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## Advanced glycation end products and risk of mortality in patients with cirrhosis: a prospective cohort study

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The role of diet in reducing the burden of liver disease and mortality attributed to cirrhosis is very imperative. The present study scrutinized the relationship between dietary advanced glycation end products (AGEs) and mortality in patients with cirrhosis. This research was a prospective cohort study on 166 ambulatory cirrhotic patients who had been diagnosed with cirrhosis for a maximum of six months. Follow-up of patients continued for 5 years until May 2024. To determine the incidence of mortality in the quartiles of dietary AGEs, cox regression models were used with the adjustment of potential confounding variables. Although the first model of the analysis by adjusting the results for age and sex failed to show a significant increase in the risk of mortality in patients ( $HR_{Q4 \text{ vs. } Q1} = 2.64$ ; 95% CI = 0.9–7.5, P trend = 0.075), after adjusting the results for further confounders in the second ( $HR_{Q4 \text{ vs. } Q1} = 3.56$ ; 95% CI = 1.1–11.6, P trend = 0.040) and third ( $HR_{Q4 \text{ vs. } Q1} = 3.3$ ; 95% CI = 1.79–13.7, P trend = 0.048) models, the P trend for the risk of mortality during the quartiles of AGEs became significant. In addition, along with increasing trend of dietary AGEs, the number of deaths increased significantly ( $P = 0.024$ ). Higher mortality risk was generally attributed to higher dietary AGEs in patients with cirrhosis.

**Keywords** Advanced glycation end products, AGEs, Mortality, Cirrhosis

Liver cirrhosis plays a major role in the morbidity and mortality of patients with chronic liver diseases<sup>1</sup>. Cirrhosis involves stages of progressive liver damage characterized by the extensive formation of fibrous tissue that transforms the lobular structure of the liver into regenerative nodules<sup>2</sup>. This process significantly impairs liver function<sup>2</sup>. Cirrhosis can lead to the development of hepatocellular carcinoma (HCC) and hepatic decompensation, which includes conditions like ascites, hepatic encephalopathy, and variceal bleeding<sup>1,3–8</sup>. Cirrhosis is one of the main causes of global mortality, accounting for 2.4% of global deaths in 2019<sup>9</sup>. Moreover, the burden of disease project in Iran in 2017 showed that cirrhosis and other liver diseases accounted for 1.42% of the total mortality rate<sup>10</sup>.

Cirrhosis has been associated with various factors including viral infections, autoimmune disorders, metabolic and genetic disorders, long-term use of some drugs<sup>11</sup>, alcohol abuse<sup>12</sup>, and diabetes mellitus (DM)<sup>13,14</sup>. In addition to the mentioned factors, diet is also considered as an operative factor in the etiology of liver

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cirrhosis<sup>15</sup>. The modern dietary patterns contain highly processed foods, which are not only high in fat, sugar, and salt, but also contain potentially harmful compounds known as advanced glycation end-products (AGEs). Previous studies have revealed that dietary AGEs are directly related to increased inflammation, oxidative stress, and insulin resistance (IR)<sup>16,17</sup>. Therefore, dietary AGEs play an important role in the pathogenesis of diseases<sup>18</sup>.

AGEs are formed through a non-enzymatic reaction where reducing sugars chemically interact with amino groups found in proteins, lipids, and nucleic acids. This sequence includes creating a Schiff base, an Amadori rearrangement, and oxidative modifications (glycoxidation), leading to the production of AGEs<sup>19-21</sup>. AGEs are produced by two main processes: one is the natural metabolic processes of the body and the other is the formation of AGEs that occurs during cooking and food processing. A significant part of these AGEs are absorbed by the digestive system<sup>22</sup>.

Direct association of AGEs with increased risk of many chronic diseases such as diabetes and its related complications, cardiovascular diseases (CVDs), obesity, kidney and neurological diseases has been proven<sup>23</sup>. Also, it has been reported that non-alcoholic fatty liver disease (NAFLD) and cirrhosis are associated with increased serum concentrations of N-carboxyethyllysine (CEL) and N-carboxymethyllysine (CML)<sup>24</sup>. There is a growing body of evidence linking AGEs to intimal thickening, plaque formation, and ultimately the development or progression of atherosclerosis, which predisposes to cardiovascular events<sup>25</sup>, which in turn are a major cause of mortality in patients with cirrhosis<sup>26</sup>. Advanced glycation end products may cause the production of oxygen free radicals through interaction with receptors involved in inflammation signaling, followed by the release of inflammatory cytokines such as interleukin-6 (IL-6) and C-reactive protein (CRP) in various cells, especially the liver<sup>24</sup>. Although the exact mechanism of the development and progression of cirrhosis is still not fully understood, growing evidence suggests that AGEs may play a role in the development of the disease and exacerbation of its complications by stimulating inflammation.

In our current study, we hypothesized that dietary AGEs may promote inflammatory cascade seen in cirrhotic patients, subsequently leading to high rate of mortality. Therefore in present prospective cohort study, we investigated the relationship between dietary AGEs and mortality in patients with cirrhosis.

## Methods and materials

### Study design and population

The current cohort study included 166 adult patients with liver cirrhosis, aged over 18 years who had been diagnosed within the past 6 months. The methods of this research have been described in detail elsewhere<sup>27,28</sup>, with the difference that the follow-up period in this study was 60 months.

Briefly, non-pregnant or lactating patients with no medical history of diseases such as renal failure, cancer, diabetes, infectious diseases, heart disease, acquired immunodeficiency syndrome (AIDS), or pancreatic insufficiency were included in this study. In this study, the participants were followed up for 5 years from the time of registration. They were contacted annually by telephone to complete a follow-up questionnaire regarding any deaths or medical events.

### Dietary assessment and AGEs calculation

Dietary intakes were collected through face-to-face interviews using a reliable and valid food frequency questionnaire (FFQ) with 168 items<sup>29</sup> at enrollment, before disease diagnosis had significant effects on patients' intakes. A trained nutritionist assessed and analyzed dietary data using Nutritionist IV software. Information on the consumption of different food items was recorded on a daily, weekly and monthly basis and subsequently converted to grams using standard household measurements. The average daily consumption of energy and essential nutrients was determined by utilizing the food composition table (FCT) provided by the United States Department of Agriculture (USDA).

Since the Iranian food composition table does not have data on the content of AGEs in foods, to calculate the intake of dietary AGEs, we used the published database of food AGEs for a multi-ethnic urban population in the northeastern United States, which was measured using a valid immunoassay method<sup>30,31</sup>. Considering that the FFQ questions were designed based on the frequency of consumption and the usual size of food, first the consumed food items reported in household measures were converted to grams, then the total consumption of AGEs per day was calculated for each participant. For data analysis, consumption was classified using quartile cutoffs. The intake of AGEs was adjusted for daily energy intake.

### Other assessments

Basic information such as age, sex, alcohol and smoking habits and the cause of cirrhosis were collected as primary data at the beginning of the study. Weight was accurately measured using digital scales, rounded to the nearest 100 g, while height was measured with a tape measure to the closest 1 cm. These measurements were taken while the participants were wearing light cloths and standing straight without shoes. Subsequently, the BMI was calculated by dividing the weight in kilograms by the square of the height in meters.

The subjective global assessment (SGA) score was calculated based on Destky et al.<sup>32</sup>. Accordingly, participants were divided into three categories including well-nourished (A), mild to moderate malnourished (B), and severe malnourished (C). Severity and prognosis of liver cirrhosis were evaluated by using clinical and biochemical indicators and determination of Child-Pugh (qualitative: A, B and C) and model for end-stage liver disease (MELD) scores (quantitative)<sup>33</sup>.

### Statistical analysis

To perform comparisons and analyses, participants were divided into four quartiles based on their dietary intake of AGEs. One-way analysis of variance (ANOVA) or chi-square ( $\chi^2$ ) test was used to compare baseline

characteristics and dietary intakes of participants among quartiles of AGEs, as desired. Multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox proportional hazards regression models to assess the relationship between dietary intakes of AGEs and mortality in patients with cirrhosis. Three different models were designed to control the potential confounding variables. Model 1: adjustments for sex (man, woman) and age (continuous). Model 2: additionally adjustments for BMI, alcohol consumption ( $> 30$  g/day), and smoking habits. Model 3: additionally adjustments for Child-Pugh classification, MELD score, and etiology of liver disease. Statistical analyses were conducted using SPSS (version 19; SPSS Inc, Chicago, IL, USA) with a significance level of  $< 0.05$ .

## Results

The final analysis was conducted on a total of 121 participants (83 men and 38 women). During the 5 years of follow-up, 50 deaths were recorded. Liver failure accounted for 55% of deaths, cardiovascular diseases 31%, carcinoma 3% and miscellaneous causes for 11% of deaths. The average intake of AGEs was estimated as  $8427.6 \pm 5114$  mg/day. As Table 1 shows, the ratio of men to women increases significantly as the average intake of dietary AGEs increases ( $P=0.006$ ). Also, smoking ( $P=0.017$ ) and alcohol use ( $P=0.032$ ) increased significantly. Although most cases of cirrhosis had a viral cause, the etiology difference between the AGE quartiles was close to the significant level ( $P=0.047$ ). No significant differences were observed in the participants' average age, anthropometric and clinical parameters.

As presented in Table 2, comparison of dietary intakes among AGE quartiles indicated a significant increase in energy intake ( $P=0.016$ ) and meats ( $P=0.001$ ). While the decrease in the percentage of carbohydrates from the total energy intake was close to a significant level ( $P=0.052$ ). No significant differences were observed between other dietary intakes across the AGE quadriles.

The results of the analysis of the relationship between dietary intakes of AGEs and mortality in patients with cirrhosis are summarized in Table 3. Although the first model of the analysis by adjusting the results for age and sex failed to show a significant increase in the risk of mortality in patients ( $HR_{Q4 \text{ vs. } Q1} = 2.64$ ; 95% CI = 0.9–7.5,  $P$  trend = 0.075), after adjusting the results for further confounders in the second ( $HR_{Q4 \text{ vs. } Q1} = 3.56$ ; 95% CI = 1.1–11.6,  $P$  trend = 0.040) and third ( $HR_{Q4 \text{ vs. } Q1} = 3.3$ ; 95% CI = 1.79–13.7,  $P$  trend = 0.048) models, the  $P$  trend for the risk of mortality during the quartiles of AGEs became significant. In addition, along with increasing trend of dietary AGEs, the number of deaths increased significantly ( $P=0.024$ ). Full adjusted hazard ratios for mortality in patients with cirrhosis in different quartiles of AGEs are depicted in Fig. 1.

## Discussion

This cohort study contributed to the expansion of knowledge about the possible association between dietary AGEs and mortality in patients with cirrhosis. What emerges from the results of this cohort is an increase in the risk of mortality by 2–3 times following an increase in AGE intake in cirrhotic patients. These findings are consistent with some previous studies that indicated the relationship between AGE intake and mortality in patients with various chronic diseases. A follow-up of postmenopausal women diagnosed with breast cancer for more than 15 years showed that a high intake of AGEs was associated with an increased risk of all-cause mortality, CVD, and breast cancer<sup>34</sup>. Similarly, a direct association of serum AGEs with increased risk of mortality of all-caused, CVD, and coronary heart disease was also reported in a large cohort study with more than 1100 participants<sup>35</sup>. However, conflicting results have been reported in some studies<sup>36–38</sup>.

Cirrhosis commonly coexists with inflammation, insulin resistance (IR) and related complications such as metabolic syndrome (MetS) which could provide an explanation for the association between AGEs and liver cirrhosis<sup>39,40</sup>, although the exact mechanism of this association has not yet been fully elucidated. Recent findings have confirmed that the interaction between AGEs and their cellular receptor (RAGE) may play a role in developing various severe conditions, including diabetic vascular problems, neurodegenerative disorders, IR, and cancers<sup>41–47</sup>. Moreover, a growing body of evidence suggests that the interaction between AGEs and RAGE elicits reactive oxygen species (ROS) and subsequently leads to inflammatory responses in different cell types, such as hepatocytes and hepatic stellate cells<sup>48–51</sup>. AGEs activate Kupffer cells, sinusoidal endothelial cells, and stellate cells, resulting in the release of oxygen radicals and cytokines like transforming growth factor (TGF)- $\beta$ 1, which promotes fibrosis<sup>52</sup>. Furthermore, AGEs can directly contribute to increased collagen deposition in the liver through cross-link formation<sup>52</sup>.

According to the findings of the present study, comparing the highest intake with the lowest quartile after adjusting for confounding factors, the dietary intake of AGEs was associated with a more than 3-fold increase in the risk of mortality in cirrhotic patients, and on the other hand, the main cause of death of patients in this study was liver failure (55%), which can be caused by AGE damage to the hepatic tissue. Hepatic stellate cells (HSCs) play a crucial role in liver fibrogenesis by producing an extracellular matrix in the liver<sup>50</sup>. Fehrenbach et al.<sup>50</sup> showed that HSCs and myofibroblasts (MFB) can express RAGE, and the activation of HSCs and their differentiation to MFB increases RAGE expression. Activation of RAGE by ligands resulted in the generation of ROS and the initiation of mitogen-activated protein kinase (MAPK) and nuclear factor-kappa B (NF- $\kappa$ B) signaling pathways HSCs, which are directly related to hepatic inflammation<sup>50,53,54</sup>. Moreover, AGEs derived from glyceraldehyde stimulate the expression of fibrosis and inflammation-related genes and proteins, such as TGF- $\beta$ 1, collagen type I alpha2, and monocyte chemoattractant protein-1, by generating ROS via NADPH oxidase in cultured HSCs<sup>51</sup>. The interaction between AGEs and RAGE triggers the activation of Rac-1, leading to the stimulation of hepatic CRP in human hepatoma cells, specifically Hep3B cells<sup>55</sup>. Previous studies have indicated that at least two separate signaling pathways contribute to the induction of the CRP gene in Hep3B cells exposed to AGEs. One pathway involves the activation of Rac-1 and the NADPH oxidase, leading to the production of ROS. Rac-1 mediates the other pathway and involves the activation of signal transducer and

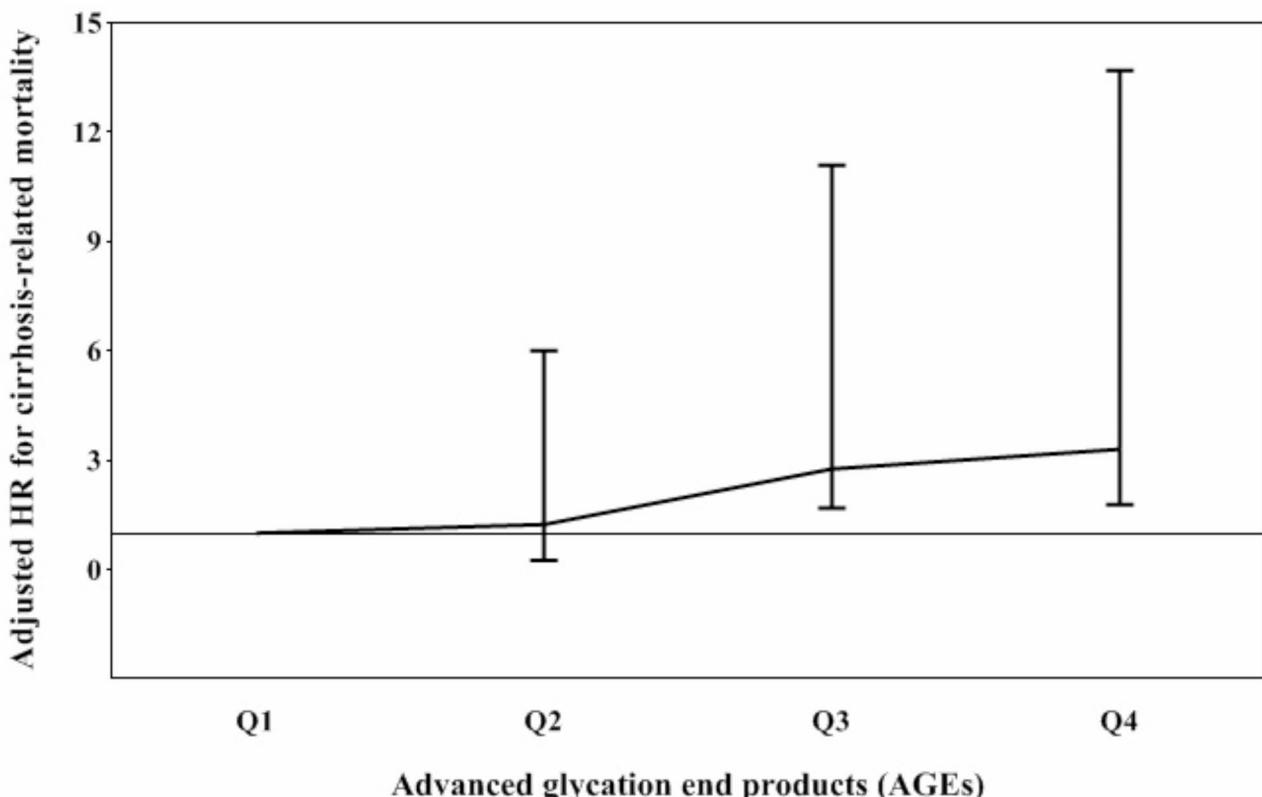
	Quartile of total AGFs				P value
	Q1 <51,867	Q2 51,87-7559	Q3 7559-10,171	Q4 >10,171	
Men, %	55.6	51.7	73.3	88.2	0.006
Age (y)	54.6 ± 10.1	53.2 ± 10.5	53.6 ± 12.7	55.4 ± 13.9	0.871
Etiology of cirrhosis					
Virus	53.8	42.3	62.1	65.6	
Autoimmune	46.2	34.6	17.2	25	0.047
Other	0	23.1	20.7	9.4	
MELD score <sup>a</sup>	10.9 ± 4.9	11.5 ± 5	12.5 ± 4.1	12.9 ± 5.2	0.459
Child Pugh category (A/B/C)					
A	59.1	72	76.9	65.4	
B, C	40.9	28	23.1	34.6	0.568
Alcohol drinker	26.9	28.6	3.6	34.4	0.032
Smoker, %	30.8	31	32.1	63.6	0.017
Weight, kg	75.6 ± 19.2	76.8 ± 17.8	71.2 ± 12.2	72.9 ± 16	0.556
Height, cm	163.7 ± 8.5	163.7 ± 8.9	167.3 ± 8.2	167 ± 8.7	0.141
Body mass index, kg/m <sup>2</sup>	28.2 ± 6.1	28.8 ± 5.6	25.8 ± 4.4	26.2 ± 4.8	0.076
Subjective global assessment					
A	29.6	41.4	27.6	32.4	
B	59.3	41.4	63.3	52.9	
C	11.1	17.2	10	14.7	0.771

**Table 1.** Characteristics of study participants by quartiles of advanced glycation end products (AGFs). Values are means ± SDs for continuous variables and percentages for categorical variables. ANOVA for quantitative variables and  $\chi^2$  test for qualitative variables

	Quartile of total AGEs				
	Q1	Q2	Q3	Q4	P value
Energy (kcal/d)	1851 ± 653	2102 ± 628	2165 ± 445	2427 ± 736	0.016
Protein (% TEI)	13.9 ± 2.4	14.3 ± 2.5	15.2 ± 2.9	15 ± 3.4	0.336
Carbohydrate (% TEI)	64.8 ± 9.7	61.2 ± 6.4	60 ± 6.2	59.5 ± 5.4	0.052
Fat (% TEI)	27.7 ± 6.6	29.2 ± 9.9	27.8 ± 5.8	28.4 ± 8.7	0.577
Fiber (1000 g/kcal)	13.7 ± 3.7	15.4 ± 3.5	14.8 ± 43.8	14.5 ± 4.1	0.510
Vegetables	209.2 ± 144.3	202.5 ± 133.7	235.1 ± 165.3	257.9 ± 167.7	0.509
Fruits	351.6 ± 228.7	406.9 ± 195.8	356.8 ± 216.4	410.1 ± 173.8	0.620
Meats	35.4 ± 15.4	63.1 ± 26.3	93 ± 43.3	96.5 ± 49.5	0.001
Cereals	134.2 ± 88.4	157.6 ± 118.4	182.4 ± 151.7	185.7 ± 130.1	0.381
Dairy	232.2 ± 159.3	241.3 ± 143.6	250.5 ± 179.6	271.3 ± 149.9	0.841

**Table 2.** Dietary intakes of study participants by quartiles of advanced glycation end products (AGEs).

AGEs	Q1	Q2	Q3	Q4	P trend
No. of deaths	6	11	13	20	0.024
Model 1	ref	2.1 (0.69–6.2)	2.47 (0.85–7.1)	2.64 (0.9–7.5)	0.075
Model 2	ref	2.54 (0.81–8)	2.75 (0.79–9.5)	3.56 (1.1–11.6)	0.040
Model 3	ref	1.24 (0.25–6)	2.76 (1.69–11.1)	3.3 (1.79–13.7)	0.048

**Table 3.** Hazard ratios (HR) and 95% confidence intervals (CI) for the association between quartiles of the advanced glycation end products (AGEs) and mortality in patients with cirrhosis.**Fig. 1.** Full adjusted hazard ratios for mortality in patients with cirrhosis in different quartiles of advanced glycation end products (AGEs).

activator of transcription 3 (STAT3) and NF-κB, but does not directly rely on ROS<sup>55</sup>. IR is another possible mechanism that explains the association between AGEs and cirrhosis. AGEs play a role in hepatic IR by causing the phosphorylation of IRS-1 at serine residues through the activation of JNK and IκB kinase, which was mediated by Rac-1 activation<sup>55</sup>. CVD was another major cause of mortality in this study, and previous studies have proven the relationship of CVD with AGEs and suggested similar mechanisms for it<sup>56–58</sup>.

To the best of our knowledge, this study was the first to investigate the relationship between dietary intake of AGEs and the risk of mortality in patients with cirrhosis, which was one of the strengths of this study. In addition, an attempt was made to increase the reliability of the study by adjusting all potential confounding factors. However, the current study has limitations that should be considered when interpreting the results, including small sample size and potential recall bias in the use of the FFQ. Also, the selection of confounding factors was based on prior knowledge, existing literature and clinical considerations. Therefore, similar to numerous observational studies, the outcomes may have been affected by residual and unmeasured confounding.

## Conclusion

In conclusion, our findings emphasize that higher intake of AGEs does increase the chance of mortality in patients with cirrhosis. Further studies are necessary to clarify the underlying mechanisms of this relationship.

## Data availability

The datasets analysed in the current study are available from the corresponding author on reasonable request.

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## Author contributions

Conceptualization, ZY and AH; Formal analysis, ZY and ZM; Methodology, MS, FPK, BH, SA and SK; Project administration, MST, MN and AH; Writing – original draft, MST, MN and ZY; Writing – review & editing, ZY and AH. All authors read and approved.

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## Declarations

### Competing interests

The authors declare no competing interests.

### Ethics approval and consent to participate

National nutrition and Food Technology Research Institute (NNFTRI) ethics committee approved the study protocol (IR. SBMU. NNFTRI.1396.186) in accordance with the Declaration of Helsinki. All participants provided written informed consent and were informed about the study.

### Conflict of interest

The authors declare that they have no competing interests.

### Additional information

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