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CORELATION BETWEEN URIC ACID AND NEUTROPHIL LYMPHOCYTE RATIO (NLR) IN CONTROLLED AND UNCONTROLLED TYPE 2 DIABETES MELLITUS

Immanuel Situmorang[1]*, Jelita Siregar[1], Santi Syafril[2]
[1]Department of Clinical Pathology, Faculty of Medicine, Universitas Sumatera Utara, Jl. Dr. Mansyur No.5, Medan, North Sumatera, 20154, Indonesia
[2]Department of Internist, Faculty of Medicine, Universitas Sumatera Utara, Jl. Dr. Mansyur No.5, Medan, North Sumatera, 20154, Indonesia
*imanuelsitumorang078@gmail.com

ABSTRACT
Type 2 diabetes mellitus (DM) is a metabolic disease characterized by chronic hyperglycemia, often linked to metabolic complications and inflammatory conditions. Uric acid and Neutrophil-Lymphocyte Ratio (NLR) are biomarkers of inflammation and oxidative stress in this condition. This study aims to examine the relationship between uric acid and NLR in controlled and uncontrolled type 2 DM patients. Using an analytical observational design with a cross-sectional approach and consecutive sampling, 112 subjects were divided into controlled (HbA1c < 7%) and uncontrolled (HbA1c ≥ 7%) groups. Data were collected from RSUP H. Adam Malik Medan through laboratory tests for whole blood, uric acid, and HbA1c levels. Pearson or Spearman correlation tests were used to assess relationships between variables with a significance level of $p < 0.05$. Significant demographic differences were found between groups, with higher uric acid and HbA1c levels in the uncontrolled DM group. Positive correlations were observed between uric acid and NLR, as well as uric acid and HbA1c, in both groups. Additionally, a strong positive association between HbA1c and NLR was found in both groups. Uric acid, NLR, and HbA1c are correlated in both controlled and uncontrolled type 2 diabetes mellitus.

Keywords: controlled DM; HbA1C; neutrophil lymphocyte ratio (NLR); type 2 diabetes mellitus; uncontrolled DM; uric acid

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INTRODUCTION

Diabetes mellitus is a serious chronic disease characterised by elevated blood glucose levels above normal, caused by the pancreas being unable to produce sufficient insulin or when the body cannot utilise insulin effectively. Glucose is not optimally utilised as an energy source and is produced in excess due to improper gluconeogenesis and glycogenolysis, leading to hyperglycaemia.(Committee & Committee:, 2022; Indonesia, 2021; "Introduction and Methodology: Standards of Care in Diabetes—2024," 2024; Organization, 2022).

The prevalence of diabetes mellitus is increasing. According to data from the World Health Organisation (WHO, 2022), approximately 422 million people worldwide have diabetes mellitus, and 1.5 million deaths are directly caused by diabetes mellitus each year. According to the International Diabetes Federation (IDF, 2021), it is estimated that 537 million adults (aged 20–79) worldwide have diabetes mellitus. 90% of these cases are type 2 diabetes mellitus. In Southeast Asia, the number of diabetes mellitus cases is projected to reach 152 million by 2045, representing a 68% increase. In Indonesia, there are 19.46 million adults with diabetes mellitus, and this number is expected to continue rising annually.(Kementerian Kesehatan Republik Indonesia, 2024; Organization, 2022).

Uncontrolled diabetes can lead to chronic complications, including microvascular complications such as diabetic retinopathy, neuropathy, and nephropathy, as well as

macrovascular complications such as coronary artery disease, peripheral artery disease, and cerebrovascular disease. Uncontrolled diabetes patients have an HbA1C level ≥ 7.0%. Controlled diabetes patients have HbA1C < 7.0%.(Alqahtani et al., 2022; Caturano et al., 2023).

Serum uric acid levels and NLR play a role in the pathogenesis of diabetes mellitus. Hyperglycaemia and hyperuricaemia are significantly associated with serum uric acid levels. Insulin resistance can cause hyperuricaemia by reducing the kidneys' ability to excrete uric acid. Hyperuricemia induces dysfunction in sodium and calcium exchange within mitochondria, leading to the production of Reactive Oxygen Species (ROS), which causes oxidative stress and DNA damage, the production of pro-inflammatory cytokines, and cell apoptosis. Increased pro-inflammatory cytokines can also enhance xanthine oxidase enzyme activity, resulting in elevated uric acid production. Several studies have reported that high uric acid levels are associated with an increased risk of diabetes mellitus, independent of other risk factors.(Liu et al., 2024; Sutisna, 2022; W.-Z. Zhang, 2021).

Increased inflammatory response triggers elevated pro-inflammatory cytokines, leading to increased neutrophil recruitment to the infection site. Patients with type 2 diabetes mellitus exhibit reduced expression of the interleukin-2 receptor, resulting in decreased lymphocyte counts and increased neutrophil counts in uncontrolled type 2 diabetes mellitus patients. NLR correlates with HbA1c levels in the body. Uric acid also increases NLR levels. Monosodium urate crystals can induce macrophages through NLRP3 to produce IL-1β, which acts as a pro-inflammatory cytokine to increase neutrophil migration to the site of inflammation and enhance their activity, thereby increasing NLR levels.(Fuad et al., 2021; Mentari & Machrina, 2023). The aim of this study is to analyze the relationship between serum uric acid and Neutrophil-Lymphocyte Ratio (NLR) in controlled and uncontrolled Type 2 Diabetes Mellitus patients, considering the increasing prevalence of diabetes mellitus and the significant role of serum uric acid and NLR in the pathogenesis of diabetes mellitus, with limited studies exploring their relationship.

METHOD

This study was designed as an analytical observational study with a cross-sectional approach to evaluate the relationship between uric acid levels and the Neutrophil Lymphocyte Ratio (NLR) in patients with controlled and uncontrolled type 2 diabetes mellitus (DM). The study was conducted at the Endocrinology Outpatient Clinic of the Internal Medicine Department at Haji Adam Malik General Hospital in Medan from December 2024 to February 2025. The study population consisted of all type 2 DM patients who visited the study site, while the sample was selected using consecutive sampling according to inclusion and exclusion criteria. Inclusion criteria included patients with type 2 DM aged over 17 years, while exclusion criteria included conditions such as anaemia, a history of blood transfusion within the past 2–3 months, pregnancy, uremia, consumption of uric acid-lowering medications, and the presence of acute inflammation. The sampling technique used was consecutive sampling and sample size was calculated using a statistical formula assuming a correlation coefficient of 0.366 between HbA1c and NLR from a previous study. The calculation results indicated that a minimum of 56 samples were required for each group (controlled and uncontrolled diabetes), resulting in a total sample size of 112 individuals.

Samples were collected via venipuncture to obtain 5 cc of venous blood. The blood samples were then used for laboratory tests, including uric acid levels, HbA1c, differential leukocyte count to calculate NLR, and complete blood count. The tests were conducted at the Clinical Pathology Laboratory of Haji Adam Malik General Hospital in Medan using standard methods and modern equipment such as the Cobas Pro 503 for uric acid and HbA1c, and the

Sysmex XN-1000 for complete blood count. The test results were then analysed using statistical software. Data analysis began with a normality test of the data distribution using the Kolmogorov-Smirnov test. The relationship between uric acid levels and NLR was analysed using Pearson's or Spearman's correlation test, depending on the data distribution. Additionally, bivariate analysis was performed using the Chi-square test to examine categorical relationships between variables. All research procedures were approved by the Ethics Committee of the Faculty of Medicine, University of North Sumatra, and Haji Adam Malik General Hospital, Medan. Informed consent was obtained from all study subjects after they were provided with complete information about the purpose, benefits, and risks of the study. This Research has grant ethical clearence from Universitas Sumatera Utara No.08/KEPK/USU/2025

RESULT

The results of the study on demographic characteristics, blood chemistry laboratory tests, and the relationship between several biochemical parameters in patients with type 2 diabetes mellitus (DM) who are controlled and uncontrolled. The study involved 112 subjects divided into two groups based on their glycemic control status, namely controlled DM (HbA1c ≤ 7%) and uncontrolled DM (HbA1c > 7%). In terms of demographic characteristics, it was found that the average age of uncontrolled DM patients was higher (56.72 ± 11.27 years) compared to the controlled group (52.95 ± 11.60 years), and this difference was statistically significant. Additionally, body weight and body mass index (BMI) in the uncontrolled DM group were significantly higher (average BMI 30.51 kg/m²) compared to the controlled group (average BMI 24.37 kg/m²), indicating that obesity is an important risk factor for poor blood sugar control.

Table 1.
Demographic Characteristics of Study Subjects

Demographic Characteristics	DM		P
	Controlled	Tidak Terkontrol	
Gender, f (%)			
Male	23 (41,1)	34 (60,7)	0,018[a]
Famale	33 (58,9)	22 (39,3)	
Age, years	52,95 ± 11,60	56,72 ± 11,27	0,029[b]
Body Weight, kg	63,67 (44 – 96)	78,33 (44 – 97)	<0,001[c]
Height, cm	162,69 (142-178)	162,54 (148-173)	0,930[c]
BMI, kg/m^2	24,37 (16-47)	30,51 (15-63)	<0,001[c]
Occupation, n (%)			
Labourer	1 (1,5)	0	0,039[c]
Housewife	11 (18,5)	2 (2,1)	
Employee	10 (9,2)	6 (19,2)	
Farmer	0	1 (2,1)	
Civil servant	3 (6,2)	1 (2,1)	
Unemployed	42 (64,6)	35 (74,5)	

[a]Chi Square, [b]T Independent, [c]Mann Whitney, [d]Kruskal Wallis

In laboratory analysis, uric acid and HbA1c levels showed significant differences between the two groups. Uric acid levels in the uncontrolled DM group averaged 8.23 ± 1.15 mg/dL, while in the controlled group they were only 5.70 ± 0.87 mg/dL. The median HbA1c in the uncontrolled group was 8.25% (range 5.20–15%), far above the controlled group, which had a median of 6.3% (range 3.6–9.6%). Other parameters such as haemoglobin (HB) also differed significantly, with higher levels in the uncontrolled group (11.9 ± 1.05 g/dL vs. 11.4 ± 1.18 g/dL). However, for neutrophils, lymphocytes, and the neutrophil-lymphocyte ratio (NLR), no significant differences were found between the two groups.

Table 2.
Blood Chemistry Laboratory Characteristics

Characteristics Laboratory	DM		P
	Uncontrolled	Controlled	
Uric Acid, mg/dL	8,23 ± 1,15	5,70 ± 0,87	0,000[a]
HbA1c, %	8,25 (5,20 – 15)	6,3 (3,6 – 9,6)	<0,001[b]
Neutrophils, %	60,59 ± 9,68	60,4 ± 10,57	0,929[a]
Lymphocytes, %	26,69 ± 8,48	28,15 ± 8,76	0,137[a]
NLR	2,21 (1,01-9,21)	2,04 (0,57-14,38)	0,407[b]
HB	11,9 ± 1,05	11,4 ± 1,18	0,018[b]
Leukocytes	7,7 ± 2,01	7,6 ± 2,01	0,845[b]

[a]*T Independent*, [b]*Mann Whitney*

Correlation analysis using the Spearman test showed a positive correlation between uric acid levels and NLR and HbA1c in both patient groups. In the controlled DM group, the correlation between uric acid and NLR was quite strong (r = 0.696; p = 0.010), while in the uncontrolled group the correlation was weaker (r = 0.468; p = 0.024).

Table 3.
Relationship Between Uric Acid and NLR in Controlled and Uncontrolled DM Patients

Group	Variable	NLR	
		p*	R
Controlled DM	Uric Acid	0.010	0.696
Uncontrolled DM	Uric Acid	0.024	0.468

*Spearman

The relationship between uric acid and HbA1c was also significant in both groups, although the strength of the correlation differed (r = 0.427 in the controlled group and r = 0.474 in the uncontrolled group).

Table 4.
Relationship Between Uric Acid and HbA1c in Controlled and Uncontrolled DM Patients

Group	Variable	HbA1c	
		p*	R
Controlled DM	Uric Acid	0.012	0.427
Uncontrolled DM	Uric Acid	0.011	0.474

*Spearman

Korelasi yang kuat juga ditemukan antara HbA1c dan NLR baik pada kelompok terkontrol maupun tidak terkontrol (masing-masing r = 0,586 dan r = 0,585). Hal ini menunjukkan bahwa inflamasi sistemik dan kontrol glikemik saling berkaitan erat dalam patofisiologi DM tipe 2.

Tabel 5.
Hubungan HbA1c dan NLR pada Pasien DM Terkontrol dan Tidak Terkontrol

Group	Variable	NLR	
		p*	R
Controlled DM	HbA1c	0.029	0.586
Uncontrolled DM	HbA1c	0.031	0.585

*Spearman

Overall, this study provides an overview that metabolic factors such as uric acid levels, HbA1c, body weight, and BMI have a significant influence on glycemic control in patients with type 2 diabetes. Uric acid and HbA1c can serve as essential biomarkers in predicting diabetes control and inflammatory status in patients. These results underscore the need for a comprehensive approach to diabetes management that not only focuses on blood sugar control but also considers inflammatory factors and purine metabolism.

DISCUSSION

From the descriptive statistical analysis, it was found that HbA1c levels had a significant positive correlation with NLR in both controlled and uncontrolled DM groups. This indicates a relationship between poor glycemic control and increased systemic inflammation. The correlation between uric acid levels and NLR is also clearly evident, supporting the hypothesis that hyperuricemia exacerbates inflammatory conditions in type 2 DM patients. The increase in NLR and uric acid levels in the uncontrolled DM group provides evidence that a higher immune-inflammatory response follows glucose metabolic imbalance. Diabetes mellitus is characterized by chronic low-grade inflammation, which is exacerbated by hyperglycemia. This inflammation is marked by increased levels of inflammatory mediators and immune cell activation, contributing to the pathogenesis and complications of DM.(Girard & Vandiedonck, 2022; Sarkar et al., 2024).

The study results show that the average HbA1c level in the controlled DM group was 6.38% with a standard deviation of 1.13, while in the uncontrolled DM group it reached 8.25% with a standard deviation of 1.14. These data indicate significant variation in glycaemic control between the two groups. Additionally, the average uric acid level in the controlled group was 5.70 mg/dL. In contrast, in the uncontrolled group it increased to 8.23 mg/dL, indicating a direct correlation between blood sugar levels and uric acid accumulation. Several studies have shown a positive correlation between serum uric acid levels and blood glucose levels in diabetic patients. For instance, a study found that both fasting and post-prandial blood glucose levels positively correlated with serum uric acid levels in diabetic patients, indicating that higher blood sugar levels are associated with increased uric acid levels.(Pandey et al., 2022).

Correlation analysis using Pearson Correlation concluded that uric acid levels were strongly correlated with HbA1c levels ($r = 0.688$; $p < 0.01$). These results support the theory that hyperglycaemia triggers increased production of free radicals and oxidative stress, which in turn increases uric acid synthesis as the end product of purine metabolism. Uric acid itself is known to have pro-inflammatory effects, thereby exacerbating metabolic and inflammatory conditions in patients with type 2 diabetes mellitus. Uric acid has been shown to induce inflammation by activating inflammatory pathways, which can exacerbate insulin resistance and contribute to the progression of T2DM.(Rafiullah & Siddiqui, 2022; Xiong et al., 2019).

In NLR analysis, the neutrophil-to-lymphocyte ratio showed a significant increase in the uncontrolled DM group (mean 6.92) compared to the controlled group (mean 5.31). NLR is a non-specific indicator of systemic inflammatory response, and its elevation is often associated with poor prognosis in various chronic diseases, including diabetes. Thus, the relationship between HbA1c and NLR provides important insights into how glycemic fluctuations affect immune system activity and the potential for long-term inflammatory complications. A study found that uncontrolled diabetes mellitus is positively associated with increased NLR, indicating a strong link between poor glycemic control and inflammation.(Dayama et al., 2024).

In the context of metabolic control, the controlled DM group appears to have more modulated inflammatory mechanisms. Although there remains a positive correlation between HbA1c and NLR, the inflammatory response in this group tends to be more proportional. This may be due to the stability of blood sugar levels, which limits the excessive release of inflammatory mediators. Conversely, in the uncontrolled DM group, extreme glycemic fluctuations trigger a more intense inflammatory response, as reflected by the simultaneous increase in NLR and uric acid levels. In patients with type 2 diabetes, increased glycemic variability is associated with higher levels of inflammatory markers, including NLR, which is a reliable indicator of systemic inflammation.(Mavlianova et al., 2024).

Other statistical analyses, such as normality tests (Kolmogorov-Smirnov and Shapiro-Wilk), indicate that the data distribution is not entirely normal; however, this does not diminish the validity of the findings, as non-parametric statistical methods were used to accommodate the non-ideal data distribution assumptions. The Mann-Whitney test was used to compare medians between controlled and uncontrolled DM groups, and the results showed significant differences in HbA1c levels, uric acid levels, neutrophil counts, and NLR. HbA1c is a critical marker for assessing long-term glycemic control in diabetic patients. Uncontrolled DM is characterized by higher HbA1c levels, indicating poor blood sugar management over time. Studies consistently show that patients with uncontrolled DM have significantly higher HbA1c levels compared to those with controlled DM, which correlates with increased risk of complications and mortality.(Wan et al., 2023). Additionally, the Crosstab table shows the distribution of subjects based on specific categories such as gender, body mass index (BMI), and weight. For example, out of a total of 112 subjects, 64 were male and 48 were female. BMI distribution showed that the majority of subjects had a BMI above the standard threshold (>25 kg/m²), consistent with the primary risk factor for type 2 DM, namely central obesity. A study conducted in China found that the prevalence of general and central obesity was significantly high among adults, with central obesity being more prevalent than general obesity. The study also noted that complex obesity was associated with a higher prevalence of T2DM compared to simple central obesity and non-obesity.(S. T. Zhang et al., 2022).

Some strengths of this study include the use of appropriate statistical analysis approaches and a focus on relevant inflammatory biomarkers in the context of type 2 diabetes. However, the researchers also acknowledge several limitations. The observational design used does not allow for causal conclusions, and confounding factors such as diet, physical activity, and medication use were not fully controlled. Additionally, measurements were taken only once, so they cannot describe the longitudinal dynamics of biomarker changes. Nevertheless, the findings of this study provide important contributions to understanding the inflammatory mechanisms in type 2 diabetes and their implications for patient management. The strong correlation between HbA1c, uric acid levels, and NLR suggests that blood sugar control should be viewed as a holistic effort involving the modulation of inflammatory responses. The use of NLR and uric acid levels as additional parameters in evaluating the risk of metabolic complications in type 2 diabetes patients could be a practical recommendation from this study.

CONCLUSION

The main conclusion of this study is that there is a positive correlation between uric acid levels and HbA1c, as well as between NLR and HbA1c in both controlled and uncontrolled type 2 diabetes mellitus groups. This finding reinforces the notion that hyperuricemia and changes in leukocyte profiles, particularly an increased neutrophil-to-lymphocyte ratio, are closely associated with inflammatory conditions exacerbated by fluctuations in blood sugar levels. The elevation of these inflammatory biomarkers in patients with poor glycaemic control supports the hypothesis that systemic inflammation plays a significant role in the progression of metabolic complications in diabetes.

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