Medical Principles and Practice

Original Paper

Med Princ Pract 2025;34:87–95
DOI: 10.1159/000541879

Received: May 3, 2024
Accepted: October 7, 2024
Published online: October 9, 2024

The Role of Advanced Glycation End Products in Saphenous Vein Graft Failure

Alkame Akgümüş[a] Bedrettin Boyraz[b] Ahmet Balun[a]

[a]Department of Cardiology, Faculty of Medicine, Bandırma Onyedi Eylül University, Balıkesir, Turkey;
[b]Cardiology Department, Medicalpark Hospital, Mudanya University, Bursa, Turkey

Highlights of the Study

- Advanced glycation end products (AGEs) cause endothelial dysfunction by reducing the availability of vasodilator NO and the production of endothelin-1, a potent vasoconstrictor.
- We observed that the levels of AGEs measured by skin autofluorescence were significantly higher in patients with a previous history of coronary artery bypass grafting and saphenous vein graft failure.

Keywords
Advanced glycation end products · Skin autofluorescence · Saphenous vein graft failure · Coronary artery bypass surgery

Abstract

Objective: We aimed to investigate the relationship between advanced glycation end product (AGE) levels in patients with saphenous vein graft (SVG) failure and in patients without SVG failure. ***Subjects and Methods:*** In our study, 55 patients with a history of previous coronary artery bypass grafting (CABG) surgery, who subsequently underwent coronary angiography for any reason and were found to have either SVG occlusion or significant lesions, were included as study patients. Additionally, 55 patients who have had CABG surgery without SVG failure for at least 1 year served as the control group. AGE values of the patients were measured using the skin autofluorescence method. ***Results:*** In our study results, we observed a significant difference in AGE levels between the two groups of patients with similar demographic characteristics (SVG failure groups AGE 3.2 [2.8–3.6] vs. control groups AGE 2.4 [2.1–2.7] $p < 0.001$). In the receiver operating characteristic curve analysis, we determined the ability of AGE levels to detect SVG failure with an area under the curve of 0.869. We found that in patients with AGE >3, it could detect SVG failure with a sensitivity of 70.9% and a specificity of 87.3%. ***Conclusions:*** Our results demonstrate that AGE levels can predict SVG failure risk inexpensively, easily, and quickly.

karger@karger.com
www.karger.com/mpp

Correspondence to:
Alkame Akgümüş, aakgumus@bandirma.edu.tr

Introduction

Coronary artery disease (CAD) caused by atherosclerosis is a leading cause of illness and death in developed nations. Each year, over a million individuals worldwide succumb to cardiovascular illness. For those with appropriate CAD, coronary artery bypass graft (CABG) surgery offers significant symptom relief and a good long-term prognosis. CABG surgery is typically recommended if a patient has left main coronary artery disease, 3-vessel disease, and proximal left anterior descending coronary artery involvement with 2-vessel disease and left ventricular systolic dysfunction. However, the long-term success of CABG is limited by insufficiency in saphenous vein grafts (SVGs). Despite the increased use of artificial arterial grafts, SVG is still commonly used in most CABG patients due to the need for multiple grafts and its ease of accessibility [1]. The cause of SVG failure is not fully understood, but possible mechanisms include thrombosis (within the first month), intimal hyperplasia (within 1 month to 1 year after surgery), and accelerated atherosclerosis (late period) [2]. Favaloro [3] discovered the first SVG for CABG. Since then, SVGs have been routinely used, but occlusion of the SVG has become a serious problem. Studies have been conducted to understand the pathologies that develop in the SVG, and efforts have been made to increase patency rates. The rate of SVG occlusion is approximately 15% in the first year after CABG surgery, 1–2% per year between the first and sixth years, and 4% per year up to the tenth year [4]. After 10 years, the SVG patency rate is around 60%, and only 50% of the patent SVGs do not have significant stenosis. Within the first year after the CABG, angina relapses in 20% of patients, and 4% annually within the next 5 years due to diseases developed in the SVGs and pathologies in the native veins [4]. The atherosclerotic plaques causing SVG occlusions are more diffuse and fragile, contain more inflammatory and foam cells, have a small fibrous capsule, and are relatively less calcified compared to the native vessels [5].

Advanced glycation end products (AGEs), are produced in the human body through the Maillard reaction. Introduced by Maillard in 1912, AGE for the first time as the "browning reaction" has been defined. AGEs are complex, sequential, and nonenzymatic reaction products [6]. Chronic accumulations of AGEs produced by enzymatic glycation have been shown in previous studies to be predictive of cardiovascular and all-cause mortality in patients with diabetes and cardiovascular or renal disease. AGE levels may be an indicator of the patient's metabolic, inflammatory, and pro-atherogenic status and may also play a role in pathophysiology [7].

Cardiovascular disease is contributed to by AGE through two mechanisms: receptor-mediated and non-receptor-mediated interactions [8]. In the receptor-mediated mechanism, AGE binds to receptors on cell surfaces, activating the signaling mechanism for various cells. The receptor of AGE (RAGE) is one of the most studied receptors and is expressed on many cell surfaces that contribute to atherosclerosis development, including vascular endothelium, vascular smooth muscle cells, lymphocytes, monocytes, and macrophages [9].

Despite advances in the field of health, especially in the diagnosis and treatment of CAD, cardiovascular disease-related deaths continue to be the main cause all over the world. Increasing technology in parallel with the developments in the field of health has resulted in less mobility in humans of today and has thus contributed to an increase in the risk of CAD. In addition, there have been developments in the food sector such as different types of food, different cooking methods, and the use of different chemicals to prevent food from spoilage. In our study, we aimed to measure the AGE levels that have the potential to cause SVG failure in patients who have had the CABG surgery and to investigate whether AGE levels have an effect in patients with SVG failure.

Materials and Methods

This is a case-control study and has been carried out after obtaining approval from the Ethics Committee. The study does not contain descriptive personal information of patients. The study included 55 patients with a history of previous CABG surgery, who subsequently underwent coronary angiography for any reason and were found to have either SVG occlusion or significant lesions, and these were included as the study patients. Additionally, 55 patients who had undergone CABG surgery without SVG lesions for at least 1 year served as the control group. 100% occlusions and stenoses requiring revascularization of 70% or more were considered SVG failure. Patients with SVG lesions less than 70%, glomerular filtration rate value <60, liver failure, active infection, and malignancy were excluded from the study. The criteria used for patient selection are presented in Figure 1.

The demographic information of patients in both groups, including comorbidities, smoking habits, cardiac medical treatments, body mass index, gender, and age, was recorded from their files and obtained directly from the patients themselves. The time elapsed since the patients' CABG surgeries and the time until SVG failure were calculated and recorded. The measurement of

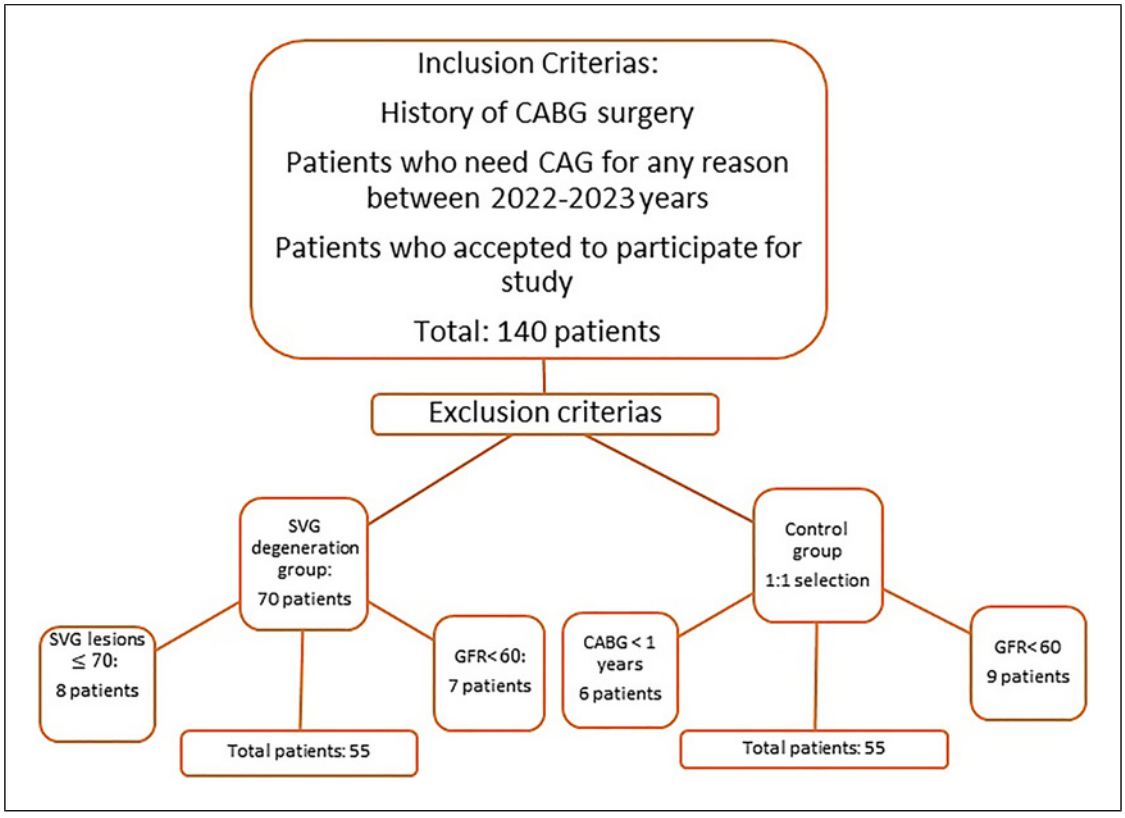

Fig. 1. Patient selection.

patients' AGE levels was performed using the AGE reader™ (Diagnoptics Technologies B.V., Groningen, The Netherlands) at the volar surface of the right forearm, 10–15 cm above the wrist, as described by the manufacturer, using the skin autofluorescence (SAF) method, and the measurements were recorded. With this device, the area measured was illuminated with a wavelength of 300–420 nm. The data reflected from the skin were measured with a spectrometer. Autofluorescence was calculated in arbitrary units by dividing the average light intensity emitted per nm in the range 420–600 nm by the average light intensity emitted per nm in the range 300–420 [10]. The healthcare personnel conducting the measurements did not know which group the patient belonged to, ensuring the impartiality of the data.

Statistical analysis was performed using SPSS 23 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.) and STATA 17 (Stata Corp. 2021. Stata Statistical Software: Release 17. College Station, TX: Stata Corp LLC) software. Categorical variables were compared using the chi-square and Fisher's exact tests, and the data were summarized as numbers (percentages). Numeric variables were first subjected to normality and variance analysis using the Kolmogorov-Smirnov test. Variables that did not show normality were compared using the non-parametric Mann-Whitney U test, and the results were summarized as median (25–75% interquartile range). Variables showing normal distribution were evaluated using the Student's *t* test, and the data were summarized as mean ± standard deviation. Receiver operating characteristic curve analysis was conducted to examine the relationship between SVG failure time and AGE values and sensitivity and specificity values were determined. A significance level of $p < 0.05$ was used, and the necessary data were summarized with 95% confidence interval (CI) values. Diabetes mellitus (DM) can increase AGE levels, so the differences in AGE levels in the groups with and without DM were also evaluated statistically.

Results

This study included 55 patients with SVG failure and 55 patients who did not have the SVG failure. There were no significant differences between the two groups in

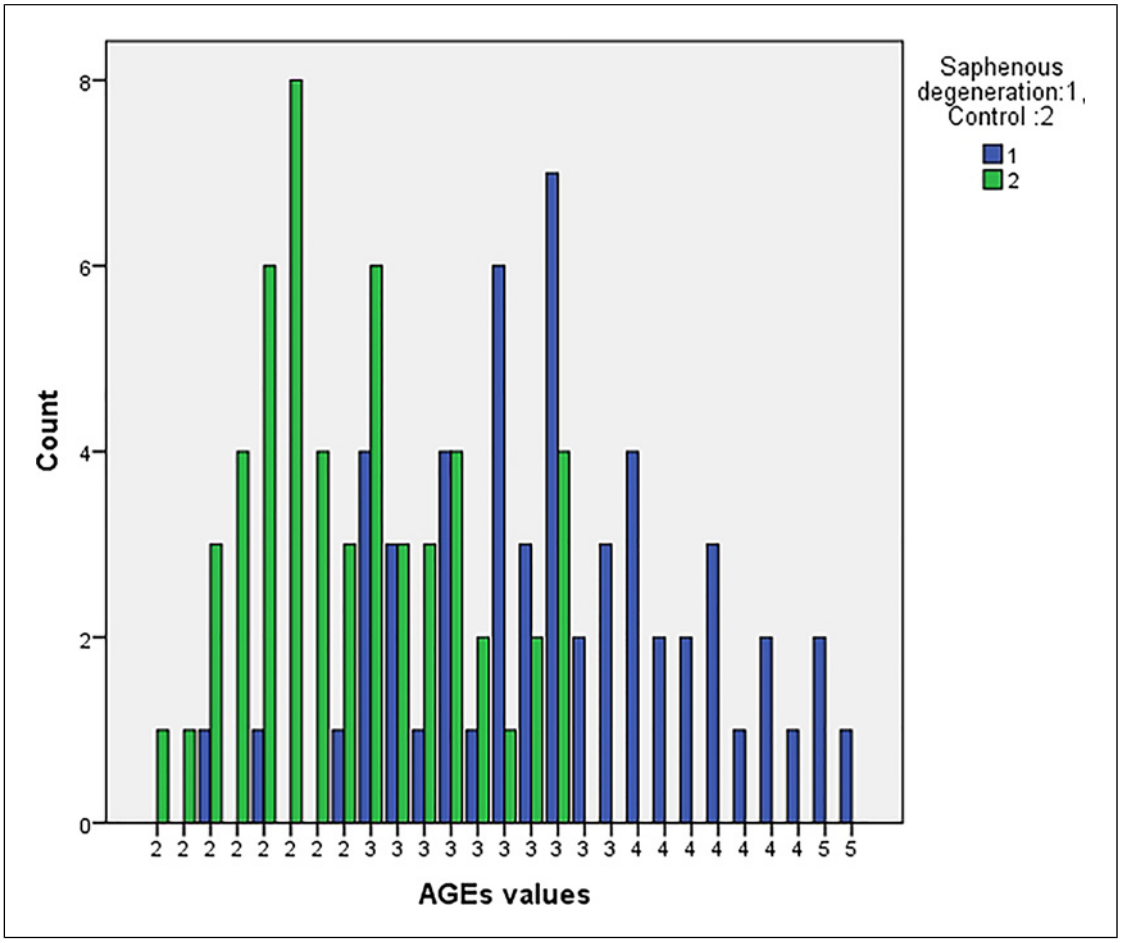

Fig. 2. AGE value bar graph of the study population.

terms of demographic characteristics such as age, gender, and smoking habits. AGE values of the study population are given in Figure 2. Ejection fraction was found to be 50% (45–55) in the group with SVG failure and 55% (45–60) in the control group. It was noted that ejection fractions were significantly lower in the group experiencing SVG failure. There was no statistical difference in the time after CABG surgery between the two groups. The median SVG failure time was found to be 6 years (range 4–10 years). There were no significant differences observed between the patient groups in terms of comorbidities such as DM, hypertension, peripheral artery disease, stroke, HF, and hyperlipidemia. While the body mass index of the patients in both groups was similar, AGE levels were significantly higher in the group with SVG failure (Table 1).

The receiver operating characteristic curve analysis resulted in an area under curve value of 0.869 with a 95% CI of 0.803–0.935 for the ability to detect SVG failure. In patients with AGE values >3, it had a sensitivity of 70.9% and a specificity of 87.3% in detecting SVG failure (shown in Fig. 3).

Logistic regression analysis for SVG failure was performed forward stepwise. In terms of SVG occlusion, only heart failure and AGE values were found to be significant in the logistic regression analysis (Nagelkerke R^2: 0.55, heart failure β: 3.96, 95% CI: 0.98–16.06, p: 0.053; AGE value β: 31.83, 95% CI: 8.83–114.08, $p < 0.001$). In the correlation analysis between SVG failure time and AGE values, the Pearson coefficient was found to be 0.186, meaning a weak relationship, but no statistically significant difference was detected (p: 0.17).

After excluding patients with DM from the statistical analysis, there were 29 patients in the group with SVG failure and 30 patients in the control group. In the analysis conducted between these groups, AGE levels were found to be significantly higher in the group with SVG failure, with a median of 3.1 (2.80–3.40), compared

Table 1. Patient demographics and AGE values

Variables	SVG failure	Control group	*p* value
Patients, *n*	55	55	
Age	67.6±10.8	65.8±9.7	0.344
Gender (male)	46 (83.6%)	42 (76.4%)	0.340
Smoking	21 (38.2%)	17 (30.9%)	0.423
Ejection fraction	50 (45–55)	55 (45–60)	0.035
Time elapsed since CABG, years	8 (6–12)	7 (5–12)	0.064
SVG failure time, years	6 (4–10)	–	–
Diabetes mellitus	26 (47.3%)	25 (45.5)	0.848
Hypertension	48 (87.3%)	51 (92.7%)	0.340
Peripheral artery disease	3 (5.5%)	1 (1.8%)	0.308
Stroke	6 (10.9%)	3 (5.5%)	0.297
Heart failure	11 (20.0%)	11 (20.0%)	1.000
Hyperlipidemia	49 (89.1%)	49 (89.1%)	1.000
BMI, kg/m^2	28.6±4.1	28.0±3.2	0.349
AGEs	3.2 (2.8–3.6)	2.4 (2.1–2.7)	<0.001

The data are summarized as mean ± standard deviations, median (25%–75% interquartile range), and numbers (percentages). AGEs, advanced glycation products; BMI, body mass index; CABG, coronary artery bypass grafting; SVG, saphenous vein graft.

to the control group with a median of 2.4 (2.20–2.80), with a p value of <0.001. A significant difference was observed in terms of AGE levels in patients with DM (SVG failure groups AGE: 3.3 [3.0–3.8] vs. control groups AGE: 2.3 [2.1–2.7], $p < 0.001$].

Discussion

The long-term benefit of the LIMA graft in patients undergoing CABG is well known. However, for complete revascularization, SVG usually needs to be used. SVGs do not have as long a lifespan as arterial grafts, and their failure is associated with significant adverse cardiac outcomes and mortality [11]. The findings we have obtained support our study's objective, as the levels of AGE were found to be higher in patients with SVG lesions compared to those without, as reported earlier [12]. The levels of AGE here may serve as an indicator of the patient's metabolic, inflammatory, and pro-atherogenic status, and they may also play a role in the pathophysiology. The histological structure of SVGs primarily consists of an intima, media, and adventitia layer, with the intima layer containing endothelium and the media layer containing smooth muscle cells. When examining SVG physiology, the endothelial layer releases prostacyclin-2 and endothelial nitric oxide. These two substances have inhibitory effects on vasospasm, platelet activation, and smooth muscle cell proliferation. In addition to these effects, they also increase the release of intracellular adhesion molecule-1 and vascular cell adhesion molecule-1 [13]. When conditions leading to SVG loss are investigated, one of them is increased platelet activation, and the endothelial NO which also plays an important role. Various conditions result due to decreases in both the production and bioavailability of NO. One of these is the elimination of inhibition of platelet aggregation [14]. AGEs reduce the bioavailability of endothelial NO, resulting in an increase in AGE production due to increased oxygen radicals in the existing environment, as well as a decrease in NO production and bioavailability. This condition reduces platelet inhibition and result in increasing the susceptibility to thrombosis. Furthermore, AGE levels also affect platelet functions both directly and through transmembrane receptors known as RAGE. In its direct effect, it upregulates the levels of platelet adhesion molecules and increases the levels of platelet glycoproteins (glycoprotein 2b) and

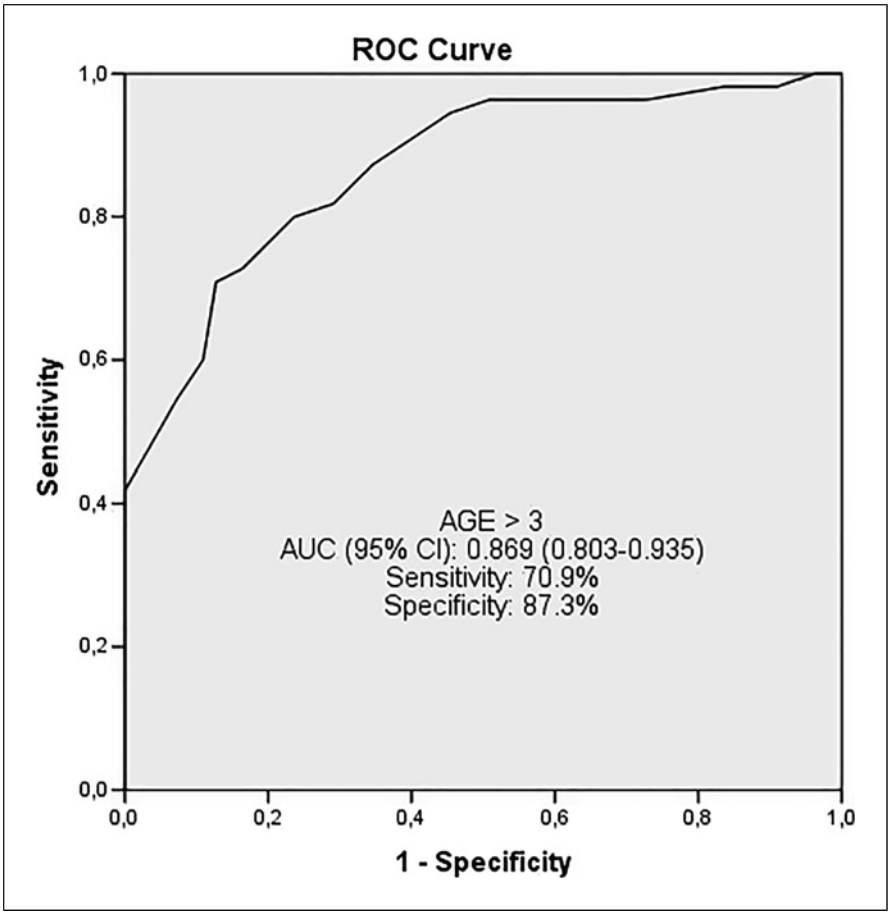

Fig. 3. ROC curve analysis of AGE levels for predicting SVG failure. ROC, receiver operating characteristic.

phospholipids, which play a role in platelet aggregation. After the AGE-RAGE interaction, studies have shown an increase in thromboxane A2 production through stimulation of the cyclooxygenase pathway, leading to increased microthrombus formation and activation of the coagulation cascade [15–17]. After AGE-RAGE interaction, there is an increase in nuclear factor kappa B transcription. Activation of nuclear factor kappa B causes inflammatory cytokines, such as endothelin-1, intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and E-selectin. It results in enhanced expression of the adhesion molecules and various mediators. Additionally, AGE-RAGE interaction reduces eNOS activity and may reduce the amount of NO [18]. Increased AGE production and increased accumulation of AGE in the vascular endothelium may be the contributing factors to the early stage increased endothelial dysfunction and SVG loss. Additionally, considering the anticipated heightened AGE-RAGE interaction in these patients, disruption in the release of mediators could lead to impaired platelet functions due to increased thrombogenicity. Of course, it is hard to believe that a single factor is solely responsible for this condition, but it would be safe to state that it may have contributed to this pathological effect.

Furthermore, another condition is the delayed graft stenosis, where the fundamental event is migration of the smooth muscle cells into intimal layer, their proliferation, extracellular matrix expansion, and the resulting intimal hyperplasia. Another effect of NO is on smooth muscle cells, in addition to inducing vasodilation in smooth muscle cells, it also suppresses their migration and proliferation. The decrease in NO due to AGE increase and reduced bioavailability has the consequence of reducing inhibitory effects on the migration and proliferation of the smooth muscle cells [19, 20]. The influence of AGE on vascular smooth muscle cells is not limited to this alone. In addition to this, AGE-RAGE interaction leads to increased proliferation of smooth muscle cells. Another effect is the suppression of autophagy in structurally impaired smooth muscle cells and an increase in osteogenic transformation [21, 22]. The proliferation of smooth muscle cells leads to

tissue thickening, and in addition, these cells experience a disruption in their structural functions, leading to fibrosis and increased stiffness in vascular muscle tissue. The proliferating smooth muscle cells migrate to the endothelial region. This situation results in impairments in the endothelial structure, affecting both the secretory functions of endothelial tissue and its physiological functions. Endothelial intimal hyperplasia occurs as a result of endothelial smooth muscle cell migration. Endothelial intimal hyperplasia is one of the major causes of both stent restenosis and SVG stenosis. One of the fundamental events here is the migration, proliferation, and calcification of vascular smooth muscle cells. Increased tissue levels of AGE stimulate the migration, proliferation, and calcification of vascular smooth muscle cells through nuclear transcription factor activation, both via NO and through the AGE-RAGE interaction [17].

AGEs affect the fundamental components of the connective tissue, such as collagen and elastin, leading to cross-linking and structural disruption in collagen fibrils. They also have similar effects on elastin. These effects on collagen and elastin result in a loss of tissue elasticity. In tissues like SVGs, there can be an increased production of AGE in the early stages due to elevated oxidative stress and oxygen radicals in the environment. The increased production of AGE leads to increased cross-linking of elastin and collagen fibrils present in vein conduits, resulting in dysfunctional collagen and elastin. Consequently, vascular dysfunctions can occur [23, 24]. One of the reasons for SVG failure is the loss of vasodilation capability and vascular stiffness. Due to the dysfunction occurring in elastin and collagen fibrils, there is a deterioration in vasodilation capability, leading to an increase in vascular stiffness. The lysyl oxidase is an important enzyme in the stabilization of the extracellular matrix structure. This enzyme increases the cross-linking of collagen and elastin. Some studies suggest that an increase in its production and activity is associated with the prevalence of atherosclerosis, neointimal hyperplasia, the development of restenosis, and an increase in the migration and proliferation of vascular smooth muscle cells. Studies suggest that increased AGE levels at the endothelial level in various tissues have an up-regulatory effect on the lysyl oxidase enzyme. The origin of this effect is believed to be through the nuclear transcription factor pathway, which is related to the AGE-RAGE interaction [25, 26]. It is possible that the high production and accumulation of AGE in SVGs could lead to the deterioration of collagen and elastin, the fundamental structural components, due to the high levels of AGE. This may result in arterial stiffness and a loss of vasodilation ability in the vessels. Additionally, by acting through the lysyl oxidase enzyme, it could disrupt the extracellular matrix and significantly contribute to SVG failure by enhancing the migration and proliferation of smooth muscle cells, which are the underlying pathophysiological causes of intimal hyperplasia. The results of the study conducted by Gelžinský et al. [27] also support our findings.

Another point to consider is the early inflammatory response that occurs. Due to the inflammatory response, there is infiltration of macrophages and lymphocytes. Additionally, this inflammatory environment increases the formation of oxygen radicals. As we know, oxidative stress contributes to AGE formation. Furthermore, in this inflammatory condition, chemoreactive substances such as IL-1, IL-6, IL-8, and TNF-alpha play a role. There are studies which show that AGE increases IL-6 levels and other studies have reported that AGE increases IL-8 levels and triggers apoptosis through IL-8 [28, 29]. AGEs not only contribute to increased inflammation but also induce apoptosis through chemoreactive substances in the tissues.

DM, both microvascular and macrovascular, is a disease that causes widespread vascular damage. Previous studies have shown that AGEs are effective in the pathogenesis of diabetes and various complications of diabetes [30]. DM can increase AGE levels, but in our study, there was no significant difference between the groups in terms of DM diagnosis.

One of the main limitations of our study is that it is not an in vivo tissue study. Therefore, we cannot establish a clear cause-and-effect relationship. In the future, tissue studies, if conducted, could provide important clues for a clear relationship in terms of a cause-and-effect perspective.

Conclusion

In our study, we observed that AGE levels measured by the SAF method were significantly higher in patients with a previous CABG history and SVG failure than in those without SVG failure. In vivo tissue studies are needed to establish a cause-effect relationship with this observation. However, the SAF method provides a possibility to detect the risk of developing SVG failure by measuring AGE levels in an inexpensive, easy, and noninvasive manner within a short period. As a result, a sedentary lifestyle and an increase in the amount of exogenous AGEs may increase the number of CAD candidates or cause existing CAD patients to worsen despite innovations in treatment. Considering that they increase health expenditures as well as mortality and morbidity, we think that AGEs should be given due consideration.

Statement of Ethics

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Istinye University (protocol code 23/15 and date of approval August 08, 2023). Written informed consent has been obtained from all the study subjects.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The funder had no role in the design, data collection, data analysis, and reporting of this study.

Author Contributions

Conceptualization, writing – original draft preparation, formal analysis, and investigation: Alkame Akgümüş and Bedrettin Boyraz; methodology, validation, and writing – review and editing: Alkame Akgümüş, Bedrettin Boyraz, and Ahmet Balun; software and data curation: Bedrettin Boyraz; resources: Alkame Akgümüş and Ahmet Balun; visualization: Ahmet Balun; supervision and project administration: Alkame Akgümüş. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author.

References

1 Gökay S, Çiçek D. Saphenous vein graft disease: causes, prevention, and contemporary treatment strategies. Turk Kardiyol Dern Ars. 2012;40(8):736–43. https://doi.org/10.5543/tkda.2012.26790
2 Parang P, Arora R. Coronary vein graft disease: pathogenesis and prevention. Can J Cardiol. 2009;25(2):e57–62. https://doi.org/10.1016/s0828-282x(09)70486-6
3 Favaloro RG. Saphenous vein autograft replacement of severe segmental coronary artery occlusion: operative technique. Ann Thorac Surg. 1968;5(4):334–9. https://doi.org/10.1016/s0003-4975(10)66351-5
4 Caliskan E, de Souza DR, Böning A, Liakopoulos OJ, Choi YH, Pepper J, et al. Saphenous vein grafts in contemporary coronary artery bypass graft surgery. Nat Rev Cardiol. 2020;17(3):155–69. https://doi.org/10.1038/s41569-019-0249-3
5 Danek BA, Karatasakis A, Alame AJ, Nguyen-Trong PKJ, Karacsonyi J, Rangan B, et al. Saphenous vein graft near-infrared spectroscopy imaging insights from the lipid core plaque association with clinical events near-infrared spectroscopy (ORACLE-NIRS) registry. Catheter Cardiovasc Interv. 2017;89(6):E172–80. https://doi.org/10.1002/ccd.26696
6 Singh R, Barden A, Mori T, Beilin L. Advanced glycation end-products: a review. Diabetologia. 2001;44(2):129–46. https://doi.org/10.1007/s001250051591
7 Cavero-Redondo I, Soriano-Cano A, Álvarez-Bueno C, Cunha PG, Martínez-Hortelano JA, Garrido-Miguel M, et al. Skin autofluorescence-indicated advanced glycation end products as predictors of cardiovascular and all-cause mortality in high-risk subjects: a systematic review and meta-analysis. J Am Heart Assoc. 2018;7(18):e009833. https://doi.org/10.1161/JAHA.118.009833
8 Del Turco S, Basta G. An update on advanced glycation end products and atherosclerosis. Biofactors. 2012;38(4):266–74. https://doi.org/10.1002/biof.1018
9 Singh S, Siva BV, Ravichandiran V. Advanced Glycation End Products: key player of the pathogenesis of atherosclerosis. Glycoconj J. 2022;39(4):547–63. https://doi.org/10.1007/s10719-022-10063-x
10 den Engelsen C, van den Donk M, Gorter KJ, Salomé PL, Rutten GE. Advanced glycation end products measured by skin autofluorescence in a population with central obesity. Dermatoendocrinol. 2012;4(1):33–8. https://doi.org/10.4161/derm.17999
11 McKavanagh P, Yanagawa B, Zawadowski G, Cheema A. Management and prevention of saphenous vein graft failure: a review. Cardiol Ther. 2017;6(2):203–23. https://doi.org/10.1007/s40119-017-0094-6
12 Sun Y, Kang L, Li J, Liu H, Wang Y, Wang C, et al. Advanced glycation end products impair the functions of saphenous vein but not thoracic artery smooth muscle cells through RAGE/MAPK signalling pathway in diabetes. J Cel Mol Med. 2016;20(10):1945–55. https://doi.org/10.1111/jcmm.12886
13 Addabbo F, Nacci C, de Benedictis L, Leo V, Tarquinio M, Quon MJ, et al. Globular adiponectin counteracts VCAM-1-mediated monocyte adhesion via AdipoR1/NF-κB/COX-2 signaling in human aortic endothelial cells. Am J Physiol Endocrinol Metab. 2011;301(6):E1143–54. https://doi.org/10.1152/ajpendo.00208.2011
14 Saito T, Kurazumi H, Suzuki R, Matsunaga K, Tsubone S, Lv B, et al. Perivascular adipose tissue is a major source of nitric oxide in saphenous vein grafts harvested via the No-touch technique. J Am Heart Assoc. 2022;11(3):e020637. https://doi.org/10.1161/JAHA.120.020637
15 Recabarren-Leiva D, Burgos CF, Hernández B, Garcïa-García FJ, Castro RI, Guzman L, et al. Effects of the age/rage axis in the platelet activation. Int J Biol Macromol. 2021;166:1149–61. https://doi.org/10.1016/j.ijbiomac.2020.10.270
16 Ortillon J, Hézard N, Belmokhtar K, Kawecki C, Terryn C, Fritz G, et al. Receptor for advanced glycation end products is involved in platelet hyperactivation and arterial thrombosis during chronic kidney disease. Thromb Haemost. 2020;120(9):1300–12. https://doi.org/10.1055/s-0040-1714101
17 Kojok K, El-Kadiry AEH, Merhi Y. Role of NF-κB in platelet function. Int J Mol Sci. 2019;20(17):4185. https://doi.org/10.3390/ijms20174185
18 Hegab Z, Gibbons S, Neyses L, Mamas MA. Role of advanced glycation end products in cardiovascular disease. World J Cardiol. 2012;4(4):90–102. https://doi.org/10.4330/wjc.v4.i4.90
19 Bucala R, Tracey KJ, Cerami A. Advanced glycosylation products quench nitric oxide and mediate defective endothelium-dependent vasodilatation in experimental diabetes. J Clin Invest. 1991;87(2):432–8. https://doi.org/10.1172/jci115014
20 Birukov A, Cuadrat R, Polemiti E, Eichelmann F, Schulze MB. Advanced glycation end-products, measured as skin autofluorescence, associate with vascular stiffness in diabetic, pre-diabetic and normoglycemic individuals: a cross-sectional study. Cardiovasc Diabetol. 2021;20(1):110. https://doi.org/10.1186/s12933-021-01296-5
21 Kosmopoulos M, Drekolias D, Zavras PD, Piperi C, Papavassiliou AG. Impact of advanced glycation end products (AGEs) signaling in coronary artery disease. Biochim Biophys Acta Mol Basis Dis. 2019;1865(3):611–9. https://doi.org/10.1016/j.bbadis.2019.01.006

22 Zhao LM, Su XL, Wang Y, Li GR, Deng XL. KCa3.1 channels mediate the increase of cell migration and proliferation by advanced glycation endproducts in cultured rat vascular smooth muscle cells. Lab Invest. 2013;93(2):159–67. https://doi.org/10.1038/labinvest.2012.163
23 Kostov K, Blazhev A. Elevated IgG and IgM autoantibodies to advanced glycation end products of vascular elastin in hypertensive patients with type 2 diabetes: relevance to disease initiation and progression. Pathophysiology. 2022;29(3):426–34. https://doi.org/10.3390/pathophysiology29030034
24 Li Y, Zheng X, Guo J, Samura M, Ge Y, Zhao S, et al. Treatment with small molecule inhibitors of advanced glycation end-products formation and advanced glycation end-products-mediated collagen cross-linking promotes experimental aortic aneurysm progression in diabetic mice. J Am Heart Assoc. 2023;12(10):e028081. https://doi.org/10.1161/jaha.122.028081
25 Chandrakumar S, Santiago Tierno I, Agarwal M, Matisioudis N, Kern TS, Ghosh K. Subendothelial matrix stiffening by lysyl oxidase enhances RAGE-mediated retinal endothelial activation in diabetes. Diabetes. 2023;72(7):973–85. https://doi.org/10.2337/db22-0761
26 Mouanness M, Merhi Z. Impact of dietary advanced glycation end products on female reproduction: review of potential mechanistic pathways. Nutrients. 2022;14(5):966. https://doi.org/10.3390/nu14050966
27 Gelžinský J, Mayer O Jr, Seidlerová J, Mateřánková M, Mareš Š, Kordíkova V, et al. Serum biomarkers, skin autofluorescence and other methods. Which parameter better illustrates the relationship between advanced glycation end products and arterial stiffness in the general population? Hypertens Res. 2021;44(5):518–27. https://doi.org/10.1038/s41440-020-00601-1
28 Nonaka K, Kajiura Y, Bando M, Sakamoto E, Inagaki Y, Lew JH, et al. Advanced glycation end-products increase IL-6 and ICAM-1 expression via RAGE, MAPK and NF-κB pathways in human gingival fibroblasts. J Periodontal Res. 2018;53(3):334–44. https://doi.org/10.1111/jre.12518
29 Mahali S, Raviprakash N, Raghavendra PB, Manna SK. Advanced glycation end products (AGEs) induce apoptosis via a novel pathway: involvement of Ca2+ mediated by interleukin-8 protein. J Biol Chem. 2011;286(40):34903–13. https://doi.org/10.1074/jbc.M111.279190
30 Ahmed N. Advanced glycation end-products--role in pathology of diabetic complications. Diabetes Res Clin Pract. 2005;67(1):3–21. https://doi.org/10.1016/j.diabres.2004.09.004