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ORIGINAL ARTICLE

Glycemic Control and Cardiovascular Risk Assessment: A Study on HbA1c and Hs-CRP Levels in Type 2 Diabetes Mellitus

Kontrol Glikemik dan Penilaian Risiko Kardiovaskular: Studi Kadar HbA1c dan Hs-CRP pada Diabetes Melitus Tipe 2

Mustika Anggiane Putri[1], Patwa Amani[1], Donna Adriani[1], Yudhisman Imran[2]

[1]Departement of Physiology, Faculty of medicine, Universitas Trisakti, Jakarta, Indonesia
[2]Department of Neurology, Faculty of medicine, Universitas Trisakti, Jakarta, Indonesia

inge.mustika@trisakti.ac.id

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ABSTRACT

Background

Type 2 diabetes mellitus (T2DM) is a major risk factor for cardiovascular disease. Patients with diabetes have a 2-4 times higher risk of developing coronary heart disease compared to those without diabetes. Cardiovascular complications are the leading cause of illness and death in diabetic patients, with cardiovascular disease-related deaths making up 65-75% of all deaths in this group. Poor glycemic control is a key factor in the development of cardiovascular problems in diabetes. Chronic high blood sugar levels activate various harmful mechanisms, including increased oxidative stress, systemic inflammation, endothelial dysfunction, and faster atherosclerosis. Hemoglobin A1C (HbA1C), a marker of long-term blood sugar control, strongly correlates with the risk of both microvascular and macrovascular complications in diabetes. This study aims to examine the relationship between glycemic control, as measured by HbA1C, and systemic inflammation, assessed through Hs-CRP, as predictors of cardiovascular risk in patients with type 2 diabetes mellitus.

Methods

An analytical cross-sectional study was conducted on 53 T2DM patients at the Prolanis Clinic in East Jakarta, using purposive sampling. HbA1c was measured with the HPLC method, and Hs-CRP with the Turbidimetric Immunoassay method at PRODIA laboratory. Correlation analysis was performed using Spearman's correlation test.

Results

The study showed an average HbA1C level of 7.2% and an average Hs-CRP level of 2.9 mg/L. Statistical analysis indicated a significant correlation between HbA1C and Hs-CRP (p-value = 0.014), with a Spearman correlation coefficient of 0.336.

Conclusions

There is a significant positive correlation between HbA1c and Hs-CRP levels.

Keywords: Cardiovascular risk; HbA1C; Hs-CRP; Inflammation; Type 2 diabetes mellitus.

ABSTRAK

Latar Belakang

Diabetes melitus tipe 2 (T2DM) merupakan faktor risiko utama penyakit kardiovaskular. Pasien diabetes memiliki risiko 2-4 kali lebih tinggi mengalami penyakit jantung koroner dibandingkan populasi non-diabetes. Komplikasi kardiovaskular menjadi penyebab utama morbiditas dan mortalitas pada pasien diabetes, dengan angka kematian akibat penyakit kardiovaskular mencapai 65-75% dari total kematian populasi diabetes. Kontrol glikemik yang buruk menjadi faktor kunci patogenesis komplikasi kardiovaskular pada diabetes. Hiperglikemia kronis memicu berbagai mekanisme patofisiologis, termasuk peningkatan stres oksidatif, inflamasi sistemik, disfungsi endotel, dan percepatan proses aterosklerosis. Hemoglobin A1C (HbA1C) sebagai parameter kontrol glikemik jangka panjang telah terbukti berkorelasi kuat dengan risiko komplikasi mikrovaskular dan makrovaskular pada diabetes. Penelitian ini bertujuan menganalisis korelasi antara kontrol glikemik yang dinilai melalui HbA1C dengan status inflamasi sistemik yang diukur melalui Hs-CRP sebagai predictor resiko kardiovaskular pada pasien diabetes melitus tipe 2.

Metode

Studi potong lintang analitik pada 53 pasien T2DM di Klinik Prolanis Jakarta Timur (purposive sampling). Pemeriksaan HbA1c dengan metode HPLC dan Hs-CRP dengan metode Turbidimetric Immunoassay dilakukan di laboratorium PRODIA. Korelasi dianalisis menggunakan uji korelasi Spearman.

Hasil

pada studi ini didapatkan rerata kadar HbA1C adalah 7.2% dan rerata Hs-CRP adalah 2.9 mg/L. Analisis statistik menunjukkan korelasi signifikan antara HbA1C dan Hs-CRP (p-value = 0.014) dengan koefisien korelasi Spearman 0.336.

Kesimpulan

Terdapat korelasi positif yang signifikan antara kadar HbA1c dan Hs-CRP.

Kata Kunci: Risiko Kardiovaskular; HbA1C; hsCR; Inflamasi; Diabetes melitus tipe 2.

INTRODUCTION

The global prevalence of type 2 diabetes mellitus (T2DM) has shown a significant increase due to changes in human lifestyle patterns and behavioral modifications.[1,2] Diabetes has become a leading cardiometabolic disorder, affecting 10.5% of the adult population (aged 20-79 years) in 2021, with projections suggesting an increase to 12.2% by 2045.[2,3] The prevalence is higher in urban areas (12.1%) compared to rural regions (8.3%), and in high-income countries (11.1%) versus low-income nations (5.5%). The most notable relative rise is expected in middle-income countries (21.1%) compared to high-income (12.2%) and low-income countries (11.9%). In Indonesia, T2DM prevalence shows an alarming trend, with rates continuously rising alongside societal changes in lifestyle and diet patterns.

Diabetes mellitus goes beyond being a simple health issue; it is a major risk factor for cardiovascular disease. Diabetic patients face a 2-4 times higher risk of developing coronary heart disease compared to non-diabetic people.[4] Cardiovascular complications are the leading cause of illness and death in diabetic patients, with cardiovascular-related deaths making up 65-75% of all mortalities in this group.[4,5] Poor control of blood sugar levels plays a key role in the development of cardiovascular problems in diabetes. Chronic high blood sugar levels activate various harmful processes, including increased oxidative stress, widespread inflammation, damage to blood vessel lining, and faster buildup of plaque in arteries.1 This creates a harmful cycle that speeds up the development of cardiovascular disease in diabetic patients.[1,2]

Hemoglobin A1c (HbA1c), a long-term indicator of glycemic control, has been shown to correlate with microvascular and macrovascular complications in diabetes.[6] HbA1C reflects the average blood glucose levels over the preceding 8-12 weeks and serves as the gold standard for

monitoring glycemic control in diabetic patients. The American Diabetes Association has recognized an HbA1c level of 6.5% or higher as a diagnostic threshold for diabetes and an HbA1c level of greater than 7% as indicative of poor glycemic control.[6] Conversely, high-sensitivity C-Reactive Protein (Hs-CRP) represents a sensitive systemic inflammatory biomarker that has been recognized as an independent predictor of cardiovascular risk. Low-grade chronic inflammation constitutes a crucial characteristic of type 2 diabetes mellitus and plays a significant role in the development of cardiovascular complications.[7] Elevated Hs-CRP levels in diabetic patients not only reflect systemic inflammatory status but also correlate with glycemic control levels and future cardiovascular event risk.[8,9] Given the concerning projected increase in diabetes prevalence, particularly in middle-income countries such as Indonesia, the identification of predictive biomarkers for cardiovascular risk becomes critically important for timely preventive interventions. Therefore, understanding the relationship between glycemic control and inflammatory status becomes essential in the comprehensive management of diabetic patients.

This study aims to analyze the correlation between glycemic control, as assessed by HbA1c, and systemic inflammatory status, as measured by Hs-CRP, in T2DM patients. Although the relationship between glycemic control and cardiovascular complications in type 2 diabetes mellitus has been extensively documented, research specifically analyzing the correlation between HbA1C and Hs-CRP as systemic inflammatory biomarkers in the Indonesian population remains limited. This study contributes novel insights into understanding the interaction between long-term glycemic control and chronic inflammatory status in T2DM patients in Indonesia, who possess distinct demographic and genetic characteristics compared to Western populations.

METHODS

This analytical cross-sectional study was conducted among participants of the Prolanis Diabetes Clinic in East Jakarta. The total clinic population consisted of 64 individuals with type 2 diabetes mellitus (T2DM, of whom 53 subjects were included using purposive sampling. Five people were excluded due to absence during blood collection, and six people were excluded for showing Hs-CRP results greater than 10 mg/L (indicating the presence of acute systemic inflammation that could be caused by various diseases).[10] Eligible participants were men and women aged 40–60 years with a diagnosis of type 2 diabetes mellitus (T2DM). Exclusion criteria included any known cardiovascular, neurological, malignancy, or pulmonary diseases, as well as any current illness or history of inflammatory conditions that could affect Hs-CRP levels, such as rheumatoid arthritis, gout, or infections.

To justify the sample size, a power estimation was conducted based on the correlation coefficient ($r = 0.81$) reported in a previous study by Reddy et al. (2024)[6], which found a strong positive relationship between HbA1c and Hs-CRP levels in patients with T2DM and myocardial infarction. Assuming a significance level of 0.05 and statistical power of 80% ($\beta = 0.20$), the minimum number of subjects required to detect a statistically significant correlation of similar strength would be considerably less than the 53 subjects included in this study. Therefore, the chosen sample size was considered statistically adequate and appropriate for the study objective.

Venous blood samples were collected and processed by the certified PRODIA Laboratory for HbA1c and Hs-CRP. Hemoglobin A1c was measured using HPLC, standardized under the National Glycohemoglobin Standardization Program (NGSP), with the Tina-quant HbA1c kit on the Cobas Integra analyzer, serving as a marker of long-term glycemic control. Hs-CRP levels were determined using a validated turbidimetric immunoassay method with i-CHROMA™ hsCRP-ALL in one kit (Boditech Med Inc.) to assess systemic inflammation and cardiovascular risk.

The study protocol was reviewed and approved by the Ethics Committee of the Faculty of Medicine, Trisakti University (No.055/KER/FK/II/2023). Descriptive statistics were used to evaluate

demographic and clinical characteristics, with means and standard deviations for continuous variables and percentages for categorical data. The correlation between HbA1c and Hs-CRP was analyzed using Spearman's rank correlation test. Data analysis was conducted with SPSS software.

RESULTS

The distribution of subject characteristics based on gender, age, blood pressure, HbA1C levels, and Hs-CRP is presented in Table 1. This study involved 53 subjects with type 2 diabetes mellitus (T2DM), comprising 36 females (67.9%) and 17 males (32.1%). The age distribution revealed that the majority of subjects were within the 40-60 years age range, accounting for 40 individuals (75.5%), while 13 subjects (24.5%) were aged 60 years or older.

Table 1. Distribution of Subject Characteristics

Variable	Frequency	min	max	mean±SD
Gender				
Men	17 (32.1%)			
Women	36 (67.9%)			
Age (year)				
40 – 60	40 (75.5%)			
>60	13 (24.5%)			
Inflammation risk categories				
Low risk (< 1.0 mg/L)	8 (15.1%)			
Intermediate risk (1.0 – 3.0 mg/L)	28 (52.8%)			
High risk (>3.0 mg/L)	17 (32.1 %)			
Tekanan Darah				
Sistolik (mmHg)		100	202	138.2 ± 19.6
Diastolik (mmHg)		70	115	87.7 ± 9.2
Serum Level				
HbA1c (%)		4.8	11.3	7.2 ± 1.8
Hs-CRP (mg/L)		0.3	9.7	2.9 ± 2.4

The mean systolic and diastolic blood pressure values in this study were 138.2 mmHg and 87.7 mmHg, respectively. The mean HbA1C level among subjects was 7.2%, indicating poor glycemic control. The study results showed a mean Hs-CRP level of 2.9 mg/dL, indicating an intermediate risk. Cardiovascular risk assessment using Hs-CRP levels according to American Heart Association criteria revealed that 8 participants (15.1%) had low risk (Hs-CRP <1 mg/L), 28 participants (52.8%) had intermediate risk (Hs-CRP 1.0-3.0 mg/L), and 17 participants (32.1%) had high risk (Hs-CRP >3 mg/L).[11]

Table 2. Correlation Analysis Between HbA1C, Blood Pressure and Hs-CRP

Variable		Hs-CRP
HbA1C	spearman Correlation	.336**
	Sig.(2-tailed)	.014*
Systolic blood pressure	spearman Correlation	.277**
	Sig.(2-tailed)	.044*
Diastolic blood pressure	spearman Correlation	.059
	Sig.(2-tailed)	.673

Spearman

**Correlation is significant at the 0.05 level (2-tailed)*

***Correlation is significant at the 0.01 level (2-tailed)*

A non-parametric Spearman correlation analysis was performed to assess the relationship between glycemic control parameters, hemodynamic variables, and Hs-CRP as a predictor of cardiovascular risk among 53 patients with T2DM. The results are shown in Table 2. The analysis found a statistically significant positive correlation between HbA1c levels and Hs-CRP concentrations (r = 0.336, p = 0.014). This indicates that higher HbA1c levels are linked with increased Hs-CRP levels, implying a connection between poor glycemic control and cardiovascular risk in diabetic patients.

Regarding hemodynamic parameters, systolic blood pressure demonstrated a significant positive correlation with Hs-CRP levels (r = 0.277, p = 0.044). This finding suggests that elevated systolic blood pressure is associated with increased inflammatory markers, potentially indicating the role of hypertension in cardiovascular risk enhancement through inflammatory pathways. Conversely, diastolic blood pressure showed no significant correlation with Hs-CRP levels (r = 0.059, p = 0.673).

DISCUSSION

Based on the research data presented in Table 2, a distinct pattern of relationship exists between Hs-CRP and the components of systolic and diastolic blood pressure. The Spearman correlation analysis revealed a significant relationship between Hs-CRP and systolic blood pressure (r = 0.277, p = 0.044); however, no significant relationship was found with diastolic blood pressure (r = 0.059, p = 0.673). This finding offers an interesting insight into the interaction between systemic inflammatory markers and cardiovascular hemodynamic parameters in patients with type 2 diabetes mellitus.[8,9] Previous studies have established the relationship between diabetes and the occurrence of hypertension.[12] Diabetes and hypertension can increase each other, and when they occur together, they significantly elevate the risk of cardiovascular disease.[12-14]

Hs-CRP is an inflammatory marker produced by the liver and elevated during inflammation, including the process of atherosclerosis, and has been proven to be a marker that can predict cardiovascular disease risk.[6] This study demonstrated a significant relationship between systolic blood pressure and Hs-CRP but not with diastolic blood pressure. This phenomenon can occur because systolic blood pressure is more sensitive to vascular inflammatory changes compared to diastolic pressure, as systolic pressure reflects the strength of cardiac contraction and the elasticity of larger arterial blood vessels.[15] When chronic inflammation occurs, as indicated by increased Hs-CRP, arterial walls become stiffer and less elastic, which directly affects systolic pressure.[15] Conversely, diastolic pressure more reflects the resistance of smaller peripheral blood vessels and is not significantly influenced by inflammatory processes occurring in larger blood vessels.[14] Poor glycemic conditions trigger systemic inflammation that increases Hs-CRP.[1,2,6] This inflammation contributes to arterial stiffening, which has a greater impact on the systolic component of blood pressure.[15] Therefore, Hs-CRP as a predictor of cardiovascular inflammation demonstrates a stronger correlation with systolic pressure because both reflect vascular damage occurring in major arterial blood vessels, while diastolic pressure remains more stable and is not significantly affected by systemic inflammatory changes measured through Hs-CRP.[15-16]

High blood pressure (hypertension) and diabetes frequently occur simultaneously and increase the risk of cardiovascular disease. Elevated blood glucose levels and high blood pressure can damage the vascular endothelium, subsequently leading to the formation of atherosclerosis.[4-

[5] The fundamental concept of atherosclerosis is arterial hardening due to the gradual accumulation of fatty plaques within the vessel walls. This plaque accumulation restricts blood flow.[4]

Atherosclerosis begins with endothelial activation, followed by a cascade of events such as lipid accumulation and fibrous proliferation.[5] Non-enzymatic glycation reactions between glucose and proteins or lipoproteins in arterial walls are one of the key mechanisms responsible for the accelerated formation of atherosclerosis under hyperglycemic conditions in type 2 diabetes mellitus.[15] Prolonged exposure to hyperglycemia is believed to be a primary factor in the development of atherosclerosis in diabetes. Hyperglycemia causes numerous changes at the cellular level of vascular tissue that can potentially speed up the atherosclerotic process. [17-18]

Another important biochemical process accompanying type 2 diabetes mellitus is the formation of Advanced Glycation End Products (AGEs). These AGEs likely also underlie the general inflammatory process.[19] The formation and accumulation of AGEs are associated with aging processes and are accelerated in diabetes.[20] AGEs are produced under hyperglycemic conditions, but their production also occurs in situations characterized by oxidative stress and inflammation.[18] Activation of AGE receptors can induce cascading inflammatory responses that cause increased inflammation, oxidative stress, enhanced calcium deposition, and increased vascular smooth muscle apoptosis. This contributes to the development of atherosclerosis. [21]

The synergistic reaction between hypertension and hyperglycemia causes atherosclerosis formation through at least two mechanisms: elevated hemodynamic pressure in hypertensive conditions damages the endothelium and upregulates the renin-angiotensin-aldosterone system, oxidative stress, and inflammation, which contribute to the close relationship between diabetes and hypertension.[22]

High-sensitivity C-reactive protein (Hs-CRP) is a systemic inflammatory marker that emerges as an independent risk factor for cardiovascular disease.[23-24] Elevated Hs-CRP levels are associated with increased risk of thrombotic events, including myocardial infarction. Increased Hs-CRP levels are also associated with increased risk of developing diabetes later in life. Furthermore, it has been found that Hs-CRP levels are higher in diabetic patients compared to those without diabetes.[25-27] This study demonstrated a significant relationship between Hs-CRP and HbA1c. This finding is consistent with studies conducted by Seo HY, Khairinisa G, and Reddy KSS, which reported that HbA1c levels increased significantly with increasing Hs-CRP levels.[6,7] In contrast to the study conducted by Sari EP (2023), which stated that her study results showed no significant correlation between HbA1c levels and CRP (p-value=0.171 and r=0.218).[8] The key differences between this study and Sari EP (2023) involve measurement sensitivity and sample size. Sari used a semi-quantitative latex agglutination method for CRP with a detection threshold of 0.6 mg/dL (6 mg/L), which is less sensitive for detecting low-grade inflammation compared to our validated turbidimetric immunoassay capable of measuring Hs-CRP below 0.1 mg/L. Hs-CRP's superior sensitivity allows identification of subtle inflammatory changes specifically relevant to cardiovascular risk assessment. The sample size difference is also crucial; Sari's 24 subjects versus our 53 participants significantly affect statistical power to detect associations.[8]

Hs-CRP directly participates in the pathogenesis of atherosclerosis by inducing inflammation in endothelial cells and coronary arterial smooth muscle cells. Hs-CRP levels in various morbidity and mortality assessments are considered one of the factors taken into account and are added to the Framingham score as predictor factors, enhancing cardiovascular risk prediction. While this study identified a statistically significant correlation between HbA1c and Hs-CRP, potential confounding factors must be acknowledged. Variables such as BMI, lipid profile, and medications—particularly statins, anti-inflammatory agents, and metformin—are known to influence systemic inflammation. Previous studies have demonstrated that metformin reduces Hs-

CRP levels by suppressing the secretion of proinflammatory cytokines in hepatocytes and macrophages, indicating anti-inflammatory properties beyond glucose control.[28] However, due to data limitations, these variables were not adjusted for in the current analysis. Future studies incorporating multivariable regression models are warranted to control for confounding variables and clarify the independent relationship between glycemic control and systemic inflammation.

CONCLUSION

This study shows a strong positive link between HbA1c and Hs-CRP levels in T2DM, indicating that poor blood sugar control is connected to increased systemic inflammation. Additionally, Hs-CRP has a significant relationship with systolic blood pressure but not with diastolic blood pressure, implying that inflammatory markers mainly influence arterial stiffness and larger vessel function. These results support using Hs-CRP as an important biomarker for assessing cardiovascular risk in diabetic patients, especially when combined with measures of glycemic control.

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AUTHORS CONTRIBUTION

The concept, analysis, and interpretation of data, drafting manuscript: Putri MA. Collecting data, assisted in developing research methodology: MAP, PA, DA, YI. Critical review of the manuscript: PA, DA, YI.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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