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Effects of dietary advanced glycation end-products restriction on renal function in patients with diabetic nephropathy; a randomized, double-blind clinical trial

Arash Dashtabi[1], Zohreh Mazloom[1*], Shahrokh Ezzatzadegan Jahromi[2], Mohammad Fararouei[3]

[1]Department of Clinical Nutrition, School of Nutrition and Food Sciences, Shiraz University of Medical Sciences, Shiraz, Iran
[2]Nephrology-Urology Research Center and Department of Internal Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
[3]School of Health, Shiraz University of Medical Sciences, Shiraz, Iran

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ABSTRACT

Introduction: It has been proposed that advanced glycation end-products (AGEs) are contributory factors in diabetic nephropathy (DN) pathogenesis. Interventions regarding restriction dietary AGEs (dAGEs) intake indicate improvement in clinical outcomes.

Objectives: The present study aimed to compare the effects of 10-week low AGEs diet (LAGEsd) based on recommended diabetic diet (DD) versus DD alone on glycemic status, lipid profile, serum creatinine (sCr), blood urea nitrogen (BUN), urine albumin to creatinine ratio, eGFR and urine albumin in patients with DN.

Patients and Methods: This randomized, double-blind clinical trial was conducted on 62 patients with DN. Patients were assigned randomly to LAGEsd (n = 31) and DD (n = 31) groups for 10 weeks. All patients were prescribed calorie adjusted diet in regards to American Diabetes Association's recommendation. In addition, patients in the LAGEsd group were instructed how to reduce dAGEs intake based on established guidelines. Demographic data were collected and dietary intakes, physical activity level, fasting blood sugar (FBS), hemoglobin A1C (HbA1c), lipid profile, sCr, blood urea nitrogen (BUN), estimated glomerular filtration rate (eGFR), urine albumin to creatinine ratio (Alb/Cr), and urine albumin were measured before and after of 10-weeks intervention, and compared between the two groups.

Results: The results showed that dAGEs intake decreased significantly in the LAGEsd group compared with the DD group ($P < 0.001$). In the LAGEsd group, eGFR improved significantly compared with the DD group (18.77 ± 20.99 mL/min/1.73 m^2 versus 1.57 ± 21.06 mL/min/1.73 m^2, $P = 0.002$); however there were no significant difference in FBS, HbA1c, lipid profile, sCr, BUN, urine Alb/Cr, and urine albumin between the two groups ($P > 0.05$).

Conclusion: In sum, dAGEs restriction plus DD is superior to DD alone in improvement of renal function marker in patients with DD.

Trial Registration: This study was registered at Iranian Registry of Clinical Trials (identifier: IRCT20191004044979N1, https://en.irct.ir/trial/42914, ethical code #IR.SUMS.REC.1398.798).

Implication for health policy/practice/research/medical education:
In a double-blind clinical trial on 62 diabetic patients with nephropathy, we found that restriction of dietary advanced glycation end products intake for 8 weeks could significantly increase the mean eGFR while there was no significant difference in other renal functional marker between groups.

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Introduction

Diabetic nephropathy (DN) is a serious complication of diabetes mellitus (DM); almost accounting for one-third of all new cases of end-stage renal disease, and has become one of the main causes of morbidity and mortality worldwide (1). The occurrence and progression of DN are likely to be as a result of interactions between complex factors and pathways, which are pathologically characterized by glomerular basement membrane thickening, mesangial expansion, and interstitial fibrosis

***Corresponding authors**: Zohreh Mazloom, Email: zmazloom@susms.ac.ir, zohreh.mazloom@gmail.com

Original

and glomerular sclerosis. DN is characterized clinically by proteinuria and decreased glomerular filtration rate (GFR) (2).

A growing body of evidence suggests a pivotal role for advanced glycation end-products (AGEs) in DN pathogenesis (3). AGEs are a group of insoluble adducts that are formed through the non-enzymatic reduction of sugars like glucose and fructose with free amino groups of proteins, nucleic acids and lipids (4). AGEs activate several intracellular signaling cascades upon interaction with receptor for AGEs (RAGEs), for instance, increase in inflammatory cytokines (interleukin-6, tumor necrosis factor alpha), which enhance reactive oxygen species generation leading to podocyte apoptosis via autophagy. Oxidative stress-induced apoptosis in nephrons causes renal fibrosis and as a result, DN occurs (3).

AGEs can be made endogenously and accelerated in hyperglycemia state; or available from exogenous sources like foods, formed during cooking via Maillard reaction (5). These dietary AGEs (dAGEs) can be partially absorbed by the intestine, contribute to body's AGEs pool, and accumulated in tissues in an excessive amount (6). Using high temperature and low moisture cooking methods such as frying, baking, grilling or roasting, for longer duration, lead to increased production of AGEs in the food, while low temperature and high moisture methods like steaming, poaching, stewing, and boiling as well as decreasing cooking time limit formation of dAGEs (7). In addition, pH value affects dAGEs formation and maximum rate occurs at pH 10 (basic state). Thus following foods pretreatment with acidic solutions decrease AGEs production (8). Based on tables presenting AGEs content of foods, meats, eggs, nuts, fats, cheese, and highly processed foods have the highest AGEs content, while grains, dairies, fruits, and vegetables have the lowest content (9).

Reduction in the intake of dAGEs has been linked to a beneficial effect on insulin sensitivity, lipid profile, or some inflammatory markers in patients with DM, and seems a promising strategy to provide an important adjunct to interventions targeting patients with DM (10). Even though the effects of low AGEs diet (LAGEsd) on DM are well documented, research on the effects of a LAGEsd on renal functional markers like serum and urine creatinine levels, blood urea nitrogen (BUN), and estimated glomerular filtration rate (eGFR) are less acknowledged. To address this shortcoming, focusing on dietary interventions with reduced intake of dAGEs in patients with DN is necessary.

Objectives

The present study aimed to compare the effects of 10-week LAGEsd based on recommended diabetic diet (DD) versus DD alone on glycemic status, lipid profile, serum creatinine (sCr), BUN, urine albumin to creatinine ratio, eGFR and urine albumin in patients with DN.

Patients and Methods

Study design

The present double-blind, randomized, placebo-controlled clinical trial was conducted on diabetic nephropathy patients referred to nephrology ward of Motahari clinic, Shiraz, Iran; affiliated with Shiraz University of Medical Sciences (SUMS) during 2019-2020. Using convenience sampling, 62 eligible patients were enrolled for a 10-week trial. The inclusion criteria were patients with confirmed diagnose of DM and nephropathy by a physician; willing for participating; using only oral agents for controlling hyperglycemia and consuming a stabilized dose of oral anti-diabetic and anti-hyperlipidemia drugs; no current weight change or use of any other dietary supplements and herbal products at least 6 months before onset of the trial (self-reported). Exclusion criteria included changing the dose or type of medications; food supplements or herbal products use throughout the study; pregnancy or lactation; clinical or laboratory signs of acute or chronic infection, inflammatory, allergic, and cardiovascular disease; hypo-/hyperthyroidism and liver or pancreatic diseases.

General demographic questionnaire (researcher-made) and International Physical Activity Questionnaire (IPAQ) were filled by face-to-face interviews, as well anthropometric parameters (height, weight, WC) and blood pressures values were measured with respect to standard protocols. Body mass index is calculated as weight (kg) divided by the height square (m). Dietary intakes were evaluated by using three 24-hour recalls (two working days and one weekend day) collected at the beginning and end of the study. Nutritionist IV software, adjusted for Iranian foods, was used to analyze the data from dietary intake. At beginning and the end of trial, 10 mL of fasting venous blood samples intended for various laboratory variables measurements (FBS [fasting blood sugar], HbA1c [hemoglobin A1c], lipid profile, sCr and BUN) and fresh morning first-void urine samples intended for urine albumin and creatinine measurements, were taken from patients, and all laboratory procedures were performed according to conditions described earlier. The eGFR was calculated using MDRD equation.

Using random number table, the patients were randomly allocated into two groups (LdAGEs or Dd) in 1:1 fashion with 31 participants in each group (Figure 1). Patients and those involved in assessing outcomes were unaware of groups; thus, the study was double blind. Patients in both groups prescribed recommended diabetic diet adjusted to their calorie requirement. According to the ADA (American Diabetes Association) recommendation, the amount of 25–35 kcal per kg of body weight was considered, that 15-20% of this energy was provided from protein, 25%-30% from fat and 55-60% from carbohydrate with emphasis on carbohydrate sources with medium and low-glycemic index. In this diet, 14 grams of fiber per 1000 kcal was considered. Only patients in the LdAGEs group,

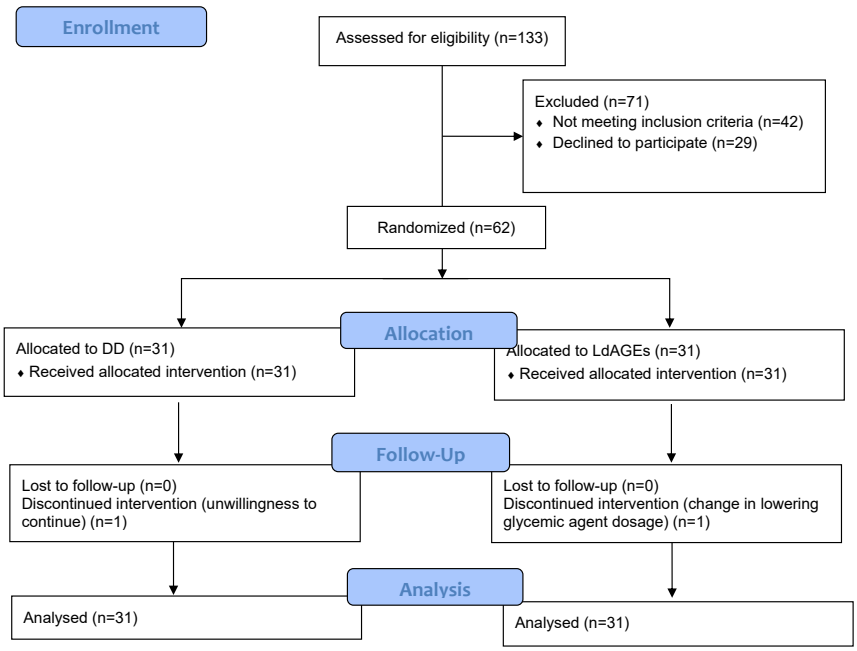

Figure 1. Flow diagram of the study.

instructed on how to reduce dietary AGEs intake to less than 15 000 kU/day (as average dAGEs intake). Reducing the time and temperature of cooking; specifically avoid exposing to dry heat similar to oven and deep frying, broiling, roasting and grilling; using cooking methods with higher amount of water content as in stewing, poaching, steaming and boiling; consuming bread without a crust, and finally soaking meats to acidic solutions like lemon juice and vinegar before cooking (marinating) can result in 40-50% dAGEs reduction via limiting new AGEs formation according to the practical guideline of Uribarri et al (9). All participants were asked to continue with their routine habits of physical activity and medication.

Statistical analysis

All analyses were performed using statistical package for social science (SPSS) software, version 16.0 (SPSS Inc., Chicago, IL, USA) and P values < 0.05 were considered statistically significant. Results were reported as mean + SD or number (percent). The Kolmogorov–Smirnov test was used to evaluate the distribution normality of data. Pearson chi-square test was applied for comparison of qualitative variables between the two groups. Independent t-test and analysis of covariance (ANCOVA) were used to compare the quantitative variables between groups. Also, paired sample Student's t test was used to compare the differences within groups between baseline and end values. To calculate the mean changes, the following equation was performed: [10-week values − baseline values].

Results

Over the study period, 133 subjects were evaluated regarding eligibility that 62 of whom met the inclusion criteria. One patient was excluded from the LdAGEs group because of change in lowering glycemic agent dosage, and one patient was excluded from the DD group because of unwillingness to continue the study. Therefore, 30 individuals completed the study in each of both groups; however, all 62 patients were analyzed based on the intention to treat method (31 patients in each group). No serious complaint was reported by the participants.

The baseline and clinical characteristics of the studied patients has been shown in Table 1. Of all, 25 patients (≈40%) were male and 37 patients (≈60%) were female. All demographic and baseline variables, including age, gender, weight, height, body mass index (BMI), waist circumference (WC), duration of T2DM (type 2 diabetes), anti-diabetic, anti-hyperlipidemia, anti-hypertension drugs usage, education, physical activity level, employment status, smoking habit, HbA1c, systolic blood pressure (SBP) and diastolic blood pressure (DBP), showed no significant differences between groups ($P>0.05$).

Table 2 shows dietary intakes of energy, macronutrients and AGEs at baseline and at the end of the study. There were no significant differences in energy and macronutrients intake between the two groups at baseline and at the end of the trial ($P>0.05$). Furthermore, comparison of mean changes between the two groups showed no significant difference. Dietary intake of AGEs was not significantly different between the two groups at baseline ($P=0.264$), but throughout the trial showed a significant greater reduction in the dAGEs group compared to the control group (-4668.87 ± 1649.30 kU/day versus -523.84 ± 1457.22 kU/day, $P<0.001$), and at the end of the trial, dietary intake of AGEs was significantly lower in dAGEs group compared to the DD group (7022.85 ± 1500.15 kU/day versus

Table 1. Baseline characteristics of participants

Variables	DD (n = 31)	LdAGEs (n = 31)	*P* value[a]
Age (years)	57.51 ± 8.72	58.91 ± 7.94	0.511
Gender (Male/Female)*	(12/19)	(13/18)	0.795[b]
Weight (kg)	73.91 ± 7.60	72.12 ± 7.11	0.342
Height (cm)	164.99 ± 8.87	166.15 ± 7.98	0.590
BMI (kg/m^2)	27.15± 4.52	26.12± 3.06	0.297
Waist circumference (cm)	101.53 ± 10.29	99.87 ± 9.66	0.515
Duration of T2DM (year)	13.62 ± 5.60	14.10 ± 6.01	0.746
Anti-diabetic drugs, n (%)*			
Mono therapy	2 (6.4%)	3 (9.6%)	0.836[b]
Two drugs	20 (64.5%)	18 (58.0%)	
Three drugs	9 (29.0%)	10 (32.2%)	
Anti-hyperlipidemia drugs (%)	30 (96.7%)	31 (100%)	1.00[c]
Educational level, n (%)*			
Under Diploma	23 (74.1%)	26 (83.8%)	0.762[d]
Diploma	7 (22.5%)	5 (16.1%)	
Higher than diploma	1 (3.2%)	0 (0.0%)	
Employed, n (%)*	5 (16.1%)	3 (9.6%)	0.448[b]
Active Smokers, n (%)*	1 (3.2%)	2 (6.4%)	0.553[b]
HbA_1c (%)	7.02 ± 1.11	6.88 ± 0.99	0.602
SBP (mmHg)	131.38 ± 10.72	132.59 ± 11.10	0.664
DBP (mmHg)	82.12 ± 9.41	81.87 ± 9.33	0.948
Anti-hypertensive drugs (%)	26 (83.8%)	28 (90.3%)	0.448[b]
Physical activity, n (%)*			
Mild	24 (77.4%)	23 (74.1%)	0.766[b]
Moderate	7 (22.5%)	8 (25.8%)	
High	0 (0.0%)	0 (0.0%)	

Abbreviations: BMI= body mass index; T2DM= Type 2 Diabetes Mellitus; HbA_1c= hemoglobin A_1c; SBP= Systolic blood pressure; DBP= Diastolic blood pressure.

Note: All outcomes reported as mean ± standard deviation except for those with * as number (percent); [a] Inter-group comparison of baseline variables was analyzed by independent *t* test; [b] Inter-group comparison of categorical variable was analyzed by chi-square test; [c] Inter-group comparison of categorical variable was analyzed by Fisher's exact test; [d] Inter-group comparison of categorical variable was analyzed by Freeman-Halton extension of Fisher's exact test.

11787.02 ± 2288.62 kU/day, $P < 0.001$).

Comparisons of metabolic factors before and after of trial are presented in Table 3. Baseline levels of FBS, HbA1c, TG, TC, HDL-c, LDL-c, sCr, BUN, urine Alb/Cr, eGFR, and urine albumin in the patients of LdAGEs and the DD groups were not significantly different. After ten weeks of intervention, significant changes were observed in levels of FBS, TG, HDL-c, sCr, eGFR within the LdAGEs group. Comparisons of mean differences showed significant greater increase in eGFR in the dAGEs group compared to the DD group (18.77 ± 20.99 mL/min/1.73 m^2 versus 1.57 ± 21.06 mL/min/1.73 m^2, $P = 0.002$).

Discussion

To the best of our knowledge, no prior study has compared standard DD with DD plus LAGEsd in clinical setting. The present study showed that the AGEs restricted diet for 10 weeks resulted in significant decrease in dAGEs intake and eGFR improvement. In our study, following DD, recommended by American Diabetes Association, leads to a reduction in total calorie intake, whether go with AGEs reduction guidelines or alone; suggesting over intake of calories by patients at baseline. No significant difference was observed in amount of calorie reduction between two groups. Moreover, both groups revealed a significant intrrgroup decrease in dietary intake of fat, carbohydrate, and protein since there were no significant differences between groups. These decreases in macronutrient intakes are consistent with observed total calorie reduction. Intake of dAGEs decreased significantly within LAGEsd group and in comparison with the DD group. In agreement with this finding, it has been reported that 8-weeks AGEs restricted diet in patients with metabolic syndrome resulted in 47% less dAGEs intake when compared to control group ($P < 0.001$) (11). Maybe implementation of a regular diet, not a standard DD, as a control group is a reason for greater reduction in dAGEs intake compared to our study, at least in part (47% versus 39%). Of note, our finding of marked differences in dAGEs intake in LAGEsd group showed patients'

Table 2. Dietary intake of participants before and after trial

Variables		DD (n=31)	LdAGEs (n=31)	*P* value[a]
Energy (kcal/d)	Baseline	2097.94± 276.15	2148.57± 278.56	0.475[b]
	End	1664.36±281.62	1699.84± 269.75	0.614
	MC	-433.58± 279.34	-440.73± 272.39	0.919
	P value[c]	<0.001	<0.001	
Carbohydrate (g/d)	Baseline	286.55± 33.91	293.55± 34.12	0.421[b]
	End	213.58± 32.14	212.20± 31.45	0.864
	MC	-72.97± 33.62	-81.35± 32.87	0.325
	P value[c]	<0.001	<0.001	
Fat (g/d)	Baseline	81.22± 12.88	84.45± 13.03	0.330[b]
	End	67.53± 11.61	72.64± 14.48	0.130
	MC	-13.69± 12.26	-11.81± 13.83	0.573
	P value[c]	<0.001	<0.001	
Protein (g/d)	Baseline	55.19± 6.46	53.58± 5.94	0.311[b]
	End	50.89± 5.94	51.32± 5.10	0.760
	MC	-4.30± 6.31	-2.26± 5.62	0.183
	P value[c]	<0.001	0.032	
Fiber (g/d)	Baseline	12.29± 3.64	11.77± 3.12	0.548[b]
	End	12.81± 4.01	12.75± 2.54	0.944
	MC	0.52± 3.98	0.98± 2.93	0.606
	P value[c]	0.472	0.072	
dAGEs (as CML, kU/day)	Baseline	12310.86± 2164.40	11691.72± 1993.87	0.246[b]
	End	11787.02± 2288.62	7022.85± 1500.15	<0.001
	MC	-523.84± 1457.22	-4668.87± 1649.30	<0.001
	P value[c]	0.054	<0.001	

Abbreviations: Dd= Diabetic diet; LdAGEs: Low dietary advanced glycation end products; dAGEs= Dietary advanced glycation end products; MC= Mean Changes.

Note: All outcomes reported as mean ± standard deviation; [a] Inter-group comparison of post-intervention and mean changes values were analyzed by ANCOVA adjusted for baseline values; [b] Inter-group comparison of baseline variables was analyzed by independent *t* test; [c] Intra-group comparison of baseline and end values of variable was analyzed by paired *t* test.

compliance to the LAGEsd protocol.

The findings of this study showed that 10 weeks of LAGEsd resulted in significant increase in the eGFR compared to DD ($P=0.002$), but failed to show any significant difference in sCr, BUN, urinary Alb/Cr, and urine albumin as compared to DN group. In consist with our study, in a meta-analysis by Baye et al (12), it has been reported that consumption of diets with low dAGEs increased eGFR compared to high AGEs diets (mean difference 1.45 mL/min/173 m^2, 95% CI 0.69 to 2.22). Notably, aforementioned meta-analysis showed merely small (mean 1.45 mL/min) increase in eGFR and resulted from only two studies (13,14), which both carried on non-diabetic patients without any apparent renal illness. More surprisingly, just the first study showed a significant difference in the eGFR between high- and low-AGE dietary groups (change from baseline; −0.8 ± 2.0 versus +2.1 ± 10.8 mL/min/173 m^2, $P=0.001$, respectively) (14), and the second study did not show any significant changes in eGFR (14). Thus, this clinically insignificant change in eGFR reported by Baye et al, warranted further researches to shed a light on effect of dAGEs restriction on measures of renal function.

Contradictory with present results, in a cross-over clinical trial published by Harcourt et al (15), urinary Alb/Cr were significantly improved following the LAGEsd in obese individuals (low- versus high-AGE diet: $P=0.02$), while no significant effect on urine albumin or sCr was observed. Regarding small sample size and single-sex samples, eleven healthy overweight males, as well as short duration of dietary intervention, two weeks each of low- and high-AGE diet separated by a 4-week wash-out period, necessitate caution in this findings' interpretation.

In this study, although FBS, TG, and HDL-c improved within LAGEsd group, but failed to show significant difference compared to the DN group. There are conflicting results that indicate LAGEd could improve glycemic status as well as lipid profile significantly. It has been reported that low calorie-AGEs diet improved FBS significantly ($P<0.01$) (11). The possible mechanism might be through the activation of AGEs receptor 1, disruption of RAGE signaling and expression of Sirtuin 1, a major part in insulin signaling and secretion (16,17). In agreement with our finding regarding lipid profile, insignificant changes of lipid profile levels after 8-week LAGEsd have been reported (11). It seems, clinical trials

Table 3. Changes in biochemical biomarkers of participants before and after trial

Variables		Baseline	End	*P* value[a]	MC
FBS (mg/dL)	Control	159.52 ± 34.57	150.44 ± 28.60	0.121	-9.08 ± 31.69
	LdAGEs	158.33 ± 32.00	139.43 ± 32.97	0.002	-18.90 ± 32.54
	P value[b]	0.888[c]	0.165		0.233
HbA_1c (%)	Control	7.02 ± 1.11	6.82 ± 1.31	0.372	-0.20 ± 1.23
	LdAGEs	6.88 ± 0.99	6.57 ± 0.92	0.082	-0.31 ± 0.96
	P value[b]	0.602[c]	0.388		0.696
TG (mg/dL)	Control	203.45 ± 100.61	211.26 ± 90.77	0.655	7.81 ± 96.52
	LdAGEs	218.86 ± 98.10	180.55 ± 95.34	0.035	-38.31 ± 97.14
	P value[b]	0.543[c]	0.198		0.065
TC (mg/dL)	Control	162.19 ± 39.33	158.19 ± 44.29	0.603	-4.00 ± 42.48
	LdAGEs	171.80 ± 39.33	172.44 ± 48.80	0.937	0.64 ± 44.86
	P value[b]	0.339[c]	0.233		0.677
HDL-c (mg/dL)	Control	39.83 ± 10.76	41.56 ± 12.19	0.403	1.73 ± 11.37
	LdAGEs	40.44 ± 11.12	55.97 ± 18.09	<0.001	15.53 ± 15.69
	P value[b]	0.827[c]	<0.001		0.409
LDL-c (mg/dL)	Control	112.14 ± 28.03	108.96 ± 25.78	0.519	-3.18 ± 27.15
	LdAGEs	107.14 ± 33.29	110.21 ± 30.15	0.596	3.07 ± 31.93
	P value[b]	0.524[c]	0.861		0.409
Serum creatinine (µmol/L)	Control	1.05 ± 0.32	1.03 ± 0.57	0.818	-0.02 ± 0.48
	LdAGEs	1.01 ± 0.36	0.80 ± 0.29	<0.001	-0.21 ± 0.33
	P value[b]	0.645[c]	0.049		0.074
BUN (mg/dL)	Control	25.29 ± 11.04	22.34 ± 16.10	0.235	-2.9 5± 13.56
	LdAGEs	26.60 ± 10.84	27.18 ± 10.25	0.762	0.58 ± 10.61
	P value[b]	0.639[c]	0.163		0.258
Urinary Alb/Cr (mg/g)	Control	150.93 ± 50.84	145.08 ± 46.90	0.506	-5.85 ± 48.39
	LdAGEs	145.10 ± 53.45	137.64 ± 52.73	0.440	-7.46 ± 53.09
	P value[b]	0.661[c]	0.559		0.901
eGFR (mL/min/1.73 $m^{2)}$	Control	65.16 ± 20.97	66.73 ± 21.23	0.068	1.57 ± 21.06
	LdAGEs	67.63 ± 19.69	86.40 ± 22.51	<0.001	18.77 ± 20.99
	P value[b]	0.634[c]	<0.001		0.002
Urine albumin (mg/L)	Control	90.55 ± 24.31	87.92 ± 28.70	0.581	-2.63 ± 26.27
	LdAGEs	86.23 ± 22.91	80.05 ± 25.42	0.163	-6.18 ± 24.11
	P value[b]	0.474[c]	0.257		0.581

Abbreviations: LdAGEs= Low dietary advanced glycation end products; MC= Mean changes; FBS= Fasting blood sugar; HbA_1c= Hemoglobin A_1c; TG= Triglyceride; TC= Total cholesterol; HDL-c= High-density lipoprotein cholesterol; LDL-c= Low-density lipoprotein cholesterol; BUN= Blood urea nitrogen, Urinary Alb/Cr= Urinary albumin to creatinine ratio; eGFR= Estimated glomerular filtration rate.
Note: n=31 in each group (DD, LdAGEs). All outcomes reported as mean ± standard deviation. [a] Intra-group comparison of baseline and end values of variable was analyzed by paired *t* test; [b] Inter-group comparison of post-intervention and mean changes values were analyzed by ANCOVA adjusted for baseline values; [c] Inter-group comparison of baseline variables was analyzed by independent *t* test.

with longer duration were able to observe significant improvements in lipid profile. For instance, Di Pino et al (18), reported significant reduction of lipid profile levels compared after 24-week of LAGEsd intervention in 62 prediabetes patients.

Conclusion

Our findings showed that the LAGEsd can ameliorate eGFR, and seems capable of clinical improvement in patients with DN, and LAGEsd plus DD is superior to DD alone. Notably, dAGE intake restriction is safe, and easy to implement. We suggest incorporating LAGEsd guidelines to a normal part of medical nutrition therapy for diabetic patients with DN.

Limitations of the study

Our study limitations were single center study, and lack of patients stratifying in terms of weight, BMI, and clinical status. Further studies with longer duration and larger sample sizes are recommended.

Authors' contribution

AD, ZM, and SEJ conducted the research. AD, ZM, and MF developed the protocol and performed it. Critical revision of the manuscript for important intellectual content was performed by AD and ZM. DA and AA prepared the final

manuscript. All authors read and signed the final paper. All authors read and signed the final manuscript.

Conflicts of interest

The authors declared no conflicts of interest

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The institutional ethical committee at Shiraz University of Medical Sciences approved all study protocols (IR.SUMS.REC.1398.798). The study protocol was registered in the Iranian Registry of Clinical Trials (identifier: IRCT20191004044979N1; https://en.irct.ir/trial/42914). Accordingly, written informed consent was taken from all participants before any intervention. This study was extracted from Ph.D thesis of Arash Dashtabi at this university (proposal # 97-01-84-18287). Moreover, Ethical issues (including plagiarism, data fabrication and double publication) were completely observed by the authors.

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