

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

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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 tentang Kadar HbA1c dan hs-CRP pada Diabetes Melitus Tipe 2

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ABSTRACT

Background: Diabetes mellitus represents a major risk factor for cardiovascular disease. Diabetic patients have a 2-4 fold higher risk of developing coronary heart disease compared to non-diabetic populations. Cardiovascular complications are the primary cause of morbidity and mortality in diabetic patients, with cardiovascular-related deaths accounting for 65-75% of total deaths in the diabetic population. Poor glycemic control is a key factor in the pathogenesis of cardiovascular complications in diabetes. Chronic hyperglycemia triggers various pathophysiological mechanisms, including increased oxidative stress, systemic inflammation, endothelial dysfunction, and accelerated atherosclerosis. Hemoglobin A1c (HbA1c) as a long-term glycemic control parameter has been proven to strongly correlate with microvascular and macrovascular complications in diabetes. This study aims to analyze the relationship between glycemic control assessed through HbA1c and systemic inflammatory status measured through hs-CRP in type 2 diabetes mellitus patients. Methods: This study employed an analytical cross-sectional design with 59 type 2 diabetes mellitus subjects. The ELISA technique was used to assess HbA1c levels as glycemic control parameters, hs-CRP as inflammatory predictors, and NT-ProBNP as heart failure risk markers. Results: 55.9% of subjects showed poor glycemic control (HbA1c $\geq$ 6.5%). Based on hs-CRP levels, 28.8% showed high inflammatory risk, 10.2% experienced acute inflammation, and 47.5% showed average risk. Statistical analysis revealed a significant correlation between HbA1c and hs-CRP (p-value = 0.026) with a Pearson correlation coefficient of 0.290. Conclusion: A significant relationship exists between HbA1c and hs-CRP as inflammatory markers.

Keywords: Cardiovascular risk; type 2 diabetes mellitus; HbA1c; hs-CRP; inflammation

ABSTRAK

Latar Belakang: Diabetes melitus 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 hubungan antara kontrol glikemik yang dinilai melalui HbA1C dengan status inflamasi sistemik yang diukur melalui hs-CRP pada pasien diabetes melitus tipe 2. Metode: Penelitian ini menggunakan desain analitik potong lintang dengan 59 responden diabetes melitus tipe 2. Teknik ELISA digunakan untuk menilai kadar HbA1C sebagai parameter kontrol glikemik, hs-CRP sebagai prediktor inflamasi, dan NT-ProBNP sebagai penanda risiko gagal jantung. Hasil: 55,9% responden menunjukkan kontrol glikemik buruk ($HbA1C \geq 6,5\%$). Berdasarkan kadar hs-CRP, 28,8% menunjukkan risiko inflamasi tinggi, 10,2% mengalami inflamasi akut, dan 47,5% menunjukkan risiko rata-rata. Analisis statistik menunjukkan korelasi signifikan antara HbA1C dan hs-CRP ($p\text{-value} = 0,026$) dengan koefisien korelasi Pearson 0,290. Kesimpulan: Terdapat hubungan signifikan antara HbA1C dan hs-CRP sebagai penanda inflamasi.

Kata kunci: Diabetes melitus tipe 2; HbA1C; hsCRP; inflamasi

INTRODUCTION

The global prevalence of type 2 diabetes mellitus (T2DM) has demonstrated a significant escalation attributable to alterations in human lifestyle patterns and behavioral modifications.^(1,2) Diabetes has emerged as a predominant cardiometabolic disorder, affecting 10.5% of the adult population (aged 20-79 years) in 2021, with projections indicating an increase to 12.2% by 2045.^(2,3) The prevalence exhibits higher rates 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 substantial relative increase is projected to occur in middle-income countries (21.1%) compared to high-income (12.2%) and low-income countries (11.9%). In Indonesia, T2DM prevalence demonstrates an alarming trend, with continuously rising incidence rates paralleling societal changes in lifestyle and dietary patterns.⁽¹⁾

Diabetes mellitus extends beyond an isolated health concern, constituting a principal risk factor for cardiovascular disease. Diabetic patients exhibit a 2-4 fold elevated risk of developing coronary heart disease compared to non-diabetic populations.⁽⁴⁾ Cardiovascular complications represent the primary cause of morbidity and mortality in diabetic patients, with cardiovascular-related deaths accounting for 65-75% of total mortality in the diabetic population.^(4,5) Poor glycemic control serves as a pivotal factor in the pathogenesis of cardiovascular complications in diabetes. Chronic hyperglycemia triggers various pathophysiological mechanisms, including enhanced oxidative stress, systemic inflammation, endothelial dysfunction, and accelerated atherosclerosis.⁽¹⁾ This condition creates a vicious cycle that accelerates the progression of cardiovascular disease in diabetic patients.^(1,2)

Hemoglobin A1C (HbA1C), as a long-term glycemic control parameter, has been demonstrated to strongly 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. 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 relationship between glycemic control assessed through HbA1c and systemic inflammatory status measured through hs-CRP in type 2 diabetes mellitus 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 the Prolanis Diabetes Clinic population in East Jakarta. A total of 59 subjects were selected using purposive sampling through questionnaire interviews, meeting inclusion criteria of male and female participants aged 40-60 years with type 2 diabetes mellitus. Exclusion criteria comprised individuals with comorbidities such as cardiovascular, neurological, malignancy, and pulmonary diseases, as well as those with current illness or history of conditions that could elevate hs-CRP levels including severe infections, non-infectious inflammatory diseases such as gout arthritis, rheumatoid arthritis, and cancer. Blood plasma samples were collected for HbA1c examination as glycemic control parameters and hs-CRP as cardiovascular risk markers, conducted professionally in collaboration with PRODIA Laboratory using ELISA technique. The research protocol was approved by the Ethics Committee of Trisakti University Faculty of Medicine (No. 055/KER/FK/II/2023). Univariate analysis was performed to present descriptive data including age, gender, blood pressure, HbA1c and hs-CRP levels, with numerical data presented as mean and standard deviation while nominal data were expressed as percentages. Data processing was conducted using SPSS statistical software with Pearson correlation analysis to assess the relationship between HbA1c and hs-CRP levels.

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 59 subjects with type 2 diabetes mellitus, comprising 41 females (69.5%) and 18 males (30.5%). The age distribution revealed that

the majority of subjects were within the 40-60 years age range, accounting for 46 individuals (77.9%), while 13 subjects (22.0%) were aged >60 years.

The mean systolic and diastolic blood pressure values in this study demonstrated a mean systolic blood pressure of 138.9 mmHg and diastolic blood pressure of 87.9 mmHg. The mean HbA1c level among subjects was 7.3%. Twenty-six subjects (44.1%) were classified as having normal glycemic control (HbA1c <6.5%), while 33 subjects (55.9%) were categorized as having diabetes ($\geq 6.5\%$), indicating poor glycemic control. The study results showed a mean hs-CRP level of 4.3 mg/dL. Based on the inflammatory risk classification according to hs-CRP levels, 17 subjects (28.8%) exhibited high inflammatory risk (>3.0 mg/L) and 6 subjects (10.2%) experienced acute inflammation (>10 mg/L). Nearly half of the participants, 28 subjects (47.5%), demonstrated average inflammatory risk (1.0-3.0 mg/L), while 8 subjects (13.6%) had low risk (<1.0 mg/L).

A non-parametric Spearman correlation analysis was conducted to examine the relationships between glycemic control parameters, hemodynamic variables, and hs-CRP as a cardiovascular risk predictor among 59 patients with type 2 diabetes mellitus. The results of the correlation analysis are presented in Table 2. The analysis revealed a statistically significant positive correlation between HbA1c levels and hs-CRP concentrations ($r = 0.386$, $p = 0.003$). This moderate correlation indicates that poorer glycemic control, as reflected by elevated HbA1c levels, is associated with increased hs-CRP levels, suggesting a relationship between chronic hyperglycemia and systemic inflammation in diabetic patients.

Regarding hemodynamic parameters, systolic blood pressure demonstrated a significant positive correlation with hs-CRP levels ($r = 0.311$, $p = 0.016$). 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 ($r = 0.092$, $p = 0.487$).

DISCUSSIONS

Based on the research data presented in Table 2, there is a distinct pattern of relationship 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 ($r=0.311$; $p=0.016$), however, no significant relationship was found with diastolic blood pressure ($r=0.092$; $p=0.487$). This finding provides an interesting insight into how systemic inflammatory markers interact with 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.(10) Diabetes can increase the risk of hypertension and vice versa, and the simultaneous presence of diabetes and hypertension can increase the risk of more serious disease complications such as cardiovascular disease.(10-12)

Hs-CRP is an inflammatory marker produced by the liver and elevated during inflammation, including in the process of atherosclerosis, and has been proven as 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.(13) When chronic inflammation occurs, as indicated by increased hs-CRP, arterial walls become stiffer and less elastic, which directly affects systolic pressure.(13) 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.(13) 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.(13,14)

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 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 (lipid accumulation, fibrous proliferation). (5) Non-enzymatic glycation reactions between glucose and proteins or lipoproteins in arterial walls represent one of the important mechanisms responsible for accelerated atherosclerosis formation under hyperglycemic conditions in type 2 diabetes mellitus. (15) Prolonged exposure to hyperglycemia is believed to be a primary factor in the pathogenesis of atherosclerosis in diabetes. Hyperglycemia induces numerous changes at the cellular level of vascular tissue that potentially accelerate the atherosclerotic process. (16)

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. (17) The formation and accumulation of AGEs are associated with aging processes and are accelerated in diabetes. (17) 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.(19)

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.(20)

High-sensitivity C-reactive protein (hs-CRP) is a systemic inflammatory marker that emerges as an independent risk factor for cardiovascular disease. 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. (21,22) This study demonstrated that hs-CRP and HbA1c showed a significant relationship between them. This is consistent with studies conducted by Yoo Han Seo, Khairinisa G, and Reddy KSS, which stated that HbA1c levels increased significantly with increasing hs-CRP.(6,7) In contrast to the study conducted by Evi Puspita Sari (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)

Hs-CRP directly participates in the pathogenesis of atherosclerosis through the inflammation of endothelial cells and coronary arterial smooth muscle cells. hs-CRP levels in various morbidity and mortality assessments are considered as one of the factors taken into account and as one of the predictor factors added to the Framingham score that enhances cardiovascular risk prediction.

CONCLUSIONS

This study demonstrates a significant positive correlation between HbA1c and hs-CRP levels in type 2 diabetes mellitus patients, indicating that poor glycemic control is associated with increased systemic inflammation. Additionally, hs-CRP showed a significant correlation with systolic blood pressure but not with diastolic blood pressure, suggesting that inflammatory markers preferentially affect arterial stiffness and larger vessel dynamics. These findings support the use of hs-CRP as a valuable biomarker for cardiovascular risk assessment in diabetic patients, particularly when combined with glycemic control parameters.

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AUTHORS CONTRIBUTION

The Concept, analysis, and interpretation of data, drafting manuscript: Putri MA. Collecting data, assisted in developing research methodology: Putri MA, Amani P, Adriani D, Imran Y. Critical review of the manuscript: Amani P, Adriani D, Imran Y.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose

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Table 1. Distribution of Subject Characteristics

Variable	Frequency	min	max	mean±SD
Gender				
Men	18 (30,5%)			
Women	41 (69,5%)			
Age (year)				
40 – 60	46 (77,9%)			
>60	13 (22,0%)			
Glycemic control status				
Good glycemic control (< 6,5%)	26 (44,1%)			
Poor glycemic control (≥6,5%)	33 (55,9%)			
Inflammation risk categories				
Low risk (< 10 mg/L)	8 (13,6%)			
Average risk (1,0 – 3,0 mg/L)	28 (47,5%)			
High risk (>3,0 mg/L)	17 (28,8%)			
Acute inflammation (> 10 mg/L)	6 (10,2%)			
Tekana Darah				
Sistolik (mmHg)		100	202	138,9 ± 18,9
Diastolik (mmHg)		70	115	87,9 ± 9,0
Serum Level				
HbA1c (%)		4.8	11.3	7.3 ± 1.9
hs-CRP (mg/L)		0.3	28.0	4.3 ± 5,1

Table 2. Correlation Analysis Between Glycemic Control Parameters and Cardiovascular Risk Markers

		Hs-CRP
HbA1C	spearman	.386**
	Correlation	
	Sig.(2-tailed)	.003*
Systolic blood pressure	spearman	.311**
	Correlation	
	Sig.(2-tailed)	.016*
Diastolic blood pressure	spearman	.092
	Correlation	
	Sig.(2-tailed)	.487

Spearman

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

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

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