

**Table 2 Non-alcoholic fatty liver disease-associated steatosis stratification according to fatty liver serum biomarkers**

	Mild (n = 182)	Moderate/severe (n = 123)	P value <sup>1</sup>
Fatty liver index	44.65 (26.71-67.91)	74.50 (54.08-88.16)	< 0.001
Hepatic steatosis index	36.66 (33.63-40.89)	41.22 (37.75-45.47)	< 0.001
Atherogenic index	0.35 (0.16-0.50)	0.44 (0.29-0.70)	< 0.001

Data were presented as median (interquartile range).

<sup>1</sup>Jonckheere-Terpstra test for trend between categories.

**Table 3 Effect of high advanced glycation end product levels on the non-alcoholic fatty liver disease-associated steatosis severity**

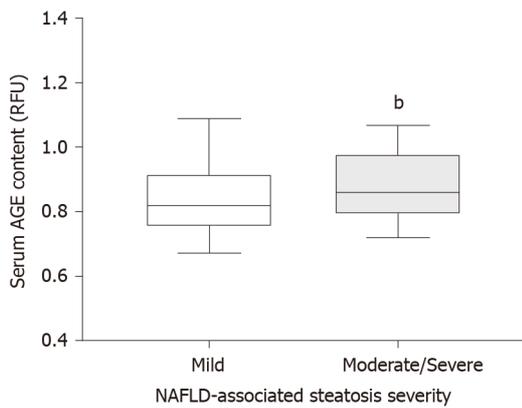
Variable	SE	OR (95%CI)	Sensitivity	Specificity	Accuracy
Crude model	0.47	2.64 (1.04-6.92)	0.62	0.61	0.61
Model 1	0.52	3.38 (1.24-9.98)	0.60	0.73	0.64
Model 2	0.55	3.34 (1.17-10.40)	0.71	0.68	0.69
Model 3	0.61	4.52 (1.44-16.28)	0.78	0.72	0.75
Model 4	0.62	4.66 (1.45-17.16)	0.77	0.77	0.77

Model 1: Adjusted for gender; Model 2: Additionally adjusted for gamma-glutamyl transferase; Model 3: Additionally adjusted for altered blood glucose (categorical  $\geq 126$ ,  $110 \leq 125$ ); Model 4: Additionally adjusted for high cholesterol. High cholesterol was defined as use of medication to treat dyslipidemia or low-density lipoprotein cholesterol  $\geq 130$ . OR: Odds ratio; CI: Confidence interval.

adjustment (0.83) would have the most clinical implications for predicting the severity of NAFLD-associated steatosis, with a sensitivity of 0.77, a specificity of 0.77, and an accuracy of 0.77, followed by model 3 (AUC = 0.81), model 2 (AUC = 0.79), model 1 (AUC = 0.72), and the crude model (AUC = 0.62) (Table 3, Supplementary Table 1, and Figure 3).

## DISCUSSION

Addressing the specific mechanisms by which NAFLD progresses could potentially open new frontiers for preventive and monitoring strategies for liver diseases. In this study, we investigated the relationship between plasmatic AGE levels and severity of NAFLD-associated steatosis in a racially/ethnically diverse cohort at baseline of the ELSA-Brasil study. Steatosis stratification based on serum biomarker indexes, that is, FLI, HSI, and AI, was associated with the ultrasonography grade of NAFLD previously described<sup>[45-47]</sup>, with higher values for moderate/severe group. Serum AGE levels were positively correlated with the steatosis stage; that is, AGE content was significantly higher in subjects with moderate/severe forms of steatosis compared to the mild form. Logistic regression analysis after adjusting for confounding variables showed that subjects with higher serum AGE content had a 4.6-fold increased chance

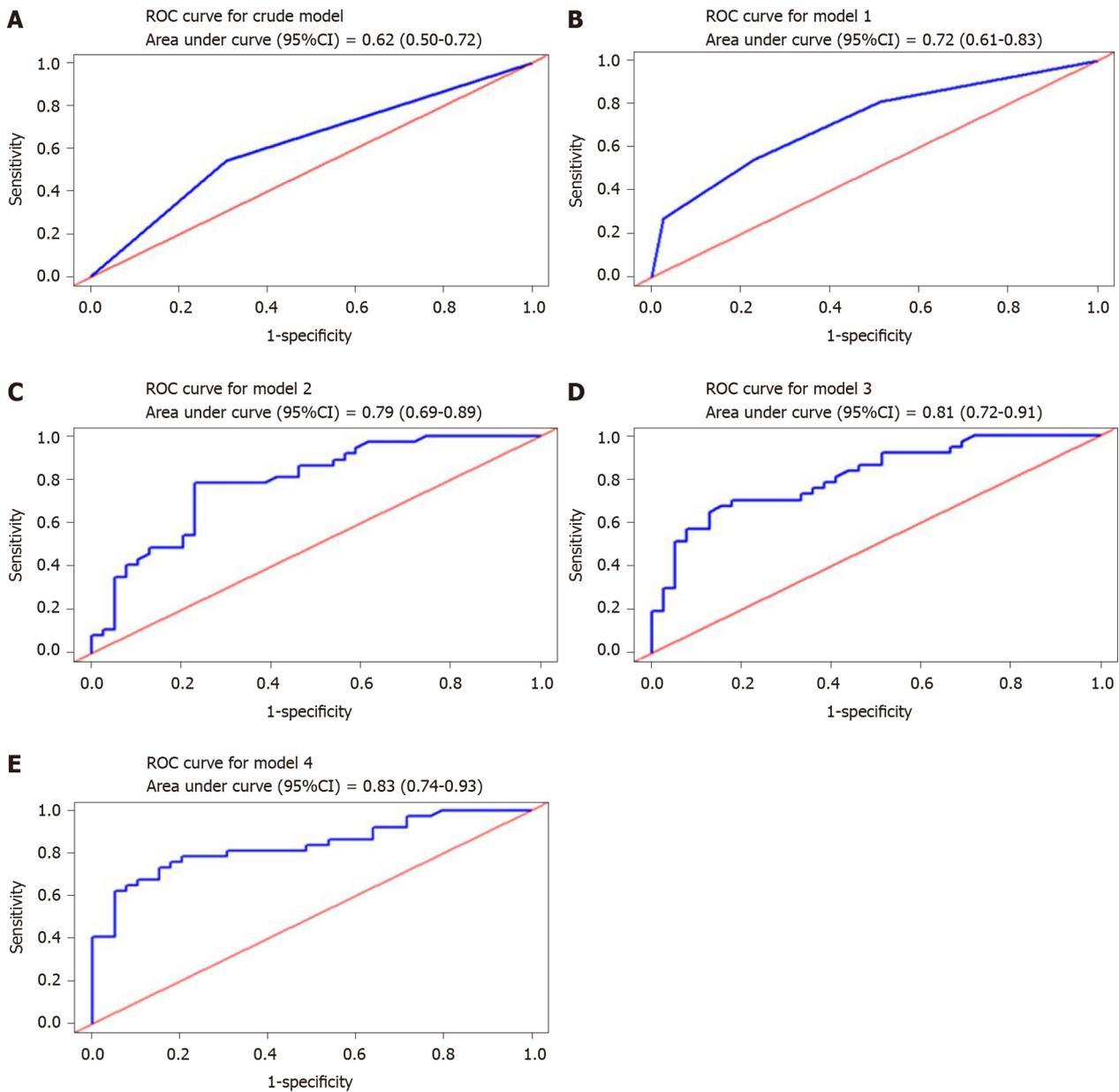


**Figure 2** Boxplot showing the distribution of advanced glycation end product values in serum in the group of participants with mild steatosis and the group of participants with moderate/severe pooled steatosis. Data are shown as median  $\pm$  inter-quartile range. <sup>b</sup> $P < 0.001$ . AGE: Advanced glycation end product; RFU: Relative fluorescent units.

of having moderate or severe forms of steatosis when compared to that in those with low levels of serum AGEs. According to the results of the ROC analyses from the current study, AGEs could be a good marker of steatosis severity in patients with NAFLD and might be a potential biomarker in predicting NAFLD progression. Therefore, fluorescent AGEs could be a potential plasmatic biomarker for risk stratification of NAFLD accordingly to the severity of hepatic steatosis.

A proposed mechanism to explain why some patients with NAFLD progress to more severe forms of NAFLD is the multiple-hit hypothesis. In this hypothesis, the deposition of fat in the liver is the first hit, whereas the progression requires the involvement of other factors[48]. Emerging evidence highlighted that AGEs can act as a critical 'hit' being one factor that drives the progression from simple NAFLD to NASH and liver fibrosis[18,49]. Previously, the correlation of CML level with the severity of disease[50]. We and others have demonstrated increased deposition of AGEs in the liver of animals with NAFLD, MetS, and diabetes[35,41,50-57], which was associated with microcirculatory disturbances[53]. Furthermore, treatment with pyridoxamine, an AGE inhibitor, reduced the microcirculatory and metabolic alterations caused by NAFLD[53]. Using biopsies, Gaens *et al*[56] showed that Ne-(carboxymethyl) lysine (CML), as assessed by immunohistochemistry, was increased in the liver of obese individuals who underwent bariatric surgery, and AGE levels were associated with the grade of hepatic steatosis and inflammation, suggesting that AGEs could contribute to NAFLD progression. Furthermore, incubation of human hepatic stellate cells with AGEs increased the expression of fibrotic and cell proliferation markers, suggesting that these compounds can contribute to the development of NASH[58]. Mechanistically, AGE formation may result in loss of hepatocyte function, while intracellular accumulation of AGEs causes cell death[59]. Moreover, the interaction of extracellular AGEs with its receptor RAGE in hepatocytes[60] promotes inflammation, a characteristic feature of NAFLD progression to NASH[61]. In addition, fatty acids stimulate CML accumulation in hepatocytes and subsequently elicit inflammatory reactions *via* RAGE activation[56].

Although some studies have highlighted the involvement of AGEs in liver diseases, only two previous studies assessed the correlation between serum AGEs and the severity of NAFLD. The study by Hyogo *et al*[34] showed that AGE levels were elevated in NASH patients compared to individuals with simple steatosis. Świdarska *et al*[62] reported that AGEs can be used as a biomarker to differentiate between patients with minimal *vs* moderate steatosis, but in a small cohort (early NAFLD  $n = 29$  and advanced NAFLD  $n = 38$ ). We addressed the AGE levels in subjects with mild and moderate/severe steatosis in a larger cohort. Presently, we assessed AGE levels by fluorescent spectroscopy, while the study by Hyogo *et al*[34] used ELISA. Fluorescence spectroscopy is an easy, rapid, and cost-effective method that has been previously proposed as a reliable tool that can be used to distinguish patients with type 1 and 2 diabetes from healthy subjects[63,64]. Recently, Heidari *et al*[65] showed that serum levels of AGEs increase progressively with increasing duration of diabetes, and proposed the monitoring of fluorescent AGEs as an estimation tool for diabetes chronicity.



**Figure 3 Receiver operating characteristic curves and corresponding areas under the curve of models to predict non-alcoholic fatty liver disease-associated steatosis.** ROC: Receiver operating characteristic; CI: Confidence interval.

Along with increasing NAFLD-associated steatosis severity, increased AGE is associated with a concomitant worsening of the metabolic profile, namely MetS, diabetes mellitus, cholesterol levels, BMI, waist circumference, blood pressure, and lipid and glycemic profile[66-70]. In our study, the results of logistic multiple regression analysis showed that, as well as AGEs, altered fasting blood glucose and high cholesterol levels were associated with the severity of steatosis in NAFLD. The risk of severe steatosis in individuals with altered fasting blood glucose and high cholesterol was 6.730 and 3.490 times higher than that in subjects with a normal range of blood glucose and cholesterol, respectively. Although the precise pathological process has not been elucidated, it has been widely accepted that excess triglyceride accumulation in the liver is a prerequisite for NAFLD development. Triglyceride showed a great correlation with NAFLD in both epidemiologic studies[71] and pre-clinical research[72]. The progression of NAFLD results from an imbalance between lipid uptake and lipid disposal and eventually causes oxidative stress and hepatocyte injury. Excess lipid accumulation may result in impaired insulin signaling through cell autonomous mechanisms or through the induction of inflammation and the subsequent production of inflammatory cytokines by macrophages, which impair insulin action[73]. Increasing evidence suggests that subjects with hyperglycemia resulting from defects in insulin secretion, insulin action, or both have a particularly

high risk for NASH, with varying degrees of liver fibrosis[74,75]. Insulin resistance may cause inflammation in the adipose tissue, which triggers the acceleration of lipolysis, resulting in increased free fatty acid export to the liver, leading to the accumulation of fat in the liver and consequently NAFLD[48,76]. It has already been demonstrated that AGE formation is accelerated under a hyperglycemic state, playing an important role in the pathogenesis of NAFLD and complications of diabetes[77,78]. Lipid peroxidation is also known to be involved in the generation of AGEs, and the glycation of lipids results in the formation of AGEs, which are related to triglyceride or HDL-C levels[79].

The current study has limitations that should be mentioned. First, it was not possible to distinguish people with NAFLD from healthy controls based on serum fluorescent AGE concentrations. Moreover, given the cross-sectional design of the study, no causal relations can be established. The sample size is higher than others in the field, but the sample size of the severe form of NAFLD-associated steatosis remains small, probably due to the study population being formed by healthy employees. Thus, the associations found here may be even greater in the general population. This might have limited our results to fully explore the relationship between glycation products and disease stages. As this was a single-center study, results and glycation levels should be extrapolated to other populations carefully.

## CONCLUSION

In conclusion, this cross-sectional analysis of the ELSA-Brasil cohort baseline study showed that high serum AGE content was associated with severe forms of steatosis, with high serum AGE levels being an important risk factor for NAFLD-associated steatosis severity. In addition, serum AGE content was positively correlated with the severity of steatosis. These data suggest that AGEs might be a potential plasmatic biomarker for NAFLD stratification accordingly to hepatic steatosis. Our findings strengthen the involvement of AGE in NAFLD pathogenesis. These findings highlight the importance of including the evaluation of AGE status as a part of health examinations and may help health policy-makers prevent or delay NAFLD among the population.

## ARTICLE HIGHLIGHTS

### **Research background**

Non-alcoholic fatty liver disease (NAFLD) is considered the hepatic manifestation of metabolic syndrome and it affects about 25% of the adult population, and can progress to hepatocellular carcinoma, death, and/or liver transplantation. The underlying mechanisms that account for disease progression are still not fully understood due to its complexity.

### **Research motivation**

Liver diseases are associated with the excess formation of advanced glycation end products (AGEs), which induce tissue inflammation and oxidative damage. However, the trend of oxidative marker levels according to NAFLD severity is unclear.

### **Research objectives**

We aim to understand whether NAFLD-associated steatosis severity was associated with serum AGE levels in the baseline data from the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) study to address the specific pathophysiological mechanisms underlying NAFLD association with AGEs in a large and mixed population cohort.

### **Research methods**

NAFLD-associated steatosis severity was classified by ultrasound hepatic attenuation: mild and moderate/severe pooled. The measurement of serum fluorescent AGE concentrations was based on spectrofluorimetric detection. Serum AGE content and clinical and laboratory characteristics of the participants were compared between groups. The correlation between serum AGE levels and the grade of steatosis was analyzed. Logistic regression analysis was used to investigate the relationship between

serum AGE levels and NAFLD-associated steatosis severity. A *P* value < 0.05 was considered statistically significant.

### Research results

According to hepatic steatosis grade in NAFLD, from mild to moderate/severe, individuals with the most severe forms of steatosis had a higher incidence of metabolic syndrome, diabetes mellitus, and high cholesterol levels. Moreover, individuals with increasing severity of NAFLD-associated steatosis presented increasing waist circumference, body mass index, systolic and diastolic blood pressure, fasting blood glucose, glycated hemoglobin, insulin, triglycerides, alanine aminotransferase, gamma-glutamyl transferase, C-reactive protein, and uric acid levels and lower high-density lipoprotein. Higher serum AGE content was present in the moderate/severe group of individuals than in the mild group. In addition, the serum AGE levels were correlated with the steatosis grade in the overall sample. Logistic regression analysis, after adjusting for confounding variables, showed that subjects with higher serum AGE content had a 4.6-fold increased chance of having moderate or severe forms of NAFLD-associated steatosis when compared to low levels of serum AGEs.

### Research conclusions

Steatosis severity in NAFLD patients was associated with serum AGE levels, thereafter AGEs could be a good marker of NAFLD stratification accordingly to steatosis grade, strengthening the involvement of AGE in NAFLD pathogenesis.

### Research perspectives

Plasmatic fluorescent AGE quantification by spectroscopy could be a promising alternative method to monitor progression from mild to severe forms of NAFLD accordingly to the severity of hepatic steatosis.

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