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ORIGINAL ARTICLE

The relationship between treatment response and precursors of advanced glycation end-products in type 2 diabetes: a prospective case-control study

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Abstract

Background In glycolysis, hydroxyl radicals emerge via the auto-oxidation pathway in a status of hyperglycemia, and by binding to proteins or lipids, form advanced glycation end-products (AGE). Glyoxal (GO) and methylglyoxal (MGO) are precursors of AGEs. The aim of this prospective, case-control study was to investigate the difference in levels of AGE precursors in patients with and without diabetes and to investigate the relationship between the change in rates of the AGE precursors and treatment in diabetic patients.

Methods The study included 21 treatment-naive patients diagnosed with type 2 diabetes and 21 age and gender-matched healthy control subjects. Throughout an observation period of 3 months, the diabetic patients were started on anti-diabetic treatment and used no additional treatment or supplementary products. The GO and MGO levels were examined with the HPLC method.

Results The GO and MGO levels were determined to be 1.74 and 0.024μg/mL respectively in the diabetic patients and 1.14 and 0.002 μg/mL in the control group. After 3 months of treatment, a statistically significant decrease compared to pre-treatment values was determined of 0.684 μg/mL in GO and 0.01989 μg/mL in MGO (p=0.001, p<0.01). No statistically significant relationship was determined between the change in HbA1c at 3 months compared to pre-treatment and the changes in GO and MGO (p>0.05).

Conclusion The level of AGE precursors was found to be significantly higher in diabetic patients than in the healthy control group. Although there was a significant decrease in AGE precursors when the HbA1c level fell in patients who followed anti-diabetic treatment and diabetes-appropriate diet recommendations, this decrease was at different rates in each patient, which demonstrated that the HbA1c level is not the only determinant of AGE level in plasma. It can be concluded that with appropriate diet and antidiabetic treatment, significant reductions can be obtained in several risk factors which increase the level of AGE precursors.

Keywords Advanced glycation end-products · Glyoxal · Methylglyoxal · Diabetes

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Introduction

Diabetes mellitus, which is basically seen as a result of insulin deficiency or insufficient insulin function, is a chronic metabolic disease characterized by impairments in the metabolism of carbohydrates, fats, and proteins, with the main finding of chronic hyperglycemia [1].

In glycolysis, hydroxyl radicals emerge via the auto-oxidation pathway in a status of hyperglycemia, and by binding to proteins or lipids, form advanced glycation end-products (AGEs). This is a non-enzymatic reaction and causes oxidative stress in the environment where there are AGEs [2, 3]. Glyoxal (GO) and methylglyoxal (MGO) are precursors of AGEs and most often occur as a result of lipid peroxidation, glucose autoxidation, and microbial fermentation [4, 5]. AGEs, which are glycotoxins, are thought to play a role in the pathogenesis of many chronic diseases, especially diabetes [6, 7]. By binding with cross-links to various body proteins or cell surface receptors, these molecules change their structures and functions. All of these events cause oxidative stress and inflammation [8]. It is accepted that oxidative stress has a significant role in the pathogenesis of complications developing associated with diabetes [9].

Glycated hemoglobin A1c (HbA1c), which is used for the diagnosis of diabetes, is an example of a glycated protein that shows average blood sugar concentrations in the previous 2- to 3-month period. HbA1c has also been shown to be correlated to complications that develop associated with diabetes [10–12]. The aim of this prospective, case-controlled, observational study was to investigate the relationship between the levels of AGE precursors and diabetes with real-life data. The difference between levels of AGE precursors was examined in patients with and without diabetes and the relationship between the change in rates of the AGE precursors and treatment in diabetic patients. It was believed that significant results would be obtained from this study that would be able to shed light on the estimated prognosis course and follow-up of diabetes.

Materials and methods

This prospective study was approved by the Ethics Committee of Bakirköy Sadi Konuk Training and Research Hospital, and in accordance with the Helsinki Declaration and its later amendments or comparable ethical standards (No:2019/312). Written informed consent was obtained from all the participants after a detailed explanation of the study protocol and it was explained that they could leave the study at any time they wished.

Study design and participants

The study included patients aged >18 years, who were being followed up in the General Internal Polyclinic between January 2019 and December 2019, had a new diagnosis of type 2 diabetes, were not yet receiving any antidiabetic treatment and had HbA1c value >8. Study exclusion criteria were defined as the presence of additional disease other than regulated hypertension, the emergence of any new disease throughout the 3-month follow-up period, or starting any additional treatment, including antibiotics, other than the antidiabetic treatment prescribed.

A control group was composed of 21 healthy volunteers, matched for age and gender to the patient group, selected from those presenting at the General Internal Polyclinic for a general check-up, with no insulin resistance, diabetes, or any other disease, including hypertension. From both groups, subjects were excluded if they had any malignancy, were using drugs that would interact with the study tests, if they had chronic diarrhea or malabsorption syndrome for any reason, inflammatory disease, or active infection, if they were smokers, were obese (BMI>30), or were taking supplementary products.

The patients diagnosed with type 2 diabetes in Group 1 were given information about the disease, were informed about the standard nutrition appropriate to diabetes and were instructed that they would maintain a diabetes-appropriate diet throughout the 3 months, not follow a different diet, not take any supplementary products, and not take any drugs other than the prescribed medication. The patients were instructed that in any unusual circumstances or when there was a need for additional drugs, they should contact the researchers and in such an event they would be withdrawn from the study.

On the day of the first presentation at the hospital and at the 3-month follow-up examination, a 2-ml venous blood sample was taken by an experienced nurse in the morning after at least 8 hours fasting. The HbA1c measurement was performed with the HPLC method on an Adams Premier Hb 9210 device (Trinity Biotech, USA).

Blood samples were taken from 40 patients initially included in the patient group. Then, a total of 19 were excluded; 5 patients had an infection that required antibiotics, 6 wished to take supplementary products, 3 started to follow a special diet program for various reasons, and 5 could not be contacted after 3 months. The blood samples taken before treatment were disposed of appropriately, and the study analysis continued with a patient group of 21 subjects.

Glyoxal, methylglyoxal, methanol, sodium acetate, 4-nitro-1,2-phenylenediamine, acetonitrile, fructose, glucose, and sucrose were obtained from Sigma-Aldrich (St. Louis, MO, USA).

HPLC determination of GO and MGO

The HPLC conditions in our study were referenced to the HPLC conditions detailed in the study of Cengiz et al. [13]. Determination of the most potent precursors of AGEs in chips,

crackers, and breakfast cereals by HPLC using precolumn derivatization with 4-nitro-1, 2-phenylenediamine.

A Shimadzu SPD-20A UV/VIS detector (Shimadzu Corporation, Kyoto, Japan) and a Shimadzu LC 20AT pump were used when setting up the HPLC system. The mobile phase consisted of methanol:water:acetonitrile (42:56:2, v/v/v) and had a wavelength of 255 nm. GO and MGO were separated with an Inersil ODS-3, 250 × 4.6 mm, 5 μm column with a flow rate of 1 mL/min.

Quality assurance/quality control (QA/QC)

AOAC guidelines [14] were used for method validation of GO and MGO analysis. Linearity was determined between 0.2 and 2.0 μg/mL for GO and MGO using five levels of calibration in triplicate. The precision of GO and MGO was evaluated for repeatability and reproducibility by analyzing one of the test samples ten times on the same day and three times on different 3 days, respectively. In addition, 2 μg/mL of GO and MGO were spiked to the test sample to check the recovery of the method. To monitor the quality control of the analyzes, the quality control material prepared in the laboratory condition was analyzed with each batch of samples. The quality control samples were prepared as follows: 1 μg/mL of GO and MGO were spiked to the test sample used for the recovery and analyzed ten times. Then, the average value was calculated with standard deviation (SD) using one-way analysis of variance (ANOVA; $p < 0.05$, Tukey's test). The upper and lower acceptable warning limits are determined by calculating the average ±2SD values, while the lower and upper precaution limits are determined by calculating the average±3SD values and recorded in the Quality Control Graph Chart [15]. All analyses were performed in triplicate ($n = 3$).

Statistical analysis

Data obtained in the study were analyzed statistically using the NCSS 2007 software (Number Cruncher Statistical System, Kaysville, UT, USA). The conformity of quantitative data to normal distribution was assessed with the Shapiro-Wilk test and graphic examinations. In the comparisons of two groups of quantitative data, the Student's t test was applied to data showing normal distribution and the Mann-Whitney U test when the data did not show normal distribution. The Wilcoxon signed-rank test was applied in the intra-group comparisons of quantitative data not conforming to normal distribution. In the comparison of qualitative data, the Pearson Chi-square test was used. Relationships between quantitative data were evaluated using Spearman correlation analysis. A value of $p<0.05$ was accepted as statistically significant.

Power analysis was applied with the G*Power (version 3.1.7) software to determine the sample number. In the pilot study applied to 10 subjects in each group, power was calculated as 0.928 so to obtain 80% power at $\alpha=0.05$, it was calculated to be necessary to have a total of 40 subjects as 20 in each group.

Results

The evaluation was made of a total of 42 subjects, comprising 26 (61.9%) females and 16 (38.1%) males with a mean age of 54.45 years (range, 39–78 years) (Table 1).

In Group 1, 10 patients with a tendency for hypertension were taking angiotensin-converting enzyme inhibitor (ACEi) treatment. All the patients diagnosed with diabetes were started on the treatment of metformin and DPP4 inhibitor. Insulin treatment was added to this treatment for 8 patients.

A statistically significant difference was determined between the groups in respect of the GO and MGO measurements ($p<0.01$). The GO and MGO levels were determined to be statistically significantly higher at 1.74 and 0.024μg/mL respectively in the diabetic patients compared to 1.14 and 0.002 μg/mL in the control group (Table 2).

After 3 months of treatment, a statistically significant decrease compared to pre-treatment values was determined of 0.684 μg/mL in GO and 0.01989 μg/mL in MGO ($p=0.001$, $p<0.01$).

A statistically significant decrease of mean 2.90 units was determined in the HbA1c measurements at 3 months compared to the pre-treatment values ($p=0.001$, $p<0.01$) (Table 3).

Table 1 Age and gender distribution by groups

		Group 1 (n=21)	Group 2 (n=21)	Total
Age (year)	*Min–max (median)*	39–71 (52)	41–78 (52)	39–78 (52)
	Mean±SD	54.10±9.43	54.81±9.93	54.45±9.57
Gender	**Women (%)**	13	13	26 (61.9)
	Men (%)	8	8	16 (38.1)

SD standard deviation

Table 2 Comparison of glyoxal and methylglyoxal levels by groups

		Group 1 (*n*=21)	Group 2 (*n*=21)	*p*
Glyoxal	*Min–max (median)*	0.87–4.2 (1.5)	0.3–1.8 (1.12)	[c]***0.004****
μg/mL	*Mean±SD*	1.74±0.79	1.14±0.35	
Methylglyoxal	*Min–max (median)*	0.006–0.203 (0.011)	0.0001–0.008 (0.0008)	[c]***0.001****
μg/mL	*Mean±SD*	0.024±0.045	0.002±0.003	

[c] Mann-Whitney *U* test, *$p<0.01$, *SD* standard deviation

The mean HbA1c of the control group without any additional disease, diabetes, or prediabetes was 4.8±0.18 (range 4–5.4%).

No statistically significant relationship was determined between the change in HbA1c at 3 months compared to pre-treatment and the changes in GO and MGO ($p>0.05$) (Table 4).

No statistically significant relationship was determined in the pre-treatment and post-treatment GO and MGO values according to the presence or absence of hypertension in the patient group ($p>0.05$) (Table 5).

Discussion

In addition to the formation of AGE by hyperglycemia, the intake of food with a high amount of AGE can cause insulin resistance and ultimately diabetes. In the most striking study on this subject, insulin resistance was seen to develop much earlier in mice fed with feed containing high amounts of AGE compared to mice fed a normal diet [16]. Several studies have shown AGE of exogenous origin to be associated with a decreased peripheral insulin response [17, 18].

The current study results demonstrated significantly higher levels of GO and MGO, which are AGE precursors, in the diabetic patients compared to the healthy control subjects with no diabetes and no insulin resistance. In the light of these findings and those of previous studies, it can be said that both GO and MGO were taken exogenously and the hyperglycemia in these patients were effective in the high GO and MGO levels determined in the current study. The effect of patient age on AGE level was taken into consideration [19] and care was taken to match the ages of the two groups. As the GO and MGO levels could be higher in smokers [20], any subjects who smoked were not included in the study.

There is known to be a relationship between tissue damage of high blood levels of AGEs and diabetic complications [21, 22]. Just as for a reduction in HbA1c, a reduction in serum AGE amounts with treatment or lifestyle changes could be a predictor of a positive response to treatment and a disease course with fewer complications. In the patient group of this study, significant reductions were observed in the GO, MGO, and HbA1c levels with antidiabetic treatment and the recommended diabetes-appropriate diet. In a previous study, type 1 and type 2 diabetes patients were given a low AGE level diet for 6 weeks, after which there was seen to be a reduction in inflammation markers together with reduced serum AGE levels [23]. In the current study, a significant decrease was determined in GO and MGO in Group 1 with diet and treatment, but it is not known to what extent this reduction can be associated with the antidiabetic drugs or the reduction in hyperglycemia with the dietary changes.

An interesting point of the current study findings was that there was no correlation between the pre-treatment HbA1c level and the reduction obtained in HbA1c with treatment and the reduction in GO and MGO levels. This demonstrates

Table 3 Comparison of glyoxal, methylglyoxal, and HbA1c levels in Group 1 before and at the 3rd month of treatment

Group 1 (*n*=21)		Before treatment	3rd month	Difference	*p*
Glyoxal μg/mL	*Min–max (median)*	0.87–4.2 (1.5)	0.4–1.61 (1.0)	0.10–3.23 (0.44)	[d]***0.001****
	Mean±SD	1.74±0.79	1.05±0.32	0.684±0.71	
Methylglyoxal μg/mL	*Min–max (median)*	0.006–0.203 (0.011)	0.0001–0.0096 (0.00001)	0.0004–0.20299 (0.00679)	[d]***0.001****
	Mean±SD	0.024±0.045	0.0025±0.0036	0.01989±0.046	
HbA1c %	*Min–max (median)*	8–15.8 (10)	6.1–9.2 (7.2)	0.3–8.6 (2.2)	[d]***0.001****
	Mean±SD	10.25±1.97	7.36±1.04	2.90±2.11	

[d] Wilcoxon signed-rank test, **$p<0.01$, *SD* standard deviation

Table 4 The relationship between HbA1c changes and glyoxal and methylglyoxal changes

	Difference HbA1c	
	r	*p*
Difference glyoxal	0.014	*0.951*
Difference methylglyoxal	0.143	*0.736*

r Spearman's correlation coefficient

that the blood glucose level reflected by the HbA1c level is not the only factor affecting the GO and MGO levels.

Studies conducted with the aim of decreasing the AGE level have shown interest in the blockage associated with the renin-angiotensin-aldosterone system in addition to nutrition with antioxidant molecules or a diet poor in AGE. The use of olmesartan (angiotensin II receptor blocker: ARB) and temocaprilate (an ACEi), which are antihypertensive agents, has been shown to have AGE-lowering effects. The effect mechanism is thought to be that these agents can have an effect by retaining carbonyl components [24]. In another study, it was demonstrated that the ARB valsartan could improve in vitro protein glycation and oxidation in various conditions and this was thought to be associated with the positive effect on the redox balance and the reduction in protein glycation [25].

In contrast to these data in the literature, no significant difference was seen between those with and without hypertension in the current study population in respect of the level of AGE precursors before or after treatment. The patients in this study were taking ACEi as an antihypertensive drug and the basic design of the study was not for the evaluation of the effect of antihypertensive drugs. Throughout the follow-up period of the study, no patient started any new antihypertensive drug or changed the dose of their existing medication. Only patients with regulated hypertension were accepted in the study. To be able to draw clearer conclusions about the effects of antihypertensive treatment on AGE precursor levels, there is a need for further studies designed accordingly with a greater number of patients.

The main limitation of this study was that although it was planned to include 40 patients, 21 could not continue for various reasons. Although the selection criteria were applied as far as possible in respect of comorbidities, smoking, and BMI, evaluations were made according to the patients' own statements of dietary habits and whether or not they were taking additional drugs.

In conclusion, with real-life data in this prospective, case-controlled study, it was shown that AGE precursor levels are significantly higher in diabetic patients than in healthy control subjects. When the HbA1c level fell in patients with antidiabetic treatment and diabetes-appropriate diet recommendations, although there was a significant decrease in the level of AGE precursors, this decrease was at different rates in each patient. This indicated that the HbA1c level is not the only determinant of plasma AGE level. Patient age, genetic factors, dietary habits, microbiota, and many other reasons such as these may have an effect on the plasma AGE level. In this study, no special diet other than a standard diabetic patient diet was applied. If factors that can be changed are focussed on, it can be said that in parallel with the reduction in HbA1c obtained with appropriate antidiabetic treatment and diet, significant reductions could be obtained in several risk factors that increase the level of AGE precursors.

Table 5 Glyoxal and methylglyoxal levels according to hypertension

		Hypertension		*p*
		No (*n*=11)	**Yes (*n*=10)**	
Glyoxal-1 μg/mL	*Min–max (median)*	0.203–4.23 (1.4595)	0.872–3.076 (1.423)	*0.36*
	Mean±SD	1.9178±0.94	1.5849±0.63	
Glyoxal-2 μg/mL	*Min–max (median)*	0.616–1.49 (0.9925)	0.374–1.612 (0.946)	*0.31*
	Mean±SD	1.068±0.3	1.014±0.37	
Methylglyoxal-1 μg/mL	*Min–max (median)*	0.0064–0.094 (0.508)	0.203–0.059 (0.0068)	*0.7*
	Mean±SD	0.018±0.026	0.264±0.0586	
Methylglyoxal-2 μg/mL	*Min–max (median)*	0.00001–0.0087 (0.00001)	0.00001–0.0096 (0.00001)	*0.83*
	Mean±SD	0.0021±0.003	0.0029±0.0041	

[c] Mann-Whitney *U* test, *SD* standard deviation

Author contribution All authors contributed to the study conception and design, material preparation, data collection and analysis. All authors read and approved the final manuscript.

Declarations

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Bakirköy Sadi Konuk Training and Research Hospital (No:2019/312).

Consent to participate Informed consent was obtained from all individual participants included in the study.

Conflict of interest The authors declare no competing interests.

References

1. Petersmann A, Müller-Wieland D, Müller UA, Landgraf R, Nauck M, Freckmann G, Heinemann L, Schleicher E. Definition, classification and diagnosis of diabetes mellitus. Exp Clin Endocrinol Diabetes. 2019;127(S01):1–7. https://doi.org/10.1055/a-1018-9078.
2. Chertow B. Advances in diabetes for the millennium: vitamins and oxidant stress in diabetes and its complications. +MedGenMed. 2004; 6(Suppl 3):4. PMID: 15647709 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1474834/
3. Johansen JS, Haris AK, Rychly DJ, Ergul A. Oxidative stress and the use of antioxidants in diabetes: linking basic science to clinical practice. Cardiovasc Diabetol. 2005;4:5. https://doi.org/10.1186/1475-2840-4-5.
4. Niyati-Shirkhodaee F, Shibamoto T. Gas chromatographic analysis of glyoxal and methylglyoxal formed from lipids and related compounds upon ultraviolet irradiation. J Agric Food Chem. 1993;41(2):227–30. https://doi.org/10.1021/jf00026a016.
5. Yamaguchi M, Ishida J, Xuan Z, Nakamura A, Yoshitake T. Determination of glyoxal, methylglyoxal, diacethyl, and 2, 3-pentanedione in fermented foods by high-performance liquid chromatography with fluorescence detection. J Liq Chromatogr Relat Technol. 1994;17(1):203–11. https://doi.org/10.1080/10826079408013445.
6. Huebschmann AG, Regensteiner JG, Vlassara H, Reusch EB. Diabetes and advanced glycoxidation end products. Diabetes Care. 2006;29:1420–32. https://doi.org/10.2337/dc05-2096.
7. Bohlender JM, Franke S, Stein G, Wolf G. Advanced glycation end products and the kidney. Am J Physiol Ren Physiol. 2005;289:645–59. https://doi.org/10.1152/ajprenal.00398.2004.
8. Sharma C, Kaur A, Thind SS, Singh B, Raina S. Advanced Glycation End-products (AGEs): an emerging concern for processed food industries. J Food Sci Technol. 2015;52:7561–76. https://doi.org/10.1007/s13197-015-1851-y.
9. Rahimi R, Nikfar S, Larijani B, Abdollahi M. A review on the role of antioxidants in the management of diabetes and its complications. Biomed Pharmacother. 2005;59:365–73. https://doi.org/10.1016/j.biopha.2005.07.002.
10. Nathan DM, Turgeon H, Regan S. Relationship between glycated haemoglobin levels and mean glucose levels over time. Diabetologia. 2007;50(11):2239–44. https://doi.org/10.1007/s00125-007-0803-0.
11. American Diabetes Association. Classification and diagnosis of diabetes. Diabetes Care. 2015;38(Suppl 1):8–16. https://doi.org/10.2337/dc15-S005.
12. World Health Organization. Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus: abbreviated report of a WHO consultation. Geneva: WHO, 2011. https://www.who.int/diabetes/publications/report-hba1c_2011.pdf
13. Cengiz S, Kişmiroğlu C, Çebi N, Çatak J, Yaman M. Determination of the most potent precursors of advanced glycation end products (AGEs) in chips, crackers, and breakfast cereals by high performance liquid chromatography (HPLC) using precolumn derivatization with 4-nitro-1,2-phenlenediamine, Microchem J 2020;158: 105170. ISSN 0026-265X, https://doi.org/10.1016/j.microc.2020.105170.
14. AOAC International. Appendix K: Guidelines for Dietary Supplements and Botanicals, Part 1 AOAC Guidelines for Single-Laboratory Validation of Chemical Methods for Dietary Supplements and Botanicals. Association of Official Analytical Chemists, Gaithersburg, MD, USA: AOAC International. 2002. https://members.aoac.org/404.aspx?aspxerrorpath=/AOAC_Prod_Imis/404.aspx
15. Montgomery DC. Statistical quality control. Wiley Global Education; 2012. ISBN: 978-1-118-53137-2. https://www.wiley.com/en-ru/Statistical+Quality+Control%3A+A+Modern+Introduction%2C+7th+Edition+International+Student+Version-p-9781118531372
16. Cai W, Ramdas M, Zhu L, Chen X, Striker GE, Vlassara H. Oral advanced glycation endproducts (AGEs) promote insulin resistance and diabetes by depleting the antioxidant defenses AGE receptor-1 and sirtuin 1. Proc Natl Acad Sci U S A. 2012;109:15888–93. https://doi.org/10.1073/pnas.1205847109.
17. Beyan H, Riese H, Hawa MI, Beretta G, Davidson HW, Hutton JC, Burger H, Schlosser M, Snieder H, Boehm BO, Leslie RD. Glycotoxin and autoantibodies are additive environmentally determined predictors of type 1 diabetes: a twin and population study. Diabetes. 2012;61:1192–8. https://doi.org/10.2337/db11-0971.
18. Uribarri J, Cai W, Ramdas M, Goodman S, Pyzik R, Chen X, Zhu L, Striker GE, Vlassara H. Restriction of advanced glycation end products improves insulin resistance in human type 2 diabetes: potential role of AGER1 and SIRT1. Diabetes Care. 2011;34:1610–6. https://doi.org/10.2337/dc11-0091.
19. Moldogazieva NT, Mokhosoev IM, Mel'nikova TI, Porozov YB, Terentiev AA. Oxidative stress and advanced lipoxidation and glycation end products (ALEs and AGEs) in aging and age-related diseases. Oxidative Med Cell Longev. 2019:3085756. https://doi.org/10.1155/2019/3085756 PMID: 31485289; PMCID: PMC6710759.
20. Nicholl ID, Stiit AW, Moore JE, Ritchie AJ, Archer DB, Bucala R. Increased levels of advanced glycation endproducts in the lenses and blood vessels of cigarette smokers. Mol Med 1998; 4:594–601. [PubMed: 9848076]
21. Huebschmann AG, Regensteiner JG, Vlassara H, Reusch JE. Diabetes and advanced glycoxidation end products. Diabetes Care. 2006;29:1420–32. https://doi.org/10.2337/dc05-2096.
22. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature. 2001;414:813–20. https://doi.org/10.1038/414813a.
23. Vlassara H, Cai W, Crandall J, Goldberg T, Oberstein R, Dardaine V, Peppa M, Rayfield EJ. Inflammatory mediators are induced by dietary glycotoxins, a major risk factor for diabetic angiopathy. Proc Natl Acad Sci U S A. 2002;99:15596–601. https://doi.org/10.1073/pnas.242407999.
24. Schalkwijk CG. Therapeutic interventions in the glyc(oxid)ation pathway. Immunol Endocr Metab Agents Med Chem. 2007;7:57–68. https://doi.org/10.2174/187152207779802491.
25. Mil KM, Gryciuk ME, Pawlukianiec C, Żendzian-Piotrowska M, Ładny JR, Zalewska A, Maciejczyk M. Pleiotropic properties of valsartan: do they result from the antiglycooxidant activity? Literature Review and In Vitro Study. Oxidative Med Cell Longev. 2021;2021:20. https://doi.org/10.1155/2021/5575545.