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Advanced Glycation End Products: A Promising Prognostic Indicator in Breast Cancer Patients

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Keywords
Advanced glycation end products · Biomarker · Breast cancer · Prognosis

Abstract
Introduction: Advanced glycation end products (AGEs) form through long-term reactions between proteins/lipids and sugars, accumulating in tissues and contributing to disease. AGEs are linked to cancer progression, with studies showing associations with colon and pancreatic cancer. ***Methods:*** This study investigates the relationship between AGEs and breast cancer. Stage 2–3 breast cancer patients and age-matched healthy controls were included. Exclusion criteria were diabetes, renal/liver disease, chronic inflammation, and infection. Blood samples were collected from patients pre-surgery and 48 h post-surgery and once from fasting controls. Glyoxal (GO) and methylglyoxal (MGO) levels were measured via liquid chromatography. A total of 60 breast cancer patients and 21 controls participated. ***Results:*** GO and MGO levels were significantly higher in patients than controls ($p < 0.001$) and decreased post-surgery. No significant differences were found between breast cancer subtypes. AGE levels did not correlate with age, lymph node involvement, or menopause status. ***Conclusion:*** The significant drop in AGE levels post-surgery suggests tumor burden influences AGE levels. While their predictive value remains uncertain, AGEs could serve as prognostic biomarkers. Monitoring AGEs may encourage lifestyle changes, and rising levels might indicate cancer recurrence or progression.

Introduction

Advanced glycation end products (AGEs) are complex molecules formed by the long-term reaction of proteins or lipids with reductive sugars. These reactions occur through nonenzymatic glycation and oxidative stress, contributing to the development of various chronic diseases [1, 2]. AGE levels are particularly

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increased in conditions such as diabetes, cardiovascular diseases, and renal failure and naturally rise with aging [2, 3].

The relationship between AGEs and cancer has become a focal point of research in recent years [4]. AGEs, whether endogenous or exogenous, can trigger a series of pathological processes at the cellular and tissue levels when accumulated in the body [3, 4]. Activation of the receptor for AGEs (RAGE) on cell surfaces increases intracellular inflammatory responses and oxidative stress [5, 6]. This can trigger cancer-associated processes such as DNA damage, changes in gene expression, and disruption of cellular signaling pathways [4, 6]. These processes can promote cell proliferation, angiogenesis (formation of new blood vessels), and metastasis (spread of cancer from one area to another), leading to tumor development and progression [4]. Additionally, AGEs can increase cellular stress and disrupt the mechanisms of apoptosis (programmed cell death) by causing proteins to misfold and aggregate [4, 6]. The combined effect of these mechanisms suggests that AGEs play a critical role in cancer development and progression, making the accumulation of AGEs and activation of RAGE a potential target for cancer treatment and prevention [6].

Research has explored the relationship between various types of cancer and blood AGE levels. For example, a study on pancreatic cancer indicated that AGEs are associated with this type of cancer and that risk factors for pancreatic cancer may increase AGE production [7].

Regarding breast cancer and AGEs, specific studies are limited. However, given the general effects of AGEs on cancer, they could potentially affect breast cancer as well. In breast cancer, body weight and physical activity are strongly associated with the risk of recurrence, making lifestyle changes an attractive strategy for improving prognosis. Trials on dietary modifications in breast cancer are promising. AGEs, compounds produced during sugar metabolism in the body, combine with exogenous AGEs from food to form the total body AGE load. AGEs can be measured or estimated from the diet and their metabolites in the blood. Studies indicate that AGEs are associated with breast cancer risk and prognosis [8].

Our study aimed to measure blood AGE levels in patients diagnosed with early-stage breast cancer before surgery and 48 h after surgery to demonstrate the change in AGE levels in the presence and absence of cancerous tissue in the same individual. We also examined the relationship between changes in AGE levels and breast cancer subtypes and menopausal status. Additionally, by examining AGE levels in healthy volunteers, we aimed to evaluate the relationship between cancer presence and AGEs.

Methods

This prospective study was approved by the Ethics Committees of our hospital (approval number: 2023/453) and was conducted in accordance with the ethical standards of the Declaration of Helsinki. Participants in our study included patients diagnosed with breast cancer (group 1) and a healthy control group (group 2) with similar age and demographic characteristics to the patients. All participants in the study were women. The first group was selected from patients who were operable, stage 2–3 according to the American Joint Committee on Cancer (AJCC) TNM Staging System for Colon Cancer 8th ed., 2017, without distant organ metastasis. Individuals under 18, pregnant women, those who did not give consent, and those with diabetes, acute or chronic renal failure, acute or chronic liver disease, chronic inflammatory disease, or acute infection were not invited to participate in the study. Demographic data, height, and weight of the patients were recorded. Individuals with a BMI >30 (body mass index, calculated by dividing body weight in kilograms by height in meters squared) were recorded as obese and were not included in the study. Postmenopausal status was defined as the absence of menstruation for at least 12 consecutive months in the absence of any other medical cause. In group 1, venous blood (1 cc) was drawn in the morning after fasting for 8 h from patients diagnosed with breast cancer, who had not received any anticancer treatment before and were planned for operation. The same patients had their venous blood (1 cc) drawn again 48 h after the operation, in the morning after fasting for 8 h. Group 2 was selected from healthy volunteers who came to our hospital's general internal medicine outpatient clinic for routine checkups, with no additional diseases, and applied to the hospital for general screening purposes. As in group 1, venous blood samples in group 2 were also collected in the morning after at least 8 h of fasting, and individuals with a BMI >30 were excluded. Measurements of glyoxal (GO) and methylglyoxal (MGO) were performed as AGEs.

Analytical Quantification of GO and MGO by Modified HPLC Method

An adapted version of a previously published high-performance liquid chromatography (HPLC) method for the quantification of GO and MGO was utilized, incorporating certain alterations suitable for our sample matrix [9]. The configuration employed encompassed a Shimadzu LC 20AT propulsion unit coupled with a Shimadzu SPD-20A UV/VIS detection mechanism (Shimadzu Corporation, Kyoto, Japan). The elution mixture was formulated from methanol, water, and acetonitrile in the volumetric ratio of 42:56:2, and the detection was conducted at a 255 nm wavelength. The separation of GO and MGO was achieved through an

Table 1. Comparison of age, GO, and MGO levels among groups

	Group		*p* value
	patient (*n* = 60)	control (*n* = 21)	
Age, median (min–max), years	57.5 (34–80)	55 (40–78)	0.490
GO, median (IQR), ng/mL	1,569 (630)	176 (157)	<0.001
MGO, median (IQR), ng/mL	72 (74)	8 (6.5)	<0.001

Wilcoxon test. GO, glyoxal; MGO, methylglyoxal.

Inersil ODS-3 column, dimensions 250 × 4.6 mm with 5 μm particle size, maintaining a solvent flow rate of 1 mL/min and a column ambient of 30°C. Power analysis was performed using the G * Power (v3.1.7) program to determine the number of samples. At the beginning of the study, it was calculated as 0.928 by taking 20 people in each group and the pilot study was applied, and it was calculated that there should be at least 20 people in each group and 40 people in total in order to obtain 80% power at the level of α = 0.05.

Validation and Quality Assurance Protocols

Following internationally harmonized guidelines for single-laboratory method validation [10], the analytical procedure for GO and MGO was validated. The linear range was established from 0.2 to 2.0 μg/mL for both GO and MGO, derived from quintuple calibration stages tested thrice. Detection and quantification thresholds were identified based on a signal-to-noise metric, set at 3 and 10 units for GO and MGO, respectively. An exemplary sample was analyzed for method precision and consistency concerning GO and MGO, with the procedure replicated tenfold consecutively and thrice across three distinct days.

Quality control was continuously monitored by analyzing in-house prepared standards with each sample batch. These control specimens were constituted by supplementing 1 μg/mL of GO and MGO into the sample intended for recovery assessment, with tenfold analysis. Subsequently, the mean and standard deviation (SD) were computed through one-way ANOVA (significance threshold $p < 0.05$, employing Tukey's test). Warning and precautionary boundaries for quality assurance were deduced by the mean ± 2 SD and mean ± 3 SD, respectively, which were then documented on the Quality Control Graph Chart [11]. The analytical procedures were executed in triplicate ($n = 3$).

Statistical Method

In this study, the SPSS 25.0 software package was used for data analysis. Data for continuous variables were presented as median (IQR) and mean ± SD. The normality assumptions of the study's data were examined in terms of Kolmogorov-Smirnov values ($p < 0.05$). From this perspective, nonparametric tests, including the Mann-Whitney U test and the Krystal-Wallis test, were conducted to determine whether there was a significant difference between various variables and groups. The Spearman correlation test, a nonparametric test, was used to determine the relationship between continuous variables. A p value of <0.05 was considered statistically significant.

Results

The study included a total of 81 participants, consisting of 60 patients diagnosed with breast cancer and 21 healthy volunteers. The median age was 57.5 years in the patient group, while it was 55 years in the control group. Among the patients, 63.3% were diagnosed with stage II and 36.7% with stage III disease, according to AJCC 8th edition criteria. Molecular subtyping revealed that 75.0% of patients had hormone receptor-positive tumors, 15.0% were human epidermal growth factor receptor 2 (HER2) positive, and 10.0% had triple-negative breast cancer. Additionally, 60.0% of the patients were postmenopausal and 40.0% were premenopausal. Examination of GO and MGO levels revealed they were notably elevated in the patient cohort compared to the control group, a finding underscored by the significant p values (GO, $p < 0.001$, MGO, $p < 0.001$) presented in Table 1.

Further analysis indicated a substantial reduction in both GO and MGO levels post-surgery in the patient group, as detailed in Table 2 (GO, $p < 0.001$, MGO, $p < 0.001$). When assessing the impact of surgery on different breast cancer subtypes – hormone receptor positive, HER2 positive, and triple negative – no significant alterations were observed (Table 3, $p > 0.05$). Table 4 illustrates the lack of a significant correlation between age and lymph node count with preoperative GO and MGO levels (preoperative GO, $p = 0.147$, preoperative MGO, $p = 0.274$, change in GO, $p = 0.493$, change in MGO, $p = 0.864$), and similarly, no substantial link was detected regarding changes in these biomarkers post-surgery (preoperative GO, $p = 0.071$, preoperative MGO, $p = 0.572$, change in GO, $p = 0.637$, change in MGO, $p = 0.404$).

Table 2. Comparison of preoperative and postoperative GO and MGO levels in patients

	Group		*p* value
	preop (*n* = 60)	postop (*n* = 60)	
GO, median (IQR), ng/mL	1,569 (630)	1,324 (511.7)	<0.001
MGO, median (IQR), ng/mL	72 (74)	23 (64.2)	<0.001

Wilcoxon test. GO, glyoxal; MGO, methylglyoxal; preop, preoperative; postop, postoperative.

Table 3. Comparison of changes caused by the operation in patient subgroups

Median (IQR), ng/mL	Group			*p* value
	HR (+) (*n* = 45)	HER2 (+) (*n* = 9)	TNBC (*n* = 6)	
Preop GO	1,524 (549.3)	1,324 (310)	1,802 (887.5)	0.122
Preop MGO	68.5 (67.7)	74 (57.9)	103.5 (127)	0.669
Change – GO	218 (317.7)	513 (4,281)	362 (870.3)	0.408
Change – MGO	32.4 (50.6)	28.9 (71.7)	31 (53.7)	0.886

Kruskal-Wallis test. HR, hormone receptor; HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer; GO, glyoxal; MGO, methylglyoxal; preop, preoperative. $p < 0.05$ is statistically significant.

Lastly, when categorizing patients into premenopausal and postmenopausal groups based on their menopausal status, our findings did not show significant differences in preoperative GO or MGO levels or their changes post-operation (Table 5, preoperative GO, $p = 0.309$, MGO, $p = 0.534$, change in GO, $p = 0.700$, and change in MGO, $p = 0.579$). Similarly, no statistically significant correlation was found between tumor size and serum AGE, GO, or MGO levels in the preoperative patient group ($p > 0.05$ for all), suggesting that tumor burden alone may not account for variations in these biomarkers.

Discussion

Studies on the relationship between AGEs and breast cancer indicate that these biochemical molecules have significant effects on the development and spread of cancer [4, 6, 12]. AGEs, in particular, may play a crucial role in breast cancer metastasis. In this context, one study revealed that AGEs promote the migration and invasion of breast cancer cells by activating the RAGE/TLR4/MyD88 signaling pathway [12]. Furthermore, it has been observed that AGE levels increase in patients with estrogen receptor-positive breast cancer and that these levels can affect the response to treatment and can be targeted through lifestyle interventions [13].

Table 4. Correlation results related to the relationship between age and lymph node with GO and MGO in the patient group

	Age	Lymph node
Preop GO		
r	0.19	−0.235
p	0.147	0.071
Preop MGO		
r	−0.145	−0.075
p	0.274	0.572
Change – GO		
r	−0.09	0.062
p	0.493	0.637
Change – MGO		
r	−0.023	0.111
p	0.864	0.404

Spearman correlation test. GO, glyoxal; MGO, methylglyoxal; preop, preoperative; postop, postoperative; *r*, Spearman correlation coefficient; *p*, *p* value for significance.

These findings highlight the capacity of AGEs to influence both the biological pathways of cancer and the role of lifestyle factors in this process. It is known that AGEs are effective in promoting the proliferation, invasion, and metastasis of cancer cells and can support tumor development and progression by leading to the activation of inflammatory response pathways.

Table 5. Comparison of GO and MGO variables according to menopausal status in the patient group

ng/mL	Group		*p* value
	premenopausal (*n* = 17)	postmenopausal (*n* = 43)	
Preop GO, median (IQR)	1,451 (753)	1,652 (546)	0.309
Preop MGO, median (IQR)	74.5 (62.7)	66 (84)	0.534
Change – GO, median (IQR)	209.5 (426.5)	232 (332)	0.700
Change – MGO, median (IQR)	32.5 (56.2)	28.9 (46.9)	0.579

Mann Whitney U test. GO, glyoxal; MGO, methylglyoxal; preop, preoperative. $p < 0.05$ is statistically significant.

The results of our study demonstrate that AGE levels are significantly higher in breast cancer patients compared to healthy individuals. This finding is consistent with the existing literature that supports the effects of AGEs on cancer pathogenesis and progression.

Furthermore, the effects of MGO, a member of AGEs, on breast cancer are particularly noteworthy. It has been shown that MGO triggers metastasis in breast cancer by activating the MEK/ERK/SMAD1 signaling pathway. These findings indicate that MGO plays a significant role in the spread and metastasis of cancer cells [14].

Another study has shown that MGO and GO are effective in the metastasis and tumor progression of breast cancer cells. Glyoxalase 1 (GLO1) and other related enzymes have significant effects on the survival and proliferation of tumor cells by regulating the levels of these metabolites. MGO is considered a potential target in cancer treatment [15] as it contributes to tumor progression through multiple signaling pathways such as MEK/ERK/SMAD1 and promotes oxidative stress and cellular damage in breast cancer cells.

While these studies demonstrate that AGEs are an important factor in the pathogenesis and treatment of breast cancer, knowledge in this area is still developing. Therefore, future research is expected to help us understand more detailed effects of these molecules on cancer. It is important to note that there is no specific criterion indicating that the measured increased levels of AGEs can directly determine the presence of cancer. Although current studies suggest that AGE levels may be associated with cancer risk, this relationship is complex, and no standard AGE level has been established for cancer detection.

In one study, the relationship between dietary intake of N-carboxymethyl-lysine (CML), an AGE, and breast cancer risk was examined. The study found that high dietary intake of CML-AGEs increased the risk of breast cancer. These findings suggest that exogenous AGEs from dietary sources may also contribute to cancer development. However, these findings are associated with cancer risk factors rather than specifying a specific AGE level for cancer detection [16]. In another study, the relationship between CML levels and the risk of pancreatic cancer was investigated. This study showed that CML and esRAGE (soluble receptor for AGEs) levels were not associated with the risk of pancreatic cancer [17].

These examples demonstrate that AGE levels are not a specific indicator that can be used for cancer diagnosis. The relationship between AGE levels and cancer can vary depending on the type of cancer and many other factors. Therefore, further research is needed on the use of AGE levels in cancer diagnosis, and findings in this area should be evaluated in conjunction with current methods used in cancer diagnosis.

Cancer cells prefer anaerobic glycolysis for energy production even in the presence of normal oxygen levels, leading to an increase in reactive intermediates. Among these intermediates is MGO, a major precursor of AGEs, whose endogenous levels increase in many types of cancer [15]. Our study supports this information. The decrease in AGE levels after surgery could be a result of the reduced tumor burden [4, 12]. With the removal of tumor cells through surgery, there may be a significant decrease in tumor-derived AGE production. However, it should be noted that the decline in GO and MGO levels may not solely be attributed to tumor removal. Postoperative metabolic alterations, inflammatory modulation, and systemic stress responses may also contribute to this reduction. Moreover, studies have reported a significant correlation between elevated serum AGE concentrations and the incidence of metastasis in breast cancer patients [12, 13]. This suggests that AGEs hold promise for use as a prognostic biomarker in cancer treatment or monitoring [4, 12].

In the literature, there has been no study found regarding AGE levels in breast cancer subtypes. In our study, despite the small number of patients, AGE levels were not statistically different in the hormone receptor-positive group, HER2 positive group, and triple-negative

group. Our research observed that menopause does not affect AGE levels. This finding seems to be consistent with previous studies in the literature that examined the effect of menopause on serum pentosidine levels, an AGE. In a study conducted using the HPLC method and involving healthy women aged 20–93, it was determined that serum pentosidine levels significantly increased with age, but the menopausal status did not have a significant impact on these levels [18].

This can be explained by the numerous endogenous and exogenous sources of AGEs. The balanced age distribution in both our control group and patient group enhances the reliability of our findings and minimizes the impact of age on AGE levels.

This study has several limitations. First, the sample size was relatively small and drawn from a single center, which may limit the generalizability of the findings. Second, we did not include long-term follow-up data or survival outcomes. Although we carefully excluded individuals with conditions known to influence AGE levels, such as diabetes, renal or hepatic failure, and obesity, it is still possible that certain unrecognized or uncontrolled factors may have influenced the results. These limitations should be considered when interpreting our findings, and future studies with larger, multicenter cohorts are needed to validate and expand upon our results.

Research related to this topic offers significant opportunities for the development of new targets and approaches in the treatment of breast cancer. To gain more insight into how MGO, GO, and other AGE members can be used in cancer treatment, it is essential to follow the outcomes of ongoing and current research focused on cancer biology and treatment. A better understanding of the effects of these molecules on the subtypes of breast cancer could contribute to the development of personalized cancer treatments.

The dietary intake of AGEs (e.g., through high-temperature processed foods) may increase cancer risk. There is evidence to suggest that dietary AGEs are particularly effective on gastrointestinal system cancers. Therefore, limiting diets high in AGE content is being considered among cancer prevention strategies [19, 20].

In light of the observed correlation between AGE levels and tumor presence, it is worth considering whether AGEs could serve as personalized biomarkers in aggressive breast cancer subtypes – such as triple negative, HER2 positive, or tumors with high Ki-67 expression. Persistent elevation of AGE levels, despite dietary regulation and the exclusion of known confounding factors, may act as a molecular early warning sign of recurrence in selected patients. Unlike classical tumor markers with standardized thresholds, AGE levels are inherently variable and likely reflect individualized metabolic and inflammatory states. This variability could, in fact, be an advantage – positioning AGEs as dynamic, patient-specific indicators that may outperform population-based cutoffs. Notably, AGEs can be measured using HPLC, a technique already widely utilized in clinical laboratories for monitoring glycosylated hemoglobin (HbA1c) in diabetes care. This methodological overlap could facilitate the integration of AGE monitoring into oncology practice without significant infrastructural burden. As precision oncology continues to evolve, monitoring AGE dynamics may help shift clinical practice from static surveillance toward proactive, individualized intervention – allowing earlier recognition of recurrence and offering new opportunities for timely therapeutic action.

Statement of Ethics

This study was conducted in accordance with the approval of the Medical Ethics Committee in Health Science University, Bakirkoy Dr. Sadi Konuk Research and Training Hospital, dated 2023, under Approval No. 2023/453. Consent to participate in the study was obtained prior to participation in the study, after informed and written consent in accordance with the requirements of the Declaration of Helsinki. The participation in the study was voluntary.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conceptualization and project administration: G.S.E., N.I., and M.C.; methodology: G.S.E., N.I., M.C., T.S.T., M.Y., E.Y.S., and E.E.C.; software: G.S.E.; validation: G.S.E., N.I., T.S.T., and M.C.; formal analysis, investigation, and resources: G.S.E., N.I., M.C., T.S.T., N.K., and D.K.; data curation and visualization: G.S.E., N.I., and T.S.T.; writing – original draft preparation and writing – review and editing: G.S.E., N.I., M.C., M.Y., E.Y.S., E.E.C., T.S.T., S.K.T., N.K., and D.K.; and supervision: N.I. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

The participants in this study did not provide explicit consent for public data sharing. To protect their privacy, the data are not available for public access. The data that support the findings of this study are available from the corresponding author (G.S.E.) upon reasonable request, provided that the request is for research purposes, the confidentiality of the data is maintained, and appropriate ethical approval is demonstrated.

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