JHeS (Journal of Health Studies)
Vol. 8, No. 2 (2024), pp. 73-83
https://doi.org/10.31101/jhes.3747

e-ISSN 2549-3353
p-ISSN 2549-3345

Original Research Paper

Correlation between ESR and hs-CRP Levels with HbA1c in diabetes mellitus patients

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Submitted: June 26, 2024 Revised: July 23, 2024 Accepted: September 18, 2024

Abstract
Subclinical inflammation and almost every indication of systemic inflammation, which is defined by elevated levels of inflammatory markers in the blood, are seen in patients with diabetes mellitus (DM). Understanding the relationship between inflammatory markers and glycemic control is essential for creating comprehensive management strategies to avoid diabetes-related complications. The aims of this study were to determine the correlation between erythrocyte sedimentation rate (ESR) and high-sensitivity C-reactive protein (hs-CRP) and glycated hemoglobin (HbA1c) in DM patients. This was an analytical observational study with a cross-sectional design that was conducted on 35 DM patients from the DM prolanis group at the Bangkalan Regency First-Level Health Facility. HbA1c and hs-CRP levels were measured using the fluorescence immunoassay (FIA) method, while ESR was assessed using the Westergren method. Statistical analysis was performed using the Spearman correlation test. Regarding the biomarkers, all respondents (100%) had HbA1c levels >8.0%, 43% had elevated hs-CRP levels associated with cardiovascular risk, and 80% had abnormal ESR values. A significant relationship was found between ESR and HbA1c ($p = 0.019$; $r = 0.394$), but no significant relationship was observed between hs-CRP and HbA1c ($p = 0.351$; $r = 0.163$). The relationship between inflammation and glycemic control in DM can be understood through the correlation of ESR, hs-CRP, and HbA1c. These findings offer practical value, particularly in monitoring disease progression and managing diabetes-related complications. Future research should investigate the effects of interventions aimed at reducing inflammation, e.g lifestyle modifications or anti-inflammatory medications, on ESR, hs-CRP, and HbA1c levels.

Keywords: diabetes melitus; erythrocyte sedimentation rate; hs-CRP; HbA1c; inflammatory

1. Introduction

Diabetes Mellitus (DM) is a group of metabolic disorders by elevated blood sugar levels (hyperglycemia). While there is no cure for this disease, blood sugar levels in patients can be managed (Puspita Sari & Sayekti, 2023). In 2021, the global prevalence of DM reached 6.1%, affecting 529 million people, and it is projected that the prevalence will increase by up to 2.5 times by 2050 (Ong et al., 2023). Based on the Indonesian Basic Health Research (Riskesdas) in 2018, the prevalence of DM in Indonesia was 1.5% or 1,017,290 people (Ministry of Health of the Republic of Indonesia, 2019). In East Java, the prevalence of DM reached 2.02%, which is higher than the national average (Ministry of Health of the Republic of Indonesia, 2019).

Metabolic disorders and insulin resistance are the main causes of Type 2 Diabetes Mellitus. The hallmark of diabetes mellitus is persistent hyperglycemia, which can lead to various complications. As a key indicator of long-term glycemic control, glycated haemoglobin (HbA1c) levels reflect the average blood glucose levels over the past two to three months. Poor glycemic control is indicated by HbA1c levels above 7%, which can double the risk of both short-term and long-term complications of diabetes (Suharni et al., 2021). These complications include diabetic nephropathy (Kang et al., 2015; Lee et al., 2018), retinopathy (Lind et al., 2019; Poshtchaman et al., 2023), and cardiovascular diseases (Adel et al., 2022; Butalia et al., 2024; Jiao et al., 2023; Sinning et al., 2021).

In the pathophysiology of diabetes, inflammation plays a crucial role in addition to glycemic control. Hyperglycemia induces the production of superoxide radicals (0_2^-), which can lead to cellular damage. Inflammatory cytokines such as IL-6, are activated in response to cell damage as part of the inflammatory response (Amelia et al., 2019). The presence of inflammation is an important factor to monitor in the progression of this disease (Elbaruni et al., 2023). Erythrocyte Sedimentation Rate (ESR) and high-sensitivity C-Reactive Protein (hs-CRP) are useful biomarkers for detecting acute-phase responses and monitoring inflammatory conditions (Elbaruni et al., 2023).

ESR values can increase due to tissue damage and inflammation caused by either acute or chronic to infection. Even in the absence of obvious infection, ESR levels in diabetic patients may be elevated, suggesting that diabetes can lead to mild inflammation (Nataliya et al., 2023). Higher blood glucose levels may exaworsen the inflammatory response, as several studies have found a substantial association between e;evated ESR values and HbA1c levels. In patients with Type 2 Diabetes Mellitus, previous studies have reported a moderate correlation ($r = 0.506$) between HbA1c and ESR, emphasizing the importance of monitoring both parameters to prevent diabetes-related complications (Nataliya et al., 2023). Elevated levels of both HbA1c and ESR are associated with an increased risk of lower extremity amputation and longer hospital stays (Al-Nimer & Ratha, 2022; Bikramjit et al., 2017).

In addition, another inflammatory marker that has been found to be associated with HbA1c levels is high-sensitivity C-reactive protein (hs-CRP). Patients with poorly managed diabetes often have elevated levels of hs-CRP, which is linked to a higher risk of cardiovascular events. This association underscores the potential use of hs-CRP, alongside HbA1c and ESR, as predictive markers for assessing the general health of diabetic patients and guiding treatment interventions (Bikramjit et al., 2017; Elbaruni et al., 2023). To develop a comprehensive management strategy focused on reducing inflammation and improving glycemic control, it is crucial to understand the relationship between ESR, hs-CRP, and HbA1c in diabetes management.

Although some previous studies have shown that higher HbA1c levels are associated with inflammatory markers such as CRP and ESR, other research has not found a significant relationship between these parameters (Ermawati et al., 2023; Permatasari et al., 2020; Wahyuningsih et al., 2019). Considered the inconsistent findings across these studies, further research is needed to better understand the relationship between inflammatory markers and glycemic control in different populations and clinical situations. This study aims to examine the correlation between Erythrocyte Sedimentation Rate (ESR), high-sensitivity C-Reactive Protein (hs-CRP), and HbA1c in patients with diabetes mellitus (DM) in the DM prolanis group.

2. Research Methods

The research was conducted between December 2023 and April 2024. The study used an analytical observational design with a cross-sectional approach. Purposive sampling was employed to select participants based on the following criteria: the participants were members of the DM Prolanis group under the First Level Health Facility Prolanis of Bangkalan Regency; they underwent HbA1c, ESR, and hs-CRP examinations at the Farmalab Medical Laboratory; and their HbA1c levels were ≥8.5%. A total of 35 individuals participated in this study.

HbA1c and hs-CRP were examined using the Fluorescence Immunoassay (FIA) method. The principle of this method is that the antibody detector in the buffer binds to the sample antigen, forming an antigen-antibody compound. This compound then migrate to the nitrocellulose matrix, where it is captured by the HbA1c antibody on the test strip. The greater the number of antigens in the sample, the more antigen-antibody complexes are formed, resulting in a stronger fluorescence signal. The intensity of the fluorescence signal from the antibody detector correlates with higher levels of HbA1c in the blood specimen.

The results of HbA1c examination were categorized into three groups: good (HbA1c < 6.5%), medium (HbA1c 6.5-8.0%), and poor (HbA1c > 8.0%) (Wibowo et al., 2019). Similarly, the hs-CRP results were categorized into three groups: normal (hs-CRP ≤ 3 mg/L), cardiovascular risk (hs-CRP 3.1-10 mg/L), and infection initiation (hs-CRP >10 mg/L) (Finecare, 2016).

The ESR examination was conducted using the Westergren method, with a 45° slope for 7 minutes. The level is determined by observing the height of the plasma column and comparing it to the scale on the tube. The ESR results are categorized into two groups: normal and abnormal. Normal ESR values are 0-15 mm/hour in males and 0-20 mm/hour in females, while abnormal ESR values are >15 mm/hour in males and >20 mm/hour in females (Hidriyah et al., 2018).

The results of the normality test indicated that the data was not normally distributed, so Spearman's correlation was used for the analysis. Data analysis was performed using IBM SPSS Statistics 22 software. This study has been declared ethically feasible by the Health Research Ethics Commission (KEPK) of the Health Polytechnic of the Ministry of Health Surabaya No.EA/2114/KEPK-Poltekkes_Sby/V/2024.

3. Results and Discussion

3.1.Results

Based on Table 1, it is clearly known that the majority of respondents are female (66%), with 23 individuals. The largest age group is the elderly (4-65 years old), comprising 27 individuals (77%).

Table 1. Distribution of respondents based on gender, age, and laboratory test results (HbA1c, ESR and hs-CRP)

Variable	Amounts	Percentages (%)
Gender		
Male	12	34
Female	23	66
Total	**35**	**100**
Age		
Adult (26 – 45 years)	2	6
Elderly (46 – 65 years)	27	77
Senior (>65 years)	6	17
Total	**35**	**100**
Levels HbA1c		
Good (<6.5%)	0	0
Moderate (6.5-8.0%)	0	0
Poor (>8.0%)	35	100
Total	**35**	**100**
ESR value		
Normal	7	20
Abnormal	28	80
Total	**35**	**100**
Level hs-CRP		
Normal (≤ 3 mg/L)	14	40
Cardiovascular Risk (3.1-10 mg/L)	15	43
Infection Risk (> 10 mg/L)	6	17
Total	**35**	**100**

Source: Primary Data, 2024

Table 1 explains that all respondents comprising 35 people (100%) fall into the group with poor HbA1c levels (HbA1c >8.0%). The majority of the results of the hs-CRP level examination indicated cardiovascular risk, with 15 people (43%) and 80% of respondents were included in the category of abnormal ESR values.

Table 2. Spearman Correlation Test

Variable	Sig. value (p-value)	Correlation Coefficient (r)
ESR with HbA1c	0.019	0.394
hs-CRP with HbA1c	0.351	0.163

Source: Primary Data, 2024

Based on the results of the Spearman correlation test presented in Table 2, it was found that there was a significant relationship between the ESR value and HbA1c (p-value 0.019<0.05). In contrast, the correlation between hs-CRP and HbA1c shiwed no significant relationship, with a p-value of 0.351. The correlation coefficient (r) between ESR and HbA1c was 0.394, indicating a moderate relationship. Meanwhile, the r value for the hs-CRP and HbA1c was 0.163, suggesting both r values low and very low levels of relationship.

3.2.Discussion

The results of this study explain that the majority of respondents are female (66%). These findings are consistent with research by Milita et al. (2021) and Mnatzaganian et al. (2024), which reported that the majority of diabetic mellitus respondents in the study were female, at 55.4% and 54.2%, respectively. Women tend to have more adipose tissue than men, which results in higher fat levels (Kautzky-Willer et al., 2016; Milita et al., 2021). After menopause phase, fat tends to accumulate in the abdominal area, increasing the risk of central obesity. Insulin resistance is closely related to an increase in visceral and subcutaneous abdominal fat (Kusters et al., 2017; Liu et al., 2018). The occurrence of an increase in excessive amounts of free fatty acids can stimulate glucose production, leading to insulin signaling disruption, because glucose cannot be properly delivered into cells (Widastra et al., 2015). According to Kautzky-Willer et al. (2023), menopause is associated with an increase in blood pressure, LDL cholesterol, and HbA1c, along with negative changes in body fat distribution, all of which contribute to impaired glucose tolerance (IGT). During menopause, estrogen levels also decrease, and this hormone plays an important role in glucose metabolism, including insulin secretion and sensitivity (Ciarambino et al., 2022; Tramunt et al., 2020). These factors may contribute to the higher incidence of DM cases in women.

In contrast to the findings of this study, some other studies have reported that diabetes mellitus (DM) is more common in men (Alrashed et al., 2024; Kautzky-Willer et al., 2016; Li et al., 2020; Tramunt et al., 2020). Biological, sociocultural, and psychosocial factors, including economic, environmental, and behavioral factors such as lifestyle, contribute to this disparity (Kautzky-Willer et al., 2016; Sujata & Thakur, 2021). Unhealthy lifestyles such as alcohol consumption and smoking are associated with an increased risk of DM in men. Compared to women, men generally have higher rates of alcohol consumption and smoking, both of which can lead to liver damage, vascular disorders, negatively affect insulin sensitivity and β-cell function (Bathna et al., 2019; Maddatu et al., 2017; Siahaan et al., 2023; Song & Lin, 2023).

More than three-quarters of the respondents in this study are classified as elderly (46-65 years old). Older age is a major risk factor for both diabetes and prediabetes (Junker et al., 2021; Xia et al., 2021). Type 2 diabetes mellitus is commonly diagnosed in individuals over the age of 45, a critical age range for increased vulnerability to the disease (Milita et al., 2021). Tanoey and Becher (2021) found that the prevalence of diabetes increases with age, with more than half of diabetes cases occurring in individuals aged >50 years.

Based on the analysis of HbA1c levels, it was found that all respondents in this study were classified in the poor category (HbA1c > 8.0%). This finding is in line with research by Nataliya et al (2023), which reported that 28 respondents (68.6%) had an HbA1c result of >7%. HbA1c provides an estimate of average blood glucose levels over the past 2-3 months, as the lifespan of glucose-bound erythrocytes is 120 days (Zulfian et al., 2020). As an indicator of glycemic control, HbA1c reflects the severity of disease progression in people with diabetes (Casadei et al., 2021). HbA1c levels exceeding >7% are associated with twice the risk of developing complications (Suharni et al., 2021). Furthermore, high levels of HbA1c (>6.0%) are associated with an increased risk of ischemic stroke by up to eight times (Nomani et al., 2016).

The researcher found that the majority of respondents had abnormal ESR scores, with 80% falling into this category. This result aligns with the research of Herman et al. (2022), where there was an increase in ESR values in 21 respondents (64%). ESR levels can increase if there is tissue damage and inflammation due to acute or chronic infection (Nataliya et al., 2023). The occurrence of vascular inflammation will trigger an increase in the release of pro-inflammatory cytokines (Niawaty, 2022). This condition causes increased levels of plasma proteins, especially fibrinogen. Fibrinogen is a plasma protein that plays a role in the blood clotting process. Fibrinogen increases in response to inflammation. Increased levels of fibrinogen increase the tendency of red blood cells to clot, facilitating the formation of rouleaux. This agglutination causes red blood cells to settle faster, resulting in a higher ESR (Herman et al., 2022; Tishkowski & Gupta, 2023). Increased ESR levels can also be observed in physiological conditions such as menstruation, pregnancy after the third month, and age factors (Ermawati et al., 2023). Based on Yuliana's research (2023), where most of the respondents are elderly, they have high ESR levels. Researchers estimate that this result is due to the fact that the respondents are experiencing inflammation, both due to infectious diseases and the entry of foreign proteins into the blood. In the elderly, there is a decrease in organ function (degenerative) which can reduce the body's immunity, making them more susceptible to disease and making the elderly tend to have weak physical conditions.

An increase in hs-CRP levels can be an indication of inflammation in the body, including chronic inflammatory conditions such as diabetes mellitus (DM) and its complications (Permatasari et al., 2020; Stanimirovic et al., 2022). According to Finecare (2016), hs-CRP results are classified into three categories: normal (≤ 3 mg/L), cardiovascular risk (3.1–10 mg/L), and indications of infection (> 10 mg/L). The results of this study show that the majority of respondents belong to the cardiovascular risk category (43%). The majority of respondents with high hs-CRP levels were also found by Puspita Sari and Sayekti (2023), which was 66.7%. Results in the range of 3.1-10 mg/L are also referred to as Low Grade Chronic Inflammation (LGCI), which is a condition in which chronic inflammation occurs in a low degree or level (Dinh et al., 2019). According to Permatasari et al (2020), DM is one of the chronic inflammatory diseases that can result in an increase in CRP synthesis, but the increase in levels is not significant. High CRP levels are generally found in DM patients as an inflammatory response to complications in patients (Kalma, 2018). Several research results show that high CRP levels can predict the risk of various complications in DMT2 patients, such as diabetic nephropathy (Lin et al., 2023; Stanimirovic et al., 2022; Tang et al., 2022), diabetic retinopathy (Naveen Nishal G et al., 2022; Qiu et al., 2020), and cardiovascular disorders (Guo et al., 2023; Tian et al., 2019).

Based on the results of the Spearman correlation test, there was a significant correlation between ESR levels and HbA1c (p-value 0.019<0.05). The finding is consistent with the previous study by Nataliya et al. (2023), which also found a positive correlation between HbA1c levels and ESR values. High levels of both HbA1c and ESR are associated with poorer clinical outcomes, particularly in conditions such as diabetic foot ulcers. Patients with elevated HbA1c and ESR are more likely to undergo lower extremity amputation and experience longer hospital stays (Bikramjit et al., 2017;

Elbaruni et al., 2023). However, the results of this study contrast with those of Ermawati et al. (2023), who reported no correlation between ESR and HbA1c. This discrepancy may be due to the influence of multiple factors on ESR levels. According to Alende-Castro et al. (2019), factors such as age, gender, unhealthy lifestyle, and metabolic disorders—including obesity—are associated with elevated ESR levels.

Physiological conditions such as menstruation, pregnancy after the third month, and aging can also affect elevated ESR levels (Ermawati et al., 2023). ESR levels will increase with age. Erythrocyte sedimentation will increase by 0.85 mm/hour with every 5-year increase in age (Long & Vodzak, 2018). The cause of the increase in ESR, when viewed from the age factor, is not a clear reason, but this is evidenced by an increase in fibrinogen levels, which is one of the factors that increase ESR levels (Masito, 2020). Increased ESR can also result from inflammation caused by other diseases, such as rheumatic fever, cancer, and bacterial or viral infectious diseases, such as hepatitis and liver cirrhosis (Yuliana, 2023).

The results of this study showed no significant correlation between hs-CRP and HbA1c. Similar findings have been reported in other studies (Permatasari et al., 2020; Wahyuningsih et al., 2019). However , other research presents contrary results. A research conducted by Seo and Shin (2021) found that as hs-CRP levels increased, HbA1c levels also rose significantly, even after adjusting for factors such as age, Body Mass Index (BMI), waist circumference, triglyceride levels, and high blood pressure. The results of the study showed that the high level of inflammation detected by hs-CRP was associated with decreased glycemic control in diabetic patients.

The synthesis of CRP in the liver begins in response to stimulation, causing the concentration of CRP in the serum to rise above 5 mg/L within a relatively short period, typically 4 to 6 hours. CRP has a half-life of 18 hours and reaches its peak level in about 48 hours. As tissue damage (inflammation) subsides, hs-CRP levels gradually return to normal values, usually within 3 to 7 days after peaking. In contrast, ESR levels rise more slowly, taking 24 to 48 hours to increase, and may take several weeks to return to normal after reaching peak levels (Mulawardi et al., 2022). In this study, the majority of respondents had hs-CRP levels within the Low-Grade Chronic Inflammation (LGCI) range, indicating a moderate increase in hs-CRP due to inflammation (Dinh et al., 2019). This explains why the normal hs-CRP results in this study were relatiely high, reaching 40%. The significant correlation observed between hs-CRP levels and HbA1c can be attributed to this moderate elevation in inflammation markers.

4. Conclusion

In this study, most respondents were female (66%) and elderly (46 – 65 years old) (77%). The majority had hs-CRP levels indicating cardiovascular risk (43%) and abnormal ESR values (80%). All respondents (100%) had poor HbA1c levels (HbA1c >8.0%). A significant relationship was found between ESR and HbA1c (p-value 0.019; r=0.394), while no significant relationship was observed between hs-CRP and HbA1c (p-value 0.351; r=0.163). The association between inflammation and glycemic management in diabetes mellitus is highlighted by the observed relationship between ESR, hs-CRP, and HbA1c. These results offer practical implications for tracking disease progression managing diabetes-related complications. Future research should explore the effects of interventions aimed at reducing inflammation (such as lifestyle modifications or anti-inflammatory medications) on ESR, hs-CRP and HbA1c levels.

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