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Background: Diabetes mellitus is a metabolic disease that can lead to macrovascular and microvascular complications that can cause death and reduce the quality of life. The level of serum AGEs increases with diabetes or a state of hyperglycemia. Increased AGEs [...]

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ORIGINAL PAPERS

Differences in AGEs and hs-CRP between Type 2 Diabetes Mellitus with and without Complications

Alfino Validita SIDIQ¹, Yetti HERNANINGSIH^{2,4}, Puspa WARDHANI^{2,4}, Soebagijo Adi SOELISTIJO^{3,4}

Abstract

Background: Diabetes mellitus is a metabolic disease that can lead to macrovascular and microvascular complications that can cause death and reduce the quality of life. The level of serum AGEs increases with diabetes or a state of hyperglycemia. Increased AGEs in patients with diabetes mellitus can increase the risk of macrovascular and microvascular complications and increase the formation of hs-CRP. This study aims to assess the differences in AGEs and hs-CRP between type 2 diabetes mellitus patients with and without complications and the relationship between AGEs and hs-CRP.

Methods: A cross-sectional study was conducted with 30 subjects of type 2 diabetes mellitus with complications and 30 subjects of diabetes mellitus without complications. Data were collected from September to December 2022. AGEs were measured using ELISA and hs-CRP using the turbidimetric method. Data were statistically processed to determine the difference and relationship between AGEs and hs-CRP.

Results: AGEs and hs-CRP values in patients with type 2 diabetes mellitus with complications were 0.671 ± 0.194 ng/mL and $2.08(0.98-15.3)$ mg/L. In patients with uncomplicated type 2 diabetes 0.561 ± 0.127 ng/mL and $1.69(0.22-9.25)$ mg/L. Differences in AGEs and hs-CRP between the two subject groups had significant results (AGEs $p=0.012$, hs-CRP $p=0.038$). The relationship between AGEs and hs-CRP in each subject group showed no significant results (With complications $r=0.659$ $p=0.659$, Without complications $r=0.253$ $p=0.253$).

Conclusion: There are differences in AGEs and hs-CRP values between patients with type 2 diabetes mellitus with and without complications and there is no relationship between AGEs and hs-CRP values in each subject

Keywords: Diabetes mellitus type 2, AGEs, hs-CRP, Complication.

Rezumat

Context: Diabetul zaharat este o boală metabolică ce poate duce la complicații macro și microvasculare care pot cauza decesul și reduce calitatea vieții. Nivelul de AGE serice crește odată cu diabetul sau cu o stare de hiperglicemie. Creșterea AGEs la pacienții cu diabet zaharat poate crește riscul de complicații macrovasculare și microvasculare și poate crește formarea de hs-CRP. Acest studiu își propune să evalueze diferențele de AGE și hs-CRP între pacienții cu diabet zaharat de tip 2 cu și fără complicații și relația dintre AGE și hs-CRP.

Metode: A fost efectuat un studiu transversal cu 30 de subiecți de diabet zaharat de tip 2 cu complicații și 30 de subiecți de diabet zaharat fără complicații. Datele au fost colectate din septembrie până în decembrie 2022. AGEs au fost măsurate prin ELISA și hs-CRP prin metoda turbidimetrică. Datele au fost prelucrate statistic pentru a determina diferența și relația dintre AGEs și hs-CRP.

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Rezultate: Valorile AGEs și hs-CRP la pacienții cu diabet zaharat de tip 2 cu complicații au fost de $0,671 \pm 0,194$ ng/mL și $2,08(0,98-15,3)$ mg/L. La pacienții cu diabet de tip 2 fără complicații $0,561 \pm 0,127$ ng/mL și $1,69(0,22-9,25)$ mg/L. Diferențele de AGE și hs-CRP între cele două grupuri de subiecți au avut rezultate semnificative (AGE $p=0,012$, hs-CRP $p=0,038$). Relația dintre AGE și hs-CRP în fiecare grup de subiecți nu a avut rezultate semnificative (Cu complicații $r=0,659$ $p=0,659$, Fără complicații $r=0,253$ $p=0,253$).

Concluzii: Există diferențe în valorile AGEs și hs-CRP între pacienții cu diabet zaharat de tip 2 cu și fără complicații și nu există nicio relație între valorile AGEs și hs-CRP în fiecare grup de subiecți.

Cuvinte cheie: AGEs și AGE: diabet zaharat tip 2, AGEs, hs-CRP, complicații.

INTRODUCTION

Diabetes mellitus is a disease caused by metabolic disorders, often characterized by increased blood glucose levels in the body due to insulin secretion abnormalities. It is the most significant cause of death worldwide¹. Type 2 diabetes mellitus is a health problem with an increasing prevalence worldwide. Indonesia is included in the top ten countries with the most estimated diabetes cases, collecting around 10.7 in 2019 and will jump to 13.7 million in 2030, then 16.6 million in 2045. The prevalence of diabetic complications, as demonstrated by multinational studies, recorded 27.2% of macrovascular complications and 53.5% of microvascular complications. In comparison, kidney complications accounted for 27.9%, eye disease 26.3%, diabetic foot 5.4%, and neuropathy 38.4%, significant causes of death in diabetic patients and reduced quality of life². In 2012 diabetes caused 1.5 million deaths and 2.2 million deaths in patients with high glucose 43% of these 3.7 million deaths occurred before the age of 70 years, most of which were because of cardiovascular disease³.

Advanced glycation end products (AGEs) belong to a heterogeneous group of compounds in general. AGEs are made by non-enzymatic condensation between the carbonyl group of reducing sugar and the free amine group of nucleic acid, protein, or lipid, resulting in a stable final product and irreversible⁴. AGEs can produce reactive oxygen species (ROS) as a source of inflammation. Serum levels of AGEs increase with age with diabetes or hyperglycemic states⁵. Patients with type 2 diabetes have hyperglycemia and low-grade inflammation, which may correlate with macrovascular diseases such as cardiovascular [6]. Receptors for advanced glycation end products (RAGE) are receptors for AGEs⁵. The presence of AGEs in the circulation that interacts with RAGE disrupts cellular

properties, one of which is an increase in nuclear factor-kappa B (NF- κ B) transcription, which triggers an increase in interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis alpha (TNF- α) and causes ROS^{7,8}. Increased inflammatory cytokines and abnormal glycated proteins can increase microvascular and macrovascular complications of diabetes⁷.

C-Reactive protein (CRP) can also be called the acute phase produced by the liver. Increasing CRP levels in the body can be a marker of inflammation⁹. In diabetes, there is a mild increase in CRP levels. CRP examination can be taken by standard test and high-sensitivity CRP (hs-CRP). Measurements using hs-CRP can accurately detect low-grade inflammatory states¹⁰. Hyperglycemia can increase CRP production. Higher levels of hs-CRP can be found in diabetic patients and indicate that microvascular and macrovascular changes have occurred in these patients¹¹.

Increased AGEs in patients with diabetes mellitus can increase the risk of microvascular and macrovascular complications. Increased AGEs can also activate NF- κ B, which triggers an increase in IL-6 and TNF- α , a stimulator of hs-CRP^{7,12,13}. Based on the explanation above, this study aimed to analyze the comparison of AGEs and hs-CRP in patients with type 2 diabetes mellitus with and without complications. This study aims to assess the differences in AGEs and hs-CRP between type 2 diabetes mellitus patients with and without complications and the relationship between AGEs and hs-CRP in each group.

METHODS

Study Design and Participant

This study was conducted in an analytical observational form with a cross-sectional by measuring serum AGEs and hs-CRP subject approach to determine whether there are differences between AGEs and hs-CRP in

subjects with type 2 diabetes mellitus with and without complications. Subjects were obtained based on patient medical record data from November - December 2022. The inclusion criteria of respondents were subjects with type 2 diabetes mellitus who were willing to be research subjects, over 18 years old, and had average body temperature. Exclusion criteria were not being an autoimmune disease, chronic infection, obesity, and taking inflammatory drugs and statins.

ETHICS

The Ethical Committee of Rumah Sakit Universitas Airlangga Surabaya approved the study with the ethical permit number 096/KEP/2022. Informed written consent was obtained from all subjects participating in the study.

Sample Size and Data Collection

The total sample in this study was 60 subjects with type 2 diabetes mellitus, consisting of 30 subjects with type 2 diabetes mellitus with complications and 30 subjects with diabetes mellitus without complications. Interviewers collected respondent data and samples from research subjects.

Assay AGEs Serum

Venous blood samples from each subject were collected into plain tubes. The serum was separated by centrifu-

gation at 3000-4000 rpm for 15 minutes. AGEs levels were determined at the Institute of Tropical Disease Airlangga University by ELISA (*Enzyme-linked immunosorbent assay*) Double antibody sandwich method using an ELISA Bio-Rad Laboratory with an ELISA kit Bioassay Technology Laboratory (Shanghai Korain Biotech Co., Ltd). The concentration of AGEs in ng/mL

Assay hs-CRP

Venous blood samples from each subject were collected into plain tubes. The serum was separated by centrifugation at 3000-4000 rpm for 15 minutes. Hs-CRP levels were determined at Airlangga University Hospital by the turbidimetric method using the TMS24 instrument (Tokyo Boeki Medisys) with Nanopia hs-CRP Reagent (Sekisui Medical Co., Ltd). This instrument automatically calculates the concentration of hs-CRP in mg/L.

Statistical Analysis

The data were processed using the statistical T-test for normally distributed data and Mann-Whitney for non-normally distributed to determine the difference in AGEs and hs-CRP values between the two subjects, and Spearman's correlation was used to determine the relationship between AGEs and hs-CRP because the data were not normally distributed with Jamovi 2.3.8.1 software assistance.

RESULTS

Characteristics of Research Subjects

A total of 60 subjects participated in this study, 30 with type 2 diabetes with complications and 30 with type 2 diabetes without complications.

Table 1. Demographics of the study population.

Demographics of the study population.	T2DM with complication (n = 30)	T2DM without complication (n =30)	p-value
Age (Years)	54,1 ± 7.47	55.3 ± 7.93	0,549 ^b
Sex			1,000 ^c
Male	16 (53,3%)	16 (53,3%)	
Female	14 (46,7 %)	14 (46,7 %)	
Smoking			0,405 ^c
Yes	8 (26,6%)	11 (36,6%)	
No	22 (73,4%)	19 (63,4%)	
Duration of T2DM			0,165 ^c
< 5 years	7 (23,3%)	12 (40%)	
> 5 years	23 (76,7%)	18 (60%)	
BMI (kg/m ²)			0,584 ^c
Normal	8 (26,6%)	11 (36,6%)	
Overweight	22 (73,4%)	19 (63,4) %	
Sistole (mmHg)	146 ± 22,2	139 ± 13,7	0,176 ^b
Diastole (mmHg)	83,5 ± 14,3	85,2 ± 9,24	0,586 ^b
Fasting plasma glucose (mg/dl)	131 (73 – 346)	120 (72 – 329)	0,544 ^a
Postprandial plasma glucose (mg/dl)	190 (125 – 426)	180 (97 – 520)	0,246 ^a

^a Mann Whitney, ^b Independent T test ^c Chi-Square, *significant p < 0,05

^d Median (Min-Max), ^e Mean ± SD

Table 1. illustrates that the research subjects have a mean age of 54.7 ± 7.67 years and the majority are male. The history of not smoking has a higher value than smoking in all study subjects. More research subjects have suffered from type 2 diabetes mellitus for more than five years from both categories. Subjects had more BMI values in the overweight category in diabetes with complications and without. The systolic value

in type 2 diabetes research subjects with complications is higher. Diastolic values have almost the same mean values in both subject categories. The median value of fasting glucose was higher in patients with type 2 diabetes with complications compared to the median value of glucose in patients with type 2 diabetes mellitus without complications, as well as the median value of postprandial glucose.

Analysis of differences in values of AGEs and hs-CRP

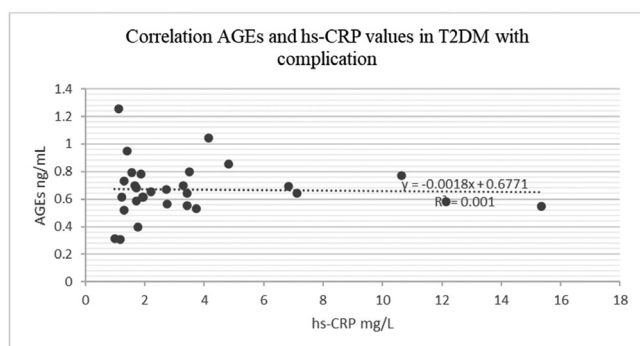
Table.2 Differences in AGEs and hs-CRP values for T2DM with and without complications

Examination	T2DM with complication (n=30)	T2DM without complication (n=30)	p-Value
AGEs (ng/mL)	0,671 ± 0,194	0,561 ± 0,127	0,012 ^a
hs-CRP (mg/L)	2,08 (0,98 – 15,3)	1,69 (0,22 – 9,25)	0,038 ^b

*a: Independent T-test, b: Mann-Whitney

The difference between variables is said to be significant if $p < 0.05$. Table 2 shows that the test results for both examinations obtained a value of < 0.05 , which means that there are differences in the two examination scores in the two categories of research subjects. AGEs and hs-CRP value examination results in type 2 diabetes mellitus subjects with complications have a higher value than those without complications.

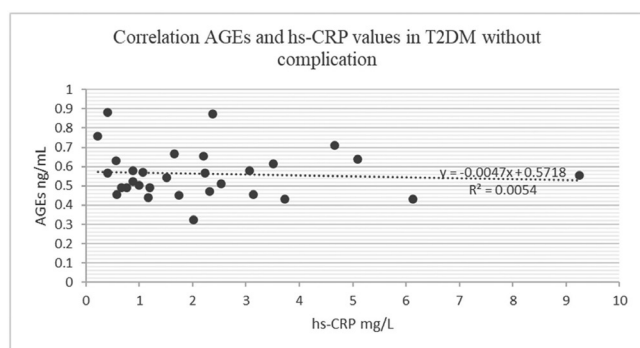
Analysis of the correlation between values of AGEs and hs-CRP



*p-value = 0,659

Figure 1. Correlation between AGEs and hs-CRP T2DM with Complication.

Figure 1 shows no correlation between AGEs and hs-CRP values in patients with type 2 diabetes mellitus with complications ($r_s = 0.084$).



*p-value = 0,253

Figure 2. Correlation between AGEs and hs-CRP T2DM without Complication.

Figure 2 shows no correlation between AGEs and hs-CRP values in subjects with type 2 diabetes mellitus without complications ($r_s = -0,255$)

DISCUSSION

Differences in AGEs values of the two categories of research subjects

AGEs examination results with a higher average were found in type 2 diabetes mellitus subjects with complications compared to those without complications. This result is in line with the results obtained by Bansal et al., 2013 which stated that the AGEs value increased in the condition of type 2 diabetes subjects with complications compared to those without complications and have significant differences between the two categories. Poor glucose values can affect AGEs values and oxidative stress parameters, although some authors report that glycemic status in type 2 diabetes mellitus patients does not affect AGE levels.¹⁴ in line with research conducted by Mostafa et al., 2007 which stated that increased AGEs were associated with the occurrence of kidney failure in diabetic patients and increased higher in patients with diabetes than without diabetes¹⁵. High AGEs values may be a predictor for diabetic nephropathy and correlate with the severity of nephropathy in diabetic patients. Higher levels of serum AGEs and inflammatory cytokines allow the development of microvascular and macrovascular complications in diabetes^{14,16}.

People with diabetes have increased formation of AGEs, AGE precursors, and oxidative stress due to increased circulating glucose¹⁷ age and the irreversible nature of AGEs, the formation of AGEs occurs due to the glycation of proteins and lipids by glucose^{18,19}. Advanced glycation Ends products which are non-enzymatic glycation products in lysine and arginine residues that accumulate in diabetic tissues, play an essential role in the pathogenesis of vascular complications in diabetics^{14,18}. AGEs is an important molecule involved in various complications of diabetes. AGEs values increase blood circulation in patients with complicated diabetes mellitus¹⁶.

The study's results stated that the presence of AGEs also plays a role in the emergence of type 2 diabetes, namely by making insulin resistance, β -cells become less functioning, and as a major player in diabetes complications.¹⁹ AGEs in diabetic tissue correlated with diabetic complications¹⁷. AGEs can increase oxidative stress and increase the oxidation of low-density lipoprotein (LDL), which is a crucial player in the pathogenesis of heart disease; oxidised LDL acts as a ligand for RAGE, causing activation of several intracellular pathways that lead to hardening of the medial lining of

blood vessels which ultimately contribute to the pathophysiology of heart disease²⁰. An increase in AGEs can be accompanied by an increase in inflammatory cytokines, which can cause various complications of conditions such as kidney, retina, nerves, and heart²¹. Arterial stiffness due to increased AGEs associated with micro-systemic inflammation can cause pressure fluctuations in the micro vessels of various organs, especially the kidneys. It can increase the risk of kidney failure.²⁰

Differences in hs-CRP values in the two categories of research subjects

The results of the hs-CRP examination found statistically significant differences between the two categories, with higher average results found in type 2 diabetes mellitus subjects with complications compared to those without complications. This increase in CRP value is to research conducted by Aryan et al., 2018 which states that an increase in CRP value can increase the incidence of microvascular and macrovascular complications. Research by Babu & Joshi., 2017 states that there is an increase in hs-CRP accompanied by an increase in blood glucose in diabetic patients, along with Babu & Joshi., 2017 study by Tan et al., 2004. Increased CRP also occurs in people with diabetes compared to those without diabetes. High glucose levels can trigger microvascular changes and increased production of inflammatory factors, including CRP, IL-6, and TNF- α ²², although a minor increase occurs in diabetics²³.

The increase in hs-CRP in diabetes mellitus subjects with this complication could be due to an increase in proinflammatory cytokines such as TNF- α as a study conducted by Navarro et al. 2015 stated that there was an increase in TNF- α in diabetic neuropathy rat models. Proinflammatory cytokines are increased in diabetic patients indicating that inflammation may be related to diabetic complications^{16,24}. CRP is also closely related to the risk of complications in people with diabetes mellitus (Gorska-Ciebiada et al., 2015; Volpe et al., 2018). Increased hs-CRP is closely related to the incidence of neuropathy, gangrene of the feet, diabetic retinopathy, and kidney failure (Aryan et al., 2018).

Previous studies have shown a close relationship between TNF- α and IL-6 in inflammation, which induces CRP transcription²⁷. A meta-analysis study by Stanimirovic et al., 2022 showed that IL-6 mediates chronic inflammation in type 2 diabetes mellitus. High levels of IL-6 and TNF- α in diabetes mellitus have

been demonstrated by several animal and human studies²⁷. CRP formed in people with diabetes is partly due to the interaction between AGEs and RAGE modulating the formation of ROS through NADPH oxidation and mitochondria, which can increase pro-inflammatory cytokines and induce the formation of CRP.

The bond between AGE-RAGE activates several signals, including p21RAS, p44/p42 mitogen-activated protein kinase (MPAK), p113K-AKT, ERK1/2, JNK, p38, PKC, and NF- κ B activation. This signal becomes a regulator of many "response to injury" genes and ultimately results in the production of cytokines, chemokines, and other proinflammatory molecules that induce inflammation, apoptosis and proliferation, including molecules IL-6, TNF- α , IL-1 β , and VCAM-1, which is regulated by AGEs²⁸.

Correlation between AGEs and hs-CRP values in the two categories of research subjects

The results of examining the relationship between AGEs and hs-CRP in the two categories of study subjects found that there was no statistically significant relationship, this is in accordance with the study of Pia de la et al 2012 which stated that AGEs values were not related to CRP in diabetic patients on anti-diabetic treatment orally or treated with insulin²⁹. Research by Isa et al 2006 states that CRP values in people with uncontrolled diabetes also do not affect the decrease in AGEs values³⁰. Factors affecting hs-CRP and AGEs results can be biased due to drugs that affect CRP and AGEs levels³¹.

Research on the administration of metformin to patients with type 2 diabetes mellitus can significantly reduce the hs-CRP value compared to before receiving metformin. This decrease may be related to metformin therapy in patients with type 2 diabetes³². Reports obtained that metformin contains anti-inflammatory. Studies conducted in Canada show that metformin therapy can reduce mortality from heart disease by more than 45% in patients with type 2 diabetes mellitus.³³

Metformin is an activator of adenosine monophosphate-activated protein kinase (AMPK), where the AMPK signal can suppress the activation of NF- κ B, thereby reducing the inflammatory response. Metformin can inhibit the inflammatory response generated by AGEs in macrophages through AMPK activation and suppression of RAGE/NF- κ B signals.³⁴ Metformin can also reduce hyperglycemia by increas-

ing peripheral insulin sensitivity. Only a tiny number of AGEs are formed in conditions with no hyperglycemia. Metformin can also increase glucose uptake in skeletal muscle and can inhibit glucose transport in the intestine so that it can reduce blood glucose levels when metformin is administered orally.³⁵

Insulin can lower blood glucose and has an anti-inflammatory effect by suppressing NF- κ B activation; by decreasing the glucose value, the formation of AGEs is also decreasing. Insulin given to subjects without diabetes can suppress NF- κ B, a factor forming CRP. Injection of low doses of insulin to healthy patients can reduce ROS and CRP values in landmark studies^{25,36} This is also consistent with a study conducted by Dwipayanan et al., 2017 that a decrease in CRP was found to be lower in the use of insulin compared to oral hypoglycemic drugs in patients with type 2 diabetes.

Smoking habits can increase CRP values, with minor increases²³ in research subjects, 31% of both categories with a smoking history. In the study, Gallus et al., 2018 stated that there was a significant relationship between hs-CRP and the duration and number of cigarettes consumed each day. This is due to the many free radicals entering the body. Advanced glycation Ends products can be sourced from within and outside, one of which is cigarettes which are also a source of AGEs from outside the body. Cigarettes are made by a process involving the formation of AGEs, and burning cigarettes can cause inhalation of AGE derivatives which can move into circulation^{20,37}. Foods processed by frying and baking can form substantial AGEs, and food processing by enhancing taste can develop food-derived AGEs, also called glycotoxins. Advanced glycation Ends products with specific characteristics can be absorbed through food 10-30 per cent, although the metabolic process of absorption AGEs has not been thoroughly explained.²⁰

Study Limitations

The limitations of this study were using a small sample, not examining A1c to measure glycemic values in patients, not examining pro-inflammatory cytokines.

CONCLUSION

This study found differences in AGEs and hs-CRP values between type 2 diabetes mellitus patients with and without complications. The values of AGEs and hs-CRP were higher in diabetic subjects with complica-

tions than those without complications. Furthermore, there is no correlation between AGEs and hs-CRP in patients with type 2 diabetes mellitus with complications and without complications.

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