ISSN 1948-9358 (online)

World Journal of *Diabetes*

World J Diabetes 2021 November 15; 12(11): 1812-1968

Published by Baishideng Publishing Group Inc

World Journal of Diabetes

Contents

Monthly Volume 12 Number 11 November 15, 2021

EDITORIAL

REVIEW

ORIGINAL ARTICLE

Basic Study

Retrospective Cohort Study

Observational Study

World Journal of Diabetes

Monthly Volume 12 Number 11 November 15, 2021

Contents

NAME OF JOURNAL

World Journal of Diabetes

ISSN

ISSN 1948-9358 (online)

LAUNCH DATE

June 15, 2010

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Lu Cai, Md. Shahidul Islam, Jian-Bo Xiao, Manfredi Rizzo

EDITORIAL BOARD MEMBERS

https://www.wjgnet.com/1948-9358/editorialboard.htm

PUBLICATION DATE

November 15, 2021

INSTRUCTIONS TO AUTHORS

https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS

https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS

https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT

https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE

https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS

https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION

https://www.f6publishing.com

World Journal of Diabetes

Submit a Manuscript: https://www.f6publishing.com

World J Diabetes 2021 November 15; 12(11): 1942-1956

DOI: 10.4239/wjd.v12.i11.1942

ISSN 1948-9358 (online)

ORIGINAL ARTICLE

Observational Study

Adherence to Mediterranean diet and advanced glycation endproducts in patients with diabetes

Marko Grahovac, Marko Kumric, Marino Vilovic, Dinko Martinovic, Ante Kreso, Tina Ticinovic Kurir, Josip Vrdoljak, Karlo Prizmic, Joško Božić

ORCID number: Marko Grahovac 0000-0002-1960-1901; Marko Kumric 0000-0002-9696-3359; Marino Vilovic 0000-0002-5433-5063; Dinko Martinovic 0000-0003-2060-5130; Ante Kreso 0000-0002-8186-9714; Tina Ticinovic Kurir 0000-0003-1695-9235; Josip Vrdoljak 0000-0001-8375-7233; Karlo Prizmic 0000-0003-2654-6661; Joško Božić 0000-0003-1634-0635.

Author contributions: Grahovac M, Kumric M, Vilovic M, Ticinovic Kurir T, Martinovic D and Božić J for conceptualization, original draft preparation, and supervision; Grahovac M, Kreso A, Prizmic K, Vrdoljak J and Vilovic M for review of literature and visualization; all authors contributed to the final draft of the manuscript, have read and agreed to the published version of the manuscript.

Institutional review board statement: The study was reviewed and approved by the Ethics Committee of University of Split School of Medicine on November 29th, 2018. (Class 003-08/18-03/0001, No. 2181-198-03-04-L8-0059).

Informed consent statement: All study participants provided informed written consent prior to

Marko Grahovac, Department of Pharmacology, University of Split School of Medicine, Split 21000, Croatia

Marko Kumric, Marino Vilovic, Dinko Martinovic, Ante Kreso, Tina Ticinovic Kurir, Josip Vrdoljak, Karlo Prizmic, Joško Božić, Department of Pathophysiology, University of Split School of Medicine, Split 21000, Croatia

Tina Ticinovic Kurir, Department of Endocrinology, University Hospital of Split, Split 21000, Croatia

Corresponding author: Joško Božić, MD, PhD, Associate Professor, Department of Pathophysiology, University of Split School of Medicine, Soltanska 2, Split 21000, Croatia. jbozic@mefst.hr

Abstract

BACKGROUND

In recent years, American Diabetes Association started to strongly advocate the Mediterranean diet (MD) over other diets in patients with diabetes mellitus (DM) because of its beneficial effects on glycemic control and cardiovascular (CV) risk factors. Tissue levels of advanced glycation endproducts (AGEs) emerged as an indicator of CV risk in DM. Skin biopsy being invasive, the use of AGE Reader has been shown to reflect tissue AGEs reliably.

AIM

To examine the association between adherence to MD and AGEs in patients with DM type II.

METHODS

This cross-sectional study was conducted on 273 patients with DM type II. A survey questionnaire was composed of 3 separate sections. The first part of the questionnaire included general data and the habits of the participants. The second part aimed to assess the basic parameters of participants' diseases and associated conditions. The third part of the questionnaire was the Croatian version of the 14-item MD service score (MDSS). AGEs levels and associated CV risk were measured using AGE Reader (DiagnOptics Technologies BV, Groningen, The Netherlands).

RESULTS

A total of 27 (9.9%) patients fulfilled criteria for adherence to MD, with a median score of 8.0 (6.0-10.0). Patients with none/limited CV risk had significantly higher percentage of MD adherence in comparison to patients with increased/definite CV risk (15.2% *vs* 6.9%, $P = 0.028$), as well as better adherence to guidelines for nuts (23.2% *vs* 12.6%, $P = 0.023$) and legumes (40.4% *vs* 25.9%, $P = 0.013$) consumption. Higher number of patients with glycated hemoglobin (HbA1c) < 7% adhered to MD when compared to patients with HbA1c > 7% (14.9% *vs* 7.3%, $P = 0.045$). Moreover, those patients followed the MDSS guidelines for eggs (33.0% *vs* 46.8%, $P = 0.025$) and wine (15.6% *vs* 29.8%, $P = 0.006$) consumption more frequently. MDSS score had significant positive correlation with disease duration ($r = 0.179$, $P = 0.003$) and negative correlation with body mass index (BMI) values ($r = -0.159$, $P = 0.008$). In the multiple linear regression model, BMI (β ± SE, -0.09 ± 0.04, $P = 0.037$) and disease duration (β ± SE, 0.07 ± 0.02, $P < 0.001$) remained significant independent correlates of the MDSS score. Patients with HbA1c > 7% think that educational programs on nutrition would be useful for patients in significantly more cases than patients with HbA1c < 7% (98.9% *vs* 92.6%, $P = 0.009$).

CONCLUSION

Although adherence to MD was very low among people with diabetes, we demonstrated that adherence to MD is greater in patients with lower CV risk, longer disease duration, and well-controlled glycaemia.

Key Words: Mediterranean diet; Cardiovascular disease; Diabetes mellitus; Advanced glycation endproducts; Dietary habits; Atherosclerosis

Core Tip: Recently, American Diabetes Association started to advocate the use of the Mediterranean diet (MD) over other diets because of its beneficial effects on glycaemic control and cardiovascular (CV) risk factors. In this cross-sectional study, we demonstrated an association between adherence to the MD and CV risk in patients with diabetes mellitus (DM) type II by measuring advanced glycation endproducts. In addition, we found that adherence to MD is very low in diabetics, especially among individuals with poorly controlled glycaemia. Finally, the duration of DM independently predicted better adherence to MD, whereas body mass index predicted poorer adherence.

Citation: Grahovac M, Kumric M, Vilovic M, Martinovic D, Kreso A, Ticinovic Kurir T, Vrdoljak J, Prizmic K, Božić J. Adherence to Mediterranean diet and advanced glycation endproducts in patients with diabetes. *World J Diabetes* 2021; 12(11): 1942-1956
URL: https://www.wjgnet.com/1948-9358/full/v12/i11/1942.htm
DOI: https://dx.doi.org/10.4239/wjd.v12.i11.1942

INTRODUCTION

Diabetes mellitus (DM) is a group of chronic disorders of carbohydrate, fat and protein metabolism caused by defects of insulin secretion, action, or both[1]. Among two of the most prominent types, DM type II accounts for 90%-95% of people with DM[2]. Around 462 million individuals worldwide are affected by DM type II, corresponding to 6.28% of the world's population[3]. The rising incidence is even more staggering, as recent estimates point that 1 in 3 people in the world will have DM type II by 2050[4]. Even though immense efforts in terms of public health measures were made, developed regions, such as Western Europe and the United States, show considerably higher prevalence rates of DM in contrast to Third World countries[4]. This highlights the implication of socio-economic development and concomitant lifestyle in the pathophysiology of DM. Hence, lifestyle changes, particularly diet, seem to be an

the study enrollment.

Conflict-of-interest statement: There are no conflicts of interest to report.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

Provenance and peer review: Invited article; Externally peer reviewed

Specialty type: Endocrinology and metabolism

Country/Territory of origin: Croatia

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: May 6, 2021
Peer-review started: May 6, 2021
First decision: June 24, 2021
Revised: July 1, 2021
Accepted: October 11, 2021
Article in press: October 11, 2021
Published online: November 15, 2021

P-Reviewer: Sorić T
S-Editor: Fan JR
L-Editor: A

P-Editor: Fan JR

essential cornerstone of DM management.

In fact, according to the American Diabetes Association (ADA), nutritional therapy is of particular importance in the treatment of DM[5]. Lately, ADA strongly advocates the Mediterranean diet (MD) over other diets because of its beneficial effects on glycaemic control and cardiovascular (CV) risk factors[5]. MD is a characteristic dietary pattern established in the coastal areas of the Mediterranean basin[6]. By definition, MD consists of three to nine servings of vegetables, one to thirteen servings of cereals, half to two servings of fruits, and up to eight servings of olive oil a day[6]. The recommended total fat intake is about 37%, 18% of which are monounsaturated and 9% saturated fats, whereas the recommended fibre intake is 33 g *per* day[6]. Furthermore, moderate consumption of red wine, especially during meals, and rare consumption of red meat are also important factors of this diet[6-8].

Pathophysiology of DM includes a myriad of detrimental molecular processes. Perhaps the critical effector arm of damage in the setting of DM is hyperglycaemia-induced overproduction of reactive oxygen species (ROS). Among multiple other effects, ROS production results in the up-regulated formation of intracellular advanced glycation endproducts (AGEs)[9]. AGEs are typically accumulated slowly in the human body during life, mostly in tissues with slow metabolism[10]. This process is accelerated in some diseases such as DM, renal failure, and various CV diseases[10]. Previous studies have shown that the values of AGEs are elevated in patients with DM and are at least in part the cause of DM-associated CV complications[11,12]. The receptors for advanced glycation endproducts (RAGEs) are found on inflammatory cells (T-lymphocytes and macrophages), endothelial cells and vascular smooth muscle cells. The binding of AGEs to RAGEs stimulates the release of proinflammatory cytokines and growth factors from macrophages, the formation of ROS from the endothelium, the procoagulant action of endothelium and macrophages, as well as interconnection of extracellular matrix proteins[10]. Previous studies have clearly shown that AGE quantity measured from skin tissue is a solid and independent predictor of CV complications, as well as CV morbidity and mortality in DM[13-15]. Unlike skin biopsy, AGE Reader recently emerged as a non-invasive yet reliable instrument for the measurement of AGEs tissue levels[14]. In addition, it has been shown that the AGEs reader has a significant additional value in determining the degree of CV risk in patients with DM[14,15]. In a study by Li *et al*[16], it was demonstrated that patients who had higher values of AGEs also had higher values of glycated hemoglobin (HbA1c), whereas the results of a cross-sectional study by Coupp é *et al*[17] show that different long-term exercise regimens can slow down the normal process of AGEs accumulation[16,17].

Although MD and AGEs levels have already been investigated in patients with DM, there is scarce information regarding their mutual interconnections. Hence, the main aim of this study was to examine the association between adherence to the MD and CV risk/AGEs skin levels, in patients with DM type II[18,19]. In addition, we examined the association of anthropometric characteristics, glycaemic control, and physical activity with AGEs levels in the same group of patients. Finally, we examined dietary attitudes and characteristics of the studied population according to DM management. In this study, we hypothesized that patients with DM type II who adhere more to the MD would have lower AGEs skin levels, reflecting lower CV risk.

MATERIALS AND METHODS

Study design and ethical considerations

This study was performed at the Regional Center for Diabetes, Endocrinology and Metabolic Diseases of the University of Split School of Medicine from 1 March 2019 to 1 June 2019. The study was approved by the Ethics Committee of the University of Split School of Medicine. The researchers informed the participants about the procedures and purpose of the study, after which all involved participants signed informed consent.

Subjects

A total of 273 patients (137 men and 136 women) with DM type II participated in this study. DM type II was diagnosed according to the criteria of the ADA[1]. All included participants were treated at the Regional Center for Diabetes, Endocrinology and Metabolic Diseases of the University Hospital of Split, and were interviewed during regular check-ups by a diabetologist. The inclusion criteria was that DM type II is diagnosed for at least a year. On the other hand, newly diagnosed DM type II, DM

type I and other types of diabetes were excluded from the study. For the present study, we initially screened 347 patients. Nineteen patients were excluded because their DM type II diagnosis was established in the past year, 37 patients were excluded because they had DM type I, whereas 10 patients were excluded because they had other types of DM. Finally, among 281 eligible patients, eight refused to participate in the study, yielding an overall acceptance rate of 97%. For the purpose of this study, we performed sample size analysis using MedCalc software. We used an estimated difference in the proportion of the adherence to MD of 0.1, with α error set at 0.05 and study power of 90%. The calculated sample size was 158 participants. To ensure additional power to the study, we collected a substantially larger sample of diabetes patients. Relevant clinical information on each participant was collected by taking anamnesis and checking their medical documentation. Participants also completed a survey on their life habits and the MD service score (MDSS) questionnaire to assess adherence to the MD. Finally, all participants were subjected to measurements of relevant anthropometric features and AGEs value using AGEs reader.

Anthropometric measurements

Participants were subjected to the following measurements of anthropometric features: Body weight and height, neck, waist and hip circumference. A calibrated medical scale with an altimeter (Seca, Birmingham, United Kingdom) was used to measure body weight and height. Body mass index (BMI) was calculated by dividing the value of body weight (kg) by the square of the value of body height (m^2). Waist circumference was measured at the upright standing position at the midline level between the bottom of the costal arch in the mid-axillary line and the apex of the iliac ridges. In the same position, the hip circumference was measured at the level of the largest circumference of the gluteal muscles, above the line connecting the large trochanters of the femur. The waist-to-hip ratio is determined by dividing the waist circumference (cm) by the hip circumference (cm). Neck circumference was measured at the midway of the neck, between the mid-cervical spine and mid anterior neck. All circumferences were measured using the same centimetre ribbon with 0.5 cm precision.

Survey

After an extensive literature review, a survey questionnaire that included 27 items divided into three main parts was compiled.

The first part consisted of 7 items that included general patients' information and basic parameters of their disease. The questions included were about: Gender, year of birth, physical activity, smoking status, year of DM diagnosis, last HbA1c levels, and type of DM therapy.

The second part of the questionnaire was MDSS, a useful instrument often used to measure overall diet quality according to the principles of the MD[20]. MDSS is based on the recommended intake of 14 food groups in the Mediterranean food pyramid [18]. While scoring the questionnaire, three points were awarded to those participants who met the appropriate recommended frequency of consumption of the following food groups: Fruits, vegetables, cereals (bread, pasta, rice), and olive oil. Two points were given to those who met the appropriate recommended frequency of dairy products and nuts consumption. Finally, one point was given to those who met the appropriate recommended frequency of consumption of potatoes, legumes, fish, eggs, red meat, white meat, sweets and wine. A score of zero was given if the number of servings of a particular food did not meet the MD recommendations. With this scoring, most points (3 points) are earned by consuming enough food that should be an integral part of every meal in the MD diet. The rest of the points are awarded for foods recommended for intake on a daily (2 points) or weekly (1 point) basis. The overall score can range from 0 to 24 points. A score of over 13.5 points is considered as good adherence to MD principles. The reliability and validity of the Croatian version of the 14-item MDSS questionnaire in assessment of adherence to MD was evaluated by Marendić *et al*[18].

Finally, the third questionnaire part included 6 items that investigated the dietary attitudes of the investigated population. All of the included statements could be answered with "yes" or "no ". Statements were about the source of information about diet, nutritionist support, getting diet information off the internet, the importance of diet in managing personal health problems, usefulness, and attendance of diet-related educational programs.

Measurement of AGEs

AGEs value and associated CV risk were measured using AGE Reader (DiagnOptics

Technologies BV, Groningen, The Netherlands). This is a non-invasive desktop device that uses the characteristic fluorescence of certain AGEs to calculate the level of accumulated AGEs in the skin. This method was confirmed to be firmly consistent with the measurement of the accumulation of AGEs in a skin biopsy sample, taken from the same site where the autofluorescence reading was performed[13].

Participants were briefly introduced to the method of measurement. There was no risk for our participants during this measurement. They were then asked to place their right forearm on the device, which is a standard and practical measuring point on the body for calculating the autofluorescence of certain AGEs from the skin[13]. A series of three consecutive measurements were performed. The results were summed and divided to obtain the mean, which was later used in the analysis. Based on the association of the obtained result with the age of the subjects, a value that classifies participants into one of the four groups (none, limited, increased, definite) depending on their CV risk was calculated. We further stratified these groups into two CV risk groups. The first group included patients with none and limited CV risk, whereas the second included patients with increased and definite CV risk. Finally, this method is observer-independent and has an intrapersonal coefficient of variation of less than 5% [14].

Statistical analysis

Statistical analysis was performed with MedCalc package (version 19.1.2, MedCalc Software, Ostend, Belgium). Categorical variables were presented as whole numbers and percentages, while differences were evaluated with the chi-squared test and Fisher's exact test. Continuous variables were presented as mean and standard deviation or median and interquartile range, according to the normality of data distribution analysis performed with D'Agostino-Pearson test. Accordingly, differences between groups were evaluated with Mann Whitney U-test and t-test for independent samples. Furthermore, the correlation between MDSS score and other selected variables was tested with Spearman's correlation coefficient, while independent factors associated with MDSS scores were evaluated with multiple linear regression analysis. For this purpose, enter algorithm was used, with a report of unstandardized beta coefficients (β), t-values, standard errors (SE), and P-values. The selected model had all assumptions in using multiple regression satisfied. Statistical significance was set at $P < 0.05$.

RESULTS

The study enrolled a total of 273 DM type II patients, with overall AGEs levels of 3.0 (2.6-3.5). Significantly higher values of AGEs were found in men when compared with women [3.1 (2.7-3.7) *vs* 2.9 (2.5-3.3), $P < 0.001$], while HbA1c values were without significant difference between genders [7.3 (6.7-8.8)% *vs* 7.5 (6.7-8.8)%, $P = 0.475$]. According to AGEs levels, patients were divided into none/limited CV risk group ($n = 99$) and increased/definite CV group ($n = 174$). According to these groups, increased CV risk group had significantly higher percentage of male patients (55.2% *vs* 41.4%, $P = 0.029$), and higher levels of HbA1c [7.65 (6.8-8.8)% *vs* 7.2 (6.5-8.5)%, $P = 0.041$]. Other baseline parameters according to the CV risk can be found in Table 1.

According to the MDSS questionnaire, a total of 27 (9.9%) patients fulfilled criteria for adherence to MD, with a median score of 8.0 (6.0-10.0). Patients with none/limited CV risk had significantly higher percentage of those who adhered to MD in comparison to patients with increased/definite CV risk (15.2% *vs* 6.9%, $P = 0.028$). In addition, those participants who followed the MDSS guidelines for nuts (23.2% *vs* 12.6%, $P = 0.023$) and legumes (40.4% *vs* 25.9%, $P = 0.013$) consumption also had significantly higher adherence (Table 2). Furthermore, analysis of MDSS according to DM type II management has shown that significantly higher number of patients with HbA1c < 7 % adhere to MD when compared to patients with HbA1c > 7 % (14.9% *vs* 7.3%, $P = 0.045$). Moreover, those patients follow the guidelines for eggs (33.0% *vs* 46.8%, $P = 0.025$) and wine (15.6% *vs* 29.8%, $P = 0.006$) consumption more frequently (Table 3).

According to gender, women followed the guidelines for red meat consumption more frequently than men (34.3% *vs* 58.8%, $P < 0.001$), while men had better follow of guidelines for cereals (70.8% *vs* 55.9%, $P = 0.011$) and wine (33.6% *vs* 7.4%, $P < 0.001$) consumption. Adherence to all food groups in MDSS according to gender can be found in Table 4.

Table 1 Baseline parameters analysis according to cardiovascular risk groups derived from advanced glycation endproducts result

Parameter	None/limited CV risk (*n* = 99)	Increased/definite CV risk (*n* = 174)	Total (*n* = 273)	*P* value[1]
Male gender, *n* (%)	41 (41.4)	96 (55.2)	137 (50.2)	0.029
Age (yr)	67.6 ± 12.4	69.1 ± 11.8	68.5 ± 12.1	0.313
Disease duration (yr)	9.0 (3.0-18.0)	14.0 (6.0-21.0)	12.0 (5.0-20.0)	0.005
BMI (kg/m^2)	29.2 ± 4.96	29.1 ± 4.85	29.2 ± 4.88	0.900
Neck circumference (cm)	38.7 ± 4.01	39.1 ± 4.17	38.9 ± 4.11	0.409
Waist circumference (cm)	98.1 ± 12.7	97.8 ± 12.7	97.9 ± 12.6	0.870
Hip circumference (cm)	106.3 ± 9.5	105.5 ±10.5	105.8 ± 10.1	0.531
WHR	0.92 ± 0.07	0.93 ± 0.08	0.92 ± 0.08	0.575
Smokers, *n* (%)	12 (12.1)	41 (23.6)	53 (19.4)	0.022
Physical activity, *n* (%)				
Not physically active	15 (15.2)	56 (32.2)	71 (26.0)	0.008
1-4 ×/mo	24 (24.2)	36 (20.7)	60 (22.0)	
> 4 ×/mo	60 (60.6)	82 (47.1)	142 (52.0)	
Therapy, *n* (%)				
OHA	56 (56.6)	90 (51.7)	146 (53.5)	0.619
Insulin	14 (14.1)	26 (14.9)	40 (14.7)	
OHA + insulin	23 (23.2)	49 (28.2)	72 (26.4)	
GLP-1 based therapy	2 (2.0)	6 (3.4)	8 (2.9)	
No medications	4 (4.0)	3 (1.7)	7 (2.6)	
HbA1c (%)	7.2 (6.5-8.5)	7.65 (6.8-8.8)	7.4 (6.7-8.8)	0.041

[1]Chi-square test, Mann-Whitney test/t-test for independent samples. Data are presented as whole numbers (%), median (IQR) or mean ± SD. Bolded parameters signify statistically significant difference. AGE: Advanced glycation endproducts; OHA: Oral hypoglycemic agents; GLP: Glucagon-like peptide; HbA1c: Glycated haemoglobin.

Further analyses have shown that MDSS score has a significant positive correlation with disease duration (r = 0.179, P = 0.003) and negative correlation with BMI values (r = -0.159, P = 0.008) (Table 5). Moreover, in the multiple linear regression model, BMI (β ± SE, -0.09 ± 0.04, P = 0.037) and disease duration (β ± SE, 0.07 ± 0.02, P < 0.001) remained significant independent correlates of MDSS score (Table 6).

Finally, attitudes regarding diet and diet behaviours were analysed. Most of the patients that get diet information from a physician (96.3%), think that a better and more controlled diet could reduce their health problems (88.6%) and would visit educational programs if they existed (81.7%). Furthermore, advice from a nutritionist was received in 16.8%of cases, while 17.9% of patients have informed themselves on the Internet regarding diet in diabetes. According to DM management, patients with worse DM control think that educational programs on nutrition would be helpful, in significantly more cases in comparison to patients with better control of DM (98.9% *vs* 92.6%, P = 0.009). Dietary attitudes of the studied population according to DM management can be seen in Table 7.

DISCUSSION

In the present cross-sectional study, we demonstrated that DM type II patients with no or limited CV risk adhere more to the MD than patients with either increased or definite CV risk. In line with this, significantly more patients with none or limited CV risk followed the recommended use of nuts and legumes. Furthermore, we showed that the subgroup of DM type II patients with lower HbA1c levels (< 7%) adheres better to the MD than the subgroup of patients with higher HbA1c levels (> 7%), markedly in terms of following the recommended use of wine and eggs. In addition,

Table 2 Adherence to individual food groups and total Mediterranean diet guidelines according to cardiovascular risk groups derived from advanced glycation endproducts levels

Parameter, *n* (%)	None/limited CV risk (*n* = 99)	Increased/definite CV risk (*n* = 174)	Total (*n* = 273)	*P* value[1]
Cereals	60 (60.6)	113 (64.9)	173 (63.4)	0.475
Potato	87 (87.9)	153 (87.9)	240 (87.9)	0.989
Olive oil	28 (28.3)	45 (25.9)	73 (26.7)	0.664
Nuts	23 (23.2)	22 (12.6)	45 (16.5)	0.023
Fresh fruit	36 (36.4)	57 (32.8)	93 (34.1)	0.546
Vegetables	10 (10.1)	13 (7.5)	23 (8.4)	0.453
Milk and dairy products	14 (14.1)	44 (25.3)	58 (21.2)	0.031
Legumes	40 (40.4)	45 (25.9)	85 (31.1)	0.013
Eggs	40 (40.4)	63 (36.2)	103 (37.7)	0.492
Fish	32 (32.3)	50 (28.7)	82 (30.0)	0.535
White meat	34 (34.3)	53 (30.5)	87 (31.9)	0.509
Red meat	39 (39.4)	88 (50.6)	127 (46.5)	0.075
Sweets	77 (77.8)	137 (78.7)	214 (78.4)	0.854
Wine	19 (19.2)	37 (21.3)	56 (20.5)	0.684
Total MDSS points	7.0 (6.0-10.75)	8.0 (6.0-10.0)	8.0 (6.0-10.0)	0.959

[1]Chi-square test or Mann-Whitney test. Data are presented as whole numbers (%) or median (IQR). Bolded parameters signify statistically significant difference. MDSS: Mediterranean diet serving score.

these subgroups mainly did not differ in dietary attitudes. Interestingly, MDSS correlated positively with disease duration and negatively with BMI, which was further confirmed in a multiple linear regression model. Finally, certain gender differences in diet adherence were also observed, as women followed guidelines for red meat consumption more frequently than men, whereas it was vice versa with respect to guidelines for cereals and wine.

Our results regarding the association between MD adherence and CV risk are in concordance with the available studies. Namely, it has so far been well established that adherence to MD improves CV outcomes[21-24]. Among an array of the conducted studies, the PREDIMED (*PREvención con DIeta MEDiterránea*) trial should be specially addressed, as insights from it provided a large body of evidence on the association between MD and diverse health outcomes[25]. The PREDIMED is a multicentre, randomized, primary prevention trial that included 7447 participants aiming to assess the long-term effects of MD on the occurrence of CV events. The trial clearly showed a 30% relative risk reduction in CV event incidence, while additionally calculating that, in a 5-year follow-up, in a hypothetic cohort of 1000 people following the MD, 13 CV events can be prevented. Notably, accounting for the advanced age of the study participants, it has been concluded that it is never too late to improve dietary regiments in terms of CV health. The main advantage of the PREDIMED trial was a continuous assessment of MD adherence, unlike most of the other follow-up studies in which dietary habits were only measured at the commencement of the study. However, it is important to point out that no effect on all-cause mortality was apparent in this trial, unlike other studies conducted on this topic[26-28]. Pathophysiological mechanisms by which MD exhibits the above-noted protective effects on the CV system are diverse[29]. Although not completely elucidated, the richness of MD nutrients in anti-oxidant and anti-inflammatory molecules is likely to be relevant[30, 31]. Nutrients can either have intrinsic anti-oxidant capacity or modulate gene and protein expression. Available studies suggest that MD exerts protective effects on the expression of several proatherogenic genes, resulting in modulation of vascular inflammation, thrombosis, and foam-cell formation[32-34]. In this sense, legumes, for which we demonstrated that patients with lower CV risk have a higher adherence, contain a lot of phytochemicals endowed with useful biological activities[35,36]. Phytochemicals were shown to have prominent antioxidant activity, improve endothelial function by increasing nitric oxide bioavailability and prevent athero-

Table 3 Adherence to individual food groups and total Mediterranean diet guidelines according to diabetes management

Parameter, *n* (%)	HbA1c > 7 % (*n* = 179)	HbA1c < 7 % (*n* = 94)	Total (*n* = 273)	*P* value[1]
Cereals	113 (63.1)	60 (63.8)	173 (63.4)	0.909
Potato	159 (88.8)	81 (86.2)	240 (87.9)	0.523
Olive oil	48 (26.8)	25 (26.6)	73 (26.7)	0.969
Nuts	27 (15.1)	18 (19.1)	45 (16.5)	0.390
Fresh fruit	57 (31.8)	36 (38.3)	93 (34.1)	0.286
Vegetables	15 (8.4)	8 (8.5)	23 (8.4)	0.971
Milk and dairy products	38 (21.2)	20 (21.3)	58 (21.2)	0.993
Legumes	50 (27.9)	35 (37.2)	85 (31.1)	0.115
Eggs	59 (33.0)	44 (46.8)	103 (37.7)	0.025
Fish	51 (28.5)	31 (33.0)	82 (30.0)	0.443
White meat	60 (33.5)	27 (28.7)	87 (31.9)	0.419
Red meat	86 (48.0)	41 (43.6)	127 (46.5)	0.487
Sweets	144 (80.4)	70 (74.5)	214 (78.4)	0.255
Wine	28 (15.6)	28 (29.8)	56 (20.5)	0.006
Total MDSS points	8.0 (6.0-10.0)	8.0 (6.0-11.0)	8.0 (6.0-11.0)	0.261

[1]Chi-square test or Mann-Whitney test. Data are presented as whole numbers (%) or median (IQR). Bolded parameters signify statistically significant difference. MDSS: Mediterranean diet serving score.

sclerosis progression by inhibition of low-density lipoprotein oxidation[37,38]. Accordingly, nutrients in nuts, for which we demonstrated better adherence among low-risk CV subgroup as well, are also associated with multiple molecular pathways which grant their beneficial CV effects. Namely, randomized trials have proven that nuts consumption is associated with attenuation of inflammation and oxidative stress burden, improvement in endothelial function and lipid status, as well as in insulin resistance[39,40].

The rationale for using AGE Reader in CV risk stratification is substantiated by multiple evidence[41]. AGEs serum or plasma levels do not reflect levels of AGEs in tissues, owing to the high protein turnover rate in the circulation[42]. Conversely, AGE Reader reliably reflects AGEs tissue levels obtained using skin biopsy by utilizing fluorescent properties that several AGEs possess[43]. Furthermore, multiple studies indicate that accelerated accumulation of AGEs was proportionally associated with higher CV risk, thus justifying the use of AGE in this setting[13,14,15,44].

Effects of MD adherence on glycaemic control in DM type II were thoroughly reviewed by Esposito *et al*[45]. Multiple authors provided evidence which points to an inverse association between MD and indices of glucose homeostasis in the general population, the elderly, and high-risk patients[46-48]. Among five conducted RCTs that evaluated the effects of MD on glycaemic control in DM type II[49-53], only one trial showed no difference in HbA1c levels between the control group[49]. Namely, Shai *et al*[49] compared three weight-loss diets in 322 moderately obese patients, 46 of which suffered from DM type II, and demonstrated no difference in HbA1c decrease between the groups assigned to the MD as compared with the low-fat diet, however, a significant decrease in fasting glucose concentration was found in the MD cohort. Our results seem to be in line with findings from the aforementioned studies. In addition, more optimal adherence for wine and eggs in the subgroup with lower HbA1c was observed in the present study. This observation could be explained by the fact that wine and eggs were both shown to exert favourable effects on the metabolic profile in patients with DM[54,55].

Although our findings that adherence to MD positively correlates with disease duration seem reasonable, conflicts with some of the available data. Austin *et al*[56] demonstrated that DM type I duration is indicative of poorer dietary self-care in adolescents[56]. Authors attributed this observation to contextual and motivational factors as posited by Self-Determination Theory. However, owing to the significant age difference and concomitant differences in psychological features between ours and

Table 4 Adherence to individual food groups and total Mediterranean diet guidelines according to gender

Parameter, *n* (%)	Men (*n* = 137)	Women (*n* = 136)	Total (*n* = 273)	*P* value[1]
Cereals	97 (70.8)	76 (55.9)	173 (63.4)	0.011
Potato	120 (87.6)	120 (88.2)	240 (87.9)	0.871
Olive oil	37 (27.0)	36 (26.5)	73 (26.7)	0.920
Nuts	18 (13.1)	27 (19.9)	45 (16.5)	0.135
Fresh fruit	42 (30.7)	51 (37.5)	93 (34.1)	0.234
Vegetables	9 (6.6)	14 (10.3)	23 (8.4)	0.269
Milk and dairy products	33 (24.1)	25 (18.4)	58 (21.2)	0.250
Legumes	38 (27.7)	47 (34.6)	85 (31.1)	0.224
Eggs	59 (43.1)	44 (32.4)	103 (37.7)	0.068
Fish	43 (31.4)	39 (28.7)	82 (30.0)	0.626
White meat	43 (31.4)	44 (32.4)	87 (31.9)	0.864
Red meat	47 (34.3)	80 (58.8)	127 (46.5)	< 0.001
Sweets	103 (75.2)	111 (81.6)	214 (78.4)	0.197
Wine	46 (33.6)	10 (7.4)	56 (20.5)	< 0.001
Total MDSS points	8.0 (6.0-10.0)	8.0 (6.0-11.0)	8.0 (6.0-10.0)	0.485
Adherence to Mediterranean Diet	12 (8.8)	15 (11.0)	27 (9.9)	0.530

[1]Chi-square test or Mann-Whitney test. Data are presented as whole numbers (%) or median (IQR). Bolded parameters signify statistically significant difference. MDSS: Mediterranean diet serving score.

Table 5 Correlation of Mediterranean diet serving score with selected parameters in study population (*n* = 273)

Parameter	MDSS score, r (*P* value[1])
Age (yr)	0.054 (0.372)
Disease duration (yr)	0.179 (0.003)
BMI (kg/m^2)	-0.159 (0.008)
Neck circumference (cm)	-0.001 (0.991)
Waist circumference (cm)	-0.010 (0.872)
Hip circumference (cm)	-0.017 (0.779)
WHR	-0.022 (0.723)
HbA1c (%)	-0.074 (0.220)
AGEs levels	-0.012 (0.839)

[1]Spearman's correlation coefficient. AGE: Advanced glycation endproducts; MDSS: Mediterranean diet serving score; BMI: Body mass index; WHR: Waist-to-hip ratio; HbA1c: Glycated hemoglobin.

Austin *et al*[56]'s study participants, their findings could hardly be extrapolated to the current study. On the other hand, multiple studies conducted on populations similar to the population present in this study also demonstrated opposite results. Most authors agree that strict dietary habits fade over time, as DM patients are under the constant threat of severe diabetic complications despite being adherent to self-care behaviours, which results in burnout[57,58]. As overall MD adherence was low in the current, but in other studies as well, a search for novel educational techniques is warranted[59-61]. This is also recognized by study participants (97%), markedly in those with higher HbA1c levels. These results may be explained by multiple factors. In both our and other studies, the first and probably the main culprit for low MD adherence are overall high prices for dietary products of which MD is comprised.

Table 6 Multiple linear regression model of independent predictors for Mediterranean diet service score

Variable	B[1]	SE[2]	*t* value	*P* value
Gender	-0.39	0.43	-0.92	0.354
Age (yr)	-0.002	0.02	-0.13	0.895
Disease duration (yr)	0.07	0.02	3.42	< 0.001
Body mass index (kg/m^2)	-0.09	0.04	-2.11	0.037
HbA1c (%)	-0.07	0.13	-0.59	0.554
AGEs levels	-0.31	0.31	-1.05	0.311

[1]Unstandardized coefficient β.
[2]Standard error.
AGE: Advanced glycation endproducts; HbA1c: Glycated hemoglobin.

Table 7 Dietary attitudes of studied population according to diabetes management

Questions	HbA1c > 7% (*n* = 179)	HbA1c < 7% (*n* = 94)	Total (*n* = 273)	*P* value[1]
Did you get diet information according to your illness from your physician (yes)	172 (96.1)	91 (96.8)	263 (96.3)	0.764
Have you visited a nutritionist to advise you on nutrition (yes)	26 (14.5)	20 (21.4)	46 (16.8)	0.157
Have you informed yourself on the Internet about the diet related to your illness (yes)	29 (16.2)	20 (21.4)	49 (17.9)	0.300
Do you think that a better and more controlled diet could reduce your health problems (yes)	156 (87.2)	86 (91.5)	242 (88.6)	0.331
Do you consider educational programs on nutrition to be useful for patients (yes)	177 (98.9)	87 (92.6)	264 (96.7)	0.009
If educational programs on nutrition existed in your community, would you visit them (yes)	145 (81.0)	78 (83.0)	223 (81.7)	0.689

Data are presented as whole numbers (%).
[1]Chi-square test.
HbA1c: Glycated hemoglobin.

Furthermore, the westernization of society has also impacted the dietary preferences of the population, shifting to high-sugar, low-fibre processed food. Finally, the knowledge concerning healthy dietary habits in our population is generally low, even among general practitioners[62,63]. Given that only 16% of our participants underwent nutritionist evaluation despite that average disease duration was 12 years, this could be a promising niche for diet improvement in patients with DM, as demonstrated by multiple authors[64,65]. Conversely, a negative correlation was found between MD adherence and BMI. These results are expected, as MD adherence was previously shown to participate in weight reduction[66,67]. In addition, patients who are more motivated for dietary self-care are more prone to weight loss[67].

The observed decrease in consumption of red meat in female participants and increased consumption of wine and cereals among men is in line with the available data[66]. Multiple authors suggest that gender differences in adherence to certain food groups could be explained by psychological dissimilarities between men and women, more frequent veganism in woman populations, and reduced accessibility of meat to women[68,69]. Results from the present study imply that patients with higher AGEs levels and concomitantly higher CV risk are less eager to remain physically active. The obtained results are in concordant with the available data, as most studies demonstrated that physical inactivity is associated with high levels of AGEs and other predictors of CV risk[70,71]. Interestingly, in a study by Rodrigues *et al*[72], the authors demonstrated that low AGEs levels in patients with human immunodeficiency virus could be restored to normal values by exercising in just a few months[72].

Our study bears several limitations. Firstly, the cross-sectional design of the study which prevents us from making any causal inferences. Secondly, in the questionnaire, we have relied on the participant's recall memory, therefore, the answers are

susceptible to subjectivity and recall bias. Finally, although considered reliable, we must bear in mind that AGE Reader has many different endogenous and exogenous components which may influence measurement of the AGEs.

CONCLUSION

In summary, this cross-sectional study brought further evidence concerning the association between AGE tissue levels and adherence to MD using a validated MDSS questionnaire. In line with this, we demonstrated that adherence to MD is very low in patients with DM type II, especially in those with poorly controlled glycaemia. Nevertheless, survey results indicate that patients seem to realize the importance of diet in DM management. Furthermore, it has been observed that dietary preferences are influenced by gender, women followed guidelines for red meat consumption more frequently than men, whereas it was vice versa in guidelines for cereals and wine. Finally, we showed that DM duration independently predicted better adherence to MD, whereas BMI predicted poorer MD adherence.

ARTICLE HIGHLIGHTS

Research background

In recent years, major diabetic organizations started to strongly advocate the use of the Mediterranean diet (MD) over other diets in patients with diabetes mellitus (DM) because of its beneficial effects on glycaemic control and cardiovascular (CV) risk factors. Evidence suggests that CV risk may be assessed using tissue levels of advanced glycation endproducts (AGEs) in patients with DM.

Research motivation

As DM prevalence is constantly rising in well-developed countries, there is an urgent need to mitigate the poor outcomes of this disease. Regarding the importance of diet in this setting, we endeavoured to bring further evidence with respect to the benefits of the use of the MD in patients with DM.

Research objectives

The main objective of this study was to examine the association between adherence to the MD, assessed by MD serving score (MDSS) and CV risk, assessed by AGEs skin levels, in patients with DM type II. Additionally, we examined the association between anthropometric characteristics, glycaemic control, and physical activity with AGEs levels among patients with DM type 2

Research methods

In this study, we employed the Croatian version of the 14-item MDSS questionnaire to assess adherence to the MD. On the other hand, in order to compare adherence to CV risk, we used skin autofluorescence-based AGE Reader that measures AGEs skin levels.

Research results

The present study demonstrated that patients with diabetes who have none or limited CV risk adhere more to the MD than patients who have either increased or definite CV risk. In addition, we showed that the subgroup of patients with diabetes with better glycaemic control adheres better to the MD than the subgroup of patients with worse glycaemic control. Altogether, these results are generally in line with the available data. It remains to be answered why adherence to MD is so low, despite being undoubtedly beneficial.

Research conclusions

By bringing additional data about the association of the MD with CV outcomes, this study addresses the need to implement novel strategies that will lead to better MD adherence in patients with diabetes.

Research perspectives

In future studies, the highlight should be placed further delineation off mechanisms by

which MD exerts its favourable effects to establish the optimal dietary pattern. Furthermore, psychological studies could be important in this setting, as the main problem of MD is low adherence. Namely, psychological studies may give a deeper insight into non-adherence, thus facilitating the resolution of this issue.

ACKNOWLEDGEMENTS

The paper has been proofread by language professional Dalibora Behmen.

REFERENCES

1 **American Diabetes Association**. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2013; **36** Suppl 1: S67-S74 [PMID: 23264425 DOI: 10.2337/dc13-S067]

2 **Genuth S**, Alberti KG, Bennett P, Buse J, Defronzo R, Kahn R, Kitzmiller J, Knowler WC, Lebovitz H, Lernmark A, Nathan D, Palmer J, Rizza R, Saudek C, Shaw J, Steffes M, Stern M, Tuomilehto J, Zimmet P; Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care* 2003; **26**: 3160-3167 [PMID: 14578255 DOI: 10.2337/diacare.26.11.3160]

3 **Khan MAB**, Hashim MJ, King JK, Govender RD, Mustafa H, Al Kaabi J. Epidemiology of Type 2 Diabetes - Global Burden of Disease and Forecasted Trends. *J Epidemiol Glob Health* 2020; **10**: 107-111 [PMID: 32175717 DOI: 10.2991/jegh.k.191028.001]

4 **Cho NH**, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, Ohlrogge AW, Malanda B. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Res Clin Pract* 2018; **138**: 271-281 [PMID: 29496507 DOI: 10.1016/j.diabres.2018.02.023]

5 **American Diabetes Association**. (4) Foundations of care: education, nutrition, physical activity, smoking cessation, psychosocial care, and immunization. *Diabetes Care* 2015; **38** Suppl: S20-S30 [PMID: 25537702 DOI: 10.2337/dc15-S007]

6 **Martínez-González MA**, Gea A, Ruiz-Canela M. The Mediterranean Diet and Cardiovascular Health. *Circ Res* 2019; **124**: 779-798 [PMID: 30817261 DOI: 10.1161/CIRCRESAHA.118.313348]

7 **Bloomfield HE**, Koeller E, Greer N, MacDonald R, Kane R, Wilt TJ. Effects on Health Outcomes of a Mediterranean Diet With No Restriction on Fat Intake: A Systematic Review and Meta-analysis. *Ann Intern Med* 2016; **165**: 491-500 [PMID: 27428849 DOI: 10.7326/M16-0361]

8 **Sofi F**, Cesari F, Abbate R, Gensini GF, Casini A. Adherence to Mediterranean diet and health status: meta-analysis. *BMJ* 2008; **337**: a1344 [PMID: 18786971 DOI: 10.1136/bmj.a1344]

9 **Yao D**, Brownlee M. Hyperglycemia-induced reactive oxygen species increase expression of the receptor for advanced glycation end products (RAGE) and RAGE ligands. *Diabetes* 2010; **59**: 249-255 [PMID: 19833897 DOI: 10.2337/db09-0801]

10 **Hanssen NM**, Beulens JW, van Dieren S, Scheijen JL, van der A DL, Spijkerman AM, van der Schouw YT, Stehouwer CD, Schalkwijk CG. Plasma advanced glycation end products are associated with incident cardiovascular events in individuals with type 2 diabetes: a case-cohort study with a median follow-up of 10 years (EPIC-NL). *Diabetes* 2015; **64**: 257-265 [PMID: 24848072 DOI: 10.2337/db13-1864]

11 **Giacco F**, Brownlee M. Oxidative stress and diabetic complications. *Circ Res* 2010; **107**: 1058-1070 [PMID: 21030723 DOI: 10.1161/CIRCRESAHA.110.223545]

12 **Brownlee M**. The pathobiology of diabetic complications: a unifying mechanism. *Diabetes* 2005; **54**: 1615-1625 [PMID: 15919781 DOI: 10.2337/diabetes.54.6.1615]

13 **den Dekker MA**, Zwiers M, van den Heuvel ER, de Vos LC, Smit AJ, Zeebregts CJ, Oudkerk M, Vliegenthart R, Lefrandt JD, Mulder DJ. Skin autofluorescence, a non-invasive marker for AGE accumulation, is associated with the degree of atherosclerosis. *PLoS One* 2013; **8**: e83084 [PMID: 24376641 DOI: 10.1371/journal.pone.0083084]

14 **Meerwaldt R**, Graaff R, Oomen PHN, Links TP, Jager JJ, Alderson NL, Thorpe SR, Baynes JW, Gans ROB, Smit AJ. Simple non-invasive assessment of advanced glycation endproduct accumulation. *Diabetologia* 2004; **47**: 1324-1330 [PMID: 15243705 DOI: 10.1007/s00125-004-1451-2]

15 **Lutgers HL**, Gerrits EG, Graaff R, Links TP, Sluiter WJ, Gans RO, Bilo HJ, Smit AJ. Skin autofluorescence provides additional information to the UK Prospective Diabetes Study (UKPDS) risk score for the estimation of cardiovascular prognosis in type 2 diabetes mellitus. *Diabetologia* 2009; **52**: 789-797 [PMID: 19274450 DOI: 10.1007/s00125-009-1308-9]

16 **Li Z**, Wang G, Zhu YJ, Li CG, Tang YZ, Jiang ZH, Yang M, Ni CL, Chen LM, Niu WY. The relationship between circulating irisin levels and tissues AGE accumulation in type 2 diabetes patients. *Biosci Rep* 2017; **37** [PMID: 28408433 DOI: 10.1042/BSR20170213]

17 **Couppé C**, Svensson RB, Grosset JF, Kovanen V, Nielsen RH, Olsen MR, Larsen JO, Praet SF, Skovgaard D, Hansen M, Aagaard P, Kjaer M, Magnusson SP. Life-long endurance running is associated with reduced glycation and mechanical stress in connective tissue. *Age (Dordr)* 2014; **36**: 9665 [PMID: 24997017 DOI: 10.1007/s11357-014-9665-9]

18 **Marendić M**, Polić N, Matek H, Oršulić L, Polašek O, Kolčić I. Mediterranean diet assessment challenges: Validation of the Croatian Version of the 14-item Mediterranean Diet Serving Score (MDSS) Questionnaire. *PLoS One* 2021; **16**: e0247269 [PMID: 33647026 DOI: 10.1371/journal.pone.0247269]

19 **Meerwaldt R**, Links T, Graaff R, Thorpe SR, Baynes JW, Hartog J, Gans R, Smit A. Simple noninvasive measurement of skin autofluorescence. *Ann N Y Acad Sci* 2005; **1043**: 290-298 [PMID: 16037251 DOI: 10.1196/annals.1333.036]

20 **Kolčić I**, Relja A, Gelemanović A, Miljković A, Boban K, Hayward C, Rudan I, Polašek O. Mediterranean diet in the southern Croatia - does it still exist? *Croat Med J* 2016; **57**: 415-424 [PMID: 27815932 DOI: 10.3325/cmj.2016.57.415]

21 **Widmer RJ**, Flammer AJ, Lerman LO, Lerman A. The Mediterranean diet, its components, and cardiovascular disease. *Am J Med* 2015; **128**: 229-238 [PMID: 25447615 DOI: 10.1016/j.amjmed.2014.10.014]

22 **Castañer O**, Corella D, Covas MI, Sorlí JV, Subirana I, Flores-Mateo G, Nonell L, Bulló M, de la Torre R, Portolés O, Fitó M; PREDIMED study investigators. In vivo transcriptomic profile after a Mediterranean diet in high-cardiovascular risk patients: a randomized controlled trial. *Am J Clin Nutr* 2013; **98**: 845-853 [PMID: 23902780 DOI: 10.3945/ajcn.113.060582]

23 **Schwingshackl L**, Hoffmann G. Mediterranean dietary pattern, inflammation and endothelial function: a systematic review and meta-analysis of intervention trials. *Nutr Metab Cardiovasc Dis* 2014; **24**: 929-939 [PMID: 24787907 DOI: 10.1016/j.numecd.2014.03.003]

24 **Martinez-Gonzalez MA**, Bes-Rastrollo M. Dietary patterns, Mediterranean diet, and cardiovascular disease. *Curr Opin Lipidol* 2014; **25**: 20-26 [PMID: 24370845 DOI: 10.1097/MOL.0000000000000044]

25 **Ros E**, Martínez-González MA, Estruch R, Salas-Salvadó J, Fitó M, Martínez JA, Corella D. Mediterranean diet and cardiovascular health: Teachings of the PREDIMED study. *Adv Nutr* 2014; **5**: 330S-336S [PMID: 24829485 DOI: 10.3945/an.113.005389]

26 **Sofi F**, Abbate R, Gensini GF, Casini A. Accruing evidence on benefits of adherence to the Mediterranean diet on health: an updated systematic review and meta-analysis. *Am J Clin Nutr* 2010; **92**: 1189-1196 [PMID: 20810976 DOI: 10.3945/ajcn.2010.29673]

27 **Sofi F**, Macchi C, Abbate R, Gensini GF, Casini A. Mediterranean diet and health status: an updated meta-analysis and a proposal for a literature-based adherence score. *Public Health Nutr* 2014; **17**: 2769-2782 [PMID: 24476641 DOI: 10.1017/S1368980013003169]

28 **Trichopoulou A**, Martínez-González MA, Tong TY, Forouhi NG, Khandelwal S, Prabhakaran D, Mozaffarian D, de Lorgeril M. Definitions and potential health benefits of the Mediterranean diet: views from experts around the world. *BMC Med* 2014; **12**: 112 [PMID: 25055810 DOI: 10.1186/1741-7015-12-112]

29 **Fitó M**, Guxens M, Corella D, Sáez G, Estruch R, de la Torre R, Francés F, Cabezas C, López-Sabater MDC, Marrugat J, García-Arellano A, Arós F, Ruiz-Gutierrez V, Ros E, Salas-Salvadó J, Fiol M, Solá R, Covas MI; PREDIMED Study Investigators. Effect of a traditional Mediterranean diet on lipoprotein oxidation: a randomized controlled trial. *Arch Intern Med* 2007; **167**: 1195-1203 [PMID: 17563030 DOI: 10.1001/archinte.167.11.1195]

30 **Salas-Salvadó J**, Garcia-Arellano A, Estruch R, Marquez-Sandoval F, Corella D, Fiol M, Gómez-Gracia E, Viñoles E, Arós F, Herrera C, Lahoz C, Lapetra J, Perona JS, Muñoz-Aguado D, Martínez-González MA, Ros E; PREDIMED Investigators. Components of the Mediterranean-type food pattern and serum inflammatory markers among patients at high risk for cardiovascular disease. *Eur J Clin Nutr* 2008; **62**: 651-659 [PMID: 17440519 DOI: 10.1038/sj.ejcn.1602762]

31 **Buil-Cosiales P**, Irimia P, Berrade N, Garcia-Arellano A, Riverol M, Murie-Fernández M, Martínez-Vila E, Martínez-González MA, Serrano-Martínez M. Carotid intima-media thickness is inversely associated with olive oil consumption. *Atherosclerosis* 2008; **196**: 742-748 [PMID: 17276438 DOI: 10.1016/j.atherosclerosis.2006.12.028]

32 **Konstantinidou V**, Covas MI, Muñoz-Aguayo D, Khymenets O, de la Torre R, Saez G, Tormos Mdel C, Toledo E, Marti A, Ruiz-Gutiérrez V, Ruiz Mendez MV, Fito M. In vivo nutrigenomic effects of virgin olive oil polyphenols within the frame of the Mediterranean diet: a randomized controlled trial. *FASEB J* 2010; **24**: 2546-2557 [PMID: 20179144 DOI: 10.1096/fj.09-148452]

33 **Llorente-Cortés V**, Estruch R, Mena MP, Ros E, González MA, Fitó M, Lamuela-Raventós RM, Badimon L. Effect of Mediterranean diet on the expression of pro-atherogenic genes in a population at high cardiovascular risk. *Atherosclerosis* 2010; **208**: 442-450 [PMID: 19712933 DOI: 10.1016/j.atherosclerosis.2009.08.004]

34 **Damasceno NR**, Sala-Vila A, Cofán M, Pérez-Heras AM, Fitó M, Ruiz-Gutiérrez V, Martínez-González MÁ, Corella D, Arós F, Estruch R, Ros E. Mediterranean diet supplemented with nuts reduces waist circumference and shifts lipoprotein subfractions to a less atherogenic pattern in subjects at high cardiovascular risk. *Atherosclerosis* 2013; **230**: 347-353 [PMID: 24075767 DOI: 10.1016/j.atherosclerosis.2013.08.014]

35 **Sikander M**, Malik S, Rodriguez A, Yallapu MM, Narula AS, Satapathy SK, Dhevan V, Chauhan SC, Jaggi M. Role of Nutraceuticals in COVID-19 Mediated Liver Dysfunction. *Molecules* 2020; **25** [PMID: 33322162 DOI: 10.3390/molecules25245905]

36 **Prakash D**, Gupta C. Role of phytoestrogens as nutraceuticals in human health. *Pharmacologyonlin***1**: 510-523

37 **Bouchenak M**, Lamri-Senhadji M. Nutritional quality of legumes, and their role in cardiometabolic

risk prevention: a review. *J Med Food* 2013; **16**: 185-198 [PMID: 23398387 DOI: 10.1089/jmf.2011.0238]

38 **Mozaffarian D**. Dietary and Policy Priorities for Cardiovascular Disease, Diabetes, and Obesity: A Comprehensive Review. *Circulation* 2016; **133**: 187-225 [PMID: 26746178 DOI: 10.1161/CIRCULATIONAHA.115.018585]

39 **Bulló M**, Lamuela-Raventós R, Salas-Salvadó J. Mediterranean diet and oxidation: nuts and olive oil as important sources of fat and antioxidants. *Curr Top Med Chem* 2011; **11**: 1797-1810 [PMID: 21506929 DOI: 10.2174/156802611796235062]

40 **Guasch-Ferré M**, Liu X, Malik VS, Sun Q, Willett WC, Manson JE, Rexrode KM, Li Y, Hu FB, Bhupathiraju SN. Nut Consumption and Risk of Cardiovascular Disease. *J Am Coll Cardiol* 2017; **70**: 2519-2532 [PMID: 29145952 DOI: 10.1016/j.jacc.2017.09.035]

41 **Atzeni IM**, van de Zande SC, Westra J, Zwerver J, Smit AJ, Mulder DJ. The AGE Reader: A non-invasive method to assess long-term tissue damage. *Methods* 2021 [PMID: 33636313 DOI: 10.1016/j.ymeth.2021.02.016]

42 **Meertens JH**, Nienhuis HL, Lefrandt JD, Schalkwijk CG, Nyyssönen K, Ligtenberg JJ, Smit AJ, Zijlstra JG, Mulder DJ. The Course of Skin and Serum Biomarkers of Advanced Glycation Endproducts and Its Association with Oxidative Stress, Inflammation, Disease Severity, and Mortality during ICU Admission in Critically Ill Patients: Results from a Prospective Pilot Study. *PLoS One* 2016; **11**: e0160893 [PMID: 27529340 DOI: 10.1371/journal.pone.0160893]

43 **Hu H**, Jiang H, Zhu L, Wu X, Han C. Accumulation of Advanced Glycation Endproducts and Subclinical Inflammation in Deep Tissues of Adult Patients With and Without Diabetes. *Can J Diabetes* 2018; **42**: 525-532.e4 [PMID: 29803627 DOI: 10.1016/j.jcjd.2018.01.003]

44 **Ninomiya H**, Katakami N, Sato I, Osawa S, Yamamoto Y, Takahara M, Kawamori D, Matsuoka TA, Shimomura I. Association between Subclinical Atherosclerosis Markers and the Level of Accumulated Advanced Glycation End-Products in the Skin of Patients with Diabetes. *J Atheroscler Thromb* 2018; **25**: 1274-1284 [PMID: 29962379 DOI: 10.5551/jat.44859]

45 **Esposito K**, Giugliano D. Mediterranean diet and type 2 diabetes. *Diabetes Metab Res Rev* 2014; **30** Suppl 1: 34-40 [PMID: 24357346 DOI: 10.1002/dmrr.2516]

46 **Kastorini CM**, Panagiotakos DB. Mediterranean diet and diabetes prevention: Myth or fact? *World J Diabetes* 2010; **1**: 65-67 [PMID: 21537429 DOI: 10.4239/wjd.v1.i3.65]

47 **Esposito K**, Maiorino MI, Di Palo C, Giugliano D; Campanian Postprandial Hyperglycemia Study Group. Adherence to a Mediterranean diet and glycaemic control in Type 2 diabetes mellitus. *Diabet Med* 2009; **26**: 900-907 [PMID: 19719711 DOI: 10.1111/j.1464-5491.2009.02798.x]

48 **Díez-Espino J**, Buil-Cosiales P, Serrano-Martínez M, Toledo E, Salas-Salvadó J, Martínez-González MÁ. Adherence to the Mediterranean diet in patients with type 2 diabetes mellitus and HbA1c level. *Ann Nutr Metab* 2011; **58**: 74-78 [PMID: 21430378 DOI: 10.1159/000324718]

49 **Shai I**, Schwarzfuchs D, Henkin Y, Shahar DR, Witkow S, Greenberg I, Golan R, Fraser D, Bolotin A, Vardi H, Tangi-Rozental O, Zuk-Ramot R, Sarusi B, Brickner D, Schwartz Z, Sheiner E, Marko R, Katorza E, Thiery J, Fiedler GM, Blüher M, Stumvoll M, Stampfer MJ; Dietary Intervention Randomized Controlled Trial (DIRECT) Group. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. *N Engl J Med* 2008; **359**: 229-241 [PMID: 18635428 DOI: 10.1056/NEJMoa0708681]

50 **Toobert DJ**, Glasgow RE, Strycker LA. Biologic and quality-of-life out- comes from the Mediterranean Lifestyle Program: a randomized clinical trial. *Diabetes Care* 2003; **26**: 2288-2293

51 **Estruch R**, Martínez-González MA, Corella D, Salas-Salvadó J, Ruiz-Gutiérrez V, Covas MI, Fiol M, Gómez-Gracia E, López-Sabater MC, Vinyoles E, Arós F, Conde M, Lahoz C, Lapetra J, Sáez G, Ros E; PREDIMED Study Investigators. Effects of a Mediterranean-style diet on cardiovascular risk factors: a randomized trial. *Ann Intern Med* 2006; **145**: 1-11 [PMID: 16818923 DOI: 10.7326/0003-4819-145-1-200607040-00004]

52 **Esposito K**, Maiorino MI, Ciotola M, Di Palo C, Scognamiglio P, Gicchino M, Petrizzo M, Saccomanno F, Beneduce F, Ceriello A, Giugliano D. Effects of a Mediterranean-style diet on the need for antihyperglycemic drug therapy in patients with newly diagnosed type 2 diabetes: a randomized trial. *Ann Intern Med* 2009; **151**: 306-314 [PMID: 19721018 DOI: 10.7326/0003-4819-151-5-200909010-00004]

53 **Elhayany A**, Lustman A, Abel R, Attal-Singer J, Vinker S. A low carbohydrate Mediterranean diet improves cardiovascular risk factors and diabetes control among overweight patients with type 2 diabetes mellitus: a 1-year prospective randomized intervention study. *Diabetes Obes Metab* 2010; **12**: 204-209 [PMID: 20151996 DOI: 10.1111/j.1463-1326.2009.01151.x]

54 **Geiker NRW**, Larsen ML, Dyerberg J, Stender S, Astrup A. Egg consumption, cardiovascular diseases and type 2 diabetes. *Eur J Clin Nutr* 2018; **72**: 44-56 [PMID: 28952608 DOI: 10.1038/ejcn.2017.153]

55 **Ditano-Vázquez P**, Torres-Peña JD, Galeano-Valle F, Pérez-Caballero AI, Demelo-Rodríguez P, Lopez-Miranda J, Katsiki N, Delgado-Lista J, Alvarez-Sala-Walther LA. The Fluid Aspect of the Mediterranean Diet in the Prevention and Management of Cardiovascular Disease and Diabetes: The Role of Polyphenol Content in Moderate Consumption of Wine and Olive Oil. *Nutrients* 2019; **11** [PMID: 31752333 DOI: 10.3390/nu11112833]

56 **Austin S**, Guay F, Senécal C, Fernet C, Nouwen A. Longitudinal testing of a dietary self-care motivational model in adolescents with diabetes. *J Psychosom Res* 2013; **75**: 153-159 [PMID: 23915772 DOI: 10.1016/j.jpsychores.2013.04.013]

57 **Ko SH**, Park SA, Cho JH, Ko SH, Shin KM, Lee SH, Song KH, Park YM, Ahn YB. Influence of the

duration of diabetes on the outcome of a diabetes self-management education program. *Diabetes Metab J* 2012; **36**: 222-229 [PMID: 22737662 DOI: 10.4093/dmj.2012.36.3.222]

58 **Eom YS**, Park HS, Kim SH, Yang SM, Nam MS, Lee HW, Lee KY, Lee S, Kim YS, Park IeB. Evaluation of stress in korean patients with diabetes mellitus using the problem areas in diabetes-Korea questionnaire. *Diabetes Metab J* 2011; **35**: 182-187 [PMID: 21738901 DOI: 10.4093/dmj.2011.35.2.182]

59 **Vrdoljak J**, Vilović M, Živković PM, Tadin Hadjina I, Rušić D, Bukić J, Borovac JA, Božić J. Mediterranean Diet Adherence and Dietary Attitudes in Patients with Inflammatory Bowel Disease. *Nutrients* 2020; **12** [PMID: 33171662 DOI: 10.3390/nu12113429]

60 **Simunovic M**, Supe-Domic D, Karin Z, Degoricija M, Paradzik M, Skrabic R, Jukic A, Bozic J, Skrabic V. The Relationship of Vitamin D Status, Adherence to the Mediterranean Diet, and Physical Activity in Obese Children and Adolescents. *J Med Food* 2021; **24**: 385-393 [PMID: 32783677 DOI: 10.1089/jmf.2020.0032]

61 **Trichopoulou A**, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. *N Engl J Med* 2003; **348**: 2599-2608 [PMID: 12826634 DOI: 10.1056/NEJMoa025039]

62 **O'Neil CE**, Keast DR, Nicklas TA, Fulgoni VL 3rd. Nut consumption is associated with decreased health risk factors for cardiovascular disease and metabolic syndrome in U.S. adults: NHANES 1999-2004. *J Am Coll Nutr* 2011; **30**: 502-510 [PMID: 22331685 DOI: 10.1080/07315724.2011.10719996]

63 **Dumic A**, Miskulin M, Pavlovic N, Orkic Z, Bilic-Kirin V, Miskulin I. The Nutrition Knowledge of Croatian General Practitioners. *J Clin Med* 2018; **7** [PMID: 30029463 DOI: 10.3390/jcm7070178]

64 **Di Onofrio V**, Gallé F, Di Dio M, Belfiore P, Liguori G. Effects of nutrition motivational intervention in patients affected by type 2 diabetes mellitus: a longitudinal study in Naples, South Italy. *BMC Public Health* 2018; **18**: 1181 [PMID: 30333012 DOI: 10.1186/s12889-018-6101-6]

65 **Mendes R**, Sousa N, Themudo-Barata J, Reis V. Impact of a community-based exercise programme on physical fitness in middle-aged and older patients with type 2 diabetes. *Gac Sanit* 2016; **30**: 215-220 [PMID: 26900099 DOI: 10.1016/j.gaceta.2016.01.007]

66 **D'Innocenzo S**, Biagi C, Lanari M. Obesity and the Mediterranean Diet: A Review of Evidence of the Role and Sustainability of the Mediterranean Diet. *Nutrients* 2019; **11** [PMID: 31181836 DOI: 10.3390/nu11061306]

67 **Estruch R**, Ros E. The role of the Mediterranean diet on weight loss and obesity-related diseases. *Rev Endocr Metab Disord* 2020; **21**: 315-327 [PMID: 32829455 DOI: 10.1007/s11154-020-09579-0]

68 **Westenhoefer J**. Age and gender dependent profile of food choice. *Forum Nutr* 2005; 44-51 [PMID: 15702587 DOI: 10.1159/000083753]

69 **Love HJ**, Sulikowski D. Of Meat and Men: Sex Differences in Implicit and Explicit Attitudes Toward Meat. *Front Psychol* 2018; **9**: 559 [PMID: 29731733 DOI: 10.3389/fpsyg.2018.00559]

70 **Sprenger HG**, Bierman WF, Martes MI, Graaff R, van der Werf TS, Smit AJ. Skin advanced glycation end products in HIV infection are increased and predictive of development of cardiovascular events. *AIDS* 2017; **31**: 241-246 [PMID: 27763891 DOI: 10.1097/QAD.0000000000001297]

71 **Kubota Y**, Evenson KR, Maclehose RF, Roetker NS, Joshu CE, Folsom AR. Physical Activity and Lifetime Risk of Cardiovascular Disease and Cancer. *Med Sci Sports Exerc* 2017; **49**: 1599-1605 [PMID: 28350711 DOI: 10.1249/MSS.0000000000001274]

72 **Rodrigues KL**, Borges JP, Lopes GO, Pereira ENGDS, Mediano MFF, Farinatti P, Tibiriça E, Daliry A. Influence of Physical Exercise on Advanced Glycation End Products Levels in Patients Living With the Human Immunodeficiency Virus. *Front Physiol* 2018; **9**: 1641 [PMID: 30574090 DOI: 10.3389/fphys.2018.01641]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com