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# The impact of medication adherence on health outcomes for patients with metabolic syndrome

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**ABSTRACT**: Cardiovascular disease is a non-communicable disease that is often associated with metabolic syndrome (MetS). MetS is a group of abnormal conditions that include hypertension, obesity, and diabetes. Patients with MetS often require multiple drugs to achieve therapeutic targets, but poor medication adherence can lead to complications. Poor medication adherence can worsen the disease and increase hospitalizations. The purpose of this study was to investigate whether medication adherence affects metabolic syndrome outcomes. This study was conducted using a cross-sectional design and purposive sampling. Our respondents were focused on patients with hypertension, diabetes mellitus, or dyslipidemia. Patients' adherence was measured using a self-made questionnaire. The study obtained data on the patient's lipid profile, HbA1c, and blood pressure (hypertension, diabetes, or dyslipidemia). The study used Spearman analysis to investigate adherence scores to lipid profile levels, HbA1c, and blood pressure. Therapeutic coverage was analyzed using a T-test. Confounding variables, such as age, HbA1c level, and blood pressure, were considered when analyzing the correlation between adherence scores and lipid profiles. The majority of patients were women or elderly, and more than 90% reported that their therapeutic needs were met. Total cholesterol and LDL-c significantly negatively correlated with adherence for patients' factor category, therapeutic regimen factor, and overall factor ($p<0.05$). Triglyceride levels correlated significantly with adherence only to category interaction factors between patients and family/health workers. Regression analysis shows that all correlations are negative to total cholesterol, LDL, HDL, and triglyceride levels ($p<0.05$).

**KEYWORDS**: Medication adherence; metabolic syndrome; therapy outcome.

## INTRODUCTION

Metabolic syndrome (MetS) is a group of metabolic dysregulations including insulin resistance, dyslipidemia, central obesity, and hypertension. MetS is associated with many risk factors from various pathophysiological mechanisms. The most common mechanism is insulin resistance, which concurrently occurs in low-level proinflammatory, prothrombotic, and oxidative physiological states [1],[2]. Insulin resistance caused by obesity can trigger the release of non-esterified free fatty acids from adipose tissue. This mechanism supports the occurrence of dyslipidemia. Adipokines that are also secreted by adipose tissue can trigger prothrombotic and proinflammatory states leading to elevated blood pressure and dyslipidemia. If left untreated, MetS can significantly increase the risk of diabetes and cardiovascular disease (CVD), where CVD is still a problem that is the leading cause of morbidity and mortality worldwide [3].

The NCEP/ATP III determines MetS criteria based on the presence of at least 3 of 5 factors: abdominal obesity, triglyceride levels, low high-density lipoprotein (HDL) cholesterol, hypertension, and impaired fasting glucose (IFG), without the exception of diabetes. The therapy goals target reducing the risk of CVD and T2DM, including lifestyle and dietary changes to lose weight, treatment of dyslipidemia, and treatment of hypertension [4],[5]. In Indonesia, using the NCEP ATP III criteria with modified criteria for Asia, MetS reported that the prevalence of metabolic syndrome in Jakarta was 28.4%. The highest component of metabolic syndrome in men was hypertension (84.7%) followed by hypertriglyceridemia (83.4%), central obesity (75.5%), hyperglycemia (50.9%), and low HDL levels (43.6%). Meanwhile, in women, the highest component of the metabolic syndrome was central obesity (91.3%), followed by hypertension (84.1%), hypertriglyceridemia (66.1%), low HDL levels (57.8%), and hyperglycemia (50.2%). Based on the results of the Riskesdas 2018, the

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prevalence of non-communicable diseases continues to increase, especially in hypertension, obesity, and diabetes mellitus [6],[7].

Clinicians usually individually evaluate each of the significant risk factors contributing to metabolic syndrome. However, there is evidence that risk factors are more than just additive. One of the main factors thought to accelerate the other risk factors is insulin resistance [3]. A primary strategy for metabolic diseases has been identifying and treating each symptom individually. This strategy uses several drugs (lipid-lowering agents, anti-hypertensive agents, and/or anti-diabetic agents) given to metabolic syndrome patients. A multi-drug regimen or polypharmacy is a significant problem in treating patients with metabolic diseases due to poor patient adherence, side effects, and drug-drug interactions [8]. Poor medication adherence can increase the incidence of hospitalization in patients with hypertension, dyslipidemia, and diabetes mellitus. In addition, poor adherence can also contribute to disease complications [9]. Therefore, we aimed to investigate how medication adherence affects the outcome of metabolic syndrome.

## MATERIALS AND METHODS

### Materials

We focused only on patients with hypertension, diabetes mellitus, or dyslipidemia. The selected patients were asked to do a blood test and complete an adherence questionnaire. The blood pressure value was obtained from the patient's last visit from the medical record. Patients were excluded if they did not want to have their blood checked or did not want to fill out the questionnaire. This study uses a self-made open-ended questionnaire instrument to assess patient adherence. The patient adherence questionnaire was compiled based on the factors influencing non-adherence consisting of 13 questions. The 13 questions are composed of three parts, namely medication adherence from patient factors (1-4), therapeutic regimen factors (5-8), and interaction factors between patients and health workers/families (9-13). Each question is scored one if it is correct and 0 if incorrect. The patients are categorized as adherence if the percentage score is >50% and non-adherence if the percentage score is ≤50%. The expert has tested the questionnaire to ensure the context is appropriate. In addition, the questionnaire has tested for validity and reliability using 30 respondents who meet the inclusion criteria for the study. We obtained that 13 questions are valid with a correlation coefficient (r) of more than 0.3. The Cronbach Alpha test indicates the questions are reliable, with a value of 0.803 [10],[11]. We used medical records to get patient data, including gender, age, blood pressure, and medication. A simple questionnaire was applied to gather information about the interaction of patients with family/health workers.

### Research design

This study is an analytical observational study with a cross-sectional design conducted in July 2022. Purposive selection of patients assisted by an internist in a hospital with criteria for patients with metabolic syndrome. This research has obtained permission from the Faculty of Medicine, Public Health and Nursing Ethics Committee of Gadjah Mada University with the letter number KE/FK/0629/EC/2022.

### Data analysis

We categorized the patient as not getting therapeutic coverage if the patient had metabolic syndrome but was not given appropriate therapy. Patients are categorized to be therapeutic uncover if blood pressure ≥140/90 mmHg but not receiving hypertension therapy [12] and HbA1C ≥6.5% but not receiving DM therapy [13]. We make therapeutic uncover criteria for antidyslipidemic agents: patients have LDL ≥190 mg/dL not receiving cholesterol-lowering therapy, DM patients aged 40-75 years old but did not receive moderate-intensity statin/high-intensity statin therapy, and TG>500 mg/dL but did not receive fibrates [14],[15].

The characteristics of participants are described in the form of mean ± SD for numerical data and n (%) for categorical data. We used Spearman's correlation coefficient to determine that adherence scores were positively correlated with lipid profiles (total cholesterol, HDL, LDL, and triglycerides) and blood pressure. Identification of the influence/difference of lipid profile on therapeutic coverage using independent t-test. We did linear regression to analyze the correlation between adherence score in each category to lipid profiles considering confounders (age, HbA1c level, and blood pressure). We considered patient factors (age and gender), therapeutic regimen, and interaction between patients with family/health workers as confounders. The significance of all the statistical tests is considered at $p<0.05$ as the threshold for statistical significance.

## RESULTS AND DISCUSSION

### Characteristics of respondents

There were 107 patients in total, but two failed to come in for blood tests, and ten were not interviewed, so 95 patients were included in the final analysis. Table 1 presents the characteristics of the respondents who participated in this study. The study participants were predominantly women and elderly. Nearly half of the patients suffer from diabetes mellitus and hypertension, and more than 90% indicated that their therapeutic needs had been covered. There was a large percentage of women and the elderly among the respondents. Researchers found the possible cause is most subjects were housewives with a sedentary lifestyle [16],[17]. The other reasons are some patients with diabetes and hypertension (particularly men) would have died by the time screening took place (survival bias), later onset diabetes indicates a weaker predisposition to diabetes, and they tend to have low health awareness [18]. According to the univariate analysis, the average age of the sample was more than 60 years old, and the mean systolic blood pressure was higher than 130 mmHg. However, the average diastolic blood pressure was still within a normal range. While the mean total cholesterol and triglycerides were high, the mean HDL and LDL were still within the normal levels. The study was conducted on a group of DM patients whose average HbA1c result was over 6.5%, but the average HbA1c obtained indicated uncontrolled diabetes in the group of patients. Most patients had diabetes mellitus and hypertension, and their average HbA1c level indicated uncontrolled blood sugar. The failure to achieve outcomes while most patients have therapeutic coverage is ironic. This event can be caused by therapeutic inertia. Therapeutic inertia is defined as the provider's failure to change the therapy when treatment goals are unmet. Therapeutic inertia may also be due to patient-related factors, including denial and refusal of treatment intensification due to non-experience with hypertension symptoms [19],[20]. In addition, the therapeutic inertia might indicate a limitation in the dosing of oral medications when maximum doses have been prescribed due to limited choice due to national insurance [21].

**Table 1.** Characteristics of respondents.

| Characteristics | n (%)/mean+SD |
|---|---|
| Female | 64 (67.4) |
| Age (year) | 61.19±9.29 |
| Systolic blood pressure (mmHg) | 134.01±18.99 |
| Diastolic blood pressure (mmHg) | 76.80±11.45 |
| Total cholesterol (mg/dL) | 200.94±58.69 |
| HDL-C (mg/dL) | 51.69±13.48 |
| LDL-C (mg/dL) | 127.01±42.12 |
| Triglycerides (mg/dL) | 192.93±156.08 |
| HbA1c (%) | 8.08±2.14 |
| Therapeutic coverage (yes) | 87 (91.6) |
| Diagnose | |
| Diabetes Mellitus | 14 |
| Hypertension | 12 |
| Dyslipidemia | 1 |
| Diabetes Mellitus + Hypertension | 39 |
| Diabetes Mellitus + Dyslipidemia | 10 |
| Hypertension + Dyslipidemia | 5 |
| Diabetes Mellitus + Hypertension + Dyslipidemia | 14 |

### Effect of therapeutic coverage on lipid profile

The cholesterol total and LDL-c are significantly correlated with adherence from the patient's factor categories, therapeutic regimen factors, and overall factors (Fig 1). Total cholesterol level has a higher correlation value than LDL-c for patient factor categories ($r=-0.38$, $p<0.01$; $r=-0.32$, $p<0.01$, respectively). As for the therapeutic regimen category, LDL had a higher correlation than total cholesterol ($r=-0.27$, $p<0.01$; $r=-0.25$, $p<0.01$, respectively). Regarding the overall adherence score, the adherence correlation was still more significant for total cholesterol than LDL ($r=-0.37$, $p<0.01$; $r=-0.31$, $p<0.01$, respectively). According to the study, there was a negative correlation between total cholesterol and LDL-c for both adherence categories. On the other hand, triglyceride levels significantly correlate with adherence only in category interaction factors between patients and family/health workers ($r=-0.21$; $p=0.04$). The outcome of therapy can be affected by changes in lifestyle that can be made as part of the treatment. Research by Sigit et al. found that patients

adhering to healthy lifestyles, including 150 mins of physical activity per week or 30 mins per day for five days, 400 g fruit and vegetable consumption, no smoking, and no alcohol consumption, may have cardiometabolic health benefits. Especially for men, middle-aged people, overweight, obese, and urban dwellers [22]. Additionally, adherence to therapy is an important thing that can affect the outcome. Treatment adherence can come from internal patients (knowledge and attitudes), drug factors (rules for use, amount of drug, drug effects, and side effects), and soc 0.3 ıpport from health workers/families [23], [24]. A cross-sectional study using a questionnaire from Alefishat et al. in 2016 involving 900 high-risk individuals with metabolic syndrome found that patients' knowledge about metabolic syndrome and attitude to health affected adherence rates in patients at high risk of metabolic syndrome [25]. In this study, we also sought to investigate the effect of therapeutic coverage on lipid profile as a confounding factor of adherence. The results in Table 2 show that there were no significant differences in all lipid profiles (total cholesterol, LDL, HDL, and triglycerides) between the group with treatment covered and the group not covered (p>0.05). Therefore, therapy coverage is not a confounding factor in research to see the effect of adherence.

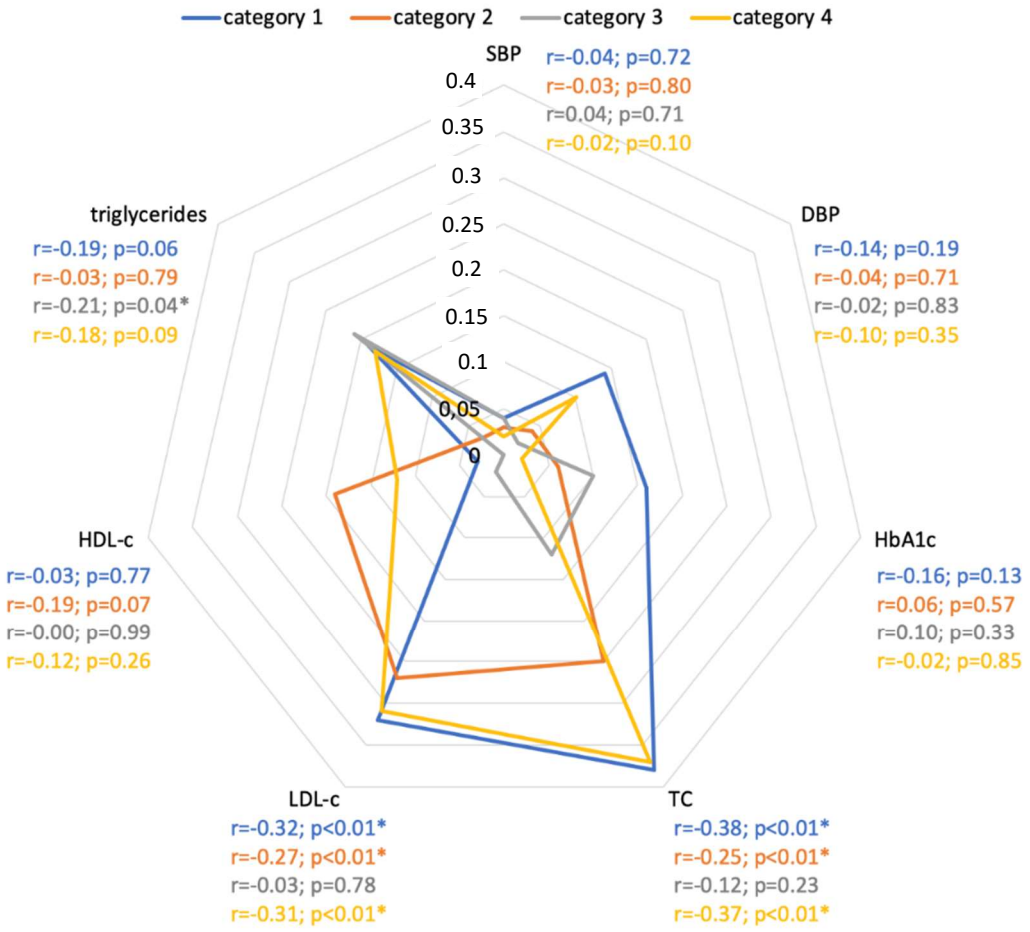


**Figure 1.** Correlation of adherence (per category) to blood pressure, HbA1c, and lipid profile. Category 1: patient factors, category 2: therapeutic regimen factors, category 3: interaction of patient factors with family/health workers factors, category 4: overall factors

**Table 2.** Effect of therapeutic coverage on lipid profile.

| Lipid profiles | Therapeutic coverage | | p-value |
|---|---|---|---|
| | Yes (n=87) | No (n=8) | |
| Total cholesterol (mg/dL) | 199.86±60.23 | 212.63±38.94 | 0.60 |
| LDL-c (mg/dL) | 126.38±41.96 | 133.88±46.30 | 0.63 |
| HDL-c (mg/dL) | 51.08±12.97 | 58.38±17.88 | 0.14 |
| Triglycerides (mg/dL) | 193.72±159.36 | 184.25±122.50 | 0.87 |

**Regression analysis**

Table 3 presents a regression analysis to see the correlation score of each adherence category on lipid profiles after adjustment for age, HbA1c, and blood pressure. Several correlations were found in the regression analysis but not in the bivariate analysis results (Figure 1). Adherence had a statistically significant correlation with total and LDL cholesterol in the categories of patient factors, treatment regimens, and overall adherence scores ($p<0.05$). Significant adherence correlation with HDL levels was only found in the patient factors and treatment regimens category. According to the statistical analysis, triglyceride levels were the only category where adherence scores were statistically significant for the category of interactions between patients and their families/health workers. It should be noted that all correlations found are negative correlations. According to the study's findings, the higher the adherence score of the patient, the lower the level of total cholesterol, LDL, HDL, and triglycerides will be. However, adherence scores with specific categories will affect the profile of each lipid. We only found a correlation between medication adherence to LDL, triglycerides, and total cholesterol. The result of this study is almost similar to research by Setiawan et al., compliance levels have no significant relationship with blood pressure, HbA1c, and lipid profiles ($p>0.05$) [26]. We suspect a strong correlation between uncontrolled HbA1c and blood pressure, so adherence may not affect either condition. An excessive level of HBA1c can be a problem with blood pressure.

Insulin resistance is more common in skeletal muscles in people with hypertension than in those with secondary hypertension. Insulin resistance can cause hyperinsulinemia, which is inherently maladaptive since other intracellular signaling pathways do not share the insulin resistance of the glucose pathway. Eventually, hyperinsulinemia stimulates growth signaling (mitogen-activated protein kinase pathway). As a result of cell proliferation, the vascular wall may remodel, stiffen, and lose its ability to regulate blood pressure [27]. Additionally, hyperinsulinemia can cause hypoglycemic events in patients with hypertension. This event activates the sympathetic nervous system, causing elevated blood pressure, associated with an increased cardiovascular risk. Patients with elderly diabetes were more likely to suffer dyslipidemia and have higher systolic and diastolic blood pressures [28]. Moreover, it was widely known that lipid profiles are influenced by diet and physical activities. A review of 30 randomized controlled trial studies declared that those factors are fundamental management for type 2 diabetes patients [29]. The low intensity of physical activities and high intake of meat could increase abnormal lipid profiles, especially total cholesterol and LDL [30]. It was notable that physical activities and diet patterns might affect our findings.

**Table 3.** Regression analysis of the effect of adherence (per category) on lipid profile.

| Variable | Adherence category** | B (95%CI)[a] | p-value |
|---|---|---|---|
| Total cholesterol | 1 | -27.49 (-43.12 □ -11.88) | <0.01* |
| | 2 | -27.40 (-35.30 □ -5.50) | <0.01* |
| | 3 | -21.86 (-49.55 □ 5.84) | 0.12 |
| | 4 | -14.71 (-22.42 □ -7.01) | <0.01* |
| LDL-c | 1 | -17.57 (-29.13 □ -6.01) | <0.01* |
| | 2 | -15.01 (-26.29 □ -3.74) | 0.01* |
| | 3 | -4.65 (-25.82 □ 16.52) | 0.66 |
| | 4 | -9.41 (-15.35 □ -3.46) | <0.01* |
| HDL-c | 1 | -2.07 (-41.13 □ -10.90) | <0.01* |
| | 2 | -3.62 (-7.14 □ - 0.09) | 0.045* |
| | 3 | -0.36 (-6.18 □ 6.89) | 0.91 |
| | 4 | -1.56 (-3.47 □ 0.35) | 0.11 |
| Triglycerides | 1 | -16.56 (-56.29 □ 23.17) | 0.41 |
| | 2 | -2.24 (-40.71 □ 36.22) | 0.91 |
| | 3 | -91.77 (-158.67 □ -24.87) | <0.01* |
| | 4 | -13.10 (-33.52 □ 7.32) | 0.21 |

[a]: adjusted for age, HbA1c, and blood pressure.
*p<0.05
**Category 1: patient factors, category 2: therapeutic regimen factors, category 3: interaction of patient factors with family/health workers factors, category 4: overall factors

### Limitations

We notice some weaknesses in this study. The result may be biased because patients are interviewed in hospitals where patients tend to answer questions from the questionnaire positively. In addition, the presence of other comorbidities that require treatment can interfere with the outcome of metabolic syndrome therapy that was not analyzed as a whole. Therefore, diet and physical activities might contribute to affecting lipid profiles.

## ▪ CONCLUSION

This study revealed a significant correlation between adherence and HDL levels for patient factors and treatment regimens, and triglycerides were the only category where adherence scores were statistically significant for interactions between patients and their families. Generally, an individual with a higher adherence score will likely have lower total cholesterol, LDL, HDL, and triglycerides. The findings of this study can serve as a foundation for further research, including prospective studies that aim to test interventions designed to increase patient compliance and optimize the management of metabolic syndrome. These results will help develop more effective treatment protocols for patients with metabolic syndrome, improving clinical outcomes through personalized protocols tailored to the patient's specific needs and characteristics.

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