

RESEARCH ARTICLE

**Uric Acid Levels Related to HbA1c Levels In Type 2 DM Patients  
Prolanis Participants  
(Chronic Disease Management Program)**

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**Abstract:** Diabetes mellitus (DM) is a metabolic disease characterized by hyperglycemia due to abnormalities in insulin secretion, insulin action or both. DM cases in the world reach 463 million people, and it is estimated that it will increase in 2045 to reach 700 million people. Almost all provinces in Indonesia have seen an increase including North Sumatra, which increased from 1.8% to 2% in 2018. HbA1c has become the most widely used and accepted test to monitor glycemic control in individuals with diabetes. This study aims to determine the relationship between uric acid levels and HbA1c levels in prolanis patients with type 2 DM. Descriptive analytical research with *a cross sectional* research design of data collection using secondary data from medical records. The study sample was patients diagnosed with type 2 DM disease who entered the inclusion criteria and exclusion was obtained using *purposive sampling* with a total of 37 patients. Data analysis was carried out using *a person* correlation test with a meaning limit if  $p < 0.05$ . The results showed that there was a significant relationship between uric acid levels and HbA1c levels ( $p = 0.014$  and  $r = 0.402$ ). This means that the higher the HbA1c level, the higher the uric acid level. There is a significant relationship between uric acid levels and HbA1c levels.

**Keywords:** uric acid levels, HbA1c, type 2 DM

## INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease characterized by hyperglycemia due to abnormalities in

insulin secretion, insulin action or both.<sup>1</sup> DM can be classified based on its cause, namely type 1 DM, type 2 DM, gestational DM, and other types of DM2. Type 2 Diabetes

Mellitus (DMT2) is the most common DM with a 95% incidence rate in the world, caused by decreased insulin secretion by the pancreatic gland.<sup>1,2</sup>

According to *The International Diabetes Federation* (IDF) in 2019, DM cases in the world reached 463 million people, and is expected to increase by 2045 to reach 700 million people.<sup>3</sup> In Indonesia itself, the prevalence of diabetes mellitus increased from 6.9% to 8.5% in 2018. Almost all provinces in Indonesia have seen an increase including North Sumatra, which increased from 1.8% to 2% in 2018.<sup>4</sup>

The criteria for type 2 diabetes were based on glycated hemoglobin (HbA1c)  $\geq 6.5\%$  or fasting blood sugar (GDP)  $\geq 126$  mg/dL or blood sugar level 2 hours after meals (GD2PP)  $\geq 200$  mg/dL or classic symptoms of hyperglycemia accompanied by random blood sugar level (GDA)  $\geq 200$  mg/dL.<sup>5</sup>

Gout is the end product of the metabolism of purine nucleotides produced in the human body. Gout is synthesized in the liver and catalyzed by the enzyme xanthine oxidase, carried by the blood to be filtered into the kidneys, reabsorbed and excreted through the urine. A state of uric acid levels in the blood exceeding the normal limit of  $>7.0$  mg/dl for men and  $>6.0$  mg/dl for women is called hyperuricemia.<sup>6</sup>

HbA1c is defined as hemoglobin that is irreversibly glycated at one or both i.e. N-terminal of the beta chain. HbA1c has become the most widely used and accepted test for monitoring glycemic control in individuals with diabetes. Once the hemoglobin molecule has been glycated, it

continues to be in red blood cells for the rest of its life (120 days). HbA1c is a reliable indicator of diabetes control except in the following situations: Situations where the average red blood cell lifespan is significantly  $<120$  days will usually result in low HbA1c results because 50% of glycation occurs in 90-120 days.<sup>7</sup>

PROLANIS is a health service system with a proactive approach that is implemented in an integrated manner involving participants, health facilities and BPJS Kesehatan in the context of health maintenance for BPJS Kesehatan participants who suffer from chronic diseases to achieve an optimal quality of life with effective and efficient health service costs.<sup>8</sup>

The state of hyperglycemia results in uric acid excretion competing with glucose excretion so that it causes a decrease in uric acid excretion from the body and hyperuricemia occurs. This happens because of excess blood glucose which will also be excreted with urine through the kidneys. High glucose in the blood causes the kidneys to be unable to filter all the glucose thus, a further state of impaired kidney performance that occurs in diabetics, and can also interfere with uric acid excretion then cause uric acid levels to increase in the blood (hyperuricemia).<sup>9</sup>

Increased serum uric acid and HbA1c in patients with diabetes mellitus are associated with reabsorption of damaged uric acid in proximal tubules in diabetic individuals. Increased uric acid levels are risk factors for peripheral artery disease, insulin resistance, and metabolic syndrome

components. Excessive gout will lead to increased production of *reactive oxygen species* (ROS) which causes inflammation and dysfunction in blood vessels.<sup>10</sup> Research conducted by Kuar Jaspinder, et al. In 2022, it was known that there was an increase in uric acid levels to HbA1c levels in DM patients. Another research was conducted by Rusdiana, et al. In 2018, there was no significant relationship between HbA1c values and uric acid levels in DM patients.

From the description above, there is a difference in the results of the relationship between uric acid levels and HbA1c levels in DM patients. In addition, there have not been many studies that have conducted research on PROLANIS participants. So the researcher wants to conduct another study, whether there is a relationship between uric acid levels and HbA1c levels in patients with type 2 diabetes who participate in PROLANIS.

## METHOD

This study uses analytical descriptive research with *a cross sectional* research design. The study sample was type 2 DM patients at Bhayangkara Hospital Medan City who were PROLANIS participants, inpatients, and patients who had complete data (HbA1c and Gout).

Many samples are determined by the Slovin formula so that the sample number is 37. Samples were selected using *the purposive sampling method*.

Research data in the form of HbA1c levels, age, gender, and uric acid levels were obtained from secondary data, namely patient medical records taken from

November 2022 to January 2023. After the data is collected, recorded, and edited, descriptive analysis is carried out manually and using SPSS software.

This study used a cross-sectional anaemic observation design to find the compatibility of the specified free variable (*viscera fat*) with the bound variable (blood pressure). This research was conducted at the Internal Medicine Polyclinic of Haji Medan Hospital on Jl. H. Hospital no. 47 Kenangan Baru, Percut Sei Tuan District, Deli Serdang Regency, North Sumatra in June 2022 - April 2023. The population taken in this study is patients with type 2 DM at the Endocrine Polyclinic of Haji Medan Hospital who have been confirmed with medical records in the period from February to May 2023.

The data analysis used consisted of univariate and bivariate analysis. Univariate analysis was used to describe the characteristics of the data, while bivariate analysis was used to determine the relationship between viscera fat variables and blood pressure. The results of the correlation test are indicated by the value of the correlation coefficient (*r*) which describes the direction and strength of the relationship. The entire analysis process was carried out using *Statistica Product and Service Solutions* (SPSS) software.

## RESULT

**Table 1. Gender of people with type 2 DM**

Gender	N	Percentage (%)
Man	24	64,9
Woman	13	35,1

Based on table 1, the distribution of patients with type 2 DM who are male is 24

patients (64.9%).

**Table 2. Age of people with type 2 diabetes**

Age	Frequency	Percentage (%)
≤60 y.o	31	83,8
>60 y.o	6	16,2

Berdasarkan tabel 2, karakteristik responden berdasarkan usia diketahui bahwa dari 37 responden, kelompok usia ≤60 tahun merupakan kelompok yang terbanyak yaitu 31 responden (83,8%).

**Table 3. HbA1c Test Results Age ≤60 Years**

HbA1c of DM patients type 2 age ≤60 years old	Frekuensi	Percentage (%)
≤7%	5	16,1
>7%	26	83,9

Based on table 3, the characteristics of respondents based on HbA1c examination in patients aged ≤60 years showed that of 31 respondents, the HbA1c value >7% was 83.9% more.

**Table 4. HbA1c Examination Results Age >60 Years**

HbA1c in type 2 DM patients aged >60 years	Frequency	Percentage (%)
≤8,5%	2	33,3
>8,5%	4	66,7

Based on table 4, the characteristics of the respondents based on the HbA1c examination in patients aged >60 years showed that out of 6 respondents, the HbA1c value >8.5% was 66.7% more.

**Table 5. Patient's Uric Acid Levels**

Gout	n	%	Mean	Min	Max
Normal	5	13,5	6,26	4,50	7,00
Hyperuricemia	32	86,5	8,65	6,20	11,90

Based on table 5, the patient's uric acid level showed that out of 37 respondents, the average value of Hyperuricemia obtained was 8.65. The description of normal gout results was 5 patients with an average of 6.26.

**Table 6. Gout Levels by Gender**

Gender	Gout		Total
	Normal	Hyperuricemia	
Male (%)	5 (13,5)	19 (51,4)	24 (64,9)
Woman (%)	0 (0,0)	13 (35,1)	13 (35,1)
<b>Total (%)</b>	<b>5 (13,5)</b>	<b>32 (86,5)</b>	<b>37 (100)</b>

Based on table 6, that of the 37 patients based on uric acid level examination and by gender, the male group was more numerous than the female group. The results of hyperuricemia in men were found as many as 19 (51.4%) and normal uric acid as many as 5 (13.5%). In women with hyperuricemia, 13 (35.1%) were found.

**Table 7. Gout Screening by Age**

Age	Gout		Total
	Normal	Hyperuricemia	
≤60 y.o	5 (16,1%)	26 (83,9 %)	31 (100%)
>60 y.o	2 (33,3%)	4 (66,7%)	6 (100%)

Based on table 7, from the examination of uric acid levels by age, the highest age group ≤60 years old was 26 (83.9%).

**Table 8. The relationship between uric acid levels and HbA1c**

Variabel	n	R	S
Gout and HbA1c	37	0,352	0,033

In this study, the relationship measured was uric acid levels with HbA1c levels using the Spearman correlation statistical test, a p value = 0.033 was obtained, which means that *the p value* < 0.05. So this shows that there is a significant relationship between uric acid levels and HbA1c.

## DISCUSSION

From table 1, it can be seen that in this study, the most type 2 DM patients occurred in men as many as 24 (64.9%), while women as many as 13 (35.1%). This study is in line with the research conducted by Made et al (2019) regarding the Prevalence of Hyperuricemia in Type 2 DM Patients at Sanglah Denpasar Bali Hospital for the July-December 2017 Period where the research was more male (68%) while female (32%).<sup>9</sup> This is also in line with the research conducted by Ayu et al. (2020) regarding the Overview of HbA1c Levels in Type 2 DM Patients at Sanglah Hospital for the July-December 2017 Period which proves that there are more men (67%), while women are (33%).<sup>10</sup> In a study conducted by Rusdiana et al (2018) regarding the relationship between HbA1c and uric acid levels in patients with type 2 diabetes at the North Sumatra Health Center, Indonesia, it was found that women (69%) were more than men (31%).<sup>11</sup> However, other journals say that this turns out that the distribution of type 2 DM disease can vary and has the same chance between men and women.<sup>12</sup>

From table 2, the results of the research that has been conducted on 37 respondents, the largest group of respondents are found to be 31 (83.3%) who have an age of  $\leq 60$  years. This is in line with the research conducted by Dian et al. (2021) regarding the Achievement of Glycemic Targets and the Analysis of Related Factors in Type 2 Diabetes Patients, the most research samples were obtained at the age of  $\leq 60$  years as many as 99 (68.28%).<sup>13</sup> This is because at the age of 40 years and above will

cause changes in the level of cells, tissues, and continue at the level of the body's organs, the age of 40 years will also experience changes in the ability of pancreatic beta cells to produce insulin later which will affect blood glucose levels.<sup>14</sup>

From table 3, it can be seen that this study patients with type 2 diabetes at the age of  $\leq 60$  years who had HbA1c increased  $>7\%$  as many as 26 patients (83.9%), while patients with normal HbA1c were only 5 patients (16.1%). From table 4.4, it can be seen that this study patients with type 2 diabetes at the age of  $>60$  years who had HbA1c increased  $>8.5\%$  as many as 4 patients (66.7%), while patients with normal HbA1c were only 2 patients (33.3%). This is in line with the research conducted by Ayu et al. (2020) regarding the Overview of HbA1c Levels in Type 2 DM Patients at Sanglah Hospital for the Period of July-December 2017 in a research sample of 64% with an increase in HbA1c.<sup>10</sup> In a study conducted by Nuril et al. (2018) regarding the Overview of HbA1c Levels in Type 2 DM Patients at Wangaya Hospital, it was found that HbA1c increased by as much as (60%) hypothesized to have *underweight*, normal, *overweight* body mass index (BMI), this happens because DM patients who have increased HbA1c can experience weight loss without a clear cause so that when HbA1c levels are checked the BMI the patient is not *overweight*. Then most of them do not exercise regularly, and do not regularly consume antidiabetic drugs.<sup>15</sup>

From table 4, it can be seen that patients with type 2 diabetes have high uric acid levels or hyperuricemia as many as 32

respondents (86.5%), while patients with normal uric acid levels are only 5 patients (13.5%). This is in line with the research conducted by Ilyas et al (2017) regarding the Overview of Gout Levels in Type 2 DM Patients at Kediri City Hospital, a research sample (84.61%) was obtained that experienced hyperuricemia in type 2 DM patients while patients who had normal uric acid levels as much as (15.38%).<sup>14</sup> This illustrates that there is an increase in uric acid levels in patients with type 2 diabetes due to inflammation in patients due to insulin resistance and eventually there will be pancreatic beta cell dysfunction. Inflammation of adipose tissue in patients plays an important role in increasing the activation of pro-inflammatory cytokines and the emergence of insulin resistance states. In addition, the increase in cytokine activity will increase cell apoptosis and tissue necrosis, which will ultimately increase uric acid levels in the serum. The activity of *the enzyme xanthine oxidase* which is a catalyst in the process of forming uric acid which will also further increase the level of uric acid and free radicals in the serum.<sup>14</sup> The kidneys are also organs of the body that play a role in removing metabolic waste that is not needed by the body, one of which is uric acid.

From table 5, it can be seen that people with type 2 diabetes have high levels of uric acid in 19 men (51.4%). This is in line with the research conducted by Made et al (2019) regarding the Prevalence of Hyperuricemia in Type 2 DM Patients at Sanglah Denpasar Hospital Bali for the July-December 2017 Period, it was found that the

research sample was more male than female as many as 36 (52.9%).<sup>9</sup> This is because high uric acid levels generally affect more men than women. This is because women have the hormone estrogen in uric acid metabolism, which is a hormone that is uricosuric. There are 3 forms of estrogen, namely, estradiol, estriol, estron. Estradiol has a special receptor in the kidneys that is able to affect the membrane of the kidney tubules so that it increases the excretion of uric acid through the urine, so that women are able to maintain lower uric acid levels than men. Estradiol is also the most widely produced form of estrogen and dominates overall estrogen levels in the premenopausal phase while in the postmenopausal phase it is dominated by estron which is the weakest group of estrogen. So this in premenopausal women has the advantage of maintaining uric acid levels within normal limits because they still have the production of the hormone estrogen which tends to be more stable.<sup>15</sup>

From table 6, it can be seen that people with type 2 diabetes have uric acid levels that occur at the age of >40 as many as 16 (43.2%). This is in line with the research conducted by Ilyas (2017) regarding the Overview of Uric Acid Levels in Type 2 DM Patients at Kediri City Hospital, it was found that many research samples occurred at the age of 40 and above (57.68%).<sup>14</sup> This is because humans experience physiological changes that drastically decline rapidly after the age of 40. Increasing age can interfere with the body's performance in the synthesis of *Hypoxanthine Guanine Phosphoribosyl Transferase* (HGRT) which has a role in

converting purines into purine nucleotides, high uric acid can be caused because uric acid in the blood, namely purines, is not properly metabolized by the HGRT enzyme so that the purine is metabolized by *the xanthine oxidase* enzyme into uric acid. The process of purine catabolism occurs due to two things, namely purines contained in food and purines contained in endogenous nucleic acids of DNA. Large amounts of uric acid are excreted by the kidneys, but can also be excreted through the gastrointestinal tract, but in small amounts. The increase in the amount of uric acid in the body is due to producing large amounts of uric acid while the excretion of uric acid through urine decreases. This happens because the purine synthesis process does not run normally so that uric acid levels increase.<sup>16</sup>

From table 7, it can be seen that in this study HbA1c increased by 33 samples (89.2%) with hyperuricemia in 32 samples (86.5%), while in controlled HbA1c only 4 samples (10.8%) and had normal uric acid levels of 5 samples (13.5%). Research conducted by Rusdiana et al. (2018) regarding the Relationship between HbA1c and Gout Levels in Patients with Type 2 DM at the North Sumatra Health Center, Indonesia did not find a significant relationship between uric acid levels and HbA1c with a  $p > 0.05$  value.<sup>11</sup> While this is different from the results of my research, in this study significant results were found with a value of  $p = 0.033$ . This is in line with the research conducted by Sanda et al. (2018) regarding uric acid levels correlated with HbA1c in type 2 DM patients, the relationship between uric acid levels and

HbA1c in type 2 DM patients with the result of  $p = 0.018$  indicates a significant positive correlation.<sup>16</sup> This is due to the fact that the higher the HbA1c level, the uric acid in the blood will also increase. The processes of hyperuricemia and insulin resistance increase the activation of *the hexose phosphate shunt* which promotes biosynthesis and purine transformation and promotes uricogenesis. At the same time, insulin can increase uric acid reabsorption in the renal tubules by stimulating *the urate anion transporter* and/or *sodium-dependent ion co-transporter* in the proximal tubule membrane of the kidney..<sup>16</sup>

Type 2 DM is closely related to microvascular damage that has an impact on the occurrence of ischemic local tissues, especially the liver. The ischemic promotes lactic production which inhibits uric acid excretion in the proximal tubules and promotes ischemically-induced *adenosine diphosphate* (ADP) degeneration to *adenine* and *xanthine*. The xanthine *substance* will then be converted by the enzyme *xanthine oxidase* (XO) intermediary into uric acid so that it has an impact on hyperuricemia.<sup>16</sup> Research conducted by Abound, et al (2022) said that Hyperuricemia can affect endothelial dysfunction, which stimulates the renin-angiotensin system while suppressing the nitric oxide system of neurons, resulting in dysregulation of the glucose absorption system.<sup>17</sup> Hyperuricemia causes oxidative stress of mitochondria in various cells, including adipocytes, and is associated with the occurrence of type 2 DM. Hyperuricemia caused by insulin resistance will increase the reabsorption of sodium in

the renal tubules and decrease uric acid excretion, so that the concentration of uric acid in the circulation increases.<sup>16</sup>

## CONCLUSION

The results of the study showed that there was a positive and significant relationship between uric acid levels and HbA1c levels. This means that the higher the HbA1c level, the higher the uric acid level.

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