Original Article

DOI: 10.14235/bas.galenos.2024.69077
Bezmialem Science 2024;12(3):368-73

The Role of Glyoxal, an Advanced Glycation Product, in Diabetic and Non-diabetic Patients with COVID-19

COVID-19 Geçiren Diyabetli ve Diyabetli Olmayan Hastalarda İleri Glikasyon Ürünü Olan Glioksalin Rolü

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ABSTRACT

Objective: The aim of this study was to investigate the effect on coronavirus disease-2019 (COVID-19) of glyoxal (GO), which is a precursor of advanced glycation end-products, in diabetic and non-diabetic patients, treated in hospital for COVID-19 who were of similar age and disease severity with similar comorbidities.

Methods: The study included 57 patients. Measurement of GO was made with the high-performance liquid chromatography method.

Results: The GO values were found to be higher in the diabetic group than in the non-diabetic group (p=0.001, p<0.01). The length of stay in hospital was longer in the diabetic group (p=0.017, p<0.05). The white blood cell, neutrophil, neutrophil/lymphocyte ratio, procalcitonin, and ferritin values were determined to be higher in the diabetic group than in the non-diabetic group (p=0.006; p=0.005, p=0.017, p=0.011, p=0.030). Although the mortality and intensive care unit admission rates were similar in the diabetic and non-diabetic patients of similar age with similar comorbidities and COVID-19 severity, the total length of stay in hospital was determined to be longer in the diabetic patients.

ÖZ

Amaç: Bu çalışmanın amacı, ileri glikasyon son ürünlerinin öncülü olan glioksalin (GO), koronavirüs hastalığı-2019 (COVID-19) nedeniyle hastanede tedavi gören benzer yaş ve benzer komorbiditeli hastalık şiddetine sahip diyabeti ve diyabeti olmayan hastalardaki etkisini araştırmaktır.

Yöntemler: Çalışmaya 57 hasta dahil edildi. GO ölçümü yüksek performanslı sıvı kromatografi yöntemiyle yapıldı.

Bulgular: Glioksal değerleri diyabetik grupta diyabetik olmayan gruba göre daha yüksek bulundu (p=0,001, p<0,01). Hastanede kalış süresi diyabetik grupta daha uzundu (p=0,017, p<0,05). Beyaz kan hücresi, nötrofil, nötrofil/lenfosit oranı, prokalsitonin ve ferritin değerlerinin diyabetik grupta diyabetik olmayan gruba göre daha yüksek olduğu belirlendi (p=0,006; p=0,005, p=0,017, p=0,011, p=0,030). Benzer yaştaki, komorbiditeleri ve COVID-19 şiddeti benzer olan diyabetik ve diyabetik olmayan hastalarda mortalite ve yoğun bakıma yatış oranları benzer olmasına rağmen, diyabetik hastaların hastanede toplam kalış süresinin daha uzun olduğu belirlendi. Diğer enflamasyon belirteçleriyle birlikte GO'nun diyabetik grupta daha yüksek olduğu belirlendi.

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Cite this article as: Işıksaçan N, Şahingöz Erdal G, Teksöz D, Kasapoğlu P, Yaman M, Uğur H, Kart Yaşar K. The Role of Glyoxal, an Advanced Glycation Product, in Diabetic and Non-diabetic Patients with COVID-19. Bezmialem Science. 2024;12(3):368-73

Received: 24.10.2023
Accepted: 16.04.2024

ABSTRACT

Together with other inflammation markers, GO, was determined to be higher in the diabetic group.

Conclusion: The results of this study showed that elevated GO could be associated with a prolonged recovery time in COVID-19.

Keywords: Advanced glycation end-products, COVID-19, diabetes, glyoxal, length of stay in hospital

ÖZ

Sonuç: Bu çalışmanın sonuçları, yüksek GO'nun COVID-19'da uzun süreli iyileşme süresiyle ilişkili olabileceğini gösterdi.

Anahtar Sözcükler: İleri glikasyon son ürünleri, COVID-19, diyabet, glioksal, hastanede kalış süresi

Introduction

The whole world has been affected by the coronavirus disease-2019 (COVID-19) pandemic for more than 2 years and as of December 2021, approximately 696 million people worldwide have contracted this disease and approximately nearly 6.9 million lives have been lost associated with the disease. In Türkiye, nearly 17.2 million people have caught the infection to date, and the number of deaths is approximately 102.174 (1). The morbidity and mortality rates of COVID-19 are known to be increased by advanced age, and comorbidities such as hypertension (HT) and diabetes (2). The frequency of type 2 diabetes is currently increasing in direct proportion to the increasing incidence of obesity and poor nutrition, especially in developed countries (3).

One of the mechanisms leading to damage in several body systems in diabetes is an increase in the level of advanced glycation end-products (AGE) (4). AGEs are a heterogenous substance group in irreversible form as a result of a non-enzymatic reaction between reducing sugars such as fructose and glucose, and proteins, lipids, or nucleic acids (5). In addition to AGE obtained directly from the diet from foods with a high level, the consumption of foods containing high amounts of simple sugars causes endogenous AGE production (6). Glyoxal (GO) is a precursor of AGE. Although the accumulation of AGEs in tissue is known to play a role in the pathogenesis of diseases such as atherosclerosis, neurodegenerative and chronic inflammatory diseases, the accelerated accumulation of AGE in conditions such as diabetes and insulin resistance in particular, leads to the early development of comorbidities (7-9).

The aim of this study was to investigate the effect on COVID-19 of GO, which is a precursor of AGE, in diabetic and non-diabetic patients, treated in hospital for COVID-19 who were of similar age and disease severity with similar comorbidities.

Methods

Approval for this prospective study was granted by the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital's Ethics Committee (desicion no: 2020-12-37, date: 08.06.2020). All the procedures were applied in compliance with the principles of the Helsinki Declaration. Prior to enrollment, each patient provided written informed consent for their participation in the study. The study included patients diagnosed as having COVID-19 from a positive real-time polymerase chain reaction test of a nasal and pharyngeal smear sample, who were admitted for treatment to our hospital between 1 March and 31 May 2021. Patients were excluded from the study if they were aged <18 years, did not wish to participate in the research, had body mass index >30, had received immunosuppressive treatment, had congenital immunosuppression or had received anti-inflammatory treatment within the last 15 days. The treatments of the patients in the study were not changed and no additional drugs were administered for the study.

The patients in the study were separated into 2 groups as those with and without type 2 diabetes according to the American Diabetes Association criteria (10). Care was taken that the groups had similar distribution of age, gender, and comorbidities. In accordance with the hospital rules, patients were only fed from the hospital canteen and received no food from outside the hospital.

On first presentation at the hospital, a 2 mL venous blood sample was taken by an experienced nurse, after at least 8 hours fasting, before the administration of any antiviral or immunosuppressive treatments, including steriods.

Hemoglobin A1c (HbA1c) was measured with the high-performance liquid chromatography (HPLC) method in an Adams Premier Hb 9210 (Trinity Biotech, USA) device.

For the measurement of GO, a system similar to HPLC with some modifications, as explained by Cengiz et al. (11) was used. The HPLC system includes a Shimadzu SPD-20A UV/VIS detector (Shimadzu Corporation, Kyoto, Japan) and a Shimadzu LC 20AT pump. The mobile phase is formed of methanol, water, and acetonitryl (42:56:2, v/v/v) and has a 254 nm wavelength. GO was separated with an Inersil ODS-3, 250x4.6 mm, 5 um column at the rate of 1 mL/min. The temperature of the column oven was 30 °C. The reference ranges in the hospital laboratory were as follows; white blood cells (WBC): 3.7-10.1x10^3/µL, neutrophils (NEU): 1.63-6.96x10^3/µL, lymphocytes (LYM): 1.09-2.99x10^3/µL, and hemoglobin (HGB): 12.9-15.9 g/dL. The upper limit was defined as 0.5 ng/mL for procalcitonin (PCT) and 5 mg/mL for C-reactive protein (CRP). Internal quality control and external quality reliability were applied for the accuracy of the tests applied. A Beckman Coulter AU5800 clinical chemistry analyzer (Beckman Coulter, Brea, CA, USA) was used to measure ferritin levels and an ADVIA 2120 hematology autoanalyzer

(Siemens Healthcare Diagnostics, Erlangen, Germany) was used for complete blood count.

Classification of the lung involvement of the patients was performed using a semi-quantitative scoring system on computed tomography images. Each of the 5 lobes of the lungs were scored from 0-5 as follows; 0: no involvement, 1 <5% involvement, 2: 25%, 3: 26-49%, 4: 50-74%, and 5: >75% involvement. For this study, the patients were separated into 3 groups according to the severity of pneumonia as mild (<25% lung involvement on CT), moderate (26-74% lung involvement), and severe (>75% involvement).

In the classification of patients according to clinical condition, those with mild symptoms and oxygen saturation within normal limits (>98%) were accepted as mild disease, patients with blood oxygen saturation of 98-94% in room air as moderate disease, and the symptoms of severe disease were accepted as evident tachypnea (respiratory rate ≥30/min), hypoxemia (oxygen saturation ≤93%, inhaled oxygen fraction ratio of partial artery oxygen pressure <300), and pulmonary leakage (>50% lung involvement) (12). Patients classified as having mild disease severity were not included in the study and analysis was only made of the two groups of patients with moderate and severe disease severity.

Statistical Analysis

Data obtained in the study were analysed statistically using NCSS software (Number Cruncher Statistical System). Descriptive statistical methods were used and data were stated as mean ± standard deviation, median, minimum, and maximum values, or number (n) and percentage (%). 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 variables, the Student's t-test was used for data with normal distribution and the Mann-Whitney U test for data not showing normal distribution. The Pearson's chi-square test and Fisher's exact test were used in the comparisons of categorical data. The level of statistical significance was accepted as $p<0.05$.

The sample size was calculated from power analysis performed using G*Power (v3.1.7) software. At the start of the study, taking 10 subjects in each group, power was calculated as 0.928, and when the pilot study was applied, it was seen to be necessary to have a total of 40 subjects with 20 in each group to obtain $\alpha=0.05$ and 80% power.

Results

The study included 57 patients treated as hospital in-patients for a diagnosis of COVID-19 pneumonia. The patients comprised 36 (63.2%) males and 21 (36.8%) females with a mean age of 63.5 years (range, 26-90 years). The patients were separated into 2 groups of diabetic and non-diabetic patients, with no difference determined between the groups in respect of age and gender distribution (Table 1).

No statistically significant difference was determined between the groups in respect of age, gender, World Health Organization classification of disease severity, admission to ICU, or mortality rates ($p>0.05$). The GO levels were determined to be significantly higher in the diabetic group than in the non-diabetic group ($p=0.001$, $p<0.01$). The length of stay in the hospital was significantly longer in the diabetic group than in the non-diabetic group ($p=0.017$, $p<0.05$) (Table 1).

No statistically significant difference was determined between the groups in respect of the rates of HT, CAD, COPD, malignancy, CRF, and cerebrovascular event (CVE), or in the distribution of pneumonia severity ($p>0.05$). CVE was seen in 1 patient in each group (Table 2).

The WBC, NEU, NLR, PCT, and ferritin values were determined to be statistically significantly higher in the diabetic group than in the non-diabetic group ($p=0.006$; $p=0.005$, $p=0.017$, $p=0.011$,

Table 1. Comparisons between the diabetic and non-diabetic groups of the demographic and clinical data and glyoxal levels

		Diabetic (n=29)	Non-diabetic (n=28)	p-value
Age (years)	Mean ± SD	64.86±11.89	62.21±15.19	[b]**0.466**
	Median (min-max)	64 (43-89)	60 (26-90)	
Glyoxal (ng/mL)	Mean ± SD	25.37±14.99	13.58±7.90	[a]**0.001****
	Median (min-max)	20.7 (3.8-64.8)	11.6 (2.1-34.6)	
Clinical disease status	**Moderate**	15 (51.7)	18 (64.3)	[c]**0.337**
	Severe	14 (48.3)	10 (35.7)	
Length of stay in hospital (days)	Mean ± SD	17.03±9.52	12.50±9.87	[a]**0.017***
	Median (min-max)	14 (5-39)	8 (4-39)	
Admission to ICU	**No**	24 (82.8)	24 (85.7)	[d]**1.000**
	Yes	5 (17.2)	4 (14.3)	
Mortality	**No**	26 (89.7)	26 (92.9)	[d]**1.000**
	Yes	3 (10.3)	2 (7.1)	

[a]Mann-Whitney U test, [b]Student's t-test, [c]Pearson's chi-square test, [d]Fisher's exact test, *p<0.05, **p<0.01, ICU: Intensive care unit, SD: Standard deviation, Min: Minimum, Max: Maximum

p=0.030, respectively). The HbA1c value was mean 8.1% in the diabetic group and 5.5% in the non-diabetic group (Table 3).

Discussion

Although the mortality rate is known to be high in COVID-19 patients with diabetes (13), the current study results showed no statistically significant difference despite the numerically higher number of diabetic patients who developed mortality (3/29 vs. 2/28). This was attributed to the low number of patients. As comorbid diseases were known to affect morbidity and mortality in COVID-19 patients (1), care was taken to have a balanced distribution of additional diseases in the diabetic and non-diabetic groups. Taking into consideration that aging had an effect on AGE, (14) attention was also paid to ensuring similar mean ages in both groups. The disease severity was similar in the patients in both groups as there was a potential effect on the AGE level of systemic changes caused by disease severity. Throughout the hospitalization period, the patients received similar oral or parenteral nutrition, thereby ensuring that the amount of GO, which is the strongest precursor of AGE, was at the forefront of the conditions related to intrinsic reasons (type 2 diabetes) in the patients.

In the clinical table of COVID-19, the role of cytokine storm, increased cytokines and the levels of inflammatory parameters have been shown to have an effect on prognosis and mortality (15). In individuals with diabetes, there is a low-grade chronic inflammation which can facilitate a cytokine storm, and this seems to be the cause of severe COVID-19 pneumonia and ultimately death in many patients (16). Higher levels of inflammatory markers [fibrinogen, CRP, D-dimer, interleukin-6 (IL-6)] have been determined in COVID-19 patients with diabetes compared to those without diabetes. Agents targeting IL-6 have been used in treatment and have provided significant benefits (17). In the current study, WBC, NEU, PCT, and ferritin levels were determined to be significantly higher in diabetic patients, supporting that there was inflammation present. Many studies have shown that high ferritin levels in COVID-19 patients are associated with severe illness and poor prognosis. Ferritin is the primary storage form of iron in the body and can increase in situations such as inflammation or tissue damage. Elevated ferritin levels in COVID-19 patients are generally considered a sign of systemic inflammation and cytokine storm. This condition can lead to overstimulation of the immune response and tissue damage. High ferritin levels

Table 2. Evaluation of additional diseases in the groups

		Diabetic (n=29)	Non-diabetic (n=28)	p-value
		n (%)	n (%)	
Hypertension	Absent	13 (44.8)	15 (53.6)	[c]0.509
	Present	16 (55.2)	13 (46.4)	
CAD	Absent	23 (79.3)	26 (92.9)	[d]0.253
	Present	6 (20.7)	2 (7.1)	
COPD	Absent	27 (93.1)	24 (85.7)	[d]0.423
	Present	2 (6.9)	4 (14.3)	
Malignancy	Absent	28 (96.9)	27 (96.4)	[d]1.000
	Present	1 (3.4)	1 (3.6)	
CRF	Absent	23 (79.3)	27 (96.4)	[d]0.102
	Present	6 (20.7)	1 (3.6)	
Pneumonia severity	Mild	12 (44.4)	8 (19.6)	[c]0.436
	Moderate	11 (40.7)	12 (44.4)	
	Severe	4 (14.8)	7 (25.9)	

[c]Pearson's chi-square test, [d]Fisher's exact test, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, CRF: Chronic renal failure

Table 3. Biochemical analysis results of the groups

		Diabetic (n=29)	Non-diabetic (n=28)	p-value
WBC	Mean ± SD	10863.45±5067.53	7480±3646.44	[b]**0.006****
	Median (min-max)	11100 (3450-23700)	6745 (2440-19430)	
LYM	Mean ± SD	1812.41±1863.42	1545.03±704.19	[a]0.609
	Median (min-max)	1320 (180-10200)	1445 (61-2890)	
NEU	Mean ± SD	8193.45±4668.21	5072.14±3378.21	[a]**0.005****
	Median (min-max)	7910 (1950-18910)	4525 (120-17410)	
NLR	Mean ± SD	8.56±10.14	3.89±3.6	[a]**0.017***
	Median (min-max)	4.8 (0-48)	2.7 (1-19)	
PCT	Mean ± SD	1.06±2.24	0.61±2.70	[a]**0.011***
	Median (min-max)	0.16 (0-10.6)	0.07 (0-14.3)	
Ferritin	Mean ± SD	366.91±307.72	176.64±169.32	[a]**0.030***
	Median (min-max)	281.8 (20.9-1070.4)	143.05 (9-694)	
HbA1c	Mean ± SD	8.90±2.19	5.65±0.36	[a]**0.001****
	Median (min-max)	8.1 (6.5-16.5)	5.5 (5.3-6.2)	

[a]Mann-Whitney U test, [b]Student's t-test, *p<0.05, **p<0.01, ICU: Intensive care unit, SD: Standard deviation, Min: Minimum, Max: Maximum, WBC: White blood cell, LYM: Lymphocyte, NEU: Neutrophil, NLR: Neutrophil/lymphocyte ratio, PCT: Procalcitonin, HbA1c: Hemoglobin A1c

have also been associated with multi-organ dysfunction and increased mortality risk in COVID-19 patients (18). AGE is a group of complex and heterogenous components, which play a role in complications related to diabetes. Just as it may be the cause of complications observed in diabetes, it may also be formed as a result of complications (19). The results of the current study demonstrated a significantly high level of GO, which is a precursor of AGE, in the diabetic group. The elevated GO level and elevated parameters related to accompanying inflammation in the diabetic group of patients diagnosed as having COVID-19 may be a reason for delayed recovery and prolonged length of stay in hospital.

Previous in vitro studies have shown that elevated AGE is a barrier to the formation of a healthy and necessary immune response. Increasing oxidant stress in particular prevents the repair and renewal of tissues (20). These views were supported by the determination of the longer recovery period in the current study of patients with a high level of GO, which is a precursor of AGE, although they had similar disease severity.

The metabolic effects of AGEs in patients, particularly in the context of COVID-19, warrant detailed elucidation. AGEs, formed through non-enzymatic reactions between reducing sugars and macromolecules, exert multifaceted effects on cellular metabolism and signaling pathways. A study by Brownlee et al. (21) highlighted the role of AGEs in exacerbating insulin resistance, impairing glucose metabolism, and promoting the development of diabetic complications. Furthermore, AGEs contribute to chronic low-grade inflammation and oxidative stress, which are key drivers of metabolic dysfunction in diabetes and other metabolic disorders. In COVID-19 patients, elevated AGE levels may exacerbate systemic inflammation and endothelial dysfunction, thereby amplifying the severity of the disease. Understanding the intricate interplay between AGEs and metabolic pathways is crucial for unraveling the pathophysiology of COVID-19 and developing targeted therapeutic interventions (21).

There are endogenous and exogenous sources of AGE in the body, and thus it was aimed in the current study to equalize the exogenous sources of AGE intake throughout the period of hospitalization. The patients were given both oral and parenteral nutrition in hospital and received no other food. The fact that all the patients had the same diet suggested a greater effect of endogenous sources of AGE on the condition.

Study Limitations

There were some limitations to this study, primarily the low number of patients and that AGEs were only examined during the period of hospitalization. The low number of patients prohibited evaluation of the relationship between low GO and mortality. Further studies of larger numbers of patients may be able to determine a statistically significant association between the level of AGE precursors and COVID-19 mortality.

Conclusion

The findings of this study underscore the complexity of COVID-19 outcomes in diabetic patients, revealing a disparity in the length of hospital stay despite comparable mortality and ICU admission rates between diabetic and non-diabetic patients with similar demographic and clinical profiles. Elevated serum AGE levels observed in diabetic COVID-19 patients, along with inflammatory markers, highlight the potential role of AGEs in influencing disease severity and recovery trajectory. These results emphasize the importance of considering metabolic factors, such as AGEs, in the management and prognosis of COVID-19 patients, particularly those with underlying diabetes. Further research is warranted to elucidate the mechanistic links between AGEs and COVID-19 outcomes, paving the way for targeted therapeutic strategies aimed at mitigating the impact of metabolic dysregulation on disease progression and recovery.

Ethics

Ethics Committee Approval: Approval for this prospective study was granted by the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital's Ethics Committee (desicion no: 2020-12-37, date: 08.06.2020).

Informed Consent: Prior to enrollment, each patient provided written informed consent for their participation in the study.

Authorship Contributions

Surgical and Medical Practices: N.I., M.Y., K.K.Y., Concept: D.T., N.I., G.Ş.E., P.K., M.Y., H.U., K.K.Y., Design: D.T., N.I., P.K., Data Collection or Processing: D.T., N.I., P.K., K.K.Y., Analysis or Interpretation: P.K., H.U., Literature Search: D.T., N.I., P.K., Writing: D.T., N.I., G.Ş.E., P.K., M.Y., H.U., K.K.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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