

Risk Factors For Metformin-Induced Side Effects Among Patients With Diabetes Mellitus At Prof. Dr. W. Z. Johannes Regional General Hospital, Kupang

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ABSTRACT

Type 2 Diabetes Mellitus (T2DM) is a chronic disease with an increasing global prevalence. Metformin is the first-line pharmacological therapy for T2DM; however, its use is frequently associated with gastrointestinal side effects, such as nausea, vomiting, and diarrhea, which may negatively affect patients' adherence to treatment. This study aimed to analyze the risk factors associated with metformin-induced side effects among patients with Type 2 Diabetes Mellitus. This observational analytic study employed a cross-sectional design involving 52 patients with Type 2 Diabetes Mellitus at Prof. Dr. W. Z. Johannes Regional General Hospital, Kupang, from January to June 2024. Data were collected from medical records and structured interviews using a standardized checklist. Bivariate analysis was performed using the Chi-square test and Fisher's Exact test, followed by multivariate logistic regression analysis to identify the dominant risk factors associated with metformin-induced side effects. Age ($p = 0.042$), Body Mass Index (BMI) ($p = 0.043$), and metformin dosage ($p = 0.001$) were significantly associated with the occurrence of metformin-induced side effects. Nausea was the most frequently reported adverse effect, accounting for 85% of all reported side effects, followed by abdominal cramps (11%) and vomiting (4%). All respondents reported taking metformin after meals, as recommended to reduce gastrointestinal adverse effects. Age, Body Mass Index (BMI), and metformin dosage were identified as the primary risk factors associated with metformin-induced side effects among patients with Type 2 Diabetes Mellitus. Nausea was the most commonly reported adverse effect. Appropriate patient education regarding metformin use is essential to minimize adverse effects, improve medication adherence, and optimize treatment outcomes.

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disease characterized by persistent hyperglycemia resulting from impaired insulin secretion, impaired insulin action, or both, and its prevalence continues to increase worldwide (Goyal et al., 2023; Purwoko & Chasanah, 2024). According to the International Diabetes Federation (IDF), approximately 463 million adults aged 20–79 years were living with diabetes worldwide in 2019, representing 9.3% of the global adult population. Diabetes mellitus is classified into four major categories, namely Type 1 Diabetes Mellitus (T1DM), Type 2 Diabetes Mellitus (T2DM), Gestational Diabetes Mellitus (GDM), and other specific types of diabetes (Soelistijo, 2021).

Type 2 Diabetes Mellitus (T2DM) is the most common form of diabetes and is strongly associated with lifestyle factors and genetic predisposition (Septiani et al., 2014). It is estimated that nearly half of individuals with diabetes in Indonesia remain undiagnosed, while only two-thirds of diagnosed patients receive either pharmacological or non-pharmacological treatment. Furthermore, only one-third of treated patients achieve adequate glycemic control, increasing the risk of chronic complications and reducing quality of life (Putra & Achmad, 2017).

According to the 2018 Indonesian Basic Health Research (Riskesdas), the prevalence of physician-diagnosed diabetes mellitus was approximately 2%. The prevalence was higher among women (1.78%) than men (1.21%), with the highest prevalence observed in individuals aged 55–64 years (6.3%) and the lowest prevalence among those aged 15–24 years (0.1%). In East Nusa Tenggara Province, the 2018 Provincial Health Profile reported 74,867 individuals with diabetes mellitus, of whom only 16,968 (22.66%) received healthcare services according to the national standard, indicating a considerable gap in diabetes management.

Metformin, a biguanide oral antihyperglycemic agent, is recommended as the first-line pharmacological therapy for patients with T2DM because of its effectiveness in lowering blood glucose levels, favorable safety profile, and relatively low cost (Soelistijo, 2021). In addition to treating T2DM, metformin may also be prescribed for individuals with prediabetes who are younger than 60 years and obese, as well as women with a history of gestational diabetes mellitus. Despite its therapeutic benefits, metformin is frequently associated with gastrointestinal adverse effects, particularly during the early phase of treatment (Soelistijo, 2021).

A clinical trial conducted in the United States involving patients with T2DM receiving metformin doses of up to 2,550 mg/day reported that more than 5% of patients experienced adverse effects, including diarrhea (53%), nausea or vomiting (26%), flatulence (12%), weakness (9%), and dyspepsia (7%). Other adverse reactions, such as abdominal pain, constipation, abdominal distension, headache, dizziness, upper respiratory tract infection, and taste disturbances, were reported in 1–5% of patients (Farahbod et al., 2021; Okayasu et al., 2012).

Previous studies have consistently demonstrated that nausea is the most common adverse effect associated with metformin therapy. Panamuan et al. (2021) reported that nausea occurred in 31.5% of patients, followed by flatulence (14.8%), hypoglycemia (13%), vomiting (9.3%), and diarrhea (3.6%). That epigastric pain (45.7%), nausea (34.8%), and abdominal bloating (19.6%) were the predominant gastrointestinal complaints among patients receiving metformin therapy (Ayu et al., 2023). Reported bloating (58%) and nausea (45%) as the most frequently observed adverse effects among patients with T2DM (Riwu et al., 2015).

The occurrence of metformin-related adverse effects during the initial phase of therapy may lead patients to discontinue treatment prematurely, resulting in poor glycemic control and failure to achieve therapeutic targets. Consequently, these adverse effects may negatively affect patients' physical well-being, quality of life, and healthcare costs (Panamuan et al., 2021; Putra & Achmad, 2017). Therefore, identifying the factors associated with metformin-related adverse effects is essential to support individualized treatment strategies, improve medication adherence, and optimize diabetes management.

RESEARCH METHODS

This study employed an observational analytic design with a cross-sectional approach. The research was conducted at Prof. Dr. W. Z. Johannes Regional General Hospital, Kupang, from January to June 2024. The study population consisted of patients diagnosed with Type 2 Diabetes Mellitus (T2DM) who received metformin therapy. A total of 52 respondents who met the inclusion and exclusion criteria were included in the study. Data were collected from patients' medical records and structured interviews using a standardized checklist (form check). The independent variables included age, sex, educational level, Body Mass Index (BMI), metformin dosage, and medication administration pattern, while the dependent variable was the occurrence of metformin-related side effects. Data analysis was performed using descriptive statistics to summarize respondent characteristics. Bivariate analysis was conducted using the Chi-square test and Fisher's Exact test to determine the association between each independent variable and the occurrence of metformin-related side effects. Variables that showed significant associations were subsequently analyzed using multivariate logistic regression to identify the dominant risk factors. Statistical significance was determined at a p-value of < 0.05.

RESULTS

Univariate analysis was conducted to describe the baseline characteristics of each study variable. Among the 52 respondents included in this study, 28 (53.8%) experienced metformin-related side effects, whereas 24 (46.2%) did not report any adverse effects. Of the respondents who experienced side effects, nausea was the most frequently reported symptom, affecting 24 respondents (85%), followed by abdominal cramps in 3 respondents (11%) and vomiting in 1 respondent (4%).

Tabel 1. Baseline Characteristics of the Study Participants

Variable	n	%
Age (years)		
41–60	25	48.1
61–80	1	50
81–90	26	1.9
Sex		
Male	19	36.5
Female	33	63.5
Educational level		
Elementary school	4	7.7
Junior high school	14	26.9
Senior high school	20	38.5
Bachelor's degree	14	26.9

Body Mass Index (BMI)		
Normal	35	67.3
Overweight	16	30.8
Obese	1	1.9
Initial metformin dose		
500 mg	33	63.5
1000 mg	10	19.2
1500 mg	9	17.3
Medication administration		
Before meals	0	0
After meals	52	100

Based on Table 1, the age distribution showed that half of the respondents (50.0%) were aged 61–80 years, while 48.1% were aged 41–60 years, and only 1.9% were aged 81–90 years. The sex distribution indicated that more than half of the respondents (63.5%) were female, whereas 36.5% were male. Regarding educational level, the largest proportion of respondents had completed senior high school education (38.5%), followed by junior high school and bachelor's degree graduates, each accounting for 26.9%, while only 7.7% had completed elementary school. Based on Body Mass Index (BMI), most respondents (71.2%) had a normal BMI, 26.9% were overweight, and only 1.9% were obese. Regarding the initial metformin dose, more than half of the respondents (63.5%) received 500 mg, while 19.2% received 1,000 mg and 17.3% received 1,500 mg. Furthermore, all respondents (100%) reported taking metformin after meals in accordance with the recommended method of administration to reduce gastrointestinal adverse effects.

Bivariate analysis was used to examine the relationship between an independent variable and the dependent variable specifically, the side effects of Metformin. Data for each variable were analyzed to determine whether there was a significant association with the occurrence of side effects.

Table 2. Bivariate Test Results Regarding Age

Age (Years)	Side Effect		Total	P Value
	Yes	No		
41–50	2	5	7	0.042*
51–60	11	4	15	
61–70	12	10	22	
71–80	3	4	7	
81–90	1	0	1	
Total	29	23	52	

Based on Table 2, most metformin-related side effects occurred in patients aged 61–70 years (12 respondents), followed by those aged 51–60 years (11 respondents). Statistical analysis showed a significant association between age and the occurrence of metformin-related side effects ($p = 0.042$).

Table 3. Bivariate Test Results Regarding Sex

Sex	Side Effect		Total	P Value
	Yes	No		
Male	12	16	28	0.416*
Female	17	7	24	
Total	29	33	52	

Based on Table 3 metformin-related side effects were reported by 17 female respondents and 12 male respondents. Although the frequency of adverse effects was higher among female patients, bivariate analysis showed no significant association between sex and the occurrence of metformin-related side effects ($p = 0.416$).

Table 4. Bivariate Test Results Regarding Education

Education	Side Effect		Total	P Value
	Yes	No		
Elementary school	2	2	4	0.494*
Junior high school	8	6	14	
Senior high school	9	11	20	
Bachelor's degree	10	4	14	
Total	29	23	52	

Based on Table 4, metformin-related side effects were most frequently reported among respondents with a bachelor's degree (10 respondents), followed by those with senior high school education (9 respondents), junior high school education (8 respondents), and elementary school education (2 respondents). However, bivariate analysis revealed no significant association between educational level and the occurrence of metformin-related side effects ($p = 0.494$), indicating that educational attainment was not associated with the risk of adverse effects among patients with Type 2 Diabetes Mellitus.

Table 5. Bivariate Test Results Regarding BMI

BMI	Side Effect		Total	P Value
	Yes	No		
Normal	17	20	35	0.043*
Overweight	11	3	16	
Obese	1	0	1	
Total	29	23	52	

Based on Table 5, metformin-related side effects were most frequently reported among respondents with a normal Body Mass Index (BMI) (17 respondents), followed by those who were overweight (11 respondents) and obese (1 respondent). Bivariate analysis demonstrated a significant association between BMI and the occurrence of metformin-related side effects ($p = 0.043$), indicating that Body Mass Index was significantly associated with the risk of adverse effects among patients with Type 2 Diabetes Mellitus.

Table 6. Bivariate Test Results Regarding Dose

Dose	Side Effect		Total	P Value
	Yes	No		
500 mg	10	23	33	0.001*
1000 mg	10	0	10	
1500 mg	9	0	9	
Total	29	23	52	

Based on Table 6, metformin-related side effects were reported in 10 respondents receiving a metformin dose of 500 mg, 10 respondents receiving 1,000 mg, and 9 respondents receiving 1,500 mg. In contrast, respondents who did not experience side effects were only found in the 500 mg dose group (23 respondents). Bivariate analysis demonstrated a significant association between metformin dosage and the occurrence of metformin-related side effects ($p = 0.001$), indicating that metformin dosage was significantly associated with the risk of adverse effects among patients with Type 2 Diabetes Mellitus.

Table 7. Bivariate Test Results Regarding Medication Adm

Medication Adm	Side Effect		Total	P Value
	Yes	No		
Before meals	0	0	0	nope*
After meals	24	24	52	
Total	28	24	52	

Based on Table 7, all respondents (100%) reported taking metformin after meals, while none of the respondents took metformin before meals. Among those who took metformin after meals, 28

respondents experienced side effects and 24 respondents did not. Since no respondents reported taking metformin before meals, statistical analysis could not be performed to determine the association between medication administration pattern and the occurrence of metformin-related side effects.

DISCUSSION

The present study demonstrated that age was significantly associated with the occurrence of metformin-related side effects ($p = 0.042$). The findings indicate that the risk of adverse effects increases with advancing age. This result is consistent with previous studies by (Panamuan et al., 2021) and (Yulianto et al., 2020) which reported that gastrointestinal side effects associated with metformin are influenced by several factors, including age, with most affected patients being older than 50 years. This may be explained by age-related physiological changes, particularly the decline in renal function. Since approximately 90% of metformin is excreted unchanged through the kidneys, reduced renal function may increase drug accumulation and consequently elevate the risk of adverse effects.

No significant association was observed between sex and the occurrence of metformin-related side effects ($p = 0.416$). The findings suggest that male and female patients have a relatively similar risk of experiencing adverse reactions during metformin therapy. This result is in agreement with the study conducted by (Ayu et al., 2023) which also reported no significant relationship between sex and gastrointestinal side effects among patients receiving metformin treatment.

Similarly, educational level was not significantly associated with metformin-related side effects ($p = 0.494$). Patients with different educational backgrounds demonstrated a comparable likelihood of experiencing adverse effects. This finding is consistent with (Purwoko & Chasanah, 2024) who reported that educational attainment does not directly influence the occurrence of metformin-related adverse reactions. Nevertheless, adequate patient education remains essential because a better understanding of medication use and its potential side effects may improve patients' ability to recognize adverse reactions early and seek appropriate medical attention. This study also found a significant association between Body Mass Index (BMI) and metformin-related side effects ($p = 0.043$). Patients with overweight or obesity tended to experience adverse effects more frequently than those with normal BMI. Differences in body composition may influence drug pharmacokinetics and alter the body's response to metformin therapy, thereby contributing to variations in gastrointestinal tolerance. This finding is consistent with previous studies indicating that nutritional status is an important factor affecting the occurrence of adverse drug reactions among patients with Type 2 Diabetes Mellitus. Furthermore, metformin dosage was significantly associated with the occurrence of side effects. Higher metformin doses were associated with an increased risk of gastrointestinal adverse reactions. These findings are in line with the study by (Ayu et al., 2023) which reported that patients receiving higher doses of metformin more frequently complained of gastrointestinal disturbances. In addition, patients with impaired renal function may experience a greater risk of adverse effects because reduced drug elimination can lead to metformin accumulation. Therefore, careful dose adjustment according to individual patient characteristics is important to minimize the risk of adverse drug reactions. All respondents (100%) reported taking metformin after meals, in accordance with current clinical recommendations for reducing gastrointestinal adverse effects such as nausea and vomiting. However, despite appropriate medication administration, several patients still experienced adverse reactions. These findings indicate that taking metformin after meals alone is insufficient to completely prevent adverse effects, as other factors, particularly metformin dosage and the patient's clinical condition, also contribute to the occurrence of gastrointestinal intolerance.

Finally, nausea was identified as the most frequently reported adverse effect, accounting for 85% of all adverse reactions, followed by abdominal cramps (11%) and vomiting (4%). These findings are consistent with the known gastrointestinal safety profile of metformin and highlight the importance of patient counseling regarding the expected adverse effects of treatment. Appropriate education on medication use, dose adherence, and early reporting of adverse reactions may improve treatment adherence and optimize therapeutic outcomes among patients with Type 2 Diabetes Mellitus.

CONCLUSIONS AND RECOMMENDATIONS

Metformin remains the first-line pharmacological therapy for the management of Type 2 Diabetes Mellitus (T2DM); however, its use is frequently associated with gastrointestinal adverse effects, particularly nausea. This study demonstrated that age, Body Mass Index (BMI), and metformin dosage were the primary factors associated with the occurrence of metformin-related side effects. Nausea was identified as the most frequently reported adverse effect among patients receiving metformin therapy. Appropriate initial dose adjustment, close clinical monitoring, and

comprehensive patient education regarding the proper use of metformin are essential to minimize adverse effects, improve medication adherence, and optimize treatment outcomes.

Healthcare providers at Prof. Dr. W. Z. Johannes Regional General Hospital, Kupang are encouraged to strengthen patient education regarding adherence to the prescribed metformin dosage and strategies for minimizing gastrointestinal side effects. Improving patients' understanding of appropriate medication use may enhance treatment adherence and patient safety.

Patients are advised to comply with the prescribed metformin dosage and promptly report any adverse effects experienced during treatment. Early identification and appropriate management of side effects may improve therapeutic effectiveness and enhance patients' quality of life.

Future studies are recommended to investigate the side effects of other oral antidiabetic agents, such as acarbose and glimepiride, as these medications may also influence medication adherence and the quality of life of patients with Type 2 Diabetes Mellitus.

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