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Metformin Role in Diabetic Patients with Tuberculosis: a Review

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Abstract

Tuberculosis (TB) epidemic is a global health challenge, and WHO estimated the incidence of the new cases reaching 11.1 million people in 2017. Indonesia is classified as a high TB burden country, with 8% of its population infected by TB and ranks third in the world. Type-2 diabetes mellitus (T2DM) is known comorbidity for TB patients. TB-T2DM patients have a higher chance of morbidity, mortality, relapse, bacterial resistance, treatment failure, and slower sputum conversion than TB patients without T2DM. Recent studies suggest that metformin may have a potential synergistic role for TB-T2DM patients. Metformin has immunomodulator properties that can improve the body's immune response and inflammatory response against TB in individuals with T2-DM.

Keywords: metformin, tuberculosis, type-2 diabetes mellitus

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1. Introduction

Tuberculosis (TB) is an infectious disease that has become a global health issue with the estimated incidence of new cases by the World Health Organization (WHO), reaching 11.1 million people in 2017. An increase in the estimated incidence of new TB cases by 600 thousand people compared to 2016. Indonesia is one of the countries with a high TB burden and ranks third with 8% after India and China. Cases of pulmonary tuberculosis have an average cure rate of 83% in the world; however, the emergence of comorbidities such as HIV infection or diabetes mellitus (DM) is susceptible to increasing the risk of TB infection accompanied by the appearance of complications in treatment [1–3]. Some literature shows that 5.4-44% of pulmonary TB

patients also have DM [4]; Indonesia has 10.3 million population aged 20-79 years with DM.

The mechanism of the increased risk of TB in DM patients is unclear, but some literature states that there is an association of T cell responses and abnormal cytokines that can increase the inflammatory process in the body [5–7] . Also, it mentioned a decrease in the function of the innate and adaptive immune response that causes latent TB patients with DM to be more active than people without DM [8,9]. Some other studies also mention a relationship between TB and DM patients and undesirable treatment outcomes such as slower sputum conversion, higher mortality rates, and a higher risk of TB relapse after being declared healed as much as three times [10].

Metformin (MET) is the first-line oral antidiabetic drug recommended for patients with type 2 DM [11]. This drug can reduce blood sugar levels in the body by reducing liver glucose production, slowing glucose absorption in the small intestine, and increasing insulin sensitivity for glucose utilization [12]. Several recent studies have concluded that MET is a potential role as an adjunct therapy to increase the effectiveness of TB treatment [11]. Another study found that the use of MET to be combined with a TB regimen increased the rate of treatment success and decreased the rate of relapse in TB patients with DM [12,13].

In an in vivo study, MET can increase the effects of autophagy on macrophages through phagolysosome fusion activated from AMP-activated by protein kinase (AMPK), triggers the production of reactive oxygen species from mitochondria (mROS), and inhibit the growth of Mycobacterium tuberculosis (Mtb) (AMB) [14–16]. The follow-up in vitro study found fewer Mycobacterium germs and lower mortality in mice given a combination of isoniazid (INH) and MET compared to mice that only got INH [14]. Besides, one cohort study also mentioned that MET administration might be useful in TB-DM patients with a complicated pulmonary cavity [17].

Considering the TB case with comorbid DM is a unique population with a high vulnerability level, we present a literature review entitled The Role of Metformin in Tuberculosis Therapy, which is expected to help Indonesia achieve the WHO's post-2015 End TB goal.

2. Experimental section

This is a review of metformin role in tuberculosis patients with type-2 diabetes mellitus. We utilized four databases for the literature searching process that consists of PubMed, Science Direct, Cochrane Library, and GoogleScholar between November 2019 and June 2020.

3. Results and Discussion

3.1. Tuberculosis and Diabetes Mellitus Epidemiology

Tuberculosis (TB) still ranks the first cause of death caused by a single microorganism in the world, even if there has been a lower death rate by active TB infection since 1990. World Health Organization (WHO) estimation in 2017 found that TB incidence only reached 11.1 million, which means an increase of 600 thousand population compared to 2016. Indonesia is a country with a high TB burden, with 8% of the population infected with TB and ranks third after India and China in the world. A strategy to eradicate the global TB epidemic was launched by WHO, End TB Strategy, in 2016 with the primary goal of reducing 90% of TB deaths and 80% of TB incidence in 2030 when compared to 2015 [3].

In recent decades, the epidemic of diabetes mellitus (DM) is one of the global health challenges with a prevalence rate that far exceeds the predictions [5]. Some causes that might increase non-communicable diseases include the aging population, urbanization, and unhealthy living style. The latest census from the International Diabetes Federation (IDF) in 2015 projected that there were 415 million people in the world with DM who would increase to 642 million by 2040. The study also mentions that 85-95% of all the world population with DM has type 2 diabetes [2].

An increase in the incidence of DM is considered only experienced by residents in developed countries with high incomes, but it is estimated that 80% of the world's population who suffer from DM live in low and middle-income countries with the highest rate of increase also occurs in residents in these countries. This increase has a significant impact on the economic sector and public health because countries with low-middle income have a high prevalence of infectious diseases and the low availability of health facilities. The confluence between infectious and non-communicable diseases increases the mortality and morbidity rates associated with comorbid diseases, increases steps to control the spread of infectious diseases, and re-emergence of intracellular bacterial infections [5].

3.2. Diabetes Mellitus-Tuberculosis Comorbidity

Individuals with DM have a higher risk of developing infectious diseases, and their complications with a higher death rate are twice as high as individuals without DM [5]. Reducing the impact of this double burden is still tricky because the mechanism underlying the increased risk of infection in DM patients remains unclear. However, various studies and research have been conducted, suggesting different cytokine responses when fighting infectious diseases [5,6]. Some literature states that there are 5.4-44% of individuals with pulmonary TB who also have DM [4,13].

The relationship between type 2 DM and TB and the effect of a combination of both as a disease in pathophysiology has been known for a long time, but there are still no studies that can scientifically prove the relationship between the two [6]. Clinicians and researchers are still unable to determine whether DM causes TB or TB to cause clinical manifestations of DM [8]. Eighty years ago, DM patients who did not die from a diabetic coma were more likely to die of TB and its complications. This phenomenon began to diminish with the discovery of insulin therapy for DM and antibiotics for TB. However, in the 1980s, the reappearance of these two diseases as comorbidities due to the DM pandemic [7] was influenced by increased obesity rates, changes in diet, decreased physical activity, and an aging population [9]. Some literature shows that 5.4-44% of pulmonary TB patients also have DM [4]; Indonesia has 10.3 million population aged 20-79 years with DM.

One meta-analysis of 13 observational studies states that patients with DM have a 3.1 times greater risk of infection with pulmonary TB when compared to individuals without DM. At the same time, more than 40 other studies, including four cohort studies, 16 retrospective studies, and 17 case-control studies, also found that patients with DM were more likely to be infected with TB when compared to individuals without DM [6,7]. Besides, patients with TB and DM also have a higher risk of morbidity, mortality, relapse, slower sputum conversion, resistance, and treatment failure when compared to TB patients without DM [9,10].

3.3. Immunity Response in Individuals with Tuberculosis and Diabetes Mellitus

Several studies have shown convincing evidence about the causal relationship between DM and decreased an individual's immunity to TB [8]. Studies in experimental animals have shown that diabetic rats intentionally given M. tuberculosis (Mtb) had more bacterial counts than mice with normal blood sugar levels [7,8]. Mice with chronic diabetes have significantly lower levels of interferon-gamma (IFN-gamma), interleukin-12 (IL-12), and T helper 1 (Th1) production in early adaptive immunity against M. tuberculosis bacterial infection [8,9]. Other literature also causes a state of hyperglycemia, and poor blood sugar control in individuals with DM will create maladaptive microvascular structures and decreased lung tissue perfusion, which results in optimized immune surveillance [7,8].

Research using human plasma cells shows that high insulin levels can depict a decrease in Th1 immunity due to an imbalance between Th1 cells and Th2 cells, IFN-gamma, and IL-4 [8]. Immunity to Mtb requires a response from Th1

and Th17 cells with IL-2. IFN-gamma, TNF-alpha, IL-17, and IL-23 also play an essential role in the induction and sustainability of a protective immune response to TB infection [6,7]. Also, one literature comparing ex vivo Th1 cytokine production shows that the nonspecific IFN-gamma levels of individuals with DM are far below those without DM [7,8]. Numerous studies have noted an inverse relationship between IFN-gamma levels and the HbA1c results of the entire population [8,9]. Individuals with DM also experience a decrease in neutrophil function due to chemotaxis and higher oxidation reactions when compared to the control group [8]. The bactericidal function of leukocytes also decreases in individuals with poor glucose control [6,8].

An in vitro study was conducted to look at the initial performance of innate immunity against TB by infecting human blood monocytes with and without DM, which shows that there is a decrease in the ability of individual monocytes with DM to bind and phagocytosis of the Mtb bacteria due to alterations in the C3 complement that serves to phagocytosis Mtb [6,7,15]. This reduction in efficiency in performing phagocytosis is believed to contribute to an increased risk of infection and prolong treatment duration. The results of this study are similar to the literature conducting in vivo studies in mice [2,8].

Several immunological studies conducted in the last few years mentioned that individuals with DM infected with TB would trigger an excess paradoxical inflammation response (paradoxical hyper-inflammatory response), which can be seen from the increase in IFN-gamma production, IL-2, TNF-alpha, and factors forming granulocyte-macrophage colonies [5,6,14,15]. This inflammation response will result in an increase in various cytokines by decreasing T-regulation (Treg) cells, which will result in a physiological decrease of innate immunity to Mtb [5,6,15].

The increased risk of relapse, treatment failure, and mortality during TB treatment in patients with DM is in line with various data from in vivo and in vitro studies, which concluded that DM could interfere with cell immunity [6,9,10]. Other in vitro studies found that poor blood sugar control, judged by HbA1c, also affects the innate immune response and type 1 cytokine [9,10,15].

3.4. Pharmacological Management Problems of Patient with Tuberculosis and Mellitus Diabetes

The combination of rifampicin, isoniazid, ethambutol, and pyrazinamide is the current gold standard treatment of anti-TB therapy [10–12]. The long duration of treatment, which is 6-12 months, and non-compliance of individuals in the consumption of this therapy led to the evolution of various Mtb strains that were resistant to treatment [11]. There are 5% of all TB cases in the world that are estimated to be Mtb that is resistant to at least one first-line anti-TB drug that makes pharmacological interventions less effective so that alternative treatments are needed outside these first-line standard standards. Based on various studies that have been carried out, bacteria can become resistant to antibiotics in two ways: genetic mutation and bacterial persistence ability when given antibiotics [5,11].

Several studies have found that TB infection can worsen glucose tolerance in individuals with or without DM (12). Patients with DM have a higher susceptibility because the use of rifampicin in TB treatment can directly cause hyperglycemia and have interactions with oral antidiabetic drugs [8–10]. A study in Indonesia showed that TB patients with DM had serum rifampicin concentrations that were 53% lower than TB patients without DM, where low serum TB drug concentrations had an association with failure of TB treatment and Mtb resistance [8]. Besides, the side effects of peripheral neuropathy from isoniazid treatment can worsen in DM patients; therefore, pyridoxine is usually given to TB patients with DM [9,10].

A retrospective population-based cohort study conducted in 2017 compared the incidence of TB in patients newly diagnosed with type 2 diabetes who were given metformin or sulfonylureas for at least two years from the

diagnosis of DM. Multivariate analysis conducted in both groups found that the group given metformin had a lower risk of contracting TB than the group given sulfonylureas [18]. This study also shows that metformin can reduce the risk of progression of active TB in patients with type 2 DM [18,19].

3.5. The Role of Metformin in Tuberculosis Therapy

Metformin hydrochloride (MET) is a first-line oral antihyperglycemic drug from the biguanide group recommended for individuals with type 2 DM [11–13]. This drug mechanism of action is to inhibit glucose production by the liver, reduce the absorption of glucose in the small intestine, and optimize the use of glucose in cells that will reduce blood sugar levels in the body [12,13]. Several recent studies have suggested that MET has the potential as an adjunct therapy to increase the effectiveness of TB treatment [11]. Other studies suggest that the use of MET combined with a TB therapy regimen can improve treatment success and reduce relapse rates in TB patients with DM [13,16].

Research in China and Korea found that the use of MET in TB patients with comorbid type 2 DM will accelerate sputum culture conversion at the end of the second month [13]. MET is known to have an immunomodulatory role in reducing inflammation by activating AMP kinase, which will reduce the growth of Mtb and the area of damaged tissue [13,14]. Another study mentioned MET's role in preventing the formation of a persistent Mtb phenotype that would make this bacterium resistant to antituberculosis drugs by inhibiting proteins that function in the biosynthesis of the NDH-1 respiration chain complex [11,13].

One observational literature found that patients who were given a combination of MET therapy and conventional antituberculosis had a 7% lower risk of death even though subjects had an older age compared to the group without MET [14]. A cohort analysis showed that DM patients given MET had a lower risk of suffering from latent TB seen from the number of IFN-gamma CFP-10 specific to fewer Mtb [11,14].

An observational study found that MET can reduce relapse rates and increase therapeutic success because it has the potential to kill intracellular Mtb that lives latently in macrophages by increasing phagocytosis, phagolysosome fusion, and autophagi from macrophages [13]. Also, an in vitro study concluded that MET-exposed macrophages have a higher ability to increase the production of reactive oxidative species (ROS) and mitochondrial reactive nitrogen (RNS) species that have mycobacteriosis contained intracellular and extracellular Mtb [11,13,14]. The P450 enzyme system does not metabolize MET, and the interaction between this drug and rifampicin will increase the expression of organic cation transporters (OCT1) and increase the uptake of liver metformin, which causes more controlled blood sugar levels. MET was also found to increase the bactericidal efficacy of isoniazid due to the activation of superoxide dismutase (SOD) and can inhibit stimulators for the proliferation of cancer cells such as insulin-like growth factor (IGF) accompanied by P13K-AKT activation. There is a positive association between MET and increased pyrazinamide efficacy through autophagy and phagocytosis of intracellular Mtb [16]. Therefore, the use of a combination of antituberculosis drugs and MET as host-directed therapy (HDT) for TB patients with DM can increase the success of short-term and long-term TB treatment [13,14,16,17].

3.6. Mechanism of Metformin in Tuberculosis Therapy

There are several mechanisms of action of MET that can be used as adjunctive therapy or HDT in the pharmacotherapy of TB patients with DM, including inhibiting the growth of Mtb with mitochondrial ROS production, increasing the efficacy of conventional anti-TB drugs, reducing tissue damaged by TB, improving immune response, reduce the inflammation process, reduce the severity of TB, improve

treatment outcomes, and reduce the incidence of latent TB [11–17].

In a study [17-19] that used 13 autophagic drugs and AMPK activation to see the ability to control the growth of intracellular M. Bovis bacillus Calmette-Guerin (BCG) in THP-1 human monocyte cells using colony-forming unit (CFU) levels was found MET can slow the growth of intracellular BCG and H37Rv Mtb strains. After 24 hours of evaluation of Mtb growth retardation, the MET effect stops when adenosine monophosphate-activated protein kinase (AMPK) is genetically or chemically activated and undergoes phosphorylation, regulates cell growth and antimicrobial function of cellular immunity. MET treatment also selectively activates the production of mitochondrial ROS triggered by inhibition of the mitochondrial complex I (NADH dehydrogenase), and this condition is proven to inhibit the growth of Mtb in vitro because it can excite the potential membrane of the mitochondria, release cytochrome-c into the cytoplasm, and initiate the intrinsic apoptotic pathway that ends in cell death.

In vivo research [11,14,17] in mice with TB concluded that MET could increase isoniazid efficacy as seen from the decrease in the amount of Mtb in mice given MET and when compared to mice that were only given isoniazid. In mice given MET and ethambutol, CFU was found in the lungs and lymph, which were lower than mice given only ethambutol. Both of these results indicate that the use of MET can improve the effectiveness of conventional antituberculosis drugs.

In the same study [14,16], pulmonary and lymphatic rats found with a combination of MET and conventional antituberculosis drugs were smaller than those only given conventional anti-tuberculosis drugs, the morphological analysis showed that the pathology lesions were smaller in size. Histopathological evaluation of tuberculosis-infected lungs from mice not given MET found more diffuse lung lesions with lots of infiltration of macrophages, lymphocytes, and intracellular acid-resistant stem cells. No granulomas were found in mice infected with TB using a combination of MET and conventional TB drugs.

Furthermore, an evaluation of Th1 cell immune response was also performed, which showed a higher number of CD4 and CD8 T cells in subjects given MET [14]. MET administration was also associated with an increase in the number and percentage of IFN-gamma producing CD8 cells.

Genetic transcription analysis was also performed with RNA isolates in mice's lungs with Mtb, and there were 1580 genes expressed due to exposure to infection. There was a 97% difference in genetic expression in the two groups, which indicated that MET administration triggered a decrease in the response of proinflammatory mediators such as IL-1beta, TNF-alpha, IL-6, MCP-1, CXCL5, and CXCL10 [14,16,17].

4. Conclusion

Tuberculosis is an infectious disease by a single microorganism with the highest prevalence in the world. Along with medical science development, lifestyle changes, and an aging population shifting infectious diseases into non-communicable diseases as a significant global health problem, one of them is diabetes mellitus. The relationship between tuberculosis and diabetes mellitus that influence each other has been known for a long time. Mortality and morbidity risk in individuals with TB will be higher if there is DM as a comorbidity. Central hypothesis of TB and DM comorbidities' relationship is the disruption of the immune response and its inflammatory response.

Metformin is an oral antidiabetic drug of the first line of biguanide, most commonly used in patients with DM. Recent studies suggest that metformin's potential role as host-directed therapy (HDT) for TB patients with DM can increase treatment success. The literature found that metformin is an immunomodulator that can improve the body's immune response and inflammatory response directly and indirectly. Many studies are still needed to prove the effectiveness of metformin as HDT for TB patients with DM.

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