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RESEARCH ARTICLE

Correlation between clozapine use and metabolic syndrome in schizophrenic patients

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Abstract

Background: Clozapine, an atypical antipsychotic agent, is effective for relapse or refractory schizophrenia that has failed to respond to other antipsychotic medications. Despite its effectiveness, clozapine has a higher risk of metabolic syndrome than other antipsychotics. **Objective:** This research aimed to identify the correlation between clozapine and metabolic syndrome, such as obesity, cholesterol, and blood glucose levels, in schizophrenic patients at Ghrasia Mental Hospital, Yogyakarta, Indonesia. **Method:** This is a cross-sectional research. Subjects who met the inclusion criteria were randomly sampled from outpatients between November 2021 and February 2022. The research collected medical record data (characteristic patients, medication patterns, and body mass index) and analysed blood profiles (cholesterol and glucose levels). The data were analysed descriptively and statistically. **Result:** Among the 71 patients in this research, 37 (52.11%) were male and 34 (47.89%) were female, with an average age of 36-45 years. The treatment patterns of patients were as follows: 44 were taking only clozapine and 27 patients did not use clozapine. Clozapine was frequently combined with risperidone and haloperidol in this research. Bivariate analysis using Fisher's Exact test revealed no significant correlation between clozapine use, clozapine regimen (single or combined), duration of clozapine therapy (>= 5 years), and clozapine dose (high or low) with obesity, hypercholesterolemia, and hyperglycemia. Meanwhile, multivariate analysis revealed a significant correlation between gender and obesity ($p < 0.05$), with women having a 0.299 higher risk than men. The effects of age and duration of schizophrenia on hypercholesterolemia and hyperglycemia were insignificant. **Conclusion:** There was no correlation found between clozapine use and metabolic syndrome. Gender was found to have a significant correlation with obesity in the research.

Introduction

Schizophrenia is a functional psychotic disorder characterised by hallucinations, delusions, and disturbances in thinking, perception, and behaviour (Crismon & Buckley, 2014). This disorder affects approximately 20 million people worldwide (WHO, 2022). Meanwhile, the prevalence of schizophrenia in Indonesia is 6.7%, which means that approximately seven people develop schizophrenia in every 100 homes (Kementerian Kesehatan, 2019). This disease frequently manifests itself in the early to mid-twenties, causing most people's productivity to plummet abruptly (Sadock & Sadock, 2007). Treatment of schizophrenia consists of pharmacological and non-pharmacological therapy. Pharmacological therapy uses antipsychotic drugs. There are two types of antipsychotics: typical antipsychotics and atypical antipsychotics (Crismon & Buckley, 2014). Atypical antipsychotics have fewer extrapyramidal side effects than traditional antipsychotics because they bind to dopamine D4 receptors with greater affinity than dopamine D2 receptors (Haidary & Padhy, 2021). Atypical antipsychotics are more likely than traditional antipsychotics to cause metabolic syndrome, which includes obesity, hyperlipidemia, and hyperglycemia

(Chokhawala & Stevens, 2021). Clozapine is a frequently used atypical antipsychotic. This drug is the only antipsychotic proven to be effective in taking care of treatment-resistant schizophrenia. However, it has long-term side effects, namely metabolic syndrome, which includes weight gain, increased risk of type 2 diabetes, and dyslipidemia, which includes elevated total cholesterol, LDL (Low-Density Lipoprotein) cholesterol, and triglycerides (Casey, 2004). Clozapine-induced metabolic syndrome affects 50-60% of patients and can occur even if the patient has no prior risk factors (Ventriglio *et al.*, 2018).

Because clozapine can affect insulin sensitivity and decrease insulin secretion, blood sugar levels are one of the parameters that must be considered when administering it (Liu *et al.*, 2017). Even if no previous risk factors exist, increased blood sugar levels can occur in two weeks to three months after clozapine administration (Aronson, 2016). The Drug Information Handbook reports that the incidence of hyperglycemia with clozapine use is less than 1%. The regimen, dose, and duration of clozapine use can impact hyperglycemia. Age, gender, and duration of schizophrenia diagnosis can influence the incidence of hyperglycemia.

However, studies on the side effects of clozapine, such as weight gain, hyperglycemia, and hypercholesterolemia, have not been widely conducted in Indonesia. Given that schizophrenia treatment requires long-term therapy, possibly even a lifetime, and that schizophrenia treatment is urgently needed to prevent relapse, the researchers believe it is necessary to research the side effects of hypercholesterolemia caused by clozapine use. The findings of this research are expected to be used as research material for monitoring the side effects of metabolic syndrome, which includes obesity, hypercholesterolemia, and hyperglycemia caused by clozapine use, particularly at Grhasia Mental Hospital of Yogyakarta and throughout Indonesia.

Methods

Research design

The ethical feasibility of this research has been registered with the Ghrasia Mental Hospital's Ethics Committee under the number No. 175/ECR-KEPKRSJG/VIII/2021. The research was conducted using a cross-sectional method on schizophrenia outpatients receiving antipsychotic therapy at Grhasia Mental Hospital of Yogyakarta. If the patients underwent outpatient control and met the inclusion criteria based on medical records, the research subjects were selected using an incidental sampling technique. Selected patients who agreed to participate in the research had their BMI (Body Mass Index), blood sugar, and cholesterol levels checked at the Grhasia Mental Hospital Laboratory of Yogyakarta. The collected data were then analysed descriptively and statistically.

Material

The inclusion criteria for this research included outpatients diagnosed with schizophrenia aged 18-60 years and the patients were regular outpatients who had received antipsychotic therapy for at least the previous six months. Meanwhile, the exclusion criterion was patients who refused to participate in the research.

Data analysis

A descriptive analysis was performed to obtain an overview of patient characteristics, disease characteristics, and antipsychotic use patterns. The analysis results were presented as frequency distribution tables and narratives. The percentage was calculated based on the total number of research subjects. The statistical analysis began with a bivariate analysis using Fisher's Exact test with a confidence level of 95% to identify the correlation between each variable, including clozapine use, clozapine regimen, clozapine dose, duration of clozapine use, age, gender, and duration of schizophrenia diagnosis, and incidence of obesity, hypercholesterolemia, and hyperglycemia. Furthermore, the analysis was continued using a multivariate logistic regression test with a confidence level of 95% to identify the correlation between the variables.

Results

The patient demographic characteristics are shown in Table I.

Table I: Patient demographic characteristics

Patient characteristics	Number of patients (n=71)	Percentage (%)
Gender		
Male	37	52.11
Female	34	47.89
Age (years old)		
17-25	3	4.23
26-35	10	14.08
36-45	29	40.85
46-55	24	33.80
56-65	5	7.04
Duration of schizophrenia (years)		
≤10	44	61.97
>10	27	38.03

Antipsychotic pattern

Antipsychotics are the cornerstone of schizophrenia treatment. There are two types of antipsychotics: first-generation or typical antipsychotics and second-generation or atypical antipsychotics. Table II shows that this research involved 71 patients, consisting of 44 taking clozapine and 27 not taking clozapine. The details of the antipsychotics used by schizophrenia outpatients at the Grhasia Mental Hospital Yogyakarta are also shown in Table II.

Table II: Antipsychotic pattern

Antipsychotic regimen	Type of antipsychotic	Drug name	Number of patients (n=71)	Percentage (%)
Single	**Atypical**	Clozapine	17	23.94
		Risperidone	6	8.45
		Aripiprazole	1	1.41
	Typical	Haloperidol	3	4.22
		Fluphenazine	1	1.41
		Trifluoperazine	2	2.82
Two drugs	**Atypical+Atypical**	Clozapine+risperidone	6	8.45
		Risperidone+aripiprazole	1	1.41
		Risperidone+quetiapine	2	2.82
		Quetiapine+aripiprazole	1	1.41
	Atypical+Typical	Clozapine+haloperidol	10	14.08
		Clozapine+ fluphenazine	6	8.45
		Klozapine+trifluoperazine	3	4.22
		Aripiprazole+ fluphenazine	3	4.22
		Risperidone+haloperidol	1	1.41
		Risperidone+chlorpromazine	2	2.82
		Risperidone+ fluphenazine	1	1.41
	Typical+Typical	Haloperidol+ fluphenazine	1	1.41
		Haloperidol+chlorpromazine	2	2.82
Three drugs	**Atypical+Typical+Typical**	Clozapine+haloperidol+ fluphenazine	1	1.41
		Clozapine+haloperidol+trifluoperazine	1	1.41
Total			**71**	**100**

Analysis of the correlation of clozapine therapy with obesity, hypercholesterolemia, and hyperglycemia

According to Table III, this research revealed no significant correlation between clozapine therapy with obesity, hypercholesterolemia, or hyperglycemia.

Table III: Analysis of the correlation of clozapine therapy with obesity, hypercholesterolemia, and hyperglycemia

Features	Clozapine	*p*	OR* (95% CI)
Obesity	Yes/No	0.401	1.43 (0.583-3.720)
Hypercholesterolemia	Yes/No	0.412	0.794 (0.525-1.201)
Hyperglycemia	Yes/No	1.000	1.841 (0.202-16.813)

**OR-Odd ratio*

Analysis of the correlation of regimen, dose, and duration of clozapine therapy with obesity, hypercholesterolemia, and hyperglycemia

The research found no significant correlation between clozapine regimens with obesity, hypercholesterolemia, or hyperglycemia (Table IV).

Analysis of the correlation of age, gender, and duration of schizophrenia with obesity, hypercholesterolemia, and hyperglycemia

Table V shows a significant correlation between gender and obesity ($p < 0.05$), with female patients having a higher prevalence than male patients. Other factors, such as age and duration of schizophrenia, were not significantly correlated with metabolic syndrome, including obesity, hypercholesterolemia, and hyperglycemia.

Table IV: Analysis of the correlation of regimen, dose, and duration of clozapine therapy with obesity, hypercholesterolemia, and hyperglycemia

Variable	*p*	OR* (95% CI)
Obesity		
Clozapine regimen	1.000	1.134 (0.428-3.005)
Combination		
Single		
Clozapine dosage	0.065	2.739 (0.854-8.782)
High		
Low		
Clozapine duration of use (years)		
>5	0.498	0.714 (0.267-1.910)
≤5		
Hypercholesterolemia		
Clozapine regimen		1.679 (0.821-3.434)
Combination	0.216	
Single		
Clozapine dosage	0.763	0.833 (0.459-1.512)
High		
Low		
Clozapine duration of use (years)		
>5	0.546	0.761 (0.420-1.380)
≤5		
Hyperglycemia		
Clozapine dosage	0.549	3.176 (0.311-32.403)
Combination		
Single		
Clozapine duration of use (years)	1.000	1.826 (0.178-18.701)
High		
Low		
Clozapine duration of use (years)		
>5	0.583	0.417 (0.041-4.265)
≤5		

*OR: Odds Ratio

Table V: Analysis of the correlation of age, gender, and duration of schizophrenia with obesity, hypercholesterolemia, and hyperglycemia

Variable	*p*	OR* (95% CI)
Obesity		
Age (years)		
18-45	0.813	1.107 (0.476-2.576)
46-60		
Gender		
Female	0.010	0.299 (0.108-0.829)
Male		
The duration of schizophrenia (years)		
>10	0.790	1.125 (0.471-2.690)
≤10		
Hypercholesterolemia		
Age (years)	1.000	1.007 (0.657-1.546)
18-45		
46-60		
Gender	0.384	1.270 (0.831-1.939)
Female		
Male		

Variable	*p*	OR* (95% CI)
The duration of schizophrenia (years)	1.000	1.019 (0.661-1.569)
>10		
≤10		
Hyperglycemia		
Age (years)	1.000	1.367 (0.204-9.161)
18-45		
46-60		
Gender	0.344	3.265 (0.356-29.902)
Female		
Male		
The duration of schizophrenia (years)		
>10	0.293	4.607 (0.504-42.105)
≤10		

*OR: Odds Ratio

Discussion

Patient demographic characteristics

Gender

The number of male schizophrenia patients participating in this research was higher than that of females. This might be because men are typically the head of the household and thus face more life pressures than women. The finding is consistent with the previous study (Hanief & Noor, 2022).

Age

Table I reveals that the age group of 36-45 years dominated the research subjects. The findings of this research support the theory of another study, which claims that up to 90% of patients diagnosed with schizophrenia is between 15 and 55 years of age (Dania *et al.*, 2019). Several studies have also found that schizophrenia patients are typically in their productive ages between 25 and 40 years of age (Mukaddas *et al.*, 2014; Aryani & Sari, 2015; Yulianty *et al.*, 2017).

Duration of schizophrenia diagnosis

The findings revealed that patients were diagnosed with schizophrenia at various durations ranging from less than a year to more than 20 years. According to Table I, 44 patients (61.97%), had been diagnosed with schizophrenia for less than ten years, and 27 other patients (38.03%) had been diagnosed for more than ten years. Schizophrenia is a chronic disease with long-term treatment, even after symptoms have subsided. This is because schizophrenia symptoms can reoccur at any time (Andari, 2017).

Antipsychotic pattern

Antipsychotics are the cornerstone of schizophrenia treatment. There are two types of antipsychotics; first-generation or typical antipsychotics and second-generation or atypical antipsychotics. Table II shows that this research involved 71 patients, consisting of 41 taking clozapine and 30 not taking clozapine. The details of the antipsychotics used by schizophrenia outpatients at the Grhasia Mental Hospital Yogyakarta are shown in Table II. In 39 patients (54.93%), the most commonly prescribed antipsychotic regimen was a combination of two drugs, which was further subdivided into atypical-atypical combinations into 10 patients (14.10%), atypical-typical combinations in 26 patients (36.62%), and typical-typical combinations in 3 patients (4.23%). Clozapine is recommended for patients who have not responded to two antipsychotic medications (J.T. DiPiro, 2020). In this research, clozapine was frequently combined with risperidone and haloperidol. Risperidone is an atypical antipsychotic used to treat acute schizophrenia. Risperidone, like clozapine, works by blocking dopamine-2 (D2) and serotonin (5-HT2A) receptors. Risperidone has no anticholinergic effects, which may be advantageous for some patients, such as the elderly with dementia (McNeil *et al.*, 2022). Haloperidol is a first-class (typical) antipsychotic that works in the brain by blocking dopamine D2 receptors. The drug has the biggest effect when 72% of dopamine receptors are blocked. Typical antipsychotic drugs, such as haloperidol, have been linked to extrapyramidal symptoms due to dopamine pathway blockade in the brain (Rahman & Marwaha, 2022).

Analysis of the correlation of clozapine therapy with obesity, hypercholesterolemia, and hyperglycemia

According to Table III, this research revealed no significant correlation between clozapine therapy with obesity, hypercholesterolemia, or hyperglycemia. The findings of this research also contradicted those of other studies that using clozapine can raise cholesterol levels from baseline to levels close to statistical significance (Krakowski *et al.*, 2009). A meta-analysis

compared 14 antipsychotics to a placebo. The results of this meta-analysis revealed that the administration of quetiapine, olanzapine, and clozapine increased total cholesterol. Clozapine was identified as the worst drug based on the degree of change in total cholesterol (Pillinger *et al.*, 2020). According to Table III, the prevalence of hyperglycemia was higher in clozapine patients than in non-clozapine patients. Hyperglycemia occurred in 3 of 41 patients (7.32%) who took clozapine and 1 of 30 patients (3.33%) who did not take clozapine. The findings revealed no significant correlation between clozapine use and the incidence of hyperglycemia.

In theory, hyperglycemia caused by clozapine use results from the drug's effect on insulin sensitivity and decreased insulin secretion because clozapine has antagonistic properties at receptors that mediate glucose homeostasis, namely muscarinic, serotonergic, and dopaminergic receptors. Acute antagonists of the M3 (muscarinic acetylcholine) and 5-HT2A (5-hydroxy-tryptamine) receptors have been shown to directly affect pancreatic cell function and reduce insulin secretion (Yuen *et al.*, 2021). Clozapine is also known to inhibit glucose uptake from the brain and peripheral tissues via the GLUT protein (Tovey *et al.*, 2005). This drug has a high risk of weight gain, one of the risk factors for hyperglycemia (Holt, 2019). Previous studies using the case-control method found that clozapine use was associated with the incidence of hyperglycemia ($p < 0.05$). This study included patients who had received antipsychotic therapy in the last 12 months (Gianfrancesco *et al.*, 2002). However, case-control studies involving 7227 case groups and 6780 control groups found that clozapine use was not correlated with hyperglycemia (adjusted OR 0.98; 95% CI 0.74 - 1.31) (Wang *et al.*, 2002).

Analysis of the correlation of regimen, dose, and duration of clozapine therapy with obesity, hypercholesterolemia, and hyperglycemia

The research found no significant correlation between the clozapine regimen with obesity, hypercholesterolemia, or hyperglycemia (Table IV). A study compared the metabolic syndrome in antipsychotic monotherapy and polytherapy patients. Polytherapy was associated with an increased prevalence of metabolic syndrome (50.0% *vs* 34.3%, $p = 0.015$) compared to antipsychotic monotherapy (Correll *et al.*, 2007). These findings contradicted previous studies that found a significant increase in cholesterol levels after two-three months of clozapine use (Casey, 2004). In fact, after five years of using clozapine, cholesterol levels can rise by at least 10% (Kumar & Sidana, 2017). There have been no studies into the correlation between the length of clozapine therapy and hypercholesterolemia. Several studies, however, have found that increasing the duration of clozapine therapy shows a trend toward the incidence of metabolic syndrome (Lamberti *et al.*, 2006; Brunero *et al.*, 2009).

The findings from Table IV revealed that hyperglycemia may occur more frequently when high doses were used. Hyperglycemia occurred in 2 of 23 patients (8.70%) receiving high-dose clozapine and 1 of 21 patients (4.76%) receiving low-dose clozapine. The research showed that there was no significant correlation between clozapine dose and the incidence of hyperglycemia. The findings of this research are consistent with the findings of another study that examined 384 case reports and found no significant correlation between clozapine dose and the incidence of hyperglycemia (Koller *et al.*, 2001). Case-control studies in 7227 cases and 6780 controls found no correlation between dose size and increased risk of hyperglycemia (Wang *et al.*, 2002). Clozapine-related blood sugar elevations typically occur about two weeks to three months after the first use (Aronson, 2016). Patients taking clozapine for six months are more likely to develop hyperglycemia (Koller *et al*., 2001). Another study found that after five years of clozapine use, 37% of patients developed hyperglycemia (Henderson, 2000). This research found that the prevalence of hyperglycemia was higher in patients who had been taking clozapine for five years. Hyperglycemia occurred in 2 of 25 patients (8.0%) who had taken clozapine for more than five years and 2 of 20 patients (10.0%) who had taken clozapine for less than five years. However, the research found that there was no significant correlation between clozapine duration and the incidence of hyperglycemia. The findings of this research are consistent with those of a case-control study, which found no correlation between the duration of clozapine use and increased risk of hyperglycemia (Wang *et al*., 2002).

Analysis of the correlation of age, gender, and duration of schizophrenia with obesity, hypercholesterolemia, and hyperglycemia

Table V shows a significant correlation between gender and obesity ($p < 0.05$), with female patients having a higher prevalence than male patients. Other factors, such as age and duration of schizophrenia, were not significantly correlated with metabolic syndrome, including obesity, hypercholesterolemia, and hyperglycemia. Women are more likely to develop hypercholesterolemia because they are more likely to be obese. In some areas, females have a higher prevalence of obesity than males; however, the degree of variation between genders varies by country (Hussain & Ali, 2021).

The previous study examined the correlation of age and gender with cholesterol levels. According to the findings, 63.3% of the obese subjects were female. Women over 45 will lose 30-50% of their total muscle mass. With age, the body's metabolism slows, and decreased mobility accelerates the conversion of muscle mass to body fat. This is why women are more susceptible to hypercholesterolemia. In addition to obesity, postmenopausal women's decreased estrogen levels contribute to higher cholesterol levels (Ujiani, 2015). Most studies show schizophrenic patients have higher serum lipid levels (cholesterol and triglycerides) than the general population. Dyslipidemia is thought to be caused by antipsychotic medications and lifestyle factors, but it also occurs in untreated schizophrenic patients. According to some evidence, the pathophysiology of schizophrenia involves immune and inflammatory pathways linked to redox regulation. Impaired redox regulation may result in abnormal lipid composition. Furthermore, oxidative stress can affect serum lipids and cause dyslipidemia (Solberg *et al*., 2016). In theory, men's and women's cholesterol levels will naturally rise with age. The body's metabolic system declines with age, as evidenced by decreased hormone production, which affects increasing blood cholesterol levels. After the age of 45, the greatest increase in cholesterol levels occurs. Women over 45 have higher total cholesterol levels than men of the same age (Chang *et al*., 2002). This is due to hormonal factors, specifically decreased function and production of the hormone estrogen. The reduced estrogen hormone will increase total cholesterol levels and change the body fat composition, which is associated with hypercholesterolemia (Akhfiya & Syamsianah, 2018).

This research's findings contradicted previous studies that found a significant correlation between age and hyperglycemia (Pahlawati & Nugroho, 2019; Komariah & Rahayu, 2020; Gunawan & Rahmawati, 2021). According to a study, the age group at risk for hyperglycemia in developed countries is >65 years, while the age group at risk in developing countries is >45 years (Pahlawati & Nugroho, 2019). Hyperglycemia risk increases with age. The mechanism underlying older people's increased risk of hyperglycemia is an increase in body fat composition that accumulates in the abdomen, resulting in central obesity. Central obesity can cause insulin resistance, which is the first step toward hyperglycemia (Suastika *et al*., 2011).

The findings of this research were consistent with those of a case-control study conducted on 132 case-group patients and 132 control group patients at the Tugu Health Center in Cimanggis Subdistrict, Depok City, West Java, Indonesia, which found no significant correlation between gender and incidence of hyperglycemia (p = 0.519). (Gunawan & Rahmawati, 2021). A cross-sectional study of 137 patients at the Proclamation Outpatient Primary Clinic in Depok City found that gender did not affect the incidence of hyperglycemia (p = 0.331) (Komariah & Rahayu, 2020). Other studies produced contradictory results that there was a correlation between gender and hyperglycemia (Usman *et al*., 2020; Arania *et al*., 2021). In theory, women are more vulnerable to hyperglycemia because they are at risk of increasing their Body Mass Index (BMI). Hormonal processes, such as monthly cycle syndrome (premenstrual syndrome), can easily accumulate body fat, putting women at a higher risk of hyperglycemia. Regarding prevalence, men and women have the same chances of developing hyperglycemia (Irawan, 2010). A cross-sectional study conducted at Mbarara Southwest Uganda Regional Referral Hospital found a significant correlation between mental disorders and metabolic syndrome, one of which was hyperglycemia, and that the risk of someone who had a mental disorder for more than ten years was 2.92 times higher (Agaba *et al.*, 2019). Hyperglycemia in schizophrenia patients can theoretically be caused by the disease itself. This is due to the increased stress hormone cortisol, which has an antagonistic effect, inhibiting hepatic glucose release while decreasing glucose utilisation in muscles and insulin receptor affinity (Dinan, 2004).

Lifestyle and behavioural patterns (such as smoking, physical activity, and diet) and genetic factors were not investigated in this research, although these play important roles in lipid and glucose profiles. Based on the research findings, a better research design is required as the number of research subjects increases.

Conclusion

According to the findings, there was no significant correlation between clozapine use and metabolic syndrome. In the research, gender was found to correlate with obesity significantly. The research revealed that women had a 0.299 higher risk of obesity than men (OR 95%CI = 0.2999 (0.108-0.829) $p < 0.05$).

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