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Association between advanced glycation end products and estimated glomerular filtration rate: a cross-sectional analysis

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Abstract

Background Chronic kidney disease (CKD) is a significant public health concern associated with high morbidity and mortality rates, particularly in populations with type 2 diabetes and hypertension. Advanced glycation end products (AGEs) are implicated in CKD pathogenesis, but their association with the estimated glomerular filtration rate (eGFR) remains unclear. We aimed to assess the associations between AGE levels and the eGFR.

Methods We conducted a cross-sectional analysis of baseline data from the Health Workers Cohort Study (2004–2006), which included 1,621 adults. AGE levels were categorized into quartiles, and the eGFR was calculated via the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2009 equation. Quantile and logistic regression models were used to assess the associations between AGEs and the eGFR, adjusting for potential confounders.

Results The median AGE level was 334 µU/ml, and the prevalence of low eGFR (< 60 mL/min/1.73 m^2) was 4.7%. Quantile regression analysis revealed a significant reduction in the eGFR, particularly in the 10th percentile. Logistic regression models revealed that a 100 µU/ml increase in AGE level was associated with increased odds of a low eGFR (OR: 1.06, 95% CI: 1.03–1.09). Participants with very high AGE levels had greater odds of having a low eGFR than those in the lowest category did (OR: 2.21, 95% CI: 1.00–4.88).

Conclusion Elevated AGE levels were associated with lower eGFRs and increased odds of low eGFRs. These findings underscore the potential role of AGEs in CKD development and suggest the importance of targeting AGE accumulation for CKD prevention and management in high-risk populations.

Keywords Advanced glycation end products, Chronic kidney disease, Glomerular filtration rate

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Introduction

Chronic kidney disease (CKD) is characterized by structural alterations or a reduction in kidney function, typically indicated by an estimated glomerular filtration rate (eGFR) of less than 60 mL/min per 1.73 m^2, persisting for at least three months [1]. CKD imposes a substantial burden of morbidity and mortality globally, particularly affecting individuals with type 2 diabetes (T2D) and hypertension [1, 2]. Projections from the Global Burden of Disease estimated that CKD could escalate to become the fifth leading cause of death by 2040 [3]. In Mexico, between 1990 and 2017, the mortality rate attributed to CKD increased by 102.3%, a significantly greater increase than the 33.0% reported in Latin America [4].

CKD risk is intricately linked to hyperglycemia, which induces renal dysfunction and deterioration [1, 5]. This process triggers a cascade of events culminating in the formation of advanced glycation end products (AGEs), toxic and irreversible compounds formed through non-enzymatic reactions between reducing sugars and proteins, lipids, or nucleic acids [6–8]. AGEs are implicated in the development and progression of a variety of hyperglycemia-related disorders, including T2D, cardiovascular disease, dementia, and CKD [9–13]. Due to the kidney's essential role in AGE clearance and reabsorption, the accumulation of AGEs disrupts the glomerular membrane, leading to glomerular sclerosis, tubulointerstitial fibrosis, and eventual kidney damage [7, 14–18]. Furthermore, the activation of AGE receptors (RAGEs) in renal vasculature and tubular epithelium promotes the production of pro-inflammatory cytokines and oxidative stress, exacerbating kidney injury [2, 19]. This cascade of inflammation, fibrosis, and glomerulosclerosis significantly compromises kidney structure and function.

AGEs, both endogenous and exogenous, contribute to the progression of CKD. Endogenously, they form during normal metabolic processes or in pathological conditions such as diabetes and kidney disease. Exogenously, they can be absorbed from foods rich in fat, sugar, or those that are grilled or processed [20]. Once accumulated, AGEs bind to RAGE, inducing inflammatory and oxidative stress pathways that damage renal tissue. Empagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, has been shown to mitigate renal and metabolic dysfunction in diabetic animal models by blocking the AGE-RAGE axis, supporting the therapeutic potential of targeting this pathway to prevent CKD in individuals with T2D and other related comorbidities [21]. Activation of the AGE-RAGE axis stimulates the production of cell growth factors and oxidative stress, releasing reactive oxygen species and inflammatory mediators that aggravate kidney damage over time [19, 22]. Environmental factors, including dietary intake, and disease conditions such as T2D, influence RAGE expression levels, which in turn modulate kidney disease progression [11, 13, 18, 23]. Elevated RAGE levels are inversely correlated with metabolic parameters like triglycerides, HbA1c, insulin resistance, and obesity, underscoring the complex relationship between molecular, environmental, and pathological factors in CKD progression [18, 19, 22].

In Mexico, where the mortality rates from T2D, hypertension, and kidney disease are among the highest in the world [4, 24], understanding the role of AGEs in CKD pathogenesis is critical. This study aims to assess the association between AGE levels and eGFR in the Mexican population, providing valuable insights for disease prevention, early detection, and targeted interventions. By elucidating the impact of AGEs in CKD, it is hoped that novel strategies to reduce AGE accumulation or modulate the AGE-RAGE axis can be developed to improve kidney health in high-risk populations.

Methods and materials

Study population

We conducted a cross-sectional analysis to assess the association of interest, utilizing baseline data (2004–2006) from the Health Workers Cohort Study (HWCS). The main purpose of the HWCS was to evaluate the associations between specific lifestyles and genetic predispositions with different health outcomes, as detailed in a prior study [25].

For this study, we included adults (aged ≥ 18 years) who participated in the baseline measurement of the cohort, had serum samples available for AGE measurement, and provided complete information on the variables of interest, including serum creatinine, age, and sex. We excluded nonadult participants (< 18 years) ($n = 163$) and those without plasma levels of AGEs ($n = 334$). We eliminated individuals with extreme and implausible levels of AGEs ($n = 1$). Following these criteria, a total of 1,621 participants were eligible for analysis (Fig. 1). The ethics committees at the Mexican Social Security Institute approved the HWCS protocol, questionnaires, procedures, and informed consent (12CEI 09 006 14). All participants signed a written informed consent form before enrollment.

Exposure variable: advanced glycation end products (AGEs)

A venous blood sample was obtained after a minimum fasting period of 8 h for hematological and chemical analysis via the Selectra XL instrument (Randox). Serum levels of AGEs derived from glucose were measured via radioimmunoassay utilizing the gamma counter Cobra II (Packard Instrument Company, Inc., Connecticut, USA). The quantification of AGEs was performed via precise titration with purified polyclonal anti-AGE antibodies against a preparation of bovine serum albumin

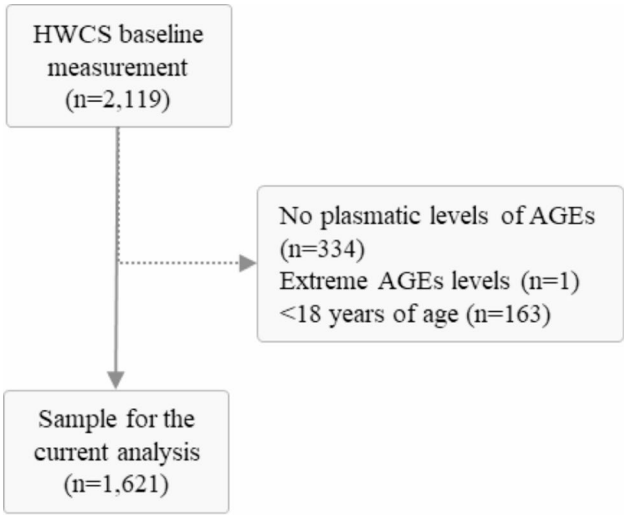

Fig. 1 Study flow chart of the study population

containing glucose dissolved in a phosphate buffer [11, 26]. This method was chosen for its cost-effectiveness and suitability for large-scale population screening. The AGE levels are expressed in μU/ml units. Quartiles were utilized to categorize AGE levels into four categories (low, medium, high, and very high) because of the lack of consensus on cutoff points or reference values.

Outcome: estimated glomerular filtration rate (eGFR)

We calculated the eGFR via the CKD-EPI 2009 equation, which incorporates serum creatinine (mg/dL), age (years), and sex as variables [27–29]. Consistent with the KDIGO 2012 Guidelines, eGFR categories were defined as low when < 60 mL/min/1.73 ^{m2} units were used [30]. Serum creatinine levels were measured via the enzymatic calorimetry method with a Selectra XL instrument (Randox Laboratories, Crumlin, United Kingdom) and are expressed as continuous values in mg/dL units [25]. We used the GFR, a key indicator of kidney function, to assess the filtering capacity of the kidneys' functional nephrons. It is highly valued for its ability to detect early kidney failure and monitor kidney function in healthy and sick individuals [30, 31]. To classify GFR levels, we applied the CKD-EPI 2009 equation, which is known for its precision in calculating higher GFRs than the MDRD equation does. This equation minimizes false-positive results and is widely regarded as the optimal index for assessing renal function in diverse populations [27–29].

Covariables

Sociodemographic and lifestyle characteristics

Sociodemographic and lifestyle information, including age, sex, education level, smoking status, leisure-time physical activity, and dietary intake, was obtained through self-report questionnaires [25]. Education level was classified into three categories: elementary school, high school, and university or more. Smoking status was categorized as never smoker, former smoker or current smoker.

Leisure-time physical activity was assessed using a validated instrument in the Mexican population and expressed in minutes/day [25, 32]. The participants were considered active if they engaged in at least 150 min of moderate-intensity aerobic physical activity per week or an equivalent combination of moderate-intensity and vigorous-intensity activity [33].

Diet was evaluated via a semiquantitative food frequency questionnaire (FFQ) validated in the Mexican population [34]. The FFQ collected data on the consumption of 116 foods during the previous year, including details on portion size and frequency. Energy intake was calculated and expressed in kcal/day [35]. AGE intake was estimated via a food database of 549 foods, following the methodology described by Robles-Rivera et al., and expressed in μU/ml/day [11, 36].

Anthropometric and clinical measurements

The anthropometric and clinical measurements were conducted by trained nurses via a standardized procedure, ensuring consistency and reliability (reproducibility assessed with kappa coefficients of 0.83 and 0.90, respectively).

Participant heights were obtained via conventional stadiometers (Seca 206, Hamburg, Germany), whereas weight was assessed via calibrated electronic scales (model BC-533; TANITA). Waist circumference was measured at the highest iliac crest point and expressed in cm units [25].

Body mass index (BMI) was calculated via the formula BMI = weight (kg)/height^2 (m^2), and the values are expressed in kg/m^2 units. The participants were categorized on the basis of their BMI as normal weight ($\geq$ 18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), or obese ($\geq$ 30 kg/m^2) [37].

Blood pressure was measured following standardized methods via a sphygmomanometer approved by the WHO (Omron HEM-7200, Omron Corporation, Matsusaka, Japan), and two measurements were taken during each visit. The average of these measurements, recorded in mm/Hg, was used for analysis [25].

Hypertension was defined on the basis of the following criteria: self-reported diagnosis of hypertension confirmed by a physician; any participant with a systolic blood pressure of $\geq$ 140 mmHg or a diastolic blood pressure of $\geq$ 90 mmHg; or participants with a prescription for any antihypertensive medication [38].

Fasting glucose samples were processed via the enzymatic calorimetry method with a Selectra XL instrument (Randox Laboratories, Crumlin, United Kingdom) [25].

Prediabetes was defined by a serum fasting glucose level ≥ 100 - < 126 mg/dL. T2D was defined on the basis of the criteria described by the American Diabetes Association (ADA) [39], which included self-reported diagnosis confirmed by a physician, serum fasting glucose ≥ 126 mg/dL, or antidiabetic drug prescription.

Statistical analysis

Descriptive analysis of baseline characteristics was estimated by AGE level categories defined by quartiles. Continuous variables are summarized using medians and interquartile ranges (P25–P75), whereas categorical variables are presented as proportions. The normality of continuous variables was assessed via the Shapiro–Wilk test prior to analysis. Differences between AGE categories were evaluated via tests for trends across ordered groups.

Two analytical approaches were employed in this study. First, quantile regression models were used to estimate the change in eGFR per unit change in AGEs (100 μU/ml) at different percentiles (10th, 25th, 50th, 75th, and 90th) of the eGFR distribution. The final quantile regression model was graphically presented to illustrate the relationship between a 100-unit change in AGEs and the eGFR across various percentiles. Quantile regression was chosen due to violations of the underlying assumptions of linear regression, such as heteroscedasticity and nonnormality of residuals [40, 41], offering a robust approach to analyze the association between AGEs and eGFR across different percentiles of the eGFR distribution.

Second, logistic regression models were employed to estimate odds ratios (ORs) to assess the associations between continuous and categorical AGEs, defined by quartiles, and low eGFRs. We conducted four models for these two analyses, each incorporating progressively different sets of covariables to examine the association between AGEs and low GFR. Model 1 was adjusted for age, sex, and education. Model 2 was additionally adjusted for physical activity, smoking status, dietary AGEs, and total energy. Model 3 was further adjusted for T2D and hypertension. Finally, Model 4 was additionally adjusted for BMI categories. Statistical significance was determined with a threshold of p values < 0.05, employing a two-tailed hypothesis. All analyses were performed via STATA version 14.0 (StataCorp, College Station, Texas, USA).

Results

The median age of the study population was 45 years (P25–P75: 36–55), and 75.5% were women. The median AGE level was 334 μU/ml (211–502), and the prevalence of low eGFR was 4.7%. Table 1 describes the population characteristics according to AGE categories defined by quartiles. The AGE values in each category ranged as follows: low (< 210.6 μU/ml), medium (210.6 to 333.7 μU/ml), high (333.8 to 502.6 μU/ml), and very high (> 502.6 μU/ml) (Table 1).

We observed that individuals in the highest category of AGEs had greater age, body mass index (BMI), waist circumference, and fasting plasma glucose levels than those in the lowest category. Additionally, the highest proportion of individuals with an elementary school education level were in the very-high-AGE category. In contrast, lower levels were observed in those with a university education or higher. We also found that the highest proportion of individuals with obesity, low eGFR, hypertension, or T2D were in the very-high-AGE category compared with the lowest category.

Associations between AGE levels and eGFRs

According to the quantile regression analysis, we only observed a statistically significant reduction in the 10th percentile of the eGFR. Across all the adjustment models, the associations remained consistent. In Model 4, for each increment of 100 units of AGEs, we observed a reduction in the eGFR of 0.48 mL/min (95% CI -0.74, -0.22) (Table 2). Additionally, Fig. 2 depicts the trend of coefficients across eGFR quantiles, illustrating the relationship between AGEs and eGFR across different percentiles.

Associations between ages and low eGFRs

We found that for every 100 μU/ml increase in plasma AGE levels, participants had greater odds of having a low eGFR, even after adjusting for age, sex, and education (OR 1.06; 95% CI 1.03–1.09). This association remained significant after adjusting for all confounding variables (1.06; 95% CI 1.03–1.09). In terms of the associations between AGE categories and low eGFRs, similar trends were observed. Compared with those in the lowest category, participants with very high levels of AGEs had significantly greater odds of having a low eGFR, even after adjusting for age, sex, and education (OR 2.22; 95% CI 1.02–4.85). This association persisted even after additional adjustments for physical activity, smoking status, dietary AGEs, total energy intake, T2D, hypertension, and BMI categories (OR 2.21; 95% CI 1.00–4.88) (Table 3).

Stratified analyses revealed differential associations between AGEs and reduced eGFR across different subgroups. The association was more marked in women (OR: 1.05; 95% CI: 1.02–1.09), whereas it did not reach statistical significance in men (OR: 1.08; 95% CI: 0.96–1.21). Participants aged ≥ 45 years showed significantly higher odds of reduced eGFR associated with AGEs (OR: 1.06; 95% CI: 1.03–1.09), while no significant association was observed in those < 45 years (OR: 0.82; 95% CI: 0.52–1.29).

Table 1 Sociodemographic and lifestyle characteristics by AGES categories

Characteristics	Low* *n* = 406 < 210.6**	Medium *n* = 405 210.6-333.7	High *n* = 405 333.8-502.6	Very-high *n* = 405 > 502.6	*P*-trend
Age, years[a]	41(33–48)	43(35–51)	49(37–58)	50(41–60)	< 0.001
Sex, %					
Women	83.0	74.7	73.8	71.1	< 0.001
Level of education, %					
Elementary school	16.8	25.9	35.1	40.7	< 0.001
High school	23.4	25.4	22.2	20.0	0.179
University or more	56.9	47.4	41.7	38.0	< 0.001
Leisure time physical activity, min/day	12.7(3.2–31.4)	12.9(4.3–35.5)	16.1(3.2–42.9)	12.9(3.2–36.4)	0.221
Active, %	29.3	32.6	40.3	32.6	0.095
Body mass index, kg/cm^2 [a]	25.4(23.0–28.0)	25.6(23.6–28.3)	26.2(23.8–29.1)	26.5(24.0-29.8)	< 0.001
Overweight, %	42.1	38.0	44.2	42.0	0.580
Obesity, %	13.4	18.1	18.9	24.1	< 0.001
Waist circumference, cm[a]	85(79–93)	89(81–97)	93(83–101)	93(84–101)	< 0.001
Systolic blood pressure, mmHg[a]	113(107–122)	115(109–124)	116(109–125)	116(108–124)	0.011
Diastolic blood pressure, mmHg[a]	70(64–77)	71(66–78)	71(65–79)	70(64–76)	0.892
Fasting plasma glucose, mg/dL[a]	87(81–94)	90(83–97)	91(84–99)	91(85–102)	< 0.001
eGFR, mL/min per 1.73 m^2 [a]	91.1(79.5-106.5)	92.7(79.5-105.8)	92.5(78.0-105.1)	92.5(77.6–105.0)	0.718
≥ 90 mL/min per 1.73 m^2,%	52.7	53.8	52.4	54.1	0.670
< 90 to 60 mL/min per 1.73 m^2, %	44.8	42.7	42.2	38.5	0.066
< 60 mL/min per 1.73 m^2, %	2.5	3.5	5.4	7.4	0.001
Smoking status, %					
Former	27.9	23.0	26.2	30.9	0.202
Current	16.3	16.3	16.8	15.3	0.751
Hypertension, %	24.4	27.7	31.1	37.8	< 0.001
Prediabetes, %	2.2	4.0	3.7	4.5	0.117
Diabetes type 2, %	5.4	5.7	8.2	13.9	< 0.001
Energy intake[a], kcal/day	2016(1550–2498)	1955(1454–2486)	1999(1557–2606)	1931(1479–2536)	0.612
AGES intake [a], µU/ml/day	6037(4639–8414)	6107(4316–8045)	6320(4707–7931)	5878(4339–7712)	0.263

[a] Median(P25-P75). *AGES categories were defined by quartiles. **AGEs range defining the AGEs categories

Table 2 Quantile regression results between AGES levels and eGFR for the different percentiles

Models	10th 68* Coefficient(95%CI)	25th 78.6 Coefficient(95%CI)	50th 91.9 Coefficient(95%CI)	75th 105.3 Coefficient(95%CI)	90th 116.6 Coefficient(95%CI)
Model 1	-0.39 (-0.63,-0.16)	-0.12 (-0.38,0.15)	-0.003 (-0.028,0.27)	0.01 (-0.10,0.13)	-0.006 (-0.13,0.12)
Model 2	-0.42 (-0.68,-0.16)	-0.14 (-0.39,0.11)	0.03 (-0.23,0.28)	0.06 (-0.05,0.17)	0.006 (-0.17,0.18)
Model 3	-0.41 (-0.66,-0.15)	-0.16 (-0.40,0.07)	0.05 (-0.20,0.30)	0.03 (-0.09,0.14)	-0.02 (-0.16,0.12)
Model 4	-0.48 (-0.74,-0.22)	-0.16 (-0.41,0.08)	0.03 (-0.21,0.28)	0.03 (-0.09,0.16)	-0.01 (-0.17,0.15)

*eGFR value at each percentile. Model 1: adjusted for age, sex, and education. Model 2: M1 + physical activity, smoking status, Dietary AGEs (Advanced Glycation End Products), and total energy intake. Model 3:M2 + diabetes and hypertension. Model 4: M3 + BMI categories. *Unit of change 100 µU/ml

Among individuals with diabetes, AGEs were significantly associated with reduced eGFR (OR: 1.12; 95% CI: 1.01–1.23), as well as in non-diabetic participants (OR: 1.05; 95% CI: 1.02–1.09). A similar pattern was observed when stratifying by hypertension status: the association remained significant in participants with hypertension (OR: 1.07; 95% CI: 1.02–1.12), but not in those without hypertension (OR: 1.04; 95% CI: 0.99–1.09).

When stratified by body mass index (BMI), the strength of the association between AGEs and reduced eGFR increased with higher BMI categories. The association was not statistically significant in participants with a normal BMI (OR: 1.04; 95% CI: 0.99–1.10). However, in

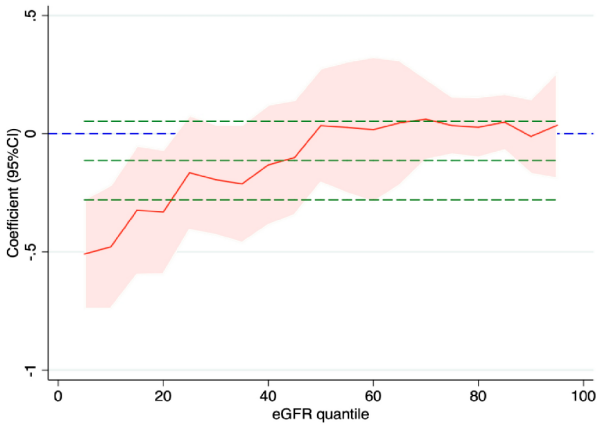

Fig. 2 Quantile plots for the effect of eGFR on AGE levels. The red line represents the coefficient with a 95% confidence interval. The solid green lines are the ordinary least square regression lines with 95% confidence intervals (dashed green lines). The unit of change was 100 µU/ml. Model adjusted for age, sex, education, physical activity, smoking status, dietary AGEs (advanced glycation end products), total energy, diabetes, hypertension, and BMI categories

overweight individuals, the association became significant (OR: 1.06; 95% CI: 1.01–1.11). The association was strongest among those with obesity (OR: 1.11; 95% CI: 1.02–1.20) (Fig. 3).

Discussion

This cross-sectional study revealed a significant association between AGEs and low GFR. Quantile regression analysis revealed a significant association for the tenth percentile of the eGFR, independent of known risk factors for kidney damage.

AGEs play a significant role in various pathological processes, contributing to tissue damage through mechanisms such as tissue deposition, in situ glycation, and interaction with the receptor for AGEs (RAGE) [7]. AGEs are known to trigger proinflammatory, profibrotic, and procoagulant cellular responses, often targeting specific organs [7]. The results of this analysis can be explained by the accumulation of AGEs in the kidney, which contributes to the progressive alteration of renal architecture and the loss of renal function by glycation of components of the glomerular filtration barrier or adjacent to it and the activation of intracellular pathways through the AGE: RAGE interaction [7].

In this study, we observed an association between AGE levels and the odds of a low GFR. Notably, 30% of the samples had hypertension, among whom 40% had a GFR < 60 mL/min, whereas 8% had T2D, of whom 10% had a GFR < 60 mL/min. This inclusion of participants with diverse health profiles adds robustness to our findings and enhances the generalizability of the results to populations with varying degrees of comorbidity. Consistent with our results, several studies have reported elevated levels of AGEs in various conditions associated with decreased GFR, such as diabetic kidney disease [10] and loss of renal function in T2D [42], with glycation considered one of the major pathways to end-organ complications in T2D [43].

In T2D individuals, a composite AGE score derived from the serum levels of five AGE-free adducts showed a robust association with kidney function decline. In the ACCORD study, this score correlated with an annual decrease in the eGFR of 20.66 mL/min per 1.73 m^2. Moreover, the AGE score was associated with a 42% increase in the risk of renal function loss (HR 1.42, 95% CI 1.13–1.78), macroalbuminuria (HR 1.53, 95% CI 1.13–2.06), and high-risk chronic kidney disease (hrCKD) (HR 1.88, 1.37–2.57) [10]. Previous studies have consistently demonstrated an association between elevated circulating levels of AGEs and a progressive decline in renal function, regardless of T2D status [10, 42, 44–47]. This broader body of evidence underscores the importance of AGEs in renal health and suggests a potential role in the pathogenesis of renal dysfunction. Importantly,

Table 3 Association between AGES levels and low glomerular filtration rate

	AGES levels* OR (95%CI)	AGES categories**				
		Low OR (95%CI)	Medium OR (95%CI)	High OR (95%CI)	Very-high OR (95%CI)	*P* trend
Model 1	1.05 (1.02–1.08)	Ref.	1.36 (0.58–3.16)	1.71 (0.77–3.81)	2.22 (1.02–4.85)	0.031
Model 2	1.05 (1.02–1.08)	Ref.	1.43 (0.61–3.35)	1.53 (0.67–3.48)	2.22 (1.01–4.86)	0.041
Model 3	1.05 (1.02–1.09)	Ref.	1.30 (0.54–3.09)	1.47 (0.65–3.36)	2.20 (0.99–4.84)	0.036
Model 4	1.06 (1.03–1.09)	Ref.	1.31 (0.55–3.11)	1.47 (0.64–3.36)	2.21 (1.00-4.88)	0.036

Model 1: adjusted for age, sex, and education. Model 2: M1 + physical activity, smoking status, Dietary AGEs (Advanced Glycation End Products), and total energy intake. Model 3: M2 + diabetes and hypertension. Model 4: M3 + BMI categories. *Unit of change 100 µU/ml. **AGES categories were defined by quartiles. Low Glomerular Filtration Rate < 60 mL/min per 1.73 m^2

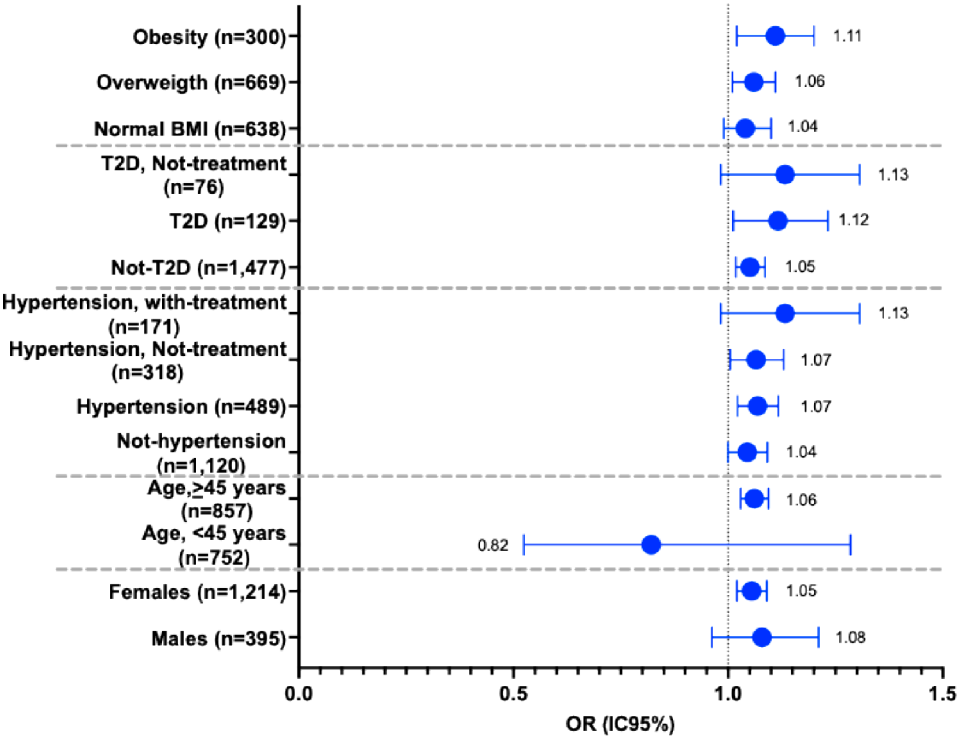

Fig. 3 Associations between AGEs and low GFR stratified by demographics and health conditions. Model adjusted for age, sex, dietary AGEs, physical activity, smoking status, total energy intake, diabetes type 2 and hypertension. For stratified analyses, the stratifying variable was not included in the model (e.g., for sex-stratified analysis, sex was not included in the model). *Unit of change 100 µU/ml

hemodialysis or peritoneal dialysis is less effective in removing AGEs from the body [42], resulting in individuals undergoing dialysis tending to exhibit higher circulating AGE concentrations than those with normal renal function [48, 49].

In the ADVANCE study involving 3763 individuals with T2D, both circulating sRAGE levels were found to be directly associated with incident or progressive CKD (HR 1.20, 95% CI 1.02–1.41) and mortality (HR 1.11, 95% CI 1.00–1.22). Additionally, AGEs were associated with incident or progressive CKD (HR 1.21, 95% CI 1.08–1.36). These findings suggest that targeting the AGE: RAGE axis could be pivotal for preventing and managing diabetic nephropathy [50].

Additionally, when we excluded participants with hypertension and T2D, the association between categorical AGE levels and renal function was not statistically significant, with the direction of the association reversing (Q4 vs. Q1 OR 0.72, 95% CI 0.26–1.96). Conversely, in the model treating AGEs as a continuous variable, each 100-unit increase in AGEs was associated with a 1.04 (95% CI 0.99, 1.09) increase in the odds ratio. Interestingly, when quantile regression was employed, the association of a 100-unit increase in AGEs remained significant at the 10th percentile, which is consistent with our findings from the complete dataset (coefficient – 0.42, 95% CI -0.72, -0.11). This finding suggests a potential modification effect of underlying medical conditions on the observed association.

The reduced sample size after excluding these participants ($n = 1039$ vs. 1621) may have contributed to this change in results. This suggests that despite the exclusion of participants with hypertension and T2D, the association between AGEs and low GFR persisted at the lower end of the GFR distribution. Notably, the loss of statistical power due to the reduced sample size, particularly the low prevalence of low GFR (< 60 mL/min), underscores the importance of considering statistical power in interpreting subgroup analyses.

This study included several strengths, including the inclusion of both sexes, a wide range of ages, validated measurements, and extensive information on lifestyle and dietary factors, as well as potential confounders of the relationship studied. Additionally, the use of quantile regression allows us to understand the relationships between variables outside the mean of the data, which is particularly useful for outcomes that are nonnormally distributed and have a nonlinear relationship with predictor variables [51].

Nonetheless, several limitations must be considered. The cross-sectional design can lead to reverse causation; it is not possible to fully determine the direction of causality. However, the results of this analysis are in line with those of previous studies. Additionally, since individuals

were unaware of their low eGFR status, it is unlikely that they changed their exposure factors, reducing the risk of reverse causality. Although we adjusted for major risk factors for kidney damage, including type 2 diabetes and hypertension—defined through self-report, medication use, and clinical measurements—residual confounding from unmeasured or imprecisely measured variables cannot be excluded. Notably, adjusting for diabetes and hypertension may also represent overadjustment, as these conditions lie on the causal pathway of AGE accumulation and CKD development, potentially attenuating the observed associations. Additionally, due to the absence of data on albuminuria or proteinuria, we could not were unable to assess whether the relationship between AGEs and kidney function is independent of early renal injury. Future research should include these parameters to understand better understand the mechanisms linking AGEs to renal impairment. Finally, our participants were middle class, with an important proportion of individuals with a high level of education. Therefore, it is likely that the findings of this study can only be extrapolated to individuals living in urban areas of Mexico.

Nevertheless, given the mechanistic nature of our objective, representativeness was not a primary concern. Finally, while we use of an in-house method for measuring AGEs, this approach allowed for the analysis of multiple samples at lower cost and has been validated in other clinical research settings.

Our results support a positive association between AGEs and low GFR. Therefore, AGEs might be among the key contributors to the development of kidney diseases, as they increase oxidative stress through multiple mechanisms and trigger an inflammatory response. These processes significantly influence the onset and worsening of kidney dysfunction [52]. Thus, therapeutic interventions aimed at preventing the formation of AGEs can potentially prevent the progression of chronic renal diseases. These findings underscore the importance of early identification of AGE levels as potential biomarkers and the development of therapeutic strategies aimed at reducing AGE formation for the prevention and management of renal diseases.

Abbreviations

CKD	Chronic kidney disease
AGEs	Advanced glycation end products
eGFR	Glomerular filtration rate
CKD-EPI	Chronic kidney disease epidemiology collaboration
OR	Odds ratio
T2D	Type 2 diabetes
RAGEs	AGE receptors
HWCS	Health workers cohort study
FFQ	Food frequency questionnaire
BMI	Body mass index
ADA	American diabetes association
hrCKD	High-risk chronic kidney disease

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Author contributions
C.A.S.A., J.S., and B.R.P.: designed the research, had primary responsibility for the final content, and conducted research; C.A.S.A., J.M.L., P.V. and B.R.P.: wrote the manuscript; C.A.S.A., and B.R.P.: analyzed the dataor performed the statistical analysis. All authors: drafted and edited the manuscript, and read and approved the final manuscript.

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Data availability
The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This research was conducted in accordance with the guidelines of the Declaration of Helsinki, and all procedures involving human subjects were approved by the Ethics Committee of the Institute. Written informed consent was obtained from all participants.

Competing interests
The authors declare no competing interests.

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References

1. Kalantar-Zadeh K, Jafar TH, Nitsch D, Neuen BL, Perkovic V. Chronic kidney disease. Lancet (London, England). England; 2021;398:786–802.
2. Fotheringham AK, Gallo LA, Borg DJ, Forbes JM. Advanced glycation end products (AGEs) and chronic kidney disease: Does the Modern Diet AGE the Kidney? Nutrients. Switzerland. 2022;14.
3. Foreman KJ, Marquez N, Dolgert A, Fukutaki K, Fullman N, McGaughey M, et al. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016–40 for 195 countries and territories. Lancet. 2018;392:2052–90.
4. Agudelo-Botero M, Valdez-Ortiz R, Giraldo-Rodríguez L, González-Robledo MC, Mino-León D, Rosales-Herrera MF, et al. Overview of the burden of chronic kidney disease in Mexico: secondary data analysis based on the global burden of disease study 2017. BMJ Open. 2020;10:e035285.
5. Ding L, Hou Y, Liu J, Wang X, Wang Z, Ding W, et al. Circulating concentrations of advanced glycation end products, carboxymethyl lysine and Methylglyoxal are associated with renal function in individuals with diabetes. J Ren Nutr Off J Counc Ren Nutr Natl Kidney Found United States. 2024;34:154–60.
6. Jung E, Kang WS, Jo K, Kim J. Ethyl pyruvate prevents renal damage induced by Methylglyoxal-Derived advanced glycation end products. J Diabetes Res Engl. 2019;2019:4058280.
7. Daroux M, Prévost G, Maillard-Lefebvre H, Gaxatte C, D'Agati VD, Schmidt AM, et al. Advanced glycation end-products: implications for diabetic and non-diabetic nephropathies. Diabetes Metab France. 2010;36:1–10.
8. Thomas MC. Advanced glycation end products. Contrib Nephrol Switz. 2011;170:66–74.
9. Clarke RE, Dordevic AL, Tan SM, Ryan L, Coughlan MT. Dietary advanced glycation end products and risk factors for chronic disease: A systematic review of randomised controlled trials. Nutrients Switz. 2016;8:125.
10. Koska J, Gerstein HC, Beisswenger PJ, Reaven PD. Advanced glycation end products predict loss of renal function and High-Risk chronic kidney disease in type 2 diabetes. Diabetes Care United States. 2022;45:684–91.

11. Robles-Rivera K, Rivera-Paredez B, Quezada-Sanchéz AD, Velázquez-Cruz R, Salmerón J. Advanced glycation end products are associated with cardiovascular risk in the Mexican population. Nutr Metab Cardiovasc Dis Neth. 2023;33:826–34.
12. Ejtahed H-S, Angoorani P, Asghari G, Mirmiran P, Azizi F. Dietary advanced glycation end products and risk of chronic kidney disease. J Ren Nutr Off J Counc Ren Nutr Natl Kidney Found United States. 2016;26:308–14.
13. Tezuka Y, Nakaya I, Nakayama K, Nakayama M, Yahata M, Soma J. Methylglyoxal as a prognostic factor in patients with chronic kidney disease. Nephrol (Carlton) Australia. 2019;24:943–50.
14. Thomas MC, Forbes JM, Cooper ME. Advanced glycation end products and diabetic nephropathy. Am J Ther United States. 2005;12:562–72.
15. Thornalley PJ. Advanced glycation end products in renal failure. J Ren Nutr Off J Counc Ren Nutr Natl Kidney Found United States. 2006;16:178–84.
16. Inagi R. RAGE and glyoxalase in kidney disease. Glycoconj J United States. 2016;33:619–26.
17. Rabbani N, Thornalley PJ. Advanced glycation end products in the pathogenesis of chronic kidney disease. Kidney Int United States. 2018;93:803–13.
18. Bettiga A, Fiorio F, Di Marco F, Trevisani F, Romani A, Porrini E, et al. The modern Western diet rich in advanced glycation End-Products (AGEs): an overview of its impact on obesity and early progression of renal pathology. Switzerland: Nutrients; 2019. p. 11.
19. Bajwa S, Luebbe A, Vo NDN, Piskor E-M, Kosan C, Wolf G, et al. RAGE is a critical factor of sex-based differences in age-induced kidney damage. Front Physiol Switz. 2023;14:1154551.
20. Ma Y, Wang X, Lin S, King L, Liu L. The potential role of advanced glycation end products in the development of kidney disease. Nutrients Switz. 2025;17.
21. Matsui T, Sotokawauchi A, Nishino Y, Koga Y, Yamagishi S-I. Empagliflozin ameliorates renal and metabolic derangements in obese type 2 diabetic mice by blocking advanced glycation end product-receptor axis. Mol Med Engl. 2025;31:88.
22. Charrin E, Faes C, Sotiaux A, Skinner S, Pialoux V, Joly P, et al. Receptor for advanced glycation end products antagonism blunts kidney damage in Transgenic townes sickle mice. Front Physiol Switz. 2019;10:880.
23. Yuan Y, Sun H, Sun Z. Advanced glycation end products (AGEs) increase renal lipid accumulation: a pathogenic factor of diabetic nephropathy (DN). Lipids Health Dis Engl. 2017;16:126.
24. Escamilla-Nuñez MC, Castro-Porras L, Romero-Martinez M, Zárate-Rojas E, Rojas-Martínez R. Detección, diagnóstico previo y tratamiento de enfermedades crónicas no transmisibles en adultos mexicanos. Ensanut 2022. Salud Publica Mex [Internet]. 2023;65:s153–62. Available from: https://saludpublica.mx/index.php/spm/article/view/14726
25. Denova-Gutierrez E, Flores YN, Gallegos-Carrillo K, Ramirez-Palacios P, Rivera-Paredez B, Munoz-Aguirre P, et al. Health workers cohort study: methods and study design. Salud Publica Mex Mexico. 2016;58:708–16.
26. Jiménez IU, Díaz-Díaz E, Castro JS, Ramos JP, León MC, Alvarado Ríos JA, et al. Circulating concentrations of advanced glycation end products, its association with the development of diabetes mellitus. Arch Med Res United States. 2017;48:360–9.
27. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150:604–12.
28. Arreola-Guerra JM, Rincón-Pedrero R, Cruz-Rivera C, Belmont-Pérez T, Correa-Rotter R, Niño-Cruz JA. Performance of MDRD-IDMS and CKD-EPI equations in Mexican individuals with normal renal function. Nefrologia Spain. 2014;34:591–8.
29. Levey AS, Inker LA. Assessment of glomerular filtration rate in health and disease: A state of the Art review. Clin Pharmacol Ther United States. 2017;102:405–19.
30. Inker LA, Astor BC, Fox CH, Isakova T, Lash JP, Peralta CA, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. Am J Kidney Dis. 2014;63:713–35.
31. Levey AS, Inker LA. GFR as the gold standard: estimated, measured, and true. Am. J. kidney dis. Off J Natl Kidney Found United States. 2016; 67: pp. 9–12.
32. Martínez-González MA, López-Fontana C, Varo JJ, Sánchez-Villegas A, Martinez JA. Validation of the Spanish version of the physical activity questionnaire used in the nurses' health study and the health professionals' Follow-up study. Public Health Nutr. 2005;8:920–7.
33. World health organization. Physical activity. World Heal. Organ. WHO. 2020.
34. Hernández-Avila M, Romieu I, Parra S, Hernández-Avila J, Madrigal H, Willett W. Validity and reproducibility of a food frequency questionnaire to assess dietary intake of women living in Mexico City. Salud Publica Mex. 1998;40:133–40.
35. Hernández-Avila M, Resoles MPS. Sistema de evaluación de hábitos nutricionales y Consumo de nutrimentos (SNUT). Cuernavaca, México: INSP; 2000.
36. Uribarri J, Woodruff S, Goodman S, Cai W, Chen X, Pyzik R, et al. Advanced glycation end products in foods and a practical guide to their reduction in the diet. J Am Diet Assoc. 2010;110:911–e1612.
37. WHO (World Health Organization). WHO obesity and overweight fact sheet 311. Obes Oveweight Fact Sheet. 2013.
38. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, et al. Seventh report of the joint National committee on prevention, detection, evaluation, and treatment of high blood pressure. Hypertension. 2003;42:1206–52.
39. Committee ADAPP. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes—2022. Diabetes Care [Internet]. 2021;45:S17–38. Available from: https://doi.org/10.2337/dc22-S002
40. Koenker R, Chernozhukov V, He X, - LPSE, editors. Handbook of quantile regression [Internet]. Handb. Quantile Regres. CRC Press. 2017; Available from: https://www.routledgehandbooks.com/doi/10.1201/9781315120256
41. Wei Y, Kehm RD, Goldberg M, Terry MB. Applications for quantile regression in epidemiology. Curr Epidemiol Reports [Internet]. 2019;6:191–9. Available from: https://doi.org/10.1007/s40471-019-00204-6
42. Saulnier P-J, Wheelock KM, Howell S, Weil EJ, Tanamas SK, Knowler WC, et al. Advanced glycation end products predict loss of renal function and correlate with lesions of diabetic kidney disease in American Indians with type 2 diabetes. Diabetes United States. 2016;65:3744–53.
43. Forbes JM, Cooper ME. Mechanisms of diabetic complications. Physiol Rev United States. 2013;93:137–88.
44. Miyata T, Ueda Y, Shinzato T, Iida Y, Tanaka S, Kurokawa K, et al. Accumulation of albumin-linked and free-form pentosidine in the circulation of uremic patients with end-stage renal failure: renal implications in the pathophysiology of pentosidine. J Am Soc Nephrol United States. 1996;7:1198–206.
45. Semba RD, Beck J, Sun K, Egan JM, Carlson OD, Varadhan R, et al. Relationship of a dominant advanced glycation end product, serum carboxymethyl-lysine, and abnormal glucose metabolism in adults: the Baltimore longitudinal study of aging. J Nutr Health Aging France. 2010;14:507–13.
46. Semba RD, Fink JC, Sun K, Bandinelli S, Guralnik JM, Ferrucci L. Carboxymethyl-lysine, an advanced glycation end product, and decline of renal function in older community-dwelling adults. Eur J Nutr Ger. 2009;48:38–44.
47. Hou FF, Ren H, Owen WFJ, Guo ZJ, Chen PY, Schmidt AM, et al. Enhanced expression of receptor for advanced glycation end products in chronic kidney disease. J Am Soc Nephrol United States. 2004;15:1889–96.
48. Peppa M, Uribarri J, Cai W, Lu M, Vlassara H. Glycoxidation and inflammation in renal failure patients. Am J Kidney Dis Off J Natl Kidney Found United States. 2004;43:690–5.
49. Agalou S, Ahmed N, Dawnay A, Thornalley PJ. Removal of advanced glycation end products in clinical renal failure by peritoneal dialysis and haemodialysis. Biochem Soc Trans Engl. 2003;31:1394–6.
50. Thomas MC, Woodward M, Neal B, Li Q, Pickering R, Marre M, et al. Relationship between levels of advanced glycation end products and their soluble receptor and adverse outcomes in adults with type 2 diabetes. Diabetes Care United States. 2015;38:1891–7.
51. Lê Cook B, Manning WG. Thinking beyond the mean: a practical guide for using quantile regression methods for health services research. Shanghai Arch Psychiatry China. 2013;25:55–9.
52. Steenbeke M, Speeckaert R, Desmedt S, Glorieux G, Delanghe JR, Speeckaert MM. The role of advanced glycation end products and its soluble receptor in kidney diseases. Int J Mol Sci Switz. 2022;23.

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