Nutrition, Metabolism & Cardiovascular Diseases (2023) **33**, 1768–1777

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

Correlation between serum advanced glycation end products and dietary intake of advanced glycation end products estimated from home cooking and food frequency questionnaires

Maria Vasilj [a,1], Leticia Goni [a,b,1], Lucía Gayoso [c,d], Cristina Razquin [a,b], María Teresa Sesma [a,b], Usune Etxeberria [c,d], Miguel Ruiz-Canela [a,b,*]

[a] *University of Navarra, Department of Preventive Medicine and Public Health, IdiSNA (Instituto de Investigación Sanitaria de Navarra), Pamplona, Spain*
[b] *CIBER Fisiopatología de la Obesidad y Nutrición (CIBERObn), Instituto de Salud Carlos III, Madrid, Spain*
[c] *Basque Culinary Center, Faculty of Gastronomic Sciences, Mondragon Unibertsitatea, Donostia-San Sebastián, Spain*
[d] *BCC Innovation, Technology Center in Gastronomy, Basque Culinary Center, Donostia-San Sebastián, Spain*

Received 13 February 2023; received in revised form 27 April 2023; accepted 18 May 2023
Handling Editor: A. Siani
Available online 24 May 2023

KEYWORDS
Serum advanced glycation end products;
Dietary advanced glycation end products;
Food frequency questionnaire;
Home cooking frequency questionnaire

Abstract *Background & aims:* To our knowledge the association between dietary advanced glycation end-products (dAGEs) and cardiometabolic disease is limited. Our aim was to examine the association between dAGEs and serum concentration of carboxymethyl-lysine (CML) or soluble receptor advanced glycation end-products (sRAGEs), and to assess the difference on dAGEs and circulating AGEs according to lifestyle and biochemical measures.
Methods and results: 52 overweight or obese adults diagnosed with type 2 diabetes were included in this cross-sectional analysis. dAGEs were estimated from a Food Frequency Questionnaire (FFQ) or from a FFQ + Home Cooking Frequency Questionnaire (HCFQ). Serum concentrations of CML and sRAGEs were measured by ELISA. Correlation tests were used to analyze the association between dAGEs derived from the FFQ or FFQ + HCFQ and concentrations of CML or sRAGEs. Demographic characteristics, lifestyle factors and biochemical measures were analyzed according to sRAGEs and dAGEs using student t-test and ANCOVA.

A significant inverse association was found between serum sRAGEs and dAGEs estimated using the FFQ + HCFQ ($r = -0.36$, $p = 0.010$), whereas no association was found for dAGEs derived from the FFQ alone. No association was observed between CML and dAGEs. dAGEs intake estimated from the FFQ + HCFQ was significantly higher among younger and male participants, and in those with higher BMI, higher Hb1Ac levels, longer time with type 2 diabetes, lower adherence to Mediterranean diet, and higher use of culinary techniques that generate more AGEs (all p values $p < 0.05$).
Conclusions: These results show knowledge on culinary techniques is relevant to derive the association between dAGEs intake and cardiometabolic risk factors.

* Corresponding author. Edificio de Investigación, Universidad de Navarra, C/ Irunlarrea, 1, 31008 Pamplona, Spain.
E-mail address: mcanela@unav.es (M. Ruiz-Canela).
[1] Equally contributor.

https://doi.org/10.1016/j.numecd.2023.05.022

1. Introduction

Advanced glycation end-products (AGEs) are a large group of heterogeneous compounds formed as a result of the Maillard reaction which occurs between reducing sugars and amino groups coming from proteins, lipids or nucleic acids [1,2]. Most commonly measured and best-studied AGEs are carboxymethyl-lysine (CML), carboxyethyl-lysine (CEL) and methylglyoxal (MG) derivatives. Endogenous AGEs are formed within the body, and their levels significantly increase in conditions like hyperglycemia and oxidative stress [3–5].

AGEs can be also originated from exogenous sources including food, and they are referred as dietary AGEs (dAGEs). Animal foods, such as beef, cheese, poultry, pork, fish, and eggs, contain the highest AGEs levels per 100 g of food. In comparison to meat, vegetables and fruits generally contain lower amounts of AGEs [2]. There is still no consensus on the content of AGEs in fats and oils group since contradictory results have been found [2,6]. Although AGEs are naturally present in food, dAGEs are markedly increased by cooking at high temperature, longer time of application of the heat, lower moisture, presence of trace metals, and higher pH of the cooking system [1,2,7]. Thus, cooking techniques such as grilling, broiling, roasting, searing, and frying generate significantly more dAGEs compared to boiling, poaching, stewing, and steaming [2,7].

Several studies have demonstrated the direct association between both endogenous AGEs and dAGEs and pathological processes of many non-communicable diseases [8–13]. Moreover, previous studies have shown that low AGEs intake may improve insulin resistance, reduced total cholesterol, low-density lipoprotein cholesterol (LDLc), leptin, as well as inflammatory (TNFα), oxidative stress (8-isoprotane), and endothelial dysfunction (VCAM-1) markers [14–16]. Meanwhile, soluble receptor advanced glycation end-products (sRAGEs) concentrations are generally lowered in different disease conditions.

It is not currently clear how dAGEs contribute to body's AGEs pool and therefore, how much effect do they have on human health. One study found that a 10% of ingested AGEs is absorbed through the intestine, of which one-third is excreted in the urine while the fate of the rest remains undetermined [17]. More recently, two studies have shown that higher intake of dAGEs is directly associated with higher levels of AGEs in plasma and urine [18,19]. However, the results have not been conclusive, possibly because a universal method to estimate dAGEs has not yet been established [20].

Most studies have derived the intake of AGEs based on food frequency questionnaires (FFQ) or 2/3 day food records [18,19,21–26]. However, these FFQ and food records did not consider in detail culinary techniques. In this sense, Luevano-Contreras et al. [27] attempted to develop and validate a specific FFQ to measure dAGEs, although the questions on the cooking methods were limited to a short number of foods.

In this study, our aim was to evaluate the correlation between dAGEs derived from a FFQ or a combination of a FFQ and a home cooking frequency questionnaire (HCFQ), and serum levels of CML or sRAGEs measured in participants of the SUKALMENA pilot study. In addition, we examined the differences in sRAGEs and dAGEs by sex, age, body mass index (BMI), glycated hemoglobin (HbA1c), years with diabetes, and dietary and culinary habits.

2. Methods

2.1. SUKALMENA study

The present work is a cross-sectional study within the SUKALMENA study, a pilot randomized controlled trial aimed at evaluating the effect of a culinary nutritional intervention on changes in health status and dietary and culinary behaviors among patients with type 2 diabetes [28]. Participants were recruited at the Basque Culinary Center (BCC, San Sebastian) or at the University of Navarra (UNAV, Pamplona). Inclusion criteria were: diagnosis of type 2 diabetes no treated with insulin, sulfonylureas or glinides; stable treatment with oral antidiabetic agents other than sulfonylureas or glinides for 3 or more months; HbA1c less than 10%; age between 18 and 70 years old; and being overweight or obesity (BMI 25–40 kg/m^2). Only baseline data were used in the present study.

The SUKALMENA trial is registered at ClinicalTrials.gov NCT04449120. The Research Ethics Committees of each recruitment center (BCC and UNAV) approved the protocol. All participants provided written informed consent after they received the information sheet and additional verbal explanation of the study characteristics.

2.2. Anthropometric, body composition, and blood pressure measurements

Anthropometric, body composition, and blood pressure measurements were taken at the beginning of the intervention by trained dietitians. Body weight and body fat were analyzed using a Tanita MC-780 MA (Tanita, Tokyo, Japan) in BCC or a Tanita RD-545 (Tanita, Tokyo, Japan) in UNAV, with the participants wearing underwear. Height was measured using a stadiometer with subjects in barefoot. BMI was calculated dividing weight (kg) by the square of height (m^2). Using a tape measure, waist circumference was measured at the midway between the lower margin of the least rib and the top of the iliac crest; and hip circumference as the widest circumference over the greater buttocks. Waist to hip ratio (waist/hip) was then calculated.

Blood pressure was measured using an automatic device (M6 AC Intellisense, OMRON, Healthcare, Hoofddorp, The Netherlands) and appropriately sized cuff. Three measurements were carried out in both arms, with the elbow at the level of the right atrium and with the subject in a sitting position with a validated automatic oscillometer (Omron M2 HEM-7102-E, The Netherlands).

2.3. Dietary and culinary assessment

Participant's dietary and culinary habits were recorded at baseline by trained dietitians using a semi-quantitative FFQ and a HCFQ, respectively. The semi-quantitative FFQ comprised a total of 138 food items and 9 consumption frequencies (never or seldom, 1–3 times/month, once weekly, 2–4 times/week, 5–6 times/week, once daily, 2–3 times/day, 4–6 times/day, and more than 6 times/day). It has been previously validated for the Spanish population [29,30]. We used Spanish food composition tables to calculate the nutrient composition of the diet, once the daily food consumption was calculated for each food item multiplying the consumption frequency by its typical portion size [31,32]. Adherence to the Mediterranean Diet (MedDiet) was measured using the score proposed by Trichopoulou et al. [33].

The HCFQ was designed, in the context of the SUKALMENA study, to evaluate participants' culinary habits and the exposure to different culinary techniques [34]. The questionnaire consists of 174 items categorized into 5 domains: cooking habits, eating habits, use of culinary techniques, use of different ingredients, and use of kitchen gadgets. For the present project, we used the information of the third domain, in which the volunteers were asked about the use of different culinary techniques for each food group (eggs, white meat, red meat, fish and seafood, vegetables, potatoes, fruits, legumes, and cereals). Each question has 8 frequency options (never or seldom, 1–3 times/month, 1–2 times/week, 3–4 times/week, 5–6 times/week, once a day, twice a day, and 3 or more times/day).

2.4. Dietary AGEs assessment

Since there is no information about AGEs in the Spanish food composition databases, the AGEs content in foods was obtained from the CML–AGEs database published by Uribarri et al. [2]. This database collects data for 549 items that represent the most consumed foods and the most applied culinary techniques in the United States of America. Therefore, not all the food items in the FFQ and the culinary techniques applied to different foods included in the HCFQ are available in such database. For those food items not included in the database, the AGEs content was estimated from similar food items based on nutrient and ingredients profile. On the other hand, when the AGEs content for a certain food prepared with a certain culinary method was not available, the AGEs content of the food prepared with a similar culinary method was used. For example, for certain foods prepared by steaming, data of AGEs content was missing and, in these cases, we applied the amount of AGEs found in the same food prepared by boiling.

Because the amount of dAGEs depends on cooking methods, we estimated dAGEs based on the information of the FFQ, or on the FFQ + HCFQ, to compare if the results obtained from the FFQ + HCFQ were more accurate than those estimated from the FFQ. Based on the FFQ, dAGEs were calculated for each participant multiplying the food intake in g/day by the concentration of AGEs expressed in kU/100 g for solid foods or in kU/100 ml for liquid foods. To estimate dAGEs intake taking into account both, the FFQ and the HCFQ, a new formula had to be developed. This formula considers the g/day of each food that were consumed according to the FFQ and the frequency/day of use of each culinary technique to cook this food. AGEs intake for each food group as well as the overall AGEs intake were calculated.

2.5. Biochemical analysis

At baseline, fasting blood samples were collected from each subject enrolled in the study and stored at -80 °C until analysis. Using standard enzymatic automated methods, serum glucose, total cholesterol, LDLc, high density lipoprotein cholesterol (HDLc), and triglycerides were determined. HbA1c and insulin were measured with an immune turbidimetric assay and a chemiluminescence immunoassay, respectively.

Serum concentrations of CML were measured using Immunotag Human CML ELISA Kit (Biosciences, USA) and sRAGEs were measured using Human RAGEs (R&D Systems, USA). The latter can measure total levels of sRAGEs without any distinction between cleaved RAGEs (cRAGEs) and endogenous secretory RAGEs (esRAGE or RAGEs v1). Generally, sRAGEs level refers to the total sRAGEs level [35].

2.6. Statistical analysis

Continuous variables were presented as mean and standard deviation (SD) whereas categorical variables were described as absolute number and percentage. Normal distribution of the main measured variables (serum CML and sRAGEs, dAGEs derived from the FFQ and from the FFQ + HCFQ) was determined using the Shapiro Wilk test. We applied the decimal logarithm transformation for those variables not normally distributed and with a log-normal distribution of their values.

To analyze the association between dAGEs derived from the FFQ or from the FFQ + HCFQ and serum concentrations of CML and sRAGEs we applied the Pearson correlation test.

To calculate the contribution of each food group to the between-person variability in dAGEs intake, after stepwise-selection regression analyses, we applied a series of nested regression models. The cumulative R^2 change reflects the additional contribution of each food group. To estimate the contribution of each food group to the total intake of dAGEs, we calculated the percentage of dAGEs content of each food group over the total dAGEs intake.

Finally, differences in sRAGEs and dAGEs derived from the FFQ + HCFQ by sex, age, BMI, HbA1c, years-with-diabetes, MedDiet adherence, and usage of culinary techniques were studied by the unpaired Student t-test and by the ANCOVA once adjusted for confounder variables (sex, age, HbA1c, BMI, and energy intake). The use of culinary

techniques was defined as the ratio between culinary techniques associated with a higher formation of AGEs (pan frying, grilling, roasting/broiling, deep frying and breading) and those techniques associated with lower AGEs formation (steaming, stewing, boiling and microwaving) [2]. For continuous variables the median was used to divide participants into two groups.

Statistical analyses were performed using STATA/SE 16.0. All p values were 2-tailed and a p value < 0.05 was considered as statistically significant.

3. Results

Of the 53 participants who started the intervention, in the present study a total of 52 individuals with complete information on food and culinary habits were included in the AGEs analyses. Among them, 18 (35%) were female, and the mean (SD) age was 57.2 (9.8) years, with the youngest participant being 25 years old and the oldest 70 years old. Baseline sociodemographic, anthropometric and biochemical characteristics of the population included in the present study are shown in Table 1. Most of the participants had university studies and were working, married and former smokers. The mean (SD) BMI, body fat mass, and waist circumference was 31.6 (4.0) kg/m^2, 32.7 (8.3) %, and 107.6 (9.6) cm, respectively. Regarding glycemic parameters, the mean (SD) fasting glucose was 129.3 (32.0) mg/dL, and the mean (SD) HbA1c was 6.8 (0.8).

Table 1 Baseline characteristics of the SUKALMENA participants included in the present study.

Characteristic	Total population (n = 52)
Age (years)	57.2 (9.8)
Sex, women	18 (34.6)
Education level	
Secondary or less	23 (44.2)
University	29 (55.8)
Civil status	
Single	15 (28.8)
Married	28 (53.9)
Others	9 (17.3)
Working status	
Working	27 (51.9)
Retired	17 (32.7)
Others	8 (15.4)
Smoking (%)	
Never	13 (25.0)
Current	6 (11.5)
Former	33 (63.5)
Physical activity (MET-h/week)	28.9 (23.6)
Weight (kg)	89.1 (12.1)
BMI (kg/m^2)	31.6 (4.0)
Body fat % (n = 51)[a]	32.7 (8.3)
WC (cm) [a]	107.6 (9.6)
Glucose (mg/dL)	129.3 (32.1)
Hb1Ac (%)	6.8 (0.8)
Insulin (mcU/mL)	9.8 (6.2)
Total cholesterol (mg/dL)	184.2 (34.7)
HDLc (mg/dL)	52.3 (10.0)
LDLc (mg/dL)	103.9 (29.5)
Triglycerides (mg/dL)	151.0 (98.3)
DBP (mmHg)	86.4 (9.9)
SBP (mmHg)	139.1 (15.6)
CML (ng/ml)	364.8 (180.0)
sRAGEs (pg/ml)[b]	695.4 (289.7)

Data are mean (SD) for continuous variables and n (%) for categorical variables.
BMI, Body mass index; CML, Nε-(Carboxymethyl)lysine; DBP, Diastolic blood pressure; Hb1Ac, Glycated hemoglobin; HDLc, High density lipoprotein cholesterol; LDLc, Low density lipoprotein cholesterol; MET, Metabolic equivalent of task; SBP, Systolic blood pressure; sRAGEs, soluble receptor advanced glycation end products; WC, Waist circumference.
[a] 51 participants.
[b] 50 participants.

Dietary and culinary habits of the study population are shown in Table 2. The mean (SD) energy intake was 2520 (712.1) kcal/day. The mean intake of fat, protein and carbohydrates was 117.8, 104.5 and 248.0 g/day, respectively. The adherence to the MedDiet was 4.4 (2.2) on a 0–9 point scale [33]. Among the 90% of participants who cooked at home, 66% cooked between 6 and 7 days a week. In general, volunteers of the SUKALMENA study were in charge of the weekly grocery shopping (96.1%), although they did not usually plan a weekly menu (57.7%). The culinary method that was most commonly used among participants was boiling (8.3 times/week), followed by pan frying (3.9 times/week).

Mean (SD) serum CML concentration was 364.8 (180.0) ng/ml and sRAGEs concentration was 695.4 (289.7) pg/ml (Table 1). Mean (SD) intake of dAGEs was 20 388 (6233) kU/day and 16 346 (6009) kU/day, derived from the FFQ and the FFQ + HCFQ, respectively (Table 2).

Table 3 shows the contribution of different food groups to the variability in total dAGEs: 98% of the variability can be explained by white meat, oils, red meat, fish and processed/ultra-processed foods intake. Oils, white and red meat were the main foods contributing to dAGEs intake.

The association of serum sRAGEs concentration with dAGEs ($r = -0.36$, $p = 0.010$) derived from the FFQ + HCFQ was inversely and statistically significant (Fig. 1). No significant association was found between sRAGEs serum levels and dAGEs derived only from the FFQ ($r = -0.13$, $p = 0.361$). Moreover, no significant association was found between the CML measured in serum and dAGEs derived from the FFQ + HCFQ or the FFQ.

Finally, we studied the differences between serum sRAGEs and dAGEs derived from FFQ + HCFQ according to different population characteristics (Table 4). sRAGEs concentration did not differ by sex, age, BMI, HbA1c, years with type 2 diabetes, MedDiet adherence, or the use of culinary techniques. After adjusting for potential confounders, the baseline intake of dAGEs was higher among male compared to female participants ($p = 0.006$), and among younger compared to older participants ($p < 0.001$). A significant difference was found for dAGEs according to BMI, where participants with high BMI showed the highest AGEs intake ($p = 0.007$). According to HbA1c levels, participants with lower levels consumed less dAGEs ($p = 0.006$). Moreover, in the adjusted model, a higher dAGEs intake was observed in participants with longer time since the diagnosis of type 2 diabetes

Table 2 Culinary and dietary habits of the SUKALMENA participants included in the present study.

Culinary habits	Total population (n = 52)
Do you plan weekly menus at home?	
Yes, I am in charge of weekly meal planning	17 (32.7)
No, but we do a weekly meal plan at home	5 (9.6)
We do not do a weekly meal plan	30 (57.7)
Are you in charge or do you participate in weekly grocery shopping?	
Yes	50 (96.1)
No	2 (3.9)
Do you cook at home?	
Yes	47 (90.4)
No	5 (9.6)
How often do you cook at home? (n = 47)	
≤5 days a week	16 (34.0)
≥6 days a week	31 (66.0)
Pan frying (times/week)	3.9 (2.4)
Deep frying (times/week)	1.5 (1.6)
Roasting/broiling (times/week)	2.4 (1.9)
Stewing (times/week)	1.3 (1.5)
Boiling (times/week)	8.3 (2.9)
Dietary habits	
Energy intake (kcal/day)	2520 (712.1)
Protein intake (g/day)	104.5 (24.6)
Carbohydrate intake (g/day)	248.0 (99.3)
Fat intake (g/day)	117.8 (32.9)
dAGEs derived from FFQ (kU/day)	20 388 (6233)
dAGEs derived from FFQ + HCFQ (kU/day)	16 346 (6009)
MedDiet adherence (0–9 points)[a]	4.4 (2.2)

Data are mean (SD) for continuous variables and n (%) for categorical variables.
dAGEs, Dietary advanced glycation end products; FFQ, Food frequency questionnaire; HCFQ, Home cooking frequency questionnaire; MedDiet, Mediterranean diet.
[a] Score proposed by Trichopoulou et al. [33].

(p = 0.010). Participants with higher adherence to the MedDiet showed a significantly lower dAGEs intake compared to those with a lower adherence (p = 0.008). As expected, the intake of dAGEs was higher in those subjects who more frequently used the culinary techniques that generate more AGEs (pan frying, grilling, roasting/broiling, deep frying and breading) than those culinary techniques that generate less AGEs (steaming, stewing, boiling and microwave) (p = 0.004). No significant differences by population characteristics were found on serum CML (Supplementary Table 1).

Table 3 Sources of variability in total dAGEs intake in a diabetic population according to food groups.

Food group	Cumulative R^2	Percentage of dAGEs
White meat	0.6591	22.0
Oils	0.7624	33.4
Red meat	0.8820	16.5
Fish	0.9479	14.9
Processed foods	0.9819	5.4

dAGEs, Dietary advanced glycation end products.

4. Discussion

This study shows a statistically significant inverse cross-sectional association between dAGEs derived from the FFQ + HCFQ and serum sRAGEs concentration. Whereas no significant association was found between dAGEs derived only from the FFQ and sRAGEs serum levels, and between the serum concentration of CML and dAGEs derived from only FFQ or FFQ + HCFQ. Moreover, the intake of dAGEs was found to be higher in younger or male participants, as well as in those with a higher BMI or a longer history of type 2 diabetes. Likewise, participants with lower HbA1c levels, better adherence to the MedDiet or those who chose culinary techniques that generate less dAGEs (boiling, steaming, stewing and microwave) had a significantly lower intake of dAGEs.

Previous studies have reported conflicting results regarding the relationship between dAGEs and circulating AGEs. Some studies have found a significant association between dAGEs and CML in serum and/or urine [19,36,37]. Moreover, despite low levels of absorption, different intervention studies have reported a decreased serum AGEs following a low AGEs diet [38,39]. However, as we observed, other studies failed to show such association between CMLs and dAGEs [20,40,41]. Although CML is the most widely studied AGEs, some studies have analyzed the relationship between dAGEs and other circulating AGEs rather than CML. For example, a previous study found a positive statistically significant association between dietary intake of CEL and Nδ-(5-hydro-5-methyl-4-imidazolon-2-yl)-ornithine (MG-H1) and their levels in plasma and urine [19]. Another study observed that a high AGEs diet (high in red and processed meat and refined grains) increased plasma CEL levels but not MG-H1 levels compared to a low AGEs diet (high in whole grains, nuts, and legumes) [42]. These conflicting results may be due in part to the complex metabolism of AGEs and how their levels may vary between individuals [43,44]. In addition, it is possible that other factors, such as inflammation and oxidative stress, both conditions present in diabetic patients, may play a role in the association between dAGEs and AGEs serum levels. Therefore, further research is needed to better understand the complex relationship between dAGEs and serum AGEs levels including those other than CML.

In our study, we found a negative association between sRAGEs and the dietary intake of AGEs. There could be several explanations for this inverse association. On the one hand, the literature suggests that while a high concentration of AGEs is associated with unhealthy effects, a low concentration of sRAGEs is associated with adverse health effects, such as diabetes, hypertension and adiposity [4,45–52]. The study carried out by Miranda et al. [53] found that obese individuals had a significantly lower circulating levels of sRAGEs compared to lean individuals. Also, participants with impaired glucose tolerance or type 2 diabetes had lower sRAGEs levels compared to those with normal glucose tolerance [53]. On the other hand, because of the potential role of sRAGEs as a decoy

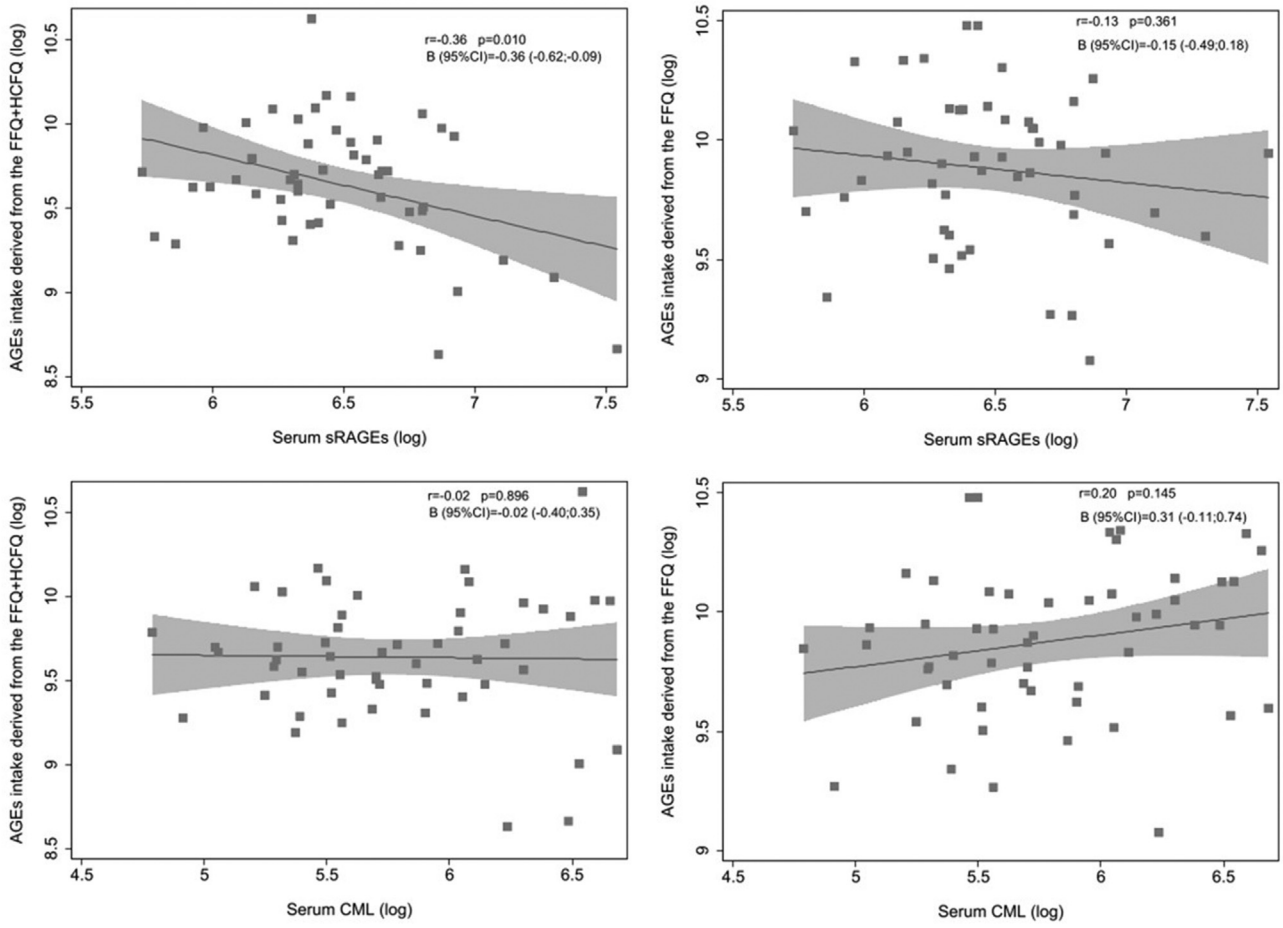

Figure 1 Association between AGEs intake derived from the FFQ + HCFQ or the FFQ and serum sRAGEs (n = 50) or serum CML (n = 52), AGEs, Advanced glycation end products; FFQ Food frequency questionnaire; HCFQ Home cooking frequency questionnaire; sRAGEs, Soluble receptor advanced glycation end products; CML, carboxymethyl-lysine.

receptor for AGEs, preventing it from binding to cell surface RAGEs and reducing the negative effects of AGEs accumulation in the body, we could hypothesize that a decrease in sRAGEs in those participants with a diet rich in dAGEs could be due to this interaction between sRAGEs and serum AGEs [54–56]. This may explain the inverse association between sRAGEs and dAGEs that we observed in our study. However, there are discrepancies in the current literature and further studies are needed [4,45–52].

Several studies have shown that different cooking methods and duration of heating are decisive for the formation of AGEs in food [2,6,57,58]. For instance 100 g of boiled chicken breast contains 1210 kU of CML, while the same amount, broiled at 450 °F for 15 min has 5828 kU. However, dAGEs intake have been previously quantified using FFQ and/or food records, but it was still lacking a specific and validated assessment method for dAGEs, which takes into account cooking methods for all foods [20,24,59]. As far as we know, only one FFQ has been developed and validated to specifically estimate the intake of AGEs but this FFQ included only 90 food items, and it used the cooking methods only for one food group (meats group) to estimate the AGEs intake [27].

Based on the association with serum sRAGEs, we suggest that a HCFQ combined with a FFQ may significantly improve the derivation of dAGEs, compared to using only a FFQ. Moreover, the mean dAGEs intake derived from the FFQ alone was higher (20 390 kU/day) than the dAGEs derived from the FFQ + HCFQ (16 707 kU/day). These results could be attributed to the fact that the mean AGEs value of all culinary techniques was used for each food item for the estimation of dAGEs based only on the FFQ. Therefore, dAGEs intake could be overestimated in those participants that usually used the techniques that generate less dAGEs (boiling, steaming, microwave etc.), while it could be underestimated in those that preferred techniques that generate more dAGEs (grilling, frying, broiling etc.). This fact, could partly explain conflicting findings between previous studies which have not taken into account the use of different culinary techniques to prepare the same food item [24,27].

In the present study, the largest part of dAGEs came from oils, being olive oil the most consumed, while in the American diet, the largest food source of dAGEs is likely to be meat [2]. First, it should be mentioned that there is limited consensus regarding the content of dAGEs in foods

Table 4 Comparison of serum sRAGE and dAGEs by population characteristics.

	Serum sRAGEs (n = 50)			dAGEs (n = 52)		
Sex	**Men**	**Women**	**p value**	**Men**	**Women**	**p value**
Crude	702.0 (330.8)	683.6 (205.0)	0.823	16 358 (6577)	16 324 (4936)	0.796
Model 1[a]	685.7 (388.2)	712.7 (533.9)	0.895	16 545 (1179)	15 970 (10 370)	0.006
Age (years)	**<58.0**	**≥58.0**	**p value**	**<58.4**	**≥58.4**	**p value**
Crude	626.5 (154.6)	764.3 (370.8)	0.237	19 103 (6481)	13 589 (3982)	<0.001
Model 1[b]	630.1 (422.8)	760.7 (422.8)	0.701	18 763 (7279)	13 929 (7279)	<0.001
BMI (kg/m^2)	**<31.0**	**≥31.0**	**p value**	**<31.0**	**≥31.0**	**p value**
Crude	731.9 (368.1)	658.8 (181.7)	0.713	15 009 (6634)	17 684 (5093)	0.063
Model 1[c]	726.2 (429.4)	664.5 (429.4)	0.961	15 732 (7843)	16 960 (7843)	0.007
HbA1c (%)	**<6.6**	**≥6.6**	**p value**	**<6.7**	**≥6.7**	**p value**
Crude	713.4 (279.7)	677.4 (303.9)	0.653	16 071 (4993)	16 621 (6970)	0.981
Model 1[d]	712.0 (422.1)	678.8 (422.1)	0.904	16 087 (7998)	16 605 (7998)	0.006
Years with diabetes	**<6.1**	**≥6.1**	**p value**	**<6.1**	**≥6.1**	**p value**
Crude	670.9 (309.3)	719.9 (272.7)	0.446	17 551 (5244)	15 142 (6570)	0.101
Model 1[e]	696.3 (468.3)	694.4 (468.3)	0.940	15 594 (8684)	17 098 (8684)	0.010
MedDiet adherence*	**<5.0**	**≥5.0**	**p value**	**<5.0**	**≥5.0**	**p value**
Crude	691.8 (305.1)	698.5 (281.7)	0.959	18 566 (7167)	14 586 (4262)	0.036
Model 1[e]	722.0 (480.9)	672.8 (438.8)	0.928	17 784 (8897)	15 206 (7782)	0.008
CTs more/less AGEs†	**<0.7**	**≥0.7**	**p value**	**<0.7**	**≥0.7**	**p value**
Crude	752.1 (358.6)	638.7 (189.8)	0.253	14 465 (4598)	18 227 (6721)	0.036
Model 1[e]	743.6 (425.6)	647.2 (425.6)	0.847	14 933 (7684)	17 760 (7684)	0.004

Data are mean (SD).
AGEs, Advanced glycation end products; BMI, Body mass index; HbA1c, Glycated hemoglobin; CTs, Culinary techniques; MedDiet, Mediterranean Diet; CTs, Culinary techniques; p50, Percentile 50; sRAGEs, Soluble receptor advanced glycation end products.
*Score proposed by Trichopoulou et al. [33].
†Ratio culinary techniques that promote the formation of AGEs more/less.
[a] Model 1: Adjusted for age, HbA1c and BMI for sRAGEs; and for age, HbA1c, BMI and energy intake for dAGEs.
[b] Model 1: Adjusted for sex, HbA1c and BMI for sRAGEs; and for sex, HbA1c, BMI and energy intake for dAGEs.
[c] Model 1: Adjusted for sex, age and HbA1c for sRAGEs; and for sex, age, HbA1c and energy intake for dAGEs.
[d] Model 1: Adjusted for sex, age and BMI for sRAGEs; and for sex, age, BMI, and energy intake for dAGEs.
[e] Model 1: Adjusted for sex, age, BMI, and HbA1c for sRAGEs; and for sex, age, BMI, HbA1c, and energy intake for dAGEs.

and beverages, especially in high fat products. The databases proposed by Goldberg et al. [7] and Uribarri et al. [2] show that oils have the highest AGEs content, whereas Scheijen et al. [6] have reported that oils are low in AGEs content. This discrepancy could be explained by the different methods used to measure the AGEs content in foods. Goldberg et al. [7] and Uribarri et al. [2] used enzyme-linked immunosorbent assay (ELISA), while Scheijen et al. [6] used ultra-performance liquid chromatography. It is also of interest to note that Uribarri et al. database includes a significantly wider variety of foods [2].

Although the scientific literature is limited, sociodemographic, health status, and lifestyle habits have been suggested as potential factors that may influence circulating levels of AGEs and the intake of dietary AGEs [25,26,60–62]. For this reason, we analyzed the effect of different factors (sex, age, BMI, HbA1c, years with diabetes, and dietary and culinary habits) on sRAGEs and dAGEs. In this sense, we found a higher dAGEs intake in men compared to women. This might be due to the fact that men tend to eat more meat than women [60,61], which is one of the food groups with a higher content in AGEs [2]. Our findings are consistent with other studies showing an inverse association between age and dAGEs [18,25,26]. This could be explained by the elevated intake of processed foods in younger population and also because of an increased concern about health and diet in older population with a clinical history of metabolic diseases. Contrary to the findings of a recent meta-analysis [62], we found a significant inverse association between dAGEs intake and BMI, which could be due to the fact that participants in the SUKALMENA study are either overweight or obese and the cross-sectional design of our analysis. According to other studies, low AGEs diets significantly reduced insulin resistance [9,62,63]. We found a lower AGEs intake among subjects with low HbA1c levels. These findings may lead to the conclusion that those participants with lower dAGEs intake, also manage their diabetes better, since the restriction of AGEs intake may significantly improve markers of inflammation and oxidative stress in type 2 diabetes [9].

The study has some limitations and strengths that should be acknowledged. First, the small sample size of the study that could lead to a lack of association or differences between groups. Second, we used self-reported FFQ and HCFQ and therefore recall bias, social desirability bias, and other potential reporting biases may have affected the results. However, the FFQ has already been validated as well as the HCFQ [29,30,34]. Third, when we asked about the culinary techniques applied to each food group we

took into account both, eating at home and at a restaurant. In this sense, we recognize that when we eat at a restaurant the information on culinary techniques used is more limited than when we cook at home and this issue could affect the results. However, it should be noted that, in our study, the number of participants who ate lunch or dinner away from home more than twice a week was low (n = 5 for lunch and n = 3 for dinner). Fourth, participants are diabetic and also overweight or obese, and therefore, the results might not be applicable to the general population. Fifth, in the analysis we did not consider the potential effect of age in circulating AGEs. However, no association was found between serum CML or sRAGEs and age (CML β −0.5 95% CI −5.1;4.1; sRAGEs β 1.3 95% CI −6.2;8.8). Sixth, the dAGEs database used in the present study had been developed in the United States of America, and not in Spain [2], and there are substantial differences between the diet consumed in North America and the diet consumed in Northern Spain [64–66]. Moreover, this database only contains CML as a marker of dAGEs, leaving out other important markers such as CEL and MG-H1. Finally, we acknowledge that the method use by Scheijen et al. [6] to develop their AGEs database, UPLC-MS/MS, is more appropriate than the used of enzyme-linked immunosorbent assay (ELISA) applied by Uribarri et al. [2]. However, we decided to use the AGEs database of Uribarri et al. [2] because it includes a much wider variety of foods and culinary techniques.

In conclusion, we have shown a significant inverse association between sRAGEs and dAGEs derived from a FFQ + HCFQ whereas no relationship was observed with dAGEs derived only from the FFQ. The combination of a FFQ + HCFQ could allow for a more detailed analysis of the dAGEs and it can result in better defined public health policies on dietary and culinary recommendations.

Author contributions

Maria Vasilj: conceptualization, methodology, writing-original draft. **Leticia Goni**: conceptualization, methodology, writing-original draft, investigation. **Lucía Gayoso**: conceptualization, methodology, investigation, writing-review and editing. **Cristina Razquin**: investigation, writing-review and editing. **María Teresa Sesma**: investigation, writing-review and editing. **Usune Etxeberria**: conceptualization, methodology, funding acquisition, writing-review and editing. **Miguel Ruiz-Canela**: conceptualization, methodology, project administration, writing-review and editing.

Funding statement

The Sukalmena study was supported by the Diputación Foral de Gipuzkoa.

Declaration of competing interest

The authors declare no conflict of interests.

Acknowledgements

The authors thanks all of the volunteers of the Sukalmena study as well as the clinical investigators from the Health Centers of Donostialdea (Centro de Salud Alza, Ambulatorio Gros, Centro de Salud Ondarreta, Centro de Salud Lasarte-Oria) for their support in the recruitment; special thanks to María Ángeles Gutíerrez Stampa, Olga Frías Oyaga, Rosalia Giribert Giral, Angel María Gómez Santamaria, Ainhoa Romero Aparicio, and Araceli Prieto Prieto. Moreover, the authors wish to acknowledge the members of the Data Safety and Monitoring Board of the SUKALMENA pilot study for their scientific support (Miguel Ángel Martínez-González, David M. Eisenber and Javier Basterra-Gortari) and all the chefs that participated in the culinary intervention (Estefanía Simón, Jon Basterretxea, Paula Torán and Nahuel Pazos). We are also grateful for the support of Plataforma de Investigación Clínica from Instituto Biodonostia in the biochemical sample analysis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2023.05.022.

References

[1] O'Brien J, Morrissey PA. Nutritional and toxicological aspects of the maillard browning reaction in foods. Crit Rev Food Sci Nutr 1989; 28:211–48. https://doi.org/10.1080/10408398909527499.
[2] 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. https://doi.org/10.1016/j.jada.2010.03.018.
[3] van Dongen KCW, Kappetein L, Miro Estruch I, Belzer C, Beekmann K, Rietjens IMCM. Differences in kinetics and dynamics of endogenous versus exogenous advanced glycation end products (AGEs) and their precursors. Food Chem Toxicol 2022;164:112987. https://doi.org/10.1016/J.FCT.2022.112987.
[4] Reynaert NL, Gopal P, Rutten EPA, Wouters EFM, Schalkwijk CG. Advanced glycation end products and their receptor in age-related, non-communicable chronic inflammatory diseases; overview of clinical evidence and potential contributions to disease. Int J Biochem Cell Biol 2016;81:403–18. https://doi.org/10.1016/J.BIOCEL.2016.06.016.
[5] Baynes JW. The role of AGEs in aging: causation or correlation. Exp Gerontol 2001;36:1527–37. https://doi.org/10.1016/S0531-5565(01)00138-3.
[6] Scheijen JLJM, Clevers E, Engelen L, Dagnelie PC, Brouns F, Stehouwer CDA, et al. Analysis of advanced glycation endproducts in selected food items by ultra-performance liquid chromatography tandem mass spectrometry: presentation of a dietary AGE database. Food Chem 2016;190:1145–50. https://doi.org/10.1016/j.foodchem.2015.06.049.
[7] Goldberg T, Cai W, Peppa M, Dardaine V, Baliga BS, Uribarri J, et al. Advanced glycoxidation end products in commonly consumed foods. J Am Diet Assoc 2004;104:1287–91. https://doi.org/10.1016/j.jada.2004.05.214.
[8] Vlassara H, Cai W, Crandall J, Goldberg T, Oberstein R, Dardaine V, et al. Inflammatory mediators are induced by dietary glycotoxins, a major risk factor for diabetic angiopathy. Proc Natl Acad Sci U S A 2002;99:15596–601. https://doi.org/10.1073/PNAS.242407999.
[9] Uribarri J, Cai W, Ramdas M, Goodman S, Pyzik R, Xue C, et al. Restriction of advanced glycation end products improves insulin resistance in human type 2 diabetes: potential role of AGER1 and SIRT1. Diabetes Care 2011;34:1610–6. https://doi.org/10.2337/dc11-0091.

[10] Cai W, Uribarri J, Zhu L, Chen X, Swamy S, Zhao Z, et al. Oral glycotoxins are a modifiable cause of dementia and the metabolic syndrome in mice and humans. Proc Natl Acad Sci U S A 2014;111:4940–5. https://doi.org/10.1073/PNAS.1316013111.
[11] Schröter D, Höhn A. Role of advanced glycation end products in carcinogenesis and their therapeutic implications. Curr Pharm Des 2019;24:261. https://doi.org/10.2174/1381612825666190130145549.
[12] Sohouli MH, Fatahi S, Sharifi-Zahabi E, Santos HO, Tripathi N, Lari A, et al. The impact of low advanced glycation end products diet on metabolic risk factors: a systematic review and meta-analysis of randomized controlled trials. Adv Nutr 2021;12:766–76. https://doi.org/10.1093/ADVANCES/NMAA150.
[13] Garay-Sevilla ME, Beeri MS, de la Maza MP, Rojas A, Salazar-Villanea S, Uribarri J. The potential role of dietary advanced glycation endproducts in the development of chronic non-infectious diseases: a narrative review. Nutr Res Rev 2020:1–14. https://doi.org/10.1017/S0954422420000104.
[14] Nowotny K, Schröter D, Schreiner M, Grune T. Dietary advanced glycation end products and their relevance for human health. Ageing Res Rev 2018;47:55–66. https://doi.org/10.1016/j.arr.2018.06.005.
[15] Van Puyvelde K, Mets T, Njemini R, Beyer I, Bautmans I. Effect of advanced glycation end product intake on inflammation and aging: a systematic review. Nutr Rev 2014;72:638–50. https://doi.org/10.1111/nure.12141.
[16] 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 2016;8. https://doi.org/10.3390/nu8030125.
[17] Koschinsky T, He CJ, Mitsuhashi T, Bucala R, Liu C, Buenting C, et al. Orally absorbed reactive glycation products (glycotoxins): an environmental risk factor in diabetic nephropathy. Proc Natl Acad Sci U S A 1997;94:6474–9. https://doi.org/10.1073/pnas.94.12.6474.
[18] Uribarri J, Cai W, Peppa M, Goodman S, Ferrucci L, Striker G, et al. Circulating glycotoxins and dietary advanced glycation endproducts: two links to inflammatory response, oxidative stress, and aging. J Gerontol Ser A Biol Sci Med Sci 2007;62:427–33. https://doi.org/10.1093/gerona/62.4.427.
[19] Scheijen JLJM, Hanssen NMJ, van Greevenbroek MM, Van der Kallen CJ, Feskens EJM, Stehouwer CDA, et al. Dietary intake of advanced glycation endproducts is associated with higher levels of advanced glycation endproducts in plasma and urine: the CODAM study. Clin Nutr 2018;37:919–25. https://doi.org/10.1016/j.clnu.2017.03.019.
[20] Semba RD, Ang A, Talegawkar S, Crasto C, Dalal M, Jardack P, et al. Dietary intake associated with serum versus urinary carboxymethyl-lysine, a major advanced glycation end product, in adults: the Energetics Study. Eur J Clin Nutr 2012;66:3–9. https://doi.org/10.1038/EJCN.2011.139.
[21] Uribarri J, Peppa M, Cai W, Goldberg T, Lu M, Baliga S, et al. Dietary glycotoxins correlate with circulating advanced glycation end product levels in renal failure patients. Am J Kidney Dis 2003;42:532–8. https://doi.org/10.1016/S0272-6386(03)00779-0.
[22] Uribarri J, Cai W, Pyzik R, Goodman S, Chen X, Zhu L, et al. Suppression of native defense mechanisms, SIRT1 and PPARγ, by dietary glycoxidants precedes disease in adult humans; relevance to lifestyle-engendered chronic diseases. Amino Acids 2014;46:301–9. https://doi.org/10.1007/s00726-013-1502-4.
[23] De la Maza MP, Bravo A, Leiva L, Gattás V, Petermann M, Garrido F, et al. Fluorescent serum and urinary advanced glycoxidation endproducts in non-diabetic subjects. Biol Res 2007;40:203–12. https://doi.org/10.4067/s0716-97602007000200011.
[24] Jara N, Leal MJ, Bunout D, Hirsch S, Barrera G, Leiva L, et al. Dietary intake increases serum levels of carboxymethil-lysine (CML) in diabetic patients. Nutr Hosp 2012;27:1272–8. https://doi.org/10.3305/nh.2012.27.4.5861.
[25] Ghorbaninejad P, Djafarian K, Babaee N, Davarzani S, Ebaditabar M, Clark CCT, et al. A negative association of dietary advanced glycation end products with obesity and body composition in Iranian adults. Br J Nutr 2021;125:471–80. https://doi.org/10.1017/S0007114520002871.
[26] Vlassara H, Cai W, Goodman S, Pyzik R, Yong A, Chen X, et al. Protection against loss of innate defenses in adulthood by low advanced glycation end products (AGE) intake: role of the anti-inflammatory age receptor-1. J Clin Endocrinol Metab 2009;94:4483–91. https://doi.org/10.1210/jc.2009-0089.
[27] Luevano-Contreras C, Durkin T, Pauls M, Chapman-Novakofski K. Development, relative validity, and reliability of a food frequency questionnaire for a case-control study on dietary advanced glycation end products and diabetes complications. Int J Food Sci Nutr 2013;64:1030–5. https://doi.org/10.3109/09637486.2013.816939.
[28] Gayoso L, Goni L, de la O V, Domper J, Razquin C, Ruiz-Canela M, et al. An intensive culinary intervention programme to empower type 2 diabetic patients in cooking skills: the SUKALMENA pilot study. Int J Gastron Food Sci 2023;32:100721. https://doi.org/10.1016/J.IJGFS.2023.100721.
[29] Martin-Moreno JM, Boyle P, Gorgojo L, Maisonneuve P, Fernandez-rodriguez JC, Salvini S, et al. Development and validation of a food frequency questionnaire in Spain. Int J Epidemiol 1993;22:512–9. https://doi.org/10.1093/ije/22.3.512.
[30] De La Fuente-Arrillaga C, Vzquez Ruiz Z, Bes-Rastrollo M, Sampson L, Martinez-González MA. Reproducibility of an FFQ validated in Spain. Public Health Nutr 2010;13:1364–72. https://doi.org/10.1017/S1368980009993065.
[31] Moreiras O, Carbajal Á, Cabrera L, Cuadrado C. Composición de Alimentos (Food Composition Tables). 16th ed. Madrid: Pirámide; 2013.
[32] Mataix Verdú J. Tabla de Composición de Alimentos (Food Composition Tables). 5th ed. Granada: Universidad de Granada; 2009.
[33] Trichopoulou A, Kouris-Blazos A, Wahlqvist ML, Gnardellis C, Lagiou P, Polychronopoulos E, et al. Diet and overall survival in elderly people. BMJ 1995;311:1457. https://doi.org/10.1136/bmj.311.7018.1457.
[34] Goni L, Gil M, de la O V, Martínez-González MÁ, Eisenberg DM, Pueyo-Garrigues M, et al. Development and validation of a new home cooking frequency questionnaire: a pilot study. Nutrients 2022;14. https://doi.org/10.3390/NU14061136.
[35] Katakami N. Can soluble receptor for advanced glycation end-product (sRAGE) levels in blood be used as a predictor of cardiovascular diseases? Atherosclerosis 2017;266:223–5. https://doi.org/10.1016/j.atherosclerosis.2017.09.007.
[36] Uribarri J, Stirban A, Sander D, Cai W, Negrean M, Buenting CE, et al. Single oral challenge by advanced glycation end products acutely impairs endothelial function in diabetic and nondiabetic subjects. Diabetes Care 2007;30:2579–82. https://doi.org/10.2337/dc07-0320.
[37] Chao PC, Huang CN, Hsu CC, Yin MC, Guo YR. Association of dietary AGEs with circulating AGEs, glycated LDL, IL-1α and MCP-1 levels in type 2 diabetic patients. Eur J Nutr 2010;49:429–34. https://doi.org/10.1007/s00394-010-0101-3.
[38] Macías-Cervantes MH, Rodríguez-Soto JMD, Uribarri J, Díaz-Cisneros FJ, Cai W, Garay-Sevilla ME. Effect of an advanced glycation end product-restricted diet and exercise on metabolic parameters in adult overweight men. Nutrition 2015;31:446–51. https://doi.org/10.1016/j.nut.2014.10.004.
[39] Birlouez-Aragon I, Saavedra G, Tessier FJ, Galinier A, Ait-Ameur L, Lacoste F, et al. A diet based on high-heat-treated foods promotes risk factors for diabetes mellitus and cardiovascular diseases. Am J Clin Nutr 2010;91:1220–6. https://doi.org/10.3945/ajcn.2009.28737.
[40] Šebeková K, Krajčovičová-Kudláčková M, Schinzel R, Faist V, Klvanová J, Heidland A. Plasma levels of advanced glycation end products in healthy, long-term vegetarians and subjects on a western mixed diet. Eur J Nutr 2001;40:275–81. https://doi.org/10.1007/S394-001-8356-3.
[41] Davis KE, Prasad C, Vijayagopal P, Juma S, Adams-Huet B, Imrhan V. Contribution of dietary advanced glycation end products (AGE) to circulating AGE: role of dietary fat. Br J Nutr 2015;114:1797–806. https://doi.org/10.1017/S0007114515003487.
[42] Kim Y, Keogh JB, Deo P, Clifton PM. Differential effects of dietary patterns on advanced glycation end products: a randomized crossover study. Nutrients 2020;12:1–11. https://doi.org/10.3390/NU12061767.
[43] Roncero-Ramos I, Delgado-Andrade C, Tessier FJ, Niquet-Léridon C, Strauch C, Monnier VM, et al. Metabolic transit of N(ε)-carboxymethyl-lysine after consumption of AGEs from bread

crust. Food Funct 2013;4:1032–9. https://doi.org/10.1039/C3FO30351A.
[44] Snelson M, Coughlan MT. Dietary advanced glycation end products: digestion, metabolism and modulation of gut microbial ecology. Nutrients 2019;11. https://doi.org/10.3390/NU11020215.
[45] Grossin N, Wautier MP, Meas T, Guillausseau PJ, Massin P, Wautier JL. Severity of diabetic microvascular complications is associated with a low soluble RAGE level. Diabetes Metab 2008;34:392–5. https://doi.org/10.1016/j.diabet.2008.04.003.
[46] Geroldi D, Falcone C, Emanuele E, D'Angelo A, Calcagnino M, Buzzi MP, et al. Decreased plasma levels of soluble receptor for advanced glycation end-products in patients with essential hypertension. J Hypertens 2005;23:1725–9. https://doi.org/10.1097/01.hjh.0000177535.45785.64.
[47] Davis KE, Prasad C, Vijayagopal P, Juma S, Imrhan V. Serum soluble receptor for advanced glycation end products correlates inversely with measures of adiposity in young adults. Nutr Res 2014;34:478–85. https://doi.org/10.1016/j.nutres.2014.04.012.
[48] Norata GD, Garlaschelli K, Grigore L, Tibolla G, Raselli S, Redaelli L, et al. Circulating soluble receptor for advanced glycation end products is inversely associated with body mass index and waist/-hip ratio in the general population. Nutr Metab Cardiovasc Dis 2009;19:129–34. https://doi.org/10.1016/j.numecd.2008.03.004.
[49] Hoonhorst SJM, Lo Tam Loi AT, Pouwels SD, Faiz A, Telenga ED, van den Berge M, et al. Advanced glycation endproducts and their receptor in different body compartments in COPD. Respir Res 2016;17:1–12. https://doi.org/10.1186/s12931-016-0363-2.
[50] Raposeiras-Roubín S, Rodiño-Janeiro BK, Grigorian-Shamagian L, Seoane-Blanco A, Moure-González M, Varela-Román A, et al. Evidence for a role of advanced glycation end products in atrial fibrillation. 2012. https://doi.org/10.1016/j.ijcard.2011.05.072.
[51] Semba RD, Ferrucci L, Sun K, Beck J, Dalal M, Varadhan R, et al. Advanced glycation end products and their circulating receptors predict cardiovascular disease mortality in older community-dwelling women. Aging Clin Exp Res 2009;21:182–90. https://doi.org/10.1007/BF03325227.
[52] Tan KC, Shiu SW, Chow WS, Leng L, Bucala R, Betteridge DJ. Association between serum levels of soluble receptor for advanced glycation end products and circulating advanced glycation end products in type 2 diabetes. Diabetologia 2006;49:2756–62. https://doi.org/10.1007/s00125-006-0394-1.
[53] Miranda ER, Somal VS, Mey JT, Blackburn BK, Wang E, Farabi S, et al. Circulating soluble RAGE isoforms are attenuated in obese, impaired-glucose-tolerant individuals and are associated with the development of type 2 diabetes. Am J Physiol Endocrinol Metab 2017;313:E631–40. https://doi.org/10.1152/AJPENDO.00146.2017/ASSET/IMAGES/LARGE/ZH100917780000002.JPEG.
[54] Schmidt AM, Hasu M, Popov D, Zhang JH, Chen J, Yan S Du, et al. Receptor for advanced glycation end products (AGEs) has a central role in vessel wall interactions and gene activation in response to circulating AGE proteins. Proc Natl Acad Sci U S A 1994;91:8807–11. https://doi.org/10.1073/PNAS.91.19.8807.
[55] Wautier JL, Zoukourian C, Chappey O, Wautier MP, Guillausseau PJ, Cao R, et al. Receptor-mediated endothelial cell dysfunction in diabetic vasculopathy. Soluble receptor for advanced glycation end products blocks hyperpermeability in diabetic rats. J Clin Invest 1996;97:238–43. https://doi.org/10.1172/JCI118397.
[56] Yan SF, Ramasamy R, Schmidt AM. Receptor for AGE (RAGE) and its ligands—cast into leading roles in diabetes and the inflammatory response. J Mol Med 2009;87:235–47. https://doi.org/10.1007/S00109-009-0439-2.
[57] Poulsen MW, Hedegaard RV, Andersen JM, de Courten B, Bügel S, Nielsen J, et al. Advanced glycation endproducts in food and their effects on health. Food Chem Toxicol 2013;60:10–37. https://doi.org/10.1016/j.fct.2013.06.052.
[58] Hull GLJ, Woodside JV, Ames JM, Cuskelly GJ. N^{*}-(carboxymethyl) lysine content of foods commonly consumed in a Western style diet. Food Chem 2012;131:170–4. https://doi.org/10.1016/j.foodchem.2011.08.055.
[59] Linkens AMA, Houben AJHM, Kroon AA, Schram MT, Berendschot TTJM, Webers CAB, et al. Habitual intake of dietary advanced glycation end products is not associated with generalized microvascular function—the Maastricht Study. Am J Clin Nutr 2021;115:444–55. https://doi.org/10.1093/AJCN/NQAB302.
[60] Sotos Prieto M, Guillen M, Sorlí JV, Asensio EM, Gillem Sáiz P, González JI, et al. Consumo de carne y pescado en población mediterránea española de edad avanzada y alto riesgo cardiovascular. Nutr Hosp 2011;26:1033–40.
[61] Love HJ, Sulikowski D. Of meat and men: sex differences in implicit and explicit attitudes toward meat. Front Psychol 2018;9:1–12. https://doi.org/10.3389/fpsyg.2018.00559.
[62] Baye E, Kiriakova V, Uribarri J, Moran LJ, De Courten B. Consumption of diets with low advanced glycation end products improves cardiometabolic parameters: meta-analysis of randomised controlled trials. Sci Rep 2017;7. https://doi.org/10.1038/s41598-017-02268-0.
[63] Kellow NJ, Savige GS. Dietary advanced glycation end-product restriction for the attenuation of insulin resistance, oxidative stress and endothelial dysfunction: a systematic review. Eur J Clin Nutr 2013;67:239–48. https://doi.org/10.1038/ejcn.2012.220.
[64] Mercasa. Informe Alimentación en España 2020. Producción, Industria, Distribución y Consumo; 2021.
[65] Ministerio de agricultura pesca y alimentación. Informe del Consumo de Alimentación en España 2021. 2022. Madrid.
[66] USDA ERS - Food Consumption and Nutrient Intakes. n.d. https://www.ers.usda.gov/data-products/food-consumption-and-nutrient-intakes/. [Accessed 25 April 2023].