ORIGINAL RESEARCH

Dietary Advanced Glycation End Products and Risk of Chronic Kidney Disease

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Objectives: To evaluate the longitudinal association between dietary advanced glycation end products (AGEs) and risk of chronic kidney disease (CKD) in a population-based study.

Design and Setting: In a longitudinal design study, participants were evaluated after approximately 3 years. Daily consumption of carboxymethyl lysine, a major type of dietary AGEs, was determined using a validated semiquantitative food frequency questionnaire. Estimated glomerular filtration rate in this study was calculated by the Modification of Diet in Renal Disease formula. CKD was defined as estimated glomerular filtration rate $<$60 mL/min/1.73 m^2 based on the national kidney foundation guidelines.

Subjects: A total of 1,692 participants, free of baseline CKD with complete follow-up data, out of 3,462 subjects, age $\geq$27 years of the third phase of Tehran Lipid and Glucose Study.

Main Outcome Measures: The association between dietary AGEs and CKD was assessed using the multivariate logistic regression models.

Results: The mean age of participants was 43.4 $\pm$ 11.4 years. The mean dietary intake of energy-adjusted AGEs was 8,336 $\pm$ 1,532 kU/day. By increasing trend of AGE consumption, the percentage of fat intake increased ($P < .001$), whereas the percentage of carbohydrates and total fiber intake decreased ($P < .001$). Longitudinal analysis indicated that compared to the first quartile category of AGE intakes from fat, in participants of the fourth quartile category, the risk of CKD increased (odds ratio: 2.02; 95% confidence interval: 1.16–3.54). The odds of CKD had increasing trends across increasing categories of AGE intakes from fat (P for trend $<$.05).

Conclusion: Higher consumption of AGEs through dietary fat was associated with higher risk of CKD incidence.

Introduction

SINCE INAPPROPRIATE DIETARY intakes may lead to kidney dysfunction, recognizing the dietary risk factors is vital to developing a comprehensive public health approach to decrease chronic kidney disease (CKD) and end stage of renal disease.[1]

Advanced glycation end products (AGEs) are a heterogeneous family of compounds formed through nonenzymatic reactions between reducing sugars and free amino groups in proteins, lipids, or nucleic acids which can lead to oxidative stress and endoplasmic reticulum stress and have toxic effects through prooxidant and inflammatory actions.[2] High levels of AGEs are associated with many chronic diseases.[3] AGEs can increase the thickness of glomerular basic membrane, glomerular sclerosis, tubular interstitial fibrosis, and finally kidney damage through different mechanisms.[4] AGE accumulation is related to renal insufficiency and correlated positively with serum creatinine and negatively with glomerular filtration rate (GFR).[5] Some kinds of AGEs like pyrrolines and dicarbonyl compounds such as methylglyoxal are formed in the food,[2] but carboxymethyl lysine (CML) is one of the most common dietary AGEs, known as a biomarker for protein damage.[6] Diets which contain more fat and meats are likely to contribute more AGEs, especially when cooked under the dry heat.[7] Consumption of high AGE diets may exert in vivo diabetogenic, hyperlipidemic, and nephrotoxic effects; induce low-grade inflammation; enhance oxidative stress; promote atherosclerosis, insulin resistance, and renal dysfunction such as proteinuria; increase kidney damages; and accelerate kidney deterioration during early phases of renal insufficiency.[8,9] Although some studies do not support the effect of dietary AGEs on circulating levels of AGEs,[10] several experimental studies show that dietary AGEs contribute substantially to the body's AGE pool and enhance circulating blood AGE content; hence, low AGE

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diets could decrease concentration of circulating AGEs[2]; decreasing serum levels of AGEs following changes in dietary pattern is considered a practical way to prevent complications.[11] Since there are limited study on dietary AGE intake and its association with the CKD, we designed this longitudinal study to assess the relation of dietary AGE intake with CKD incidence after 3 years of follow-up in an Iranian population-based study, the Tehran Lipid and Glucose study (TLGS).

Materials and Methods

Study Population

This study was conducted on 3,462 subjects, aged ≥27 years, randomly selected from among 12,523 participants of the third phase (2006–2008) of TLGS, a population-based study initiated in 1999, aimed at determining and preventing noncommunicable diseases among a representative sample of residents' district 13 of Tehran, the capital city of Iran. Study participants are evaluated approximately every 3 years, until the fourth phase (2009–2011). Participants without any data on covariates (n = 8), those with underreporting or overreporting of dietary intakes (<800 kcal/day or >4,200 kcal/day, respectively) (n = 59), and those on specific diets or those with a history of cancer (n = 7) were excluded; the final analysis was conducted on 2,382 individuals (1,285 women).

For prospective analyses, participants with baseline CKD (n = 390) were excluded and the rest of them were followed up to the fourth survey (2009–2011; follow-up rate: 87%). After excluding subjects with missing data on follow-up (n = 11), 1,692 participants remained for the final analysis.

The ethical committee of the Research Institute for Endocrine Sciences, affiliated to the Shahid Beheshti University of Medical Sciences, approved the protocol of this study, and written informed consents were taken from all subjects.

Dietary Assessment

Experienced dietitians questioned participants regarding consumption frequency for each food item, during the past year on a daily, weekly, or monthly basis, using a validated semiquantitative 168-item food frequency questionnaire (FFQ).[12] Participants were asked to report their usual frequency and portion size of consumed food items in household measures, values which were then converted to grams. Since CML is one of the most abundant in vivo and the first to be characterized in foods, it is selected as a marker of AGEs in foods in most studies.[13] As the Iranian Food Composition Table has no data on the AGE contents of foods, we had to use the published food CML-AGE database for 549 commonly consumed food items for the Northeastern American multiethnic urban population which was measured, using a validated immunoassay method (AGE-specific, enzyme-linked immune sorbent assay)[7,14]; CML-AGE values (kUnit [kU]) in 100-g solid food or 100-mL liquid were calculated for 168 food items evaluated by the FFQ of the third phase of TLGS. The CML-AGE values were directly available for some food items and were estimated for others, regarding the existing data. For example, since CML-AGE values were not available for each fruit or vegetable, we used the mean values of fruits or vegetables available to substitute for the others. Moreover, for some specific Iranian food items, for example, some kinds of bread and confectionaries, CML-AGE values were estimated from similar food items for which the CML-AGE values were available.[15] Finally, the CML-AGE values for 151 food items (out of 168) in the FFQ of third phase of the third TLGS were computed, and 17 items which had no similar items in the main list were considered as missing.

The daily CML-AGE intake was calculated for each study subject and was adjusted for daily energy intake. The CML-AGE intakes were categorized by using quartile cutoffs (<6,218, 6,231–7,988, 7,992–9,906, >9,908 kU/day). Participants with dietary AGE intakes <6,218 kU/day were set as the reference group. Since among the food groups, fats and meats groups contain more amounts of AGEs,[7] the total AGE intake from these two groups were calculated separately and then categorized into quartile cutoffs as mentioned above. We summed up the AGEs of all kinds of oils, butters, creams, margarine, mayonnaise, and nuts for fats group and all kinds of red meats, sausage, poultries, and fish for meats group.

Data Collection

All participants were interviewed to collect data on demographics, smoking status, medical history, and physical activity levels (MET hour/week). Participants who smoked daily or occasionally were considered current smokers, and those who had never smoked or those who stopped smoking were considered nonsmokers. The Persian translated Modifiable Activity Questionnaire with high reliability and moderate validity was used for estimating physical activity level in each subject.[16] The participants were asked about the frequency and time spent on light, moderate, hard, and very hard intensity activities over the past year, and the activity data were converted into metabolic equivalent hours per week (METs hour/week).[17]

Each subject's weight was recorded while wearing light clothing and no shoes, to the nearest 100 g. Height was measured to the nearest 0.5 cm using a tape meter, in a standing position, without shoes. Body mass index (BMI) was calculated as weight (kg) divided by square of height (m^2). Blood pressure was measured twice on the right arm in a seated position after a 15-minute rest, using a standardized mercury sphygmomanometer, and the mean of the two measurements was considered as the participant's systolic and diastolic blood pressure.