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Adherencia a la dieta mediterránea y riesgo cardiovascular: explorando el papel de los productos de glicación avanzada a través del análisis de autofluorescencia en la piel

Mediterranean diet adherence and cardiovascular risk: exploring the role of advanced glycation end-products via skin autofluorescence analysis

10.20960/nh.05465

09/05/2025

OR 5465

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Adherencia a la dieta mediterránea y riesgo cardiovascular: explorando el papel de los productos de glicación avanzada a través del análisis de autofluorescencia en la piel

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Received: 30/07/2024
Accepted: 14/06/2025
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Conflict of interest: The authors declare no conflict of interest.

Artificial intelligence: The authors declare not to have used artificial intelligence (AI) or any AI-assisted technologies in the elaboration of the article.

ABSTRACT

Introduction: advanced glycation end-products contribute to oxidative stress and inflammation, which are linked to chronic diseases like cardiovascular disease and type-2 diabetes.

Objectives: the aim of this study is to explore the relationship between adherence to the Mediterranean diet and cardiovascular risk, focusing on the influence of advanced glycation end-products assessed through skin autofluorescence analysis.

Methods: anthropometric measurements including waist circumference, hip circumference, height, and body weight were recorded for 200 healthy individuals. Body mass index, waist-to-hip ratio, and waist-to-height ratio were calculated based on these measurements. Levels of advanced glycation end-products were assessed using the AGE Reader, while adherence to the Mediterranean diet was evaluated using the Mediterranean Diet Adherence Scale.

Results: a significant negative correlation was found between high adherence to the Mediterranean diet and levels of advanced glycation end-products ($p < 0.05$). Conversely, advanced glycation end-product levels showed significant positive correlations with age, body weight, body mass index, waist circumference, hip circumference, and waist-to-height ratio ($p < 0.05$).

Conclusion: this study demonstrates that individuals who adhere closely to the Mediterranean diet exhibit lower levels of advanced glycation end-products, which are established risk factors for cardiovascular disease.

Keywords: Mediterranean diet. Advanced glycation end-products. Skin autofluorescence.

RESUMEN

Introducción: los productos finales de la glicación avanzada contribuyen al estrés oxidativo y la inflamación, los cuales están relacionados con enfermedades crónicas como las cardiovasculares y la diabetes de tipo 2.

Objetivos: el objetivo de este estudio es explorar la relación entre la adherencia a la dieta mediterránea y el riesgo cardiovascular, centrándose en la influencia de los productos finales de la glicación avanzada, evaluados a través del análisis de autofluorescencia cutánea.

Métodos: se registraron medidas antropométricas como la circunferencia de la cintura, la circunferencia de la cadera, la altura y el peso corporal de 200 individuos saludables. El índice de masa corporal, la relación cintura-cadera y la relación cintura-altura se calcularon en base a estas medidas. Los niveles de los productos finales de la glicación avanzada se evaluaron utilizando el AGE Reader, mientras que la adherencia a la dieta mediterránea se evaluó utilizando la Escala de Adherencia a la Dieta Mediterránea.

Resultados: se encontró una correlación negativa significativa entre la alta adherencia a la dieta mediterránea y los niveles de productos finales de la glicación avanzada ($p < 0,05$). Por el contrario, los niveles de los productos finales de la glicación avanzada mostraron correlaciones positivas significativas con la edad, el peso corporal, el índice de masa corporal, la circunferencia de la cintura, la circunferencia de la cadera y la relación cintura-altura ($p < 0,05$).

Conclusión: este estudio demuestra que los individuos que se adhieren estrechamente a la dieta mediterránea exhiben niveles más bajos de productos finales de la glicación avanzada, que son factores de riesgo establecidos de las enfermedades cardiovasculares.

Palabras clave: Dieta mediterránea. Productos finales de glicación avanzada. Autofluorescencia cutánea.

INTRODUCTİON

Advanced glycation end products (AGEs) are created through non-enzymatic interactions between the free amino groups of proteins, lipids, and nucleic acids and the carboxyl groups of reducing sugars (1). Although the generation of AGEs is a natural byproduct of metabolism, excessive accumulation of AGEs in body tissues causes oxidative stress and inflammation and significantly accelerates the onset of numerous chronic illnesses, including cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM) (2). In addition to the endogenous formation of AGEs, it contributes exogenously to the AGE pool in cases such as smoking and consuming AGE-rich foods (3). Modern diets contain high levels of AGEs, largely due to exposure to heat treatments. AGE production in foods is affected by factors such as nutrient composition, heat treatment, humidity, pH, and cooking time (4,5).

The pathogenic effects of AGEs impact the body in two distinct ways: through AGE receptor-mediated and AGE receptor-independent mechanisms. AGEs change their functions and structures by cross-linking directly with body proteins. In addition, they exert a proinflammatory effect through AGE receptors (6).

AGEs are currently detected using a variety of methods in tissues, biological fluids, and foods. Because serum and plasma contain short-lived proteins, AGEs assessed in these fluids did not appear to adequately reflect tissue AGE levels. Therefore, skin biopsies have been established as the definitive method for assessing AGE levels in tissues. Skin Autofluorescence (SAF) is suggested as a simple, non-invasive method for evaluating AGE accumulation in tissues. The AGE reader is a device designed to assess SAF levels in human skin. This technology has been validated by skin biopsies in healthy and chronically ill individuals (7).

The Mediterranean diet (MD) is a well-balanced diet that involves vegetables, fruits, legumes, whole grains, seafood, olive oil, and nuts, which have a low AGE content (8). Moderate consumption of red meat, dairy products, and alcohol is permitted. MD provides a high intake of monounsaturated fatty acids, low trans fatty acids, high dietary fibers, antioxidants, polyphenols and magnesium (9). The beneficial effects of MD primarily stem from its anti-inflammatory and antioxidative properties. Long-term MD consumption enhances blood pressure and lipid profiles, reduces endothelial inflammation and insulin resistance, and promotes a healthy body weight (10).

Under inflammatory and oxidative stress conditions, the generation and accumulation of AGEs increases (11). Healthy lifestyle habits, such as the MD, can affect the formation of AGEs. However, there are limited studies showing the effect of healthy lifestyle habits on AGE formation (12,13).

Our hypothesis is that greater adherence to the MD results in lower SAF-AGE levels and better anthropometric measures. In addition, it is predicted that high adherence to the MD will lead to a decrease in CVD risk due to SAF-AGE values. In light of this, our goal is to examine the impact of MD adherence on SAF-AGE levels, age, body weight, height, BMI, waist-hip ratio, waist-height ratio, and the relation between these parameters and CVD risk.

MATERİAL AND METHODS

Population sample of the study

This descriptive cross-sectional study was conducted with 200 volunteer, 92 male and 108 female, healthy young adults between February and March 2022.

Inclusion and exclusion criteria

The research included participants aged between 18 and 30 who were willing to take part. Exclusion criteria encompassed individuals with scars or tattoos on the inner arm, those with dark skin potentially affecting SAF-AGE measurements, pregnant or nursing individuals, those with chronic conditions, and those facing language barriers hindering effective communication.

Ethical approval

The study was approved by the Non-Interventional Research Ethics Committee of Istanbul Esenyurt University, dated 17.02.2022, and numbered 2022/02-11. The researchers explained the procedures and objectives of the study to the participants. Before participating, each subject provided written and verbal informed consent. All study protocols followed the Helsinki Declaration's ethical requirements.

Data collection method and tools

In the general information section, participants' gender, age, marital status, whether they have any diagnosed disease, and if so, what it is, smoking and/or alcohol usage and dietary habits were questioned.

The researchers measured the anthropometric features of the participants. A stadiometer (Portstad HM200P Portable Stadiometer, Charder, Taichung City, Taiwan) was used to measure each participant's height as they stood with their feet together, their heads in the Frankfurt plane, and without wearing any shoes. Tanita SC 330 (Tokyo, Japan) body weight measurements were taken while the subjects were wearing light clothing and no shoes on a flat area. By dividing the participant's body weight in kilograms by the square of their height (kg/m^2), the body mass index (BMI) results were determined. Using a 0.1 cm precision non-stretchable tape measure, the participants' waists were measured along the midpoint of the line connecting the iliac crest and the lowest rib. The individual's circumference of the hip was measured while they were standing, perpendicular to the floor, at the widest region of the hip. The ratios of waist circumference to hip circumference and waist circumference to height were calculated using the data.

The AGE Reader (DiagnOptics Technologies, Groningen, The Netherlands) is a non-invasive device that determines the level of

AGEs that exist in the skin by using the distinctive fluorescence features of some AGEs. The measurement procedure has been described in detail in previous studies (7). In this study, participants were classified into two groups: mild to moderate risk and increased risk. Individuals with AGE levels below the average were categorized as mild to moderate risk, whereas those with levels above the average were classified as increased risk.

The Mediterranean Diet Adherence Scale (MEDAS) was used to determine the adherence of individuals to the MD. MEDAS is a scale consisting of 14 questions. Each question is assigned 1 or *0* points, and the overall score is calculated. A total score of ≤ 5 was classified as low compliance, 6-9 as moderate compliance, and ≥ 9 as high compliance (14).

Statistical analysis

Power analysis was used to establish the study's sample size. The sample size was computed as 184, with 92 in each group, using the G*power 3.1 program, with an effect size of 0.50, a margin of error of 0.05, a confidence level of 0.95, and a population representation of 0.90.

The SPSS 29 (Statistical Program in Social Sciences 29) program was used to analyse the data that had been gathered for the study. The data gathered for the study were examined to see if they fit the normal distribution using the Kolmogorov-Smirnov test. For comparison tests, 0.05 was set as the significance level (p).

Non-parametric test procedures were used to continue the research since the variables did not have a normal distribution ($p > 0.05$).

Comparisons in independent pairs were made with the Mann-Whitney U-test. The Spearman correlation coefficient was used in the correlation analysis. The chi-square test was used to analyse categorical data. Since one of the boxes was below 1 during the chi-square test, the p-value obtained from Yates' correction for continuity for the chi-square test was used.

A test for multicollinearity has been done before selecting independent variables. Multiple regression analysis was used because of the relationship between different parameters, apart from the individual effects of the variables. Considering the data distribution situation, the partial least squares (PLS) regression model was used, and the number of latent factors was limited to 5.

RESULTS

A total of 200 healthy adult individuals with a median (25^{th}, 75^{th} quartiles) SAF AGE level of 1.4 (1.3, 1.6) AU participated in the study. In the study's participants, there was no statistically significant gender difference in the SAF AGE values ($p > 0.05$) (Table I).

The participants were divided into two groups: ''mild to moderate CVD risk" and "severe CVD risk" by using an application provided by the manufacturer according to their SAF AGE values (15). It was determined that there were 102 individuals in the mild to moderate CVD risk group and 98 individuals in the CVD risk group, which was formed according to the SAF AGE levels obtained. Compared to these groups, the rate of women individuals in the increased CVD risk group is higher, but it is not statistically significant (48.9 % in men vs 49.1 % in women, $p = 0.98$). Other basic parameters according to CVD risk are given (Table II).

While there was no statistically significant difference in terms of height, waist circumference, hip circumference, and waist/hip ratio data ($p > 0.05$) in terms of CVD risk according to SAF AGE levels among the participants included in the study, statistically significant differences were found in terms of SAF AGE level, body weight, BMI, waist/height ratio and age ($p < 0.05$).

According to the MEDAS, the median MD score was 6 (1-11). The study's participants' gender and their level of adherence to the MD did not have any statistically significant relationship ($p > 0.05$) (Table III). It was observed that individuals with increased CVD risk had significantly lower adherence to the MD (Table IV).

In the chi-square analysis, since the value obtained in one of the boxes as a result of the examination of people with high adherence to the MD was 0, correction for continuity was used by combining the medium and high compliance groups, and the relevant *p* value was given. Further analysis showed that significant positive correlations were found between SAF AGE values and age, body weight, BMI, waist circumference, hip circumference, and waist/height ratio values. In addition, a statistically significant negative correlation was found between SAF AGE values and MD score ($p < 0.005$) (Table V). Test for multicollinearity has been done before selecting independent variables. According to the analysis age and MEDAS scores are found to be independent variables (Table VI).

According to the results of the partial least square (PLS) regression analysis, the latent factor (LF) 1 explains 46.2 % of the variables. Variable importance in the projection models are MEDAS score, BMI, BW, HC, WHtR, WC, age, WHR, and H, respectively. According to latent factor 1, age, BW, H, BMI, WC, HC, WHR, and WHtR showed a positive relationship with SAF AGE, while MEDAS score showed a negative relationship (Table VII).

DİSCUSSİON

To our knowledge, this study is the first to explore the association between adherence to the Mediterranean diet and cardiovascular risk, with a specific focus on assessing the impact of advanced glycation end-products using skin autofluorescence analysis. Our study shows that increased adherence to the MD is associated with lower SAF levels.

The MD seems to be a healthy diet model that has come to the fore in the prevention and treatment of many diseases in recent years, and it is also the focus of dietary studies on the prevention of CVD. It has been proven that atherosclerosis risk factors such as inflammation and endothelial function are reduced in people following the MD (16). These benefits of the MD are thought to be due to its rich content of fruits, vegetables, whole grain foods, oilseeds, olive oil, and fibre (17,18). AGEs are believed to have an important role in the development and progression of CVD.

Studies examining the effect of the MD on AGE levels are limited to the serum concentration of AGE (19,20). There are limited studies investigating this effect with SAF (20,21). In the Assessing the Prevalence of Subclinical Vascular Disease and Hidden Kidney Disease (ILERVAS) study conducted on middle-aged individuals, a negative correlation was found between serum AGE level and adherence to the MD (20). In elderly individuals, consumption of the MD for 4 weeks has been shown to be associated with lower levels of fasting and postprandial AGEs, especially Nε-carboxymethyl lysine (CML) and methylglyoxal (MG), than the Western diet (22). Similarly, in a study of middle-aged individuals without any known history of CVD or T2DM, people who adhered to an MD were found to have lower SAF levels (20). In another study conducted on individuals with T2DM, it was determined that individuals with limited/high CVD risk according to SAF values had lower adherence to the MD (20,21). In our study of healthy young adults, parallel to other studies, the MD was shown to be associated with lower SAF AGE levels. A decrease in the risk of CVD due to SAF AGE levels was observed with the increase in the score of adherences to the MD. Consumption of more vegetables and fruits can limit oxidative stress and AGE formation, while a high intake of processed foods rich in sugar and fat can increase AGE accumulation (23).

Obesity causes the secretion of high amounts of inflammatory cytokines such as TNF-α and interleukin 6 (IL-6). These cytokines trigger chronic inflammation by stimulating the production of CRP in the liver. Chronic inflammation causes AGE production and accumulation. Our study showed that SAF was significantly associated with body weight, BMI, waist circumference, hip circumference, and waist/height ratio values. This situation is similar to studies reporting a positive relationship between AGE levels and anthropometric measurements. Excess body weight, particularly abdominal obesity, is associated with SAF in these studies (13,24).

According to our research, there is no correlation between maintaining the MD and body weight, BMI, waist/hip ratio, hip circumference, or waist/height ratio. It is debatable if following the MD has an impact on anthropometric measurements. In the literature, large variations are observed in the results regarding this association. According to some studies, increased adherence to the MD has been associated with decreased adiposity, whereas other studies find no association (25-28). Evidence shows that diet is more effective for weight loss by reducing energy rather than changing macronutrient composition (29).

As a result of our study, MD compliance was found to be low for both genders. It was determined that CVD risk due to SAF AGE levels, increased as MD compliance decreased. This descriptive cross-sectional study has some limitations. The first of these is that due to the cross-sectional design of our study, the individuals participating in the study consisted of young adults. Another limiting factor is that the scale of adherence to the MD depends on the individual. Studies with participants from all age groups and health conditions are required to corroborate our findings. Since the sample studied included only young adults, it is not possible to make inferences about other age ranges and generalize to all age groups. Conducting more comprehensive studies is important in terms of reproducibility and generalizability of the results. As a result, since no similar study has been done in the literature, the relevant study makes an important contribution to the field.

CONCLUSION

This cross-sectional study adds further evidence to the state of evidence on the connection between SAF AGE levels and MD adherence. In parallel, it has been shown that the adherence to the MD of the individuals participating in our study is very low. The relationship between SAF AGE level and adherence to an MD requires further research. In addition, it is essential to implement health strategies to increase adherence to the MD in order to reduce the risk of CVD in healthy populations in our country and all over the world.

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Table I. Comparison of AGE values by gender

Values	**Unit**	**Groups**	**μ (Q_1, Q_3)**	***p*-value**
SAF AGE	AU	*Man*	1.4 (1.3, 1.5)	0.76
		Woman	1.4 (1.3, 1.6)	

Mann-Whitney U-Test, μ (Q_1, Q_3): median (25^{th}, 75^{th} quartiles). SAF: skin autofluorescence; AGE: advanced glycation end products; AU: arbitrary units.

Table II. Comparison of different variables according to CVD risk

Variables	**Unit**	**Groups**	**μ (Q_1, Q_3)**	***p*-values**
SAF AGE	AU	*Mild to moderate risk*	1.3 (1.2, 1.4)	0.000†
		Increased risk	1.6 (1.5, 1.7)	
BW	kg	*Mild to moderate risk*	62.5 (57, 73)	0.01*
		Increased risk	70 (55, 83)	
H	m	*Mild to moderate risk*	1.7 (1.64, 1.75)	0.66
		Increased risk	1.68 (1.63, 1.78)	
BMI	(kg/m^2)	*Mild to moderate risk*	22.02 (19.87, 24.46)	0.003†
		Increased risk	23.55 (20.79, 27.24)	
WC	cm	*Mild to moderate risk*	75 (69, 82)	0.06
		Increased risk	80 (69, 90)	
HC	cm	*Mild to moderate risk*	96 (91, 102)	0.06
		Increased risk	99.5 (99, 106.5)	
WHR	cm	*Mild to moderate risk*	0.79 (0.74, 0.82)	0.54
		Increased risk	0.8 (0.75, 0.83)	
WHtR	cm	*Mild to moderate risk*	0.44 (0.41, 0.47)	0.02*
		Increased risk	0.46 (0.42, 0.51)	

Mann-Whitney U-test, μ (Q_1, Q_3): median (25^{th}, 75^{th} quartiles). *$p < 0.05$; †$p < 0.005$; *p*-values < 0.05 were statistically significant. BW: body weight; H: height; BMI: body mass index; WC: waist circumference; HC: hip circumference; WHR: waist-hip ratio; WHtR: waist-to-height ratio; SD: standard deviation.

Table III. The relationship between the status of adherence to the MD and gender

		Mediterranean diet			**Total**	***p*-value**
		Low compliance	**Moderate compliance**	**High compliance**		
Man	*n*	43	45	4	92	0.882
	%	46.7	48.9	4.3	100	
Woman	*n*	54	49	5	108	
	%	50	45.4	4.6	100	

Chi-square test, p-values < 0.05 were statistically significant; n: number.

Table IV. Relation between increased CVD risk and adherence to MD

Group		For CVD: Mild to moderate risk	For CVD: Increased risk	Total	*p*-value
Low compliance with MD	***n***	36	61	97	*0.000**
	%	37.1	62.9	100	
Moderate to high compliance with MD	***n***	66	37	94	
	%	64.1	35.9	100	

Chi-square test with Yates's correction for continuity; **p* < 0.005, *p*-values < 0.05 were considered to be statistically significant; *n*: number.

Table V. Correlation between SAF AGE levels and Age, MEDAS Score, and anthropometric variables

	Age	**BW**	**H**	**BMI**	**WC**	**HC**	**WHR**	**WHtR**	**MEDAS Score**
SAF AGE R-values	0.21	0.29	0.01	0.31	0.22	0.23	0.07	0.24	0.410
p-values	0.002*	0.000*	0.84	0.000*	0.002*	0.001*	0.31	0.000*	0.000*

Spearman's correlation coefficients, *$p < 0.005$, *p*-values < 0.05 were considered to be statistically significant. MEDAS: Mediterranean Diet Adherence Scale.

Table VI. Multicollinearity analysis to identify dependent variables to SAF-AGE

Variable	VIF value
Age	1.03
BW	443.38
H	154.72
BMI	316.86
WC	2305.07
HC	136.2
WHR	95.05
WHtR	1935.39
MEDAS Score	1.04

Multicollinearity analysis. VIF: variance inflation factor.

Table VII. Weights and variable importance in the projection models according to the association between SAF AGE levels with Age, MEDAS Score and anthropometric variables

	LF										SAF AGE R^2 values
	1		2		3		4		5		
	W	VIP	W	VIP	W	VIP	W	VIP	W	VIP	
Age	0.22	0.68	0.37	0.87	0.18	0.86	-0.26	0.85	0.71	0.86	0.01
BW	0.4	1.21	0.03	0.97	0.43	0.98	0.75	1.05	0.38	1.05	0.004
H	0.002	0.005	-0.37	0.68	0.23	0.98	-0.13	0.67	-0.34	0.67	-0.22
BMI	0.47	1.43	0.23	1.22	0.29	0.98	0.78	1.26	0.05	1.26	0.01
WC	0.28	0.86	-0.24	0.81	-0.2	0.81	-0.41	0.82	-0.05	0.82	-0.02
HC	0.34	1.03	-0.05	0.82	-0.58	0.87	-0.51	0.9	-0.03	0.9	0.03
WHR	0.7	0.2	-0.3	0.58	0.36	0.61	-0.02	0.6	-0.07	0.6	-0.04
WHtR	0.33	0.99	-0.12	0.82	-0.36	0.83	-0.47	0.86	-0.12	0.86	-0.22
MEDAS Score	-0.48	1.46	-0.84	1.92	-0.16	1.88	0.17	1.86	0.52	1.86	-0.03

Partial least squares regression analysis. LF: latent factor; VIP: variable importance in the projection.