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ANALYSIS OF LIVER FUNCTION AND HAEMOGLOBIN LEVELS IN PULMONARY TUBERCULOSIS PATIENTS WITH ANTI-TUBERCULOSIS DRUG

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ABSTRACT

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium Tuberculosis*. Today, Tuberculosis disease is still a major health problem and a global health problem, as the leading cause of death in millions of people every year worldwide. The main TB treatments with Drug Anti-tuberculosis are isoniazid, rifampicin, ethambutol, strep-etamycin, and pyrazinamide. Although most Drugs for tuberculosis are acceptable in therapy, they have a toxic potential to affect especially side hepatotoxic reactions. Many studies have reported rifampicin and INH as a cause of *cutaneous eruptions, a flu-like syndrome*, anemia, *respiratory insufficiency*, acute renal failure, agranulocytosis, eosinophilia, and thrombocytopenia. The aim of the study is to analyze liver function tests and hemoglobin levels before and after ATD therapy within 3 months in pulmonary tuberculosis patients in 5 Jambi City Health Centers. This research method is observation with a total of 42 respondents (total sampling). All the patients were diagnosed with pulmonary tuberculosis, and no respondents dropped out. Data collection was carried out from January to June 2023. Liver function and Hb levels were evaluated before and after 3 months of taking anti-tuberculosis drugs. Examinations were carried out in the hematology laboratory of the Health Polytechnic of the Ministry of Health, Jambi. Liver function test results are an increase in total bilirubin of 0.23 mg/dl after 3 months of respondents taking anti-tuberculosis drugs, as well as ALT and AST, each of which increased. However, they are still within normal limits. The average hemoglobin level is included in the anemia group, and there is a significant decrease from 11.94 gr/d to 11.21 gr/dl. There is a risk of hepatotoxicity due to consumption of anti-tuberculosis drugs. In contrast to the average hemoglobin levels being below normal before and after therapy, there is a decrease in hemoglobin levels after 3 months of treatment. It is best to check liver function and Hemoglobin levels periodically to detect liver function abnormalities and anemia in pulmonary tuberculosis sufferers during the treatment period.

Kata Kunci:

Ekstrak biji durian; Kadar glukosa; darah puasa; Resistensi insulin; Sindrom metabolik

Tuberkulosis (TB) merupakan penyakit menular yang disebabkan bakteri *Mycobacterium Tuberculosis*. Penyakit Tuberkulosis sampai sekarang masih menjadi masalah kesehatan utama dan masalah kesehatan global, sebagai penyebab utama kematian pada jutaan orang setiap tahun di seluruh dunia. Pengobatan TB dengan *Obat Anti Tuberkulosis* (OAT) utama yaitu *isoniazid, rifampisin, etambutanol, streptomisin*, dan *pirazinamid*. Walaupun sebagian besar OAT dapat diterima dalam terapi, namun mempunyai efek toksik yang potensial terhadap efek samping terutama reaksi hepatotoxic dan hematologik. Beberapa penelitan melaporkan rifampisin dan INH sebagi penyebab erupsi kulit, purpura trombositopenia, hepatitis, sindrom flu, anemia hemolitik syock, insufiensi pernafasan dan gagal ginjal akut, agranulositosis, eosinofilia dan trombositopenia. Tujuan penelitian ini menganalisis tes fungsi hati dan kadar hemoglobin sebelum dan sesudah terapi ATD dalam 3 bulan pada pasien tuberculosis paru di 5 Puskesmas Kota Jambi. Metode penelitian observasi dengan jumlah responden 42 penderita (total sampling) yang seluruhnya didiagnosa tuberkulosis paru, dan tidak terdapat responden yang drops out. Pengumpulan data dilakukan dari Bulan Januari sampai Juni 2023. Fungsi hati dan kadar Hb di evaluasi sebelum dan setelah 3 bulan mengkonsumsi obat anti tuberkulosis, pemeriksaan dilakukan di laboratroium Hematologi Poltekkes Kemenkes Jambi. Hasil penelitian menunjukkan bilirubin total meningkat sebesar 0,23 mg/dl setelah 3 bulan responden mengkonsumsi obat anti tuberkulosis, demikian juga dengan ALT dan AST masing-masing terjadi peningkatan walaupun masih dalam batas normal. Rata-rata kadar hemoglobin termasuk dalam kelompok anemia dan terjadi penurunan yang signifikan dari 11,94gr/dl menjadi 11,21 gr/dl. Sebaiknya dilakukan pemeriksaan fungsi hati dan

kadar Hb secara periodik oleh petugas kesehatan untuk mendeteksi kelainan fungsi hati dan anemia pada penderita tuberkulosis paru dalam masa pengobatan.

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INTRODUCTION

Pulmonary Tuberculosis (TB) is an infectious disease caused by Mycobacterium Tuberculosis. The bacteria can spread through droplets infected with tuberculosis bacilli. Pulmonary tuberculosis is still a major health problem today and is a global health problem as the main cause of death in millions of people every year throughout the world (Sari, 2018).

Data from the WHO Global TB Report in 2020, there are 10 million people in the world suffering from tuberculosis (TB), and it causes 1.2 million people to die every year. Indonesia is in 3rd place in the country with the highest TB cases in the world after India and China. Indonesia is one of the countries with the highest TB burden in the world, with an estimated 845,000 with a death rate of 98,000 or the equivalent of 11 deaths/hour (WHO, 2023). Of these cases, only 67% were found and treated, so as many as 283,000 TB patients have not been treated and are at risk of becoming a source of infection for people around them. Based on data from the Jambi Provincial Health Service (2022), the number of tuberculosis cases in Jambi is 2.405 cases (Kementrian Keseharan Kota Jambi, 2023). The treatment of TB with OAT affects the occurrence of hepatotoxicity (Mega et al., 2023).

According to WHO recommendations, TB treatment uses Anti-Tuberculosis Drugs consisting of Rifampicin (RIF), Isoniazid (INH), Ethambutol (EMB), Streptomycin, and Pyrazinamide (PZA). Tuberculosis treatment lasts for 6 months, namely the intensive phase for 2 months and the continuation phase for up to 6 months; during the treatment phase, there are sufferer complaints (Kementrian Kesehatan Republik Indonesia, 2020). Anti-tuberculosis drugs are the most hepatotoxic group of drugs. Hepatotoxicity is mainly associated with the administration of isoniazid (INH), rifampicin (RIF), and pyrazinamide (PZA) in the first-line Anti-Tuberculosis Drugs group (RI Ministry of Health, 2023). Manifestations of hepatotoxicity vary from only liver function abnormalities to acute liver failure (Banjuradia and Gurmeet, 2020). Rifampicin is able to bind the bacterial DNA-dependent RNA polymerase enzyme, thereby inhibiting the transcription of DNA into RNA and inhibiting protein synthesis. Most liver toxicities occur when RIF and INH are administered simultaneously. This is thought to be because RIF can induce the INH hydrolysis reaction to form hydrazine compounds, which are hepatotoxic (Kim et al, 2017).

Apart from that, many studies report rifampicin as a cause of cutaneous eruptions, thrombocytopenia purpura, hepatitis, a flu-like syndrome, hemolytic shock anemia, respiratory insufficiency, and acute renal failure. Rifampicin causes transient elevations in liver enzymes, usually within the first 8 weeks of therapy in 10 - 15% of patients, with less than 1% of patients showing hepatotoxicity. A total of 16 in 500,000 patients who received rifampicin were reported to have died due to rifampicin hepatotoxicity (Yansensius et al, 2023).

Anti-tuberculosis drugs cause changes in hematology, such as thrombocytopenia, anemia, agranulocytosis, and eosinophilia. Research by Riscova (2019) shows that the number of erythrocytes decreased by 75%. Isoniazid and rifampicin can cause hemolytic anemia by an immune complex mechanism; antibody drugs bind to red blood cell membranes and trigger complement activity, causing hemolysis of red blood cells and destruction of red blood cells (Riscova and Risma, 2019). Isoniazid and pyrazinamide can disrupt vitamin metabolism. B6 (pyridoxine) and increased excretion through urine cause vitamin B6 deficiency, which is a crucial nutrient for stimulating the development of the brain, nervous system, and skin. Vitamin B6 is essential in the process of forming energy, which comes from fat, protein, carbohydrates, antibodies, and red blood cells or erythrocytes. The deficiency of vitamin B6 disrupts heme biosynthesis, which results in sideroblastic anemia (Situmorang, 2020).

An early marker of hepatotoxicity is an increase in transaminase enzymes in the serum consisting of Aspartate Amino Transferase/Serum Glutamate Oxaloacetate Transaminase (AST/SGOT), which is secreted in parallel with Alanine Amino Transferase/Serum Glutamate Pyruvate Transaminase (ALT/SGPT) which is a more specific marker to detect liver damage. In 2012, the World Health

Organization classified hepatotoxicity into 4 gradations. Grade I is characterized by an increase in ALT 1.25 - 2.5 times normal, grade II ALT increases 2.6 - 5 times normal, and grade III ALT increases 5.1 - 10 times normal, and grade IV when ALT increases > 10 times the normal value (Melinia and Widodo, 2021).

Anemia and impaired liver function are risk factors for TB C; Therefore, early diagnosis screening and treatment must be promoted to the community to reduce the burden of TB (Yemataw Gelaw et al, 2021). Laboratory tests are used to detect anemia by examining hemoglobin levels and liver function abnormalities, namely serum levels of total bilirubin, alanine aminotransferase (ALT)/Serum Glutamic Pyruvic Transaminase (SGPT), aspartate aminotransferase (AST)/Serum Glutamic Oxaloacetic Transaminase (SGOT), total protein, albumin, and globulin. Monitoring of hemoglobin levels in liver function tests is carried out after 3 months of OAT treatment (Yasta and Deta, 2018).

Until now, research regarding the side effects of treatment for pulmonary tuberculosis, especially in Jambi Province, is still very limited, while OAT is still part of the Program of the Ministry of Health of the Republic of Indonesia to treat and eradicate pulmonary tuberculosis. Therefore, we wanted to analyze liver function tests and hemoglobin levels before and after administering OAT within 3 months in ray tuberculosis patients at the Community Health Center in Jambi City.

This study provides epidemiological data on the prevalence of liver function disorders and anemia in tuberculosis patients in Jambi Province. Monitoring hemoglobin levels and liver function tests are part of the treatment protocol to monitor drug side effects and prevent severe anemia in patients.

METHOD

This is descriptive research with a case series on pulmonary tuberculosis patients who have come to public health center Kasang Pudak, Penyengat Olak, Pondok Meja, and Suko Awin Jaya, from January to June 2022, with a total sample of 42 people (total sampling). The inclusion criteria were new tuberculosis patients who had been diagnosed with and had not received anti-tuberculosis drug therapy, were willing to be involved in this research by signing an informed consent form, and were between 18 and 60 years old. Exclusion criteria included pregnancy, patients taking systemic drugs for other diseases or other hepatotoxic drugs, chronic alcohol consumption, and a history of other liver diseases.

Research subjects who had signed the informed consent form had their blood taken for liver function examination, which includes total serum bilirubin, ALT, AST before anti-tuberculosis medication, and hemoglobin levels. This subject then had blood taken again for liver function tests after 3 months of anti-tuberculosis medication. Data was collected and analyzed using statistical software. Descriptive analysis was conducted to determine the mean value and standard deviation of the studied variables. This research was carried out after obtaining ethical permission from the Jambi Ministry of Health Polytechnic Research Ethics Committee with the number LB.02.06/2/422/2022. Liver function tests and examination of H hemoglobin levels were carried out at the Jambi Ministry of Health Polytechnic Hematology Laboratory.

RESULT

This study involved 42 patients obtained from 5 health centers: Kasang Pudak Health Center, Penyengat Olak, Pondok Meja, and Suko Awin Jaya Health Center. All respondents have been diagnosed with pulmonary tuberculosis; no respondents dropped out.

Table 1. Frequency Distribution of Respondent Characteristics (n = 42)

Respondent Characteristics	Indicators	n	Percentage
Sex	male	27	64.2
	Female	15	35.8
Age	< 20 years	1	2,4
	21-40 years old	16	38.1
	> 40 years	25	59.5
Occupation	Employed	23	54.7
	Unemployed	19	45.3

The characteristics of the respondents can be seen in Table 1. The majority of patients are male (64.2%), and most are older than 40 years (59.5 %). If we look at occupation, most of the respondents

work in different types of work, namely farmers, laborers, employees, and self-employed. The results of research on liver function tests and H hemoglobin levels before and during treatment can be seen in Table 2.

Table 2. Liver Function Test and Hemoglobin Level in Tuberculosis Patients with Anti-Tuberculosis Drugs

Variables	Indicators	Before anti-tuberculosis drugs	After 3 Months	
Liver function test	Total Bilirubin	0. 49 ±0.2 4	0. 72 ±0.2 7	mg/dl
	ALT/SGPT	2 5.4 ±1 5.23	30. 7 ±21.9 8	U/L
	AST/SGOT	2 8.4 ±1 4.31	3 3.7 ±2 3.52	U/L
Hemoglobin	Hemoglobin Level	11.94 ± 1.21	11.21 ± 1.09	gr/dl

Table 2 shows that total bilirubin increased by 0.23 mg/dl after 3 months of respondents taking tuberculosis drugs, as well as ALT and AST, each of which increased although they are still within normal limits. The average hemoglobin level is included in the anemia group, and there is a significant decrease from 11.94 gr/dl (SD ± 1.21) to 11.21 gr/dl (SD ± 1.09).

DISCUSSION

This research involved 42 respondents, and the majority of them are male and aged ≥ 40 years. Data on TB patients in Indonesia for 2021 and 2022 also shows that more people suffering from pulmonary tuberculosis are male than female, with the highest age group being 45-54 years old (Ministry of Health of the Republic of Indonesia, 2022). According to several studies, there is a relationship between age and gender in the incidence of pulmonary tuberculosis (Fanesa et al, 2022; Sunarmi, 2022). This is likely to occur because men interact more with others because of work and, therefore, are more vulnerable to infection compared to women (Baymakova et al., 2017). Evaluation of liver function before anti-tuberculosis drug therapy is carried out shows an increase, although it is still within the normal range. Several studies show an increase in serum bilirubin in tuberculosis sufferers due to various factors, especially the effect of therapy (Anggarini Sri Rasyid, 2020; Melinia Putri, 2021).

Treatment using anti-tuberculosis drugs in pulmonary tuberculosis sufferers can cause liver dysfunction, which is usually caused by Rifampicin ((Ivan banjuradja, 2020b); Pollock et al, 2012). The administration of isoniazid (INH), rifampicin (RIF), and pyrazinamide (PZA) in the first-line OAT group influences the occurrence of hepatotoxicity (Yunita and Novi, 2019). Providing Anti-Tuberculosis Drug (OAT) treatment at this stage initial and advanced stages (Mutia et al, 2023), but the side effects, especially anti-tuberculosis drug-induced liver injury (ATDILI), cannot be overlooked (Zhang N, Shavic RM and et al, 2021). Metabolism of rifampicin and dapsone both occur in the liver, including hydroxylation and oxidation by cytochrome P450 enzyme (Liu X, Ren S and et al, 2021).

In research subjects, laboratory examination of liver function in the 3rd month after taking anti-tuberculosis drugs has shown an increase in the values of each parameter. However, they are still within normal limits. Most patients can tolerate the improper effects of the rifampicin dose (Zing N, RM et al, 2021; Banjuradia and Gurmeet, 2020). However, evaluating functions still needs to be performed carefully to identify abnormalities in liver function as early as possible (Ivan banjuradja, 2020b).

The results of the analysis of patients' hemoglobin levels before and after taking OAT have shown an average decrease from 11.94 mg/dl to 11.21 mg/dl. In line with Gafar's (2017) research, the results obtained from 30 respondents are that 21 people (70%) have decreased hemoglobin levels. Low hemoglobin levels in pulmonary tuberculosis sufferers are caused by malnutrition or a lack of calories, vitamins, and iron, which affects the patient's immune system. Patients with active pulmonary tuberculosis are often malnourished and experience macro-nutrient deficiencies as well as weight loss and decreased appetite. It is necessary to provide nutritional supplements to prevent an incident of tuberculosis (Bhargava et al 2023). The cause of anemia is disruption of the mechanism for the formation of red blood cells in the body system or erythropoiesis (Xingren et al, 2021). Apart from that, due to the use of anti-tuberculosis drugs, anemia occurs in sufferers. The results have shown that the majority

(54%) of pulmonary TB sufferers have hemoglobin levels below normal values; there is an influence on the comparison of hemoglobin levels before and after anti-tuberculosis drug treatment (Evi et al, 2021).

Nutritional status is one of the factors that influences hemoglobin levels because if nutritional intake is not met in the body, it can cause a person to experience anemia or a lack of hemoglobin levels, especially iron (Yansensius et al, 2023). The weakness of this research is that there is no comparison group, which makes it possible to evaluate the differences between the case and control groups. Other factors that influence the research results have not been controlled.

CONCLUSION AND SUGGESTION

Current research shows that the results of liver function tests are normal before taking anti-tuberculosis drugs, namely total bilirubin, ALT/SGPT, and AST/SGOT. After 3 months of taking anti-tuberculosis drugs, there is no difference between the two before taking anti-tuberculosis drugs and after 3 months of taking anti-tuberculosis drugs. However, there is a risk of hepatotoxicity. Therefore, we recommend carrying out regular liver function tests for early detection of liver function abnormalities.

Pulmonary tuberculosis patients who take tuberculosis drugs are at risk of hepatotoxicity and anemia. Therefore, we recommend periodically carrying out liver function tests and hemoglobin levels for early detection of liver function abnormalities and anemia. We also suggest expanding the location and number of research samples for future researchers using the cohort research method.

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