Original Article

Impact of Dietary Advanced Glycation End-Product Restriction on Insulin Resistance and Anthropometric Indices in Coronary Artery Patients Treated with Percutaneous Coronary Intervention: A Randomized Controlled Trial

Elaheh Honarkar-Shafie, MD[1], Mohammad Javad Hosseinzadeh-Attar, MD[1], Fatemeh Taheri, MD[1], Najme-Sadat Moosavi, MD[2], Mehdi Yaseri, MD[3], Mohammad Alidoosti, MD[4], Ali Vasheghani-Farahani, MD[5*]

[1]*Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran.*
[2]*Tehran Heart Center, Tehran University of Medical Sciences, Tehran, Iran.*
[3]*Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran.*
[4]*Department of Cardiology, Tehran Heart Center, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.*
[5]*Cardiac Primary Prevention Research Center, Cardiovascular Disease Research Institute, Tehran University of Medical Sciences, Tehran, Iran.*

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Abstract

Background: *Insulin resistance (IR), even in its subclinical state, is a significant risk factor for the onset and progression of coronary artery disease (CAD). IR is a multifactorial condition, and dietary composition is a factor associated with its development. Elevated advanced glycation end products (AGEs) in the body, secondary to highly processed food consumption, can impair glucose metabolism. The present study investigated whether a restricted AGE diet could affect insulin sensitivity and anthropometric indices reflecting visceral adipose tissue in nondiabetic CAD patients.*

Methods: *This trial randomly allocated 42 angioplasty-treated patients to follow either low-AGE or control diets based on the AHA/NCEP guidelines for 12 weeks. Serum levels of total AGEs, insulin, HbA1c, and fasting blood sugar, as well as anthropometric measurements, were evaluated before and after the intervention. The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) and anthropometric indices were calculated according to the proposed formula. The patients' health status was assessed using the Seattle Angina Questionnaire (SAQ) at baseline and after the intervention.*

Results: *Our study showed a significant reduction in anthropometric indices in the low-AGE group after 12 weeks. Insulin levels and IR decreased during the low-AGE diet. No significant changes were observed in the other serum biochemical markers. All SAQ domains significantly decreased in both groups, except for Treatment Satisfaction.*

Conclusion: *A low-AGE diet for 12 weeks had beneficial effects on HOMA-IR and insulin levels in patients with CAD. Regarding the fundamental role of AGE in IR development and body fat distribution, AGE restriction may positively affect these patients.*

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[*]**Corresponding Author:** ***Ali Vasheghani-Farahani,*** *Professor of Clinical Cardiac Electrophysiology, Department of Electrophysiology, Tehran University of Medical Sciences, Tehran Heart Center, North Karegar Street, Tehran, Iran. 14111713138. Tel: +98 21 88029242. Fax: +98 21 66954709. E-mail: Avasheghani@tums.ac.ir.*

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Keywords: *Dietary advanced glycation end products; Insulin resistance; Visceral fat*

Introduction

Coronary artery disease (CAD) remains the leading cause of death in diabetic and nondiabetic individuals despite significant progress in managing its critical risk factors.[1] One of the most significant risk factors related to CAD onset and progression is insulin resistance (IR).[2] A strong correlation between IR and CAD risk has been established,[3] even in the absence of hyperglycemia.[4] Under physiological conditions, insulin increases glucose uptake and utilization in multiple tissues, including cardiac, skeletal muscle, liver, and adipose tissues.[5] Nonetheless, in IR conditions, these tissues fail to respond to the normal level of circulating insulin and need a higher concentration of insulin for normal function.[6] Several theories have been suggested to understand the mechanisms associated with IR and CAD. IR could cause dyslipidemia,[2] and it might lead to lipoprotein profile alterations.[7] Another theory posits that IR could cause hypertension and endothelial dysfunction by affecting several pathways.[8]

IR, even in the absence of hyperglycemia, has a strong link to cardiovascular disease (CVD). In addition, disturbances in insulin signaling on endothelial and vascular smooth muscle cells can cause plaque progression.[1] Therefore, reducing IR in patients with CAD could be crucial.

There is an increasing trend of IR and CVD concurrent with the rising rate of obesity, and excessive body fat is considered the primary culprit for IR.[9, 10] Several investigations have shown that adiposity and its distribution patterns are major IR determinants.[11, 12] Epidemiological studies have reported that newly-developed anthropometric indices such as the body roundness index (BRI), the waist-to-height ratio (WHR), and the lipid accumulation product (LAP) determine the accumulation of visceral fat better than the body mass index (BMI), the traditional anthropometric measurement of obesity as it fails to differentiate lean mass from fat mass. These indices have a high ability to detect IR[13-15] because visceral fat can increase IR and the risk of CVD and diabetes independent of overall obesity.[16, 17] On the other hand, although class I treatment for CAD is percutaneous coronary intervention,[18] approximately 26% of the patients undergoing the procedure are likely to develop in-stent restenosis. Hence, it seems crucial to identify risk factors that may lead to in-stent restenosis.[19] Advanced glycation end products (AGEs) make an essential contribution to restenosis in the stent position.[18]

AGEs comprise a heterogeneous pro-oxidant and cytotoxic group of compounds formed from the Maillard reaction.[20] Nutrient composition and food processing methods are the most critical factors determining the content of exogenous AGEs. Roasting, frying, and grilling produce more AGEs, such as carboxymethyl-lysine and methylglyoxal, in food than boiling or steaming.[21] The endogenous formation in the human body is also a prominent source of AGEs. In healthy individuals, small amounts of endogenous AGEs are generated as a consequence of normal metabolism,[22] representing a minor component of the total body load of AGEs.[21] Nevertheless, they accumulate to a greater extent in many chronic diseases, such as insulin-resistant states.[23] Animal and recent human studies have indicated that dietary AGEs, especially methylglyoxal derivatives, contribute to impaired insulin signaling, increased insulin levels, and IR.[24-26] While the increased endogenous production of AGEs results from high blood sugar concentrations, AGEs themselves can contribute to pancreatic β-cell dysfunction development of type II diabetes and activate intracellular pathways, associated with IR development.[27]

Evidence indicates that a diet low in AGEs may contribute to decreased fasting insulin and the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) in diabetics and overweight/obese subjects.[28, 29]

To our knowledge, no study has been conducted to investigate the effects of a long-term AGE-restricted diet on nondiabetic individuals undergoing angioplasty. The present study, therefore, aimed to compare the effects of 2 diets: a low-AGE diet considering the American Heart Association (AHA)/National Cholesterol Education Program (NCEP) recommendations as the intervention group and a diet based on the AHA/NCEP recommendations as the comparison group. AGE formation can be increased by increasing the cooking time and temperatures and reducing humidity by grilling as recommended in the AHA/NCEP guidelines for lowering dietary fat. Based on these observations, we hypothesized that a low-AGE diet alongside the AHA/NCEP recommendations in CAD patients without diabetes might improve insulin sensitivity as a risk factor for CVD progression.

Methods

Male and female subjects between 50 and 65 years of age and a BMI between 18.5 kg/m^2 and 35 kg/m^2 were included in the study. The participants did not have a previous history of diabetes, thyroid disorders, chronic kidney disease, autoimmune disease, cancer, familial hypercholesterolemia, and hypertriglyceridemia. They were nonsmokers. All the participants had not received multivitamin, mineral, or antioxidant supplements over the preceding 3 months, nor had they followed any weight loss diets over the past year. No participant had a history of heart attack, stroke, or angioplasty over the preceding 3 months. Postmenopausal women were included.

Patients who had undergone angioplasty treatment due to atherosclerosis in 1 or 2 vessels and met the eligibility criteria for enrollment were asked to return to the hospital 1 month after angioplasty to continue the study. All the included patients provided written informed consent before participation.

This study was an open-labeled controlled randomized clinical trial to explore the effects of an AGE-restricted diet on IR. Patients were recruited from September 2020 through June 2021 at Tehran Heart Center. Forty-eight patients were randomly assigned to 2 groups: a low-AGE group and a comparison group. Stratified randomization was used to control the sex variable. For the random allocation of eligible patients to the groups, a computer-based generated random sequence was utilized based on sex-stratified permuted block randomization with a random block length of 2 and 4. Blood sampling, body composition, and anthropometric measurements were evaluated at baseline and the day after the completion of the intervention in the morning after a 12-hour fast. Additionally, the Seattle Angina Questionnaire (SAQ) was employed to measure the health status of the included patients at baseline and the end of the study. Along with optimal medical therapy according to the healthcare protocol of the hospital, each group adhered to its specific diet for 12 weeks.

The present single-center trial was approved by the Research Ethics Committee of Tehran University of Medical Sciences before study commencement (IR.TUMS.VCR.REC1398.113). The study protocol was registered in the Iranian Clinical Trial Site (IRCT20131125015536N10).

The eligible patients were randomly assigned to a low-AGE diet group and a comparison group. The energy level for each patient was adjusted to the basal metabolic rate after body composition analysis. All diet plans were individualized for each participant's weight stability and habitual diet. In addition, the percentage of dietary macronutrients was similar in both groups. Any recommendation to increase physical activity or lose weight was not included.

In our study, both dietary models shared common characteristics in the major components based on the dietary recommendations of the AHA/NCEP for CVD (<25%-30% total fat: <20% monounsaturated fatty acids, <10% polyunsaturated fatty acids, and <7% saturated fatty acids; 15% protein; and 50%-60% carbohydrates), restricting the intake of added sugar (<100 kcal/d for women and 150 kcal/d for men), sodium (≤2300 mg/d), and cholesterol (200 mg/d). The comparison group received only the recommendations of the AHA/NCEP guidelines. The low-AGE group received written recommendations for food preparation, modifying the cooking time and temperature without changing the composition of food and a food-choice list including "restricted" or "not allowed" foods in addition to the recommendations of the AHA/NCEP guidelines. The food-choice list contained examples of foods commonly available in Iran with high dietary AGE contents.[21] The low-AGE group was encouraged to boil, poach, stew, or steam its food and was instructed to avoid broiling, grilling, deep frying, and roasting. Adherence in the 2 groups was monitored by 6 dietary recalls (4 working days and 2 weekends). Moreover, a dietitian contacted the participants by telephone to resolve their problems.

Demographic characteristics and health data were collected using a researcher-made checklist. All data were collected at baseline and the end of the intervention. Weight was measured without shoes and with minimal clothing with a precision of 100 g while the participants were fasting. In addition, height was measured without shoes in a standing position using a tape measure with the nearest 0.5 cm. For the calculation of BMI, BRI, WHR, and LAP in both groups.

IR was estimated using HOMA-IR as an index of changes in insulin sensitivity according to the following formula: HOMA-IR = (fasting insulin (mU/l) × fasting glucose (mmol/l)/ 22.5).

Fasting venous blood samples were collected at baseline and the end of the intervention to measure the serum levels of total AGEs, insulin (ELISA, IBT, Netherlands), HbA1c, and fasting blood sugar (FBS) (the photometric method by BT1500, Biotecnica Instruments, Italy; Pars-Azmoon, Iran). The Nutritionist IV software, modified for Iranian foods, was used to obtain the nutrient contents. Food items were obtained from each recall to estimate the dietary AGE contents. Then, each person's AGE contents of recalls were calculated based on the reference list of dietary AGE levels.[21]

SAQ has been validated and established to be sensitive to changes in disease over time.[30] It is a self-administered questionnaire to measure the health status of patients with CAD in 5 domains: Physical Limitation, Angina Stability, Angina Frequency, Treatment Satisfaction, and Disease Perception. We assessed the health status of our patients with a 19-item version of SAQ[31] before and after the intervention.

Physical activity was assessed using the metabolic

equivalent of task (MET), calculated for each participant according to the recorded activities over the past 24 hours alongside the time spent doing each activity for 3 days.[32]

The primary outcome was HOMA-IR, calculated based on the relevant formula. The secondary variables were insulin, FBS, HbA1C, and SAQ. The number of participants in each group was 21, providing a test power of 80%.

The data were analyzed using the SPSS software (version 24.0; SPSS). First, the normal distribution of all variables was examined using the Kolmogorov–Smirnov test. Parametric tests for variables with normal distributions and nonparametric tests for variables without normal distributions were conducted. Quantitative and qualitative variables were described as the mean±the standard error of the mean (SEM) and frequencies (percentages), respectively. The qualitative variables were compared between the 2 groups using the χ^2 test. The changes within each group during the dietary intervention were examined using paired *t* tests or the Wilcoxon signed ranks test. The differences between the 2 groups were analyzed using the independent *t* or Mann–Whitney *U* Test. For the comparison of the quantitative variables between the 2 groups after adjustments for the baseline values, the ANCOVA model was used. The correlation between HOMA-IR and anthropometric indices was assessed using the Spearman rank correlation test. A *P* value of less than 0.05 was considered statistically significant.

Results

A total of 1098 patients who had undergone angioplasty were assessed for eligibility, and 42 patients were enrolled and randomly assigned to 2 groups. Finally, 39 participants completed the 12-week trial (Figure 1).

The baseline clinical and metabolic characteristics of the study population are presented in Table 1. No significant differences were observed at baseline regarding the examined variables between the randomized dietary groups.

Table 1. Patient characteristics at baseline

Characteristic	Groups		*P*
	Low-AGE Group (n=20)	Comparison Group (n=19)	
Age (y)	58.20±1.41	56.61±1.21	0.391
Women (%)	19.00	19.00	1.000
Weight (kg)	81.25±2.09	82.00±2.35	0.823
BMI (kg/m^2)	28.48±0.69	29.31±0.83	0.429
Waist circumference (cm)	96.82±2.00	101.49±2.00	0.110

*Values are reported as mean±SEM.
**Calculated using the independent t test
AGE, Advanced glycation end product; BMI, Body mass index

The diets of the low-AGE and comparison groups were statistically isocaloric. After the assessment of the intake of macronutrients and micronutrients, the mean intake values of energy, protein, fat, and carbohydrates were similar between

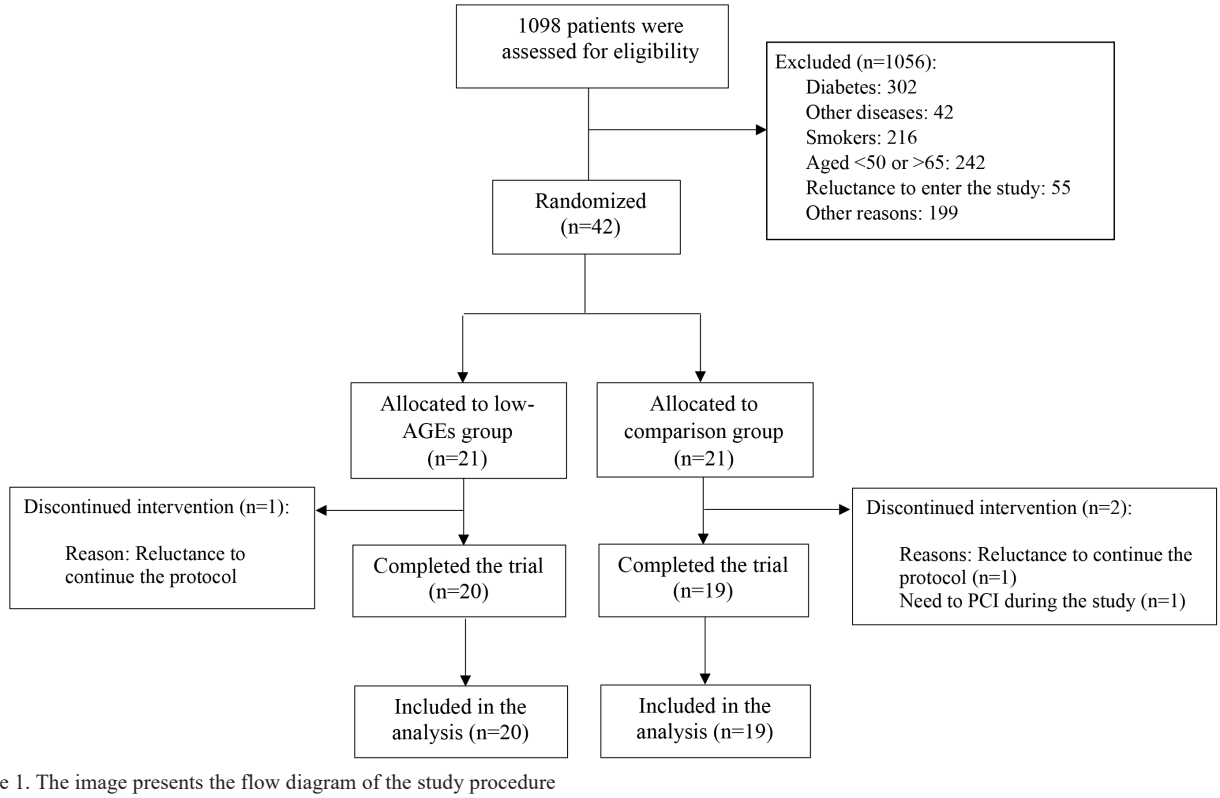

Figure 1. The image presents the flow diagram of the study procedure

Table 2. Nutritional intakes and physical activities of the study participants*

	Low-AGE Group (n=20)	Comparison Group (n=19)	P**
Energy	1941.00±64.01	2076.61±90.32	0.191
Protein			
g/d	76.52±16.31	81.10±4.19	0.395
Percentage of energy	15.80±0.65	15.73±0.78	0.112
Carbohydrate			
g/d	271.74±14.79	299.72±17.17	0.224
Percentage of energy	55.80±1.73	57.41±1.85	0.709
Fat			
g/d	60.91±3.45	61.54±4.54	0.914
Percentage of energy	28.24±1.80	26.71±1.80	0.313
MUFA			
g/d	25.91±1.45	26±2.22.00	0.968
Percentage of energy	12.51±0.69	11.31±0.89	0.307
PUFA			
g/d	18.18±1.13	16.33±1.81	0.382
Percentage of energy	8.75±0.55	7.13±0.70	0.091
SFA			
g/d	12.44±1.01	14.00±0.93	0.283
Percentage of energy	5.77±0.40	6.11±0.33	0.652
Fiber (g/d)	18.30±1.02	16.61±0.75	0.201
Cholesterol (mg/d)	187.79±18.51	207.09±18.92	0.277
Added sugar (kcal/d)			
Men	74.01±11.00	81.31±14.78	0.665
Women	33.00±6.91	42.65±13.52	0.542
Sodium (mg/d)	1726.90±51.35	1858.93±253.41	0.100
Dietary AGEs	7368.81±665.69	18952.82±2285.76	0.001
Physical activity (MET-h/day)	33.31±0.90	31.77±1.00	0.283

*Data are reported as mean±SEM.
**Calculated using the independent *t* test
PUFA, Polyunsaturated fatty acid; MUFA, Monounsaturated fatty acid; SFA, Saturated fatty acid; AGEs, Advanced glycation end products

Table 3. Anthropometric measures and serum biomarkers in both groups at baseline and the end of the study

	Low-AGE Group (n=20)			Comparison Group (n=19)			*P*
	Baseline	12-week follow-up	*P*	Baseline	12-week follow-up	*P*	
Weight (kg)†	81.25±2.09	78.58±2.21	0.001	82.00±2.35	81.00±2.33	0.021	0.021
BMI (kg/m²)†	28.48±0.69	27.61±0.75	0.001	29.31±0.83	29.01±0.85	0.061	0.062
WC (cm)†	96.82±2.00	94.00±2.01	0.002	101.49±2.00	100.10±2.27	0.220	0.225
Total AGEs (ng/L)†	648.71±144.40	617.9±122.8	0.650	581.91±124.11	632.15±121.90	0.339	0.338
FBS (mg/dL)†	110.93±4.52	110.00±3.02	0.711	106.94±2.64	108.18±4.21	0.140	0.601
HbA1c (%)†	6.11±0.85	6.01±0.80	0.397	6.10±0.13	6.14±0.083	0.501	0.893
Insulin (kg)‡	8.66(8.23,10.03)	8.56(8.05,9.78)	0.042	8.51(8.19,9.37)	8.31(7.8,10.05)	0.784	0.531
HOMA-IR (kg/m²)‡	2.37(2.01,3.14)	2.34(2.11,2.7)	0.048	2.27(2.1,2.57)	2.19(1.95,2.74)	0.910	0.367
BRI†	3.10±0.22	2.80±0.20	0.002	3.51±0.24	3.42±0.20	0.075	0.213
WHR†	0.57±0.01	0.55±0.01	0.001	0.62±0.01	0.59±0.009	0.072	0.189
LAP†	65.61±7.28	52.41±5.73	0.002	59.77±10.32	60.12±12.00	0.928	0.015

†Data are reported as mean±SEM.
‡Data are reported as median (IQR). The Wilcoxon signed ranks and Mann–Whitney *U* tests were used for within and between-group comparisons.
The paired t test and ANCOVA were used for within and between-group comparisons.
AGE, Advanced glycation end product; BMI, Body mass index; WC, Waist circumference; HbA1c, Hemoglobin A1C; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; BRI, Body roundness index; WHR, Waist-to-height ratio; LAP, Lipid accumulation produce

Table 4. Correlation between changes in anthropometric indices and HOMA-IR in both groups during the study

	HOMA-IR	
	Estimate	*P**
BRI	0.45	0.004
WHR	0.42	0.008
LAP	0.40	0.020

*Calculated using the Spearman rank correlation test
HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; BRI, Body roundness index; WHR, Waist-to-height ratio; LAP, Lipid accumulation index

Table 5. Score of the Seattle Angina Questionnaire in both groups at baseline and the end of the study*

	Low-AGE Group (n=20)			Comparison Group (n=19)			P***
	Baseline	12-week follow-up	P**	Baseline	12-week follow-up	P**	
Physical limitation	85.55±3.31	93.79±2.11	0.004	84.42±4	93.74±1.95	0.003	0.778
Angina stability	61.93±6.42	89.13±4.08	0.001	70.21±6.33	88.11±5.10	0.011	0.330
Angina frequency	82.64±3.40	90.90±2.91	0.011	78.08±4.21	90.93±2.62	0.014	0.387
Treatment satisfaction	82.78±3.50	89.64±4.25	0.073	86±3.61	92.46±3.91	0.220	0.972
Disease perception	51.41±5.00	64.10±2.63	0.014	48±4.40	62.58±3.62	0.001	0.754

*Data are reported as mean±SEM.
**Calculated using the paired *t* test
***Calculated using ANCOVA

the groups throughout the dietary intervention. Moreover, the essential factors recommended in the AHA/NCEP guidelines (ie, sodium, added sugar, and cholesterol) were not different between the 2 groups (Table 2). The estimated mean daily carboxymethyl-lysine intake, according to the records of the study participants, was 7368 in the low-AGE group and 18952 in the comparison group (P=0.001). Despite the decreasing trend of the serum total AGEs in the low-AGE group, the trend was not statistically significant. The average MET did not differ significantly between the 2 groups during the intervention.

After the consumption of both diets, weight significantly decreased in both groups (P<0.05) (Table 3), which was significantly greater in the low-AGE group (P=0.021) (Table 3). Although the difference in BMI reduction between the 2 groups was nonsignificant (P=0.062), its reduction was significant in the low-AGE group (P=0.001). Waist circumference decreased in both groups over the 12-week period, but it was statistically significant only in the low-AGE group (P=0.002).

Table 3 shows that the low-AGE diet significantly decreased BRI, WHR, and LAP after the 12-week period (P=0.002, P=0.001, and P=0.002, respectively). Nonetheless, changes in anthropometric indices were nonsignificant in the comparison group (P=0.075, P=0.072, and P=0.928, respectively). Although a decreasing trend in BRI and WHR was seen in the comparison group, a low-AGE diet produced a higher decrease in BRI and WHR throughout the follow-up. Among anthropometric indices, LAP significantly decreased in the low-AGE group compared with the comparison group (P=0.015).

During the low-AGE dietary period, fasting plasma insulin and HOMA-IR exhibited significant improvements (P=0.042 and P=0.48, respectively), whereas they did not change significantly in the comparison group (P=0.784 and P=0.910, respectively). No significant changes were observed in HbA1c and FBS in the 2 groups after the 12-week intervention. Furthermore, no significant differences were reported in FBS (P=0.601), HbA1c (P=0.893), insulin (P=0.531), and HOMA-IR (P=0.367) between the study groups at the end of the trial.

HOMA-IR showed a significant positive correlation with BRI (r=0.45, P=0.004), WHR (r=0.42, P=0.008), and LAP (r=0.40, P=0.020) (Table 4).

The scores of 4 domains of SAQ significantly improved in both groups from baseline to the end of the study (P<0.05) (Table 5). More improvements in the score of the Angina Stability domain were seen in the low-AGE group than in the comparison group (27.2±6.81 vs 17.9±6.74). The scores of the Treatment Satisfaction domain did not change significantly in the 2 groups during the intervention. No significant difference was observed in the domains of SAQ between the low-AGE and comparison groups at the end of the intervention (P>0.05).

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Discussion

In the present study, we aimed to investigate whether dietary AGE restrictions for 12 weeks could improve IR in patients with CAD. We found that the consumption of a low-AGE diet for 12 weeks resulted in a marked decrease in fasting plasma insulin and improved HOMA-IR significantly. Further, all anthropometric indicators improved significantly in the low-AGE group. In the comparison group, we observed no end-of-study effects on fasting blood glucose, HbA1c, fasting plasma insulin, HOMA-IR, and all anthropometric indicators.

It has been established that dietary macronutrient composition is associated with the development of IR.[33] In our study, diets in both groups were matched for macronutrient

and important micronutrient contents. Therefore, the effect of macronutrients on changes in IR is ruled out.

Obesity, abnormal or excessive fat accumulation (especially abdominal obesity), is a well-established risk factor for CVD. Indeed, it has been established that adipose tissue distribution is strongly associated with IR, one of the major risk factors for CVD.[34] Numerous prospective studies have indicated that impaired glucose tolerance and IR are independent predictors of the incidence of CVD in nondiabetic subjects.[35, 36] The risk of CAD is approximately 3 times larger in those who develop IR than in those without IR. Normalizing IR reduces CVD risk by nearly 55%.[35]

The most common IR indices used in studies is HOMA-IR[34]; therefore, we assessed IR by HOMA-IR in the current study. A prior investigation showed that IR in patients with diabetes or without diabetes resulted in a higher relative risk of a cardiovascular event.[37] Moreover, a cohort study conducted on patients undergoing coronary angiography revealed that HOMA-IR (independently of diabetes status) could predict vascular events.[38] Hence, it seems that ameliorating IR is beneficial in patients with CAD, which occurred in the low-AGE group in our study.

Dietary macronutrient composition consistently impacts IR development via different mechanisms.[33] Some animal models and clinical studies have demonstrated that higher diet-derived AGE intakes could induce IR.[25, 39] We observed a significant improvement in fasting plasma insulin and HOMA-IR in the low-AGE group. Similar to our study, 2 trials indicated that higher diet-derived AGE intakes for 2 or 4 weeks could lead to IR or reduced insulin sensitivity.[40, 41] The effect of consuming a low-AGE diet on HOMA-IR was reported in both diabetic[42] and nondiabetic[43] patients.

Although IR is a multifactorial condition, visceral fat is predominantly related to the development of IR.[44] A recent study showed that the carboxymethyl-lysine level of diabetic subjects was negatively correlated with BMI and WHR.[45] Another investigation indicated that the level of carboxymethyl-lysine was associated with lower WHR, BMI, and central obesity in nondiabetic subjects.[46] In contrast, a study showed that a low-AGE diet compared with a regular diet for 1 year ameliorated IR in obese subjects but exerts no effects on visceral fat.[28] Our observations showed that visceral fat decreased significantly in the low-AGE group after 12 weeks, while its change was not significant in the comparison group.

Even though the best methods for measuring fat distribution are magnetic resonance imaging and computed tomography, the procedures are inconvenient, expensive, and time-consuming. Anthropometric indices have been recently used as an alternative method to estimate visceral fat because they are simple, fast, and cost-effective. Thomas et al[47] introduced BRI as a good index for estimating the percent visceral adipose tissue and probably a good indicator to assess IR. Another investigation reported that BRI had the optimal potential to determine the presence of IR in both sexes compared with WC and WHR.[48] LAP is a reliable anthropometric tool that reflects the total volume of visceral fat by including waist circumference and serum triglyceride levels. Among the triglyceride/high-density lipoprotein-cholesterol ratio, the visceral obesity index, LAP, and the triglyceride glucose index, only LAP exhibited a significant association with insulin sensitivity.[14] LAP is also a better predictor of CVD.[49] Another index assessed in our study is WHR considering its significant positive associations with IR.[50] We investigated whether there was a relationship between visceral fat and improved IR and observed a significant positive correlation between changes in HOMA-IR and anthropometric indices reflecting visceral fat. Accordingly, the beneficial effects of an AGE-restricted diet on IR might have occurred through the reduction of visceral fat.

Although dietary AGE intakes were significantly reduced in our low-AGE group, the decreasing trend of serum total AGEs was not statistically significant. A larger sample size might yield significant results.

SAQ was introduced over 3 decades ago and has been used in numerous studies since. SAQ integrates patients' experiences into clinical care and quantifies the symptoms and function of patients with CAD. It is, therefore, recommended as a quality measure in managing patients with CAD.[51] According to our results, the scores of 4 domains of SAQ significantly improved in both groups throughout the study. We observed higher scores in the Angina Stability domain in the low-AGE group at the end of the study. To our knowledge, no study has investigated the effects of a diet on CAD patients with this questionnaire. Still, other studies have evaluated the effects of dietary supplementations or the levels of nutrients in the body on these patients using the SAQ questionnaire. A clinical trial showed that dietary supplementation for 2 weeks with arginine-rich medical food improved the summary score of SAQ.[52] Another study demonstrated that the omega-3 index was not associated with angina status measured by SAQ in patients with heart disease.[53]

The results of the current study should be interpreted in light of its limitations. The open-label design of our study increases the risk of biased results. However, it should be noted that it was impossible to blind the participants and the researchers to the dietary intervention. Further, we used HOMA to estimate IR, while the best method for the assessment of IR is the euglycemic insulin clamp technique, which was not practical in our study.

Conclusion

The results of the present study showed a significant reduction in anthropometric indices in the low-AGE group

after 12 weeks. Moreover, IR improved during the AGE-restricted diet based on the AHA/NCEP guidelines. Hence, a positive correlation could exist between reduced visceral fat and improved IR. A low-AGE diet may, therefore, be beneficial to nondiabetic CAD patients.

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References

1. Bornfeldt KE, Tabas I. Insulin resistance, hyperglycemia, and atherosclerosis. Cell Metab 2011;14:575-585.
2. Ormazabal V, Nair S, Elfeky O, Aguayo C, Salomon C, Zuñiga FA. Association between insulin resistance and the development of cardiovascular disease. Cardiovasc Diabetol 2018;17:122.
3. Gast KB, Tjeerdema N, Stijnen T, Smit JW, Dekkers OM. Insulin resistance and risk of incident cardiovascular events in adults without diabetes: meta-analysis. PLoS One 2012;7:e52036.
4. DeFronzo RA. Insulin resistance, lipotoxicity, type 2 diabetes and atherosclerosis: the missing links. The Claude Bernard Lecture 2009. Diabetologia 2010;53:1270-1287.
5. Reaven G. Insulin resistance and coronary heart disease in nondiabetic individuals. Arterioscler Thromb Vasc Biol 2012;32:1754-1759.
6. Wang CC, Goalstone ML, Draznin B. Molecular mechanisms of insulin resistance that impact cardiovascular biology. Diabetes 2004;53:2735-2740.
7. Pont F, Duvillard L, Florentin E, Gambert P, Vergès B. Early kinetic abnormalities of apoB-containing lipoproteins in insulin-resistant women with abdominal obesity. Arterioscler Thromb Vasc Biol 2002;22:1726-1732.
8. Andreozzi F, Laratta E, Sciacqua A, Perticone F, Sesti G. Angiotensin II impairs the insulin signaling pathway promoting production of nitric oxide by inducing phosphorylation of insulin receptor substrate-1 on Ser312 and Ser616 in human umbilical vein endothelial cells. Circ Res 2004;94:1211-1218.
9. Després JP, Lemieux I, Bergeron J, Pibarot P, Mathieu P, Larose E, Rodés-Cabau J, Bertrand OF, Poirier P. Abdominal obesity and the metabolic syndrome: contribution to global cardiometabolic risk. Arterioscler Thromb Vasc Biol 2008;28:1039-1049.
10. Patel P, Abate N. Body fat distribution and insulin resistance. Nutrients 2013;5:2019-2027.
11. Gao H, Salim A, Lee J, Tai ES, van Dam RM. Can body fat distribution, adiponectin levels and inflammation explain differences in insulin resistance between ethnic Chinese, Malays and Asian Indians? Int J Obes (Lond) 2012;36:1086-1093.
12. Brotons C, de la Figuera M, Franch J, Aristegui I, Rodríguez Azeredo R, García M, Gomis R; Investigation group of PRED-IR Study. Predicción de la glucemia basal alterada y resistencia a la insulina mediante el uso de medidas antropométricas de adiposidad central: estudio PRED-IR [Prediction of glucose and insulin resistance disorders by using anthropometric parameters of central adiposity: PRED-IR study]. Med Clin (Barc) 2008;131:366-370.
13. Schreiner PJ, Terry JG, Evans GW, Hinson WH, Crouse JR 3rd, Heiss G. Sex-specific associations of magnetic resonance imaging-derived intra-abdominal and subcutaneous fat areas with conventional anthropometric indices. The Atherosclerosis Risk in Communities Study. Am J Epidemiol 1996;144:335-345.
14. Fiorentino TV, Marini MA, Succurro E, Andreozzi F, Sesti G. Relationships of surrogate indexes of insulin resistance with insulin sensitivity assessed by euglycemic hyperinsulinemic clamp and subclinical vascular damage. BMJ Open Diabetes Res Care 2019;7:e000911.
15. Liu J, Fan D, Wang X, Yin F. Association of two novel adiposity indicators with visceral fat area in type 2 diabetic patients: Novel adiposity indexes for type 2 diabetes. Medicine (Baltimore) 2020;99:e20046.
16. Huxley R, Mendis S, Zheleznyakov E, Reddy S, Chan J. Body mass index, waist circumference and waist:hip ratio as predictors of cardiovascular risk--a review of the literature. Eur J Clin Nutr 2010;64:16-22.
17. Meisinger C, Döring A, Thorand B, Heier M, Löwel H. Body fat distribution and risk of type 2 diabetes in the general population: are there differences between men and women? The MONICA/KORA Augsburg cohort study Am J Clin Nutr 2006;84:483-489.
18. Kosmopoulos M, Drekolias D, Zavras PD, Piperi C, Papavassiliou AG. Impact of advanced glycation end products (AGEs) signaling in coronary artery disease. Biochim Biophys Acta Mol Basis Dis 2019;1865:611-619.
19. Cassese S, Byrne RA, Tada T, Pinieck S, Joner M, Ibrahim T, King LA, Fusaro M, Laugwitz KL, Kastrati A. Incidence and predictors of restenosis after coronary stenting in 10 004 patients with surveillance angiography. Heart 2014;100:153-159.
20. Henle T. Protein-bound advanced glycation endproducts (AGEs) as bioactive amino acid derivatives in foods. Amino Acids 2005;29:313-322.
21. Uribarri J, Woodruff S, Goodman S, Cai W, Chen X, Pyzik R, Yong A, Striker GE, Vlassara H. Advanced glycation end products in foods and a practical guide to their reduction in the diet. J Am Diet Assoc 2010;110:911-16.e12.
22. Fournet M, Bonté F, Desmoulière A. Glycation Damage: A Possible Hub for Major Pathophysiological Disorders and Aging. Aging Dis 2018;9:880-900.
23. Soldatos G, Cooper ME, Jandeleit-Dahm KA. Advanced-glycation end products in insulin-resistant states. Curr Hypertens Rep 2005;7:96-102.
24. Hofmann SM, Dong HJ, Li Z, Cai W, Altomonte J, Thung SN, Zeng F, Fisher EA, Vlassara H. Improved insulin sensitivity is associated with restricted intake of dietary glycoxidation products in the db/db mouse. Diabetes 2002;51:2082-2089.
25. Cai W, Ramdas M, Zhu L, Chen X, Striker GE, Vlassara H. Oral advanced glycation endproducts (AGEs) promote insulin resistance and diabetes by depleting the antioxidant defenses AGE receptor-1 and sirtuin 1. Proc Natl Acad Sci U S A 2012;109:15888-15893.
26. Vlassara H, Striker GE. AGE restriction in diabetes mellitus: a paradigm shift. Nat Rev Endocrinol 2011;7:526-539.
27. Sergi D, Boulestin H, Campbell FM, Williams LM. The Role of Dietary Advanced Glycation End Products in Metabolic Dysfunction. Mol Nutr Food Res 2021;65:e1900934.
28. Vlassara H, Cai W, Tripp E, Pyzik R, Yee K, Goldberg L, Tansman L, Chen X, Mani V, Fayad ZA, Nadkarni GN, Striker GE, He JC, Uribarri J. Oral AGE restriction ameliorates insulin resistance in obese individuals with the metabolic syndrome: a randomised controlled trial. Diabetologia 2016;59:2181-2192.
29. Goudarzi R, Sedaghat M, Hedayati M, Hekmatdoost A, Sohrab G. Low advanced Glycation end product diet improves the central obesity, insulin resistance and inflammatory profiles in Iranian patients with metabolic syndrome: a randomized clinical trial. J Diabetes Metab Disord 2020;19:1129-1138.
30. Dougherty CM, Dewhurst T, Nichol WP, Spertus J. Comparison of three quality of life instruments in stable angina pectoris: Seattle Angina Questionnaire, Short Form Health Survey (SF-36), and Quality of Life Index-Cardiac Version III. J Clin Epidemiol 1998;51:569-575.
31. Spertus JA, Winder JA, Dewhurst TA, Deyo RA, Prodzinski J, McDonell M, Fihn SD. Development and evaluation of the Seattle Angina Questionnaire: a new functional status measure for coronary artery disease. J Am Coll Cardiol 1995;25:333-341.

32. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, O'Brien WL, Bassett DR, Jr, Schmitz KH, Emplaincourt PO, Jacobs DR, Jr, Leon AS. Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exerc 2000;32(9 Suppl):S498-504.
33. Deer J, Koska J, Ozias M, Reaven P. Dietary models of insulin resistance. Metabolism 2015;64:163-171.
34. Zhang M, Hu T, Zhang S, Zhou L. Associations of Different Adipose Tissue Depots with Insulin Resistance: A Systematic Review and Meta-analysis of Observational Studies. Sci Rep 2015;5:18495.
35. Adeva-Andany MM, Martínez-Rodríguez J, González-Lucán M, Fernández-Fernández C, Castro-Quintela E. Insulin resistance is a cardiovascular risk factor in humans. Diabetes Metab Syndr 2019;13:1449-1455.
36. Pyörälä M, Miettinen H, Laakso M, Pyörälä K. Hyperinsulinemia predicts coronary heart disease risk in healthy middle-aged men: the 22-year follow-up results of the Helsinki Policemen Study. Circulation 1998;98:398-404.
37. Robins SJ, Rubins HB, Faas FH, Schaefer EJ, Elam MB, Anderson JW, Collins D; Veterans Affairs HDL Intervention Trial (VA-HIT). Insulin resistance and cardiovascular events with low HDL cholesterol: the Veterans Affairs HDL Intervention Trial (VA-HIT). Diabetes Care 2003;26:1513-1517.
38. Saely CH, Aczel S, Marte T, Langer P, Hoefle G, Drexel H. The metabolic syndrome, insulin resistance, and cardiovascular risk in diabetic and nondiabetic patients. J Clin Endocrinol Metab 2005;90:5698-5703.
39. Forbes JM, Sourris KC, de Courten MP, Dougherty SL, Chand V, Lyons JG, Bertovic D, Coughlan MT, Schlaich MP, Soldatos G, Cooper ME, Straznicky NE, Kingwell BA, de Courten B. Advanced glycation end products (AGEs) are cross-sectionally associated with insulin secretion in healthy subjects. Amino Acids 2014;46:321-326.
40. Birlouez-Aragon I, Saavedra G, Tessier FJ, Galinier A, Ait-Ameur L, Lacoste F, Niamba CN, Alt N, Somoza V, Lecerf JM. A diet based on high-heat-treated foods promotes risk factors for diabetes mellitus and cardiovascular diseases. Am J Clin Nutr 2010;91:1220-1226.
41. de Courten B, de Courten MP, Soldatos G, Dougherty SL, Straznicky N, Schlaich M, Sourris KC, Chand V, Scheijen JL, Kingwell BA, Cooper ME, Schalkwijk CG, Walker KZ, Forbes JM. Diet low in advanced glycation end products increases insulin sensitivity in healthy overweight individuals: a double-blind, randomized, crossover trial. Am J Clin Nutr 2016;103:1426-1433.
42. Uribarri J, Cai W, Ramdas M, Goodman S, Pyzik R, Chen X, Zhu L, Striker GE, Vlassara H. Restriction of advanced glycation end products improves insulin resistance in human type 2 diabetes: potential role of AGER1 and SIRT1. Diabetes Care 2011;34:1610-1616.
43. Mark AB, Poulsen MW, Andersen S, Andersen JM, Bak MJ, Ritz C, Holst JJ, Nielsen J, de Courten B, Dragsted LO, Bügel SG. Consumption of a diet low in advanced glycation end products for 4 weeks improves insulin sensitivity in overweight women. Diabetes Care 2014;37:88-95.
44. Kurniawan LB, Bahrun U, Hatta M, Arif M. Body Mass, Total Body Fat Percentage, and Visceral Fat Level Predict Insulin Resistance Better Than Waist Circumference and Body Mass Index in Healthy Young Male Adults in Indonesia. J Clin Med 2018;7:96.
45. Foroumandi E, Kheirouri S, Nosrati R, Ghodsi R. Association of dietary intake, medication and anthropometric indices with serum levels of advanced glycation end products, caspase-3, and matrix metalloproteinase-9 in diabetic patients. J Diabetes Metab Disord 2021;20:719-725.
46. Foroumandi E, Alizadeh M, Kheirouri S, Asghari Jafarabadi M. Exploring the role of body mass index in relationship of serum nitric oxide and advanced glycation end products in apparently healthy subjects. PLoS One 2019;14:e0213307.
47. Thomas DM, Bredlau C, Bosy-Westphal A, Mueller M, Shen W, Gallagher D, Maeda Y, McDougall A, Peterson CM, Ravussin E, Heymsfield SB. Relationships between body roundness with body fat and visceral adipose tissue emerging from a new geometrical model. Obesity (Silver Spring) 2013;21:2264-2271.
48. Li G, Wu HK, Wu XW, Cao Z, Tu YC, Ma Y, Li BN, Peng QY, Cheng J, Wu B, Zhou Z. The feasibility of two anthropometric indices to identify metabolic syndrome, insulin resistance and inflammatory factors in obese and overweight adults. Nutrition 2019;57:194-201.
49. Ganguly S, Ray L, Kuruvila S, Nanda SK, Ravichandran K. Lipid Accumulation Product Index as Visceral Obesity Indicator in Psoriasis: A Case-control Study. Indian J Dermatol 2018;63:136-140.
50. Lim SM, Choi DP, Rhee Y, Kim HC. Association between Obesity Indices and Insulin Resistance among Healthy Korean Adolescents: The JS High School Study. PLoS One 2015;10:e0125238.
51. Thomas M, Jones PG, Arnold SV, Spertus JA. Interpretation of the Seattle Angina Questionnaire as an Outcome Measure in Clinical Trials and Clinical Care: A Review. JAMA Cardiol 2021;6:593-599.
52. Maxwell AJ, Zapien MP, Pearce GL, MacCallum G, Stone PH. Randomized trial of a medical food for the dietary management of chronic, stable angina. J Am Coll Cardiol 2002;39:37-45.
53. Cai S, Coates AM, Buckley JD, Berry NM, Burres L, Beltrame J, Howe PR, Schrader G. There is No Association Between the Omega-3 Index and Depressive Symptoms in Patients With Heart Disease Who Are Low Fish Consumers. Heart Lung Circ 2017;26:276-284.