INTERACTION OF TUBERCULOSIS IN DIABETES MELLITUS AS A RISK POPULATION-HOW TO PREVENT IT

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ABSTRACT

Diabetes mellitus (DM) is a challenge in controlling Pulmonary Tuberculosis (PTB) cases. The increase in DM cases is one of the reasons that Indonesia is the second highest contributor of PTB cases in the world. The relationship between these two diseases impacts morbidity and mortality globally. This condition is based on the role of each individual's immune system against Mycobacterium tuberculosis (Mtb) infection. Impairment of the innate and adaptive immune system in eliminating Mtb infection influences the increase of PTB cases with DM. Early prevention is important in the interaction of DM and PTB.

Keywords: Diabetes Mellitus, Tuberculosis, Interaction, Risk Population

ABSTRAK

Diabetes Mellitus (DM) merupakan tantangan dalam pengendalian kasus TB Paru. Peningkatan kasus DM merupakan salah satu yang penyebab Indonesia sebagai kontributor kasus TB Paru tertinggi kedua di dunia. Hubungan antara kedua penyakit ini berdampak terhadap morbiditas dan mortalitas secara global. Kondisi ini didasari oleh peran sistem imun setiap individu terhadap infeksi Mycobacterium tuberculosis (Mtb). Gangguan sistem imun bawaan dan adaptif dalam mengeliminasi infeksi Mtb mempengaruhi peningkatan kasus TB Paru dengan DM. Pencegahan dini penting untuk diperhatikan dalam interaksi DM dan TB Paru.

Kata kunci: Diabetes Mellitus, Tuberkulosis, Interaksi, Populasi Berisiko

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INTERACTION COMPLEXITY OF DIABETES MELLITUS AND TUBERCULOSIS

INTRODUCTION

Tuberculosis (TB) is a disease caused by *Mycobacterium tuberculosis* (Mtb) that generally infects the pulmonary organs and some others in the extrapulmonary organs. Pulmonary Tuberculosis (PTB) is a highly contagious infection that is among the top ten causes of death in the world. PTB cases are estimated to cause 1.5 million deaths and an incidence of 10 million cases globally in 2020.[1,2] The increase in PTB cases since 1980 is due to several factors, such as human immunodeficiency virus (HIV) opportunistic infections, high DR-TB cases, and an increase in diabetes mellitus (DM) comorbidity cases.[3]

Studies by Guay et al. show that a quarter of the world's population has latent tuberculosis infection (LTBI). Individuals with LTBI do not infect others with the bacteria but could cause active PTB due to reactivation of the infection. This situation occurs because granulomas are lysed, especially in individuals with impaired immunity, such as in HIV and DM conditions.[3,4] Cellular immunity is an important component in the defense of the host against attenuated Mtb and is at risk of increased reactivation of Mtb bacilli. Risk factors for PTB with impaired immunity may include HIV, DM, malnutrition, chronic renal failure, chronic lung disease, and long-term immunosuppressant usage.[2]

DM is a complex and multifactorial disease caused by insufficient insulin production, insulin resistance, or both. The disease is characterized by hyperglycemia (postprandial and postabsorptive), impaired insulin secretion by pancreatic cells, and insulin resistance. Insulin resistance is the failure of insulin to stimulate glucose uptake in the body. Some factors that cause insulin resistance are genetic disorders, fetal malnutrition, and/or increased visceral adiposity. The condition of insulin resistance causes liver cells to be unable to suppress the release of glucose into the blood, resulting in hyperglycemia.[2,5]

Globally, approximately 500 million cases of DM were recorded in 2017, with an expected increase of 7079/100.000 people in 2030. The incidence of metabolic diseases, especially DM, has become a major health problem in South Asian countries, with an estimated increase in DM prevalence of more than 51% from 2000 to 2020. The prevalence of DM in active PTB cases also increased globally, especially in South Asia in 2000. The risk of DM patients acquiring MTB infection has increased threefold. Since 2009, the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease (IUATLD) have recommended screening for PTB-DM simultaneously and establishing integrated management for both diseases.[2,6]

There is a significant immunological interaction between PTB and DM, so this article is expected to provide additional knowledge for the diagnosis and management of PTB management with DM as an at-risk population. The administration of Anti-Tuberculosis Drugs (ATD) as a preventive therapy for LTBI in the DM population is also expected to be applied in daily practice.

INTERACTION OF PTB IN DIABETES MELLITUS

In general, patients with DM who are male are at higher risk of PTB infection than females, although the cause of this condition remains unclear. This could be due to factors such as smoking and exposure to environmental

pollution. Based on age criteria, DM patients over 40 years old have a higher risk of developing PTB. The aging process causes alterations in the respiratory system, such as decreased strength and rigidity of the respiratory muscles, decreased cilia activity, reduced lung elasticity, and decreased cough reflexes. In the condition of old age with DM, the body's defense system will concomitantly attenuate, which has the potential to cause secondary infections, including PTB.[7]

DM patients who have a history of contact with PTB patients have a three-time higher risk of developing active PTB than non-DM patients. WHO recommends DM screening for PTB patients at the initiation of treatment, but DM screening is not recommended to be universally performed at present. The prevalence of PTB has been highest in patients with DM for more than 10 years. A long history of DM can decrease the immune system and predispose to PTB infection. PTB cases in DM can also occur due to malnutrition due to defects in metabolism.[7,8] DM is a chronic metabolic disease characterized by hyperglycemia due to insulin deficiency and/or impairment of insulin function associated with impaired immune function. Metabolic disorders in DM lead to immunological interactions towards the occurrence of the infection process described in Figure 1.[9,10]

Complement System

The complement system is one of the main immune systems involved in the natural immune system, composed of serum with surface proteins whose main function is to signal the opsonization and phagocytosis of microorganisms through macrophages and neutrophils so as to induce the lysis of these microorganisms. In addition, complement activation products will provide a second signal to activate B lymphocyte cells and antibody production. Based on several studies, it is reported that CD4 deficiency occurs in patients with DM, which is associated with polymorphonuclear dysfunction and reduced cytokine responses.[9,10]

Inflammatory Cytokine

In individuals with diabetes mellitus, mononuclear cells and monocytes will release fewer interleukin (IL)-1 and IL-6 in reaction to lipopolysaccharide stimulation. Some studies report that increased glycation can inhibit the production of IL-10 by myeloid cells, Interferon Gamma (IFN-γ) and Tumor Necrosis Factor (TNF)-α by T cells. The glycation process will also reduce the expression of Major Histocompatibility Complex (MHC) Class I on the surface of myeloid cells so that it will cause damage to cell immunity.[9,10]

Polymorphonuclear and Mononuclear Leukocytes

Hyperglycemia causes reduced movement or mobility in polymorphonuclear leukocytes, chemotaxis and phagocytic activit y. The immune system in hyperglycemia conditions will inhibit antimicrobial function by inhibiting the enzyme glucose-6-phosphate dehydrogenase (G6PD), increasing apoptosis activity in polymorphonuclear leukocytes, and reducing the transmission of polymorphonuclear leukocytes to the endothelial area. In tissues that do not use insulin for glucose transport, a cell environment with an atmosphere of hyperglycemia will increase intracellular glucose levels, which will then be metabolized using Nicotinamide Adenine Dinucleotide

Phosphate (NADPH) as a cofactor. Low levels of NADPH will prevent the regeneration of any molecules that play an important role in the cell's antioxidant mechanism, leading to increased cell resistance to oxidation stress.[9,10]

Antibody and Adherence

Immunoglobulin glycation occurs in DM patients who are experiencing elevated HbA1c.This impacts the biological function of antibodies. The ability of the host immune system to adhere microorganisms to each epithelial or mucosal cell is a very important stage in explaining the mechanism or pathogenesis of DM patients who are susceptible to various infections. For example, DM patients will be highly susceptible to MTB infection transmitted through inhaled droplets.[9,10]

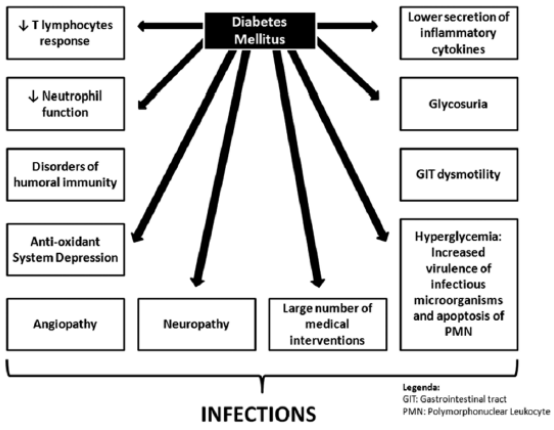

Figure 1. Pathophysiology of Infections Associated with Diabetes Mellitus[10]

The increased risk of PTB in patients with DM is multifactorial and occurs through various mechanisms of decreased immunity, including decreased number and function of T cells, low neutrophil count, and decreased cytokine responses of T-helper (Th)-1, TNF-α and TNF-β, IL-1 and IL-6. In general, the process of PTB in DM patients is caused by the reduced number and function of T cells, especially the Th-1 cytokine inhibitor Mtb. Other mechanisms can also occur due to decreased IL-2 production, causing macrophage dysfunction caused by Mtb. The oxidative stress response contributes to the blood glucose disorder mediated by IL-1, IL-2 and TNF-α.[11,12]

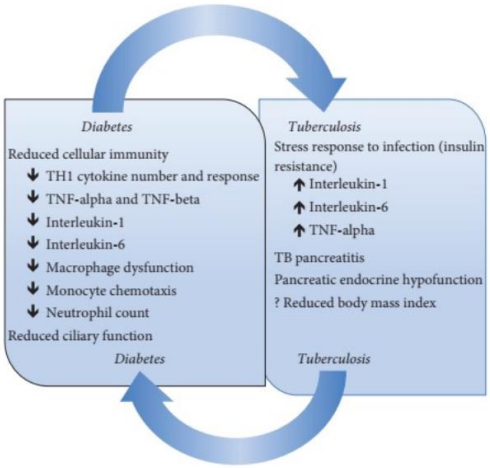

Figure 2. Immunologic Interaction between DM and PTB[12]

PREVENTION STRATEGY

The prevention that can be done in patients includes LTBI treatment, early diagnosis and screening, and vaccination. LTBI treatment is an MTB infection that occurs in individuals who do not have symptoms of an active PTB infection. LTBI patients do not transmit to others and do not activate MTB infection. Immunologic status is a contributing factor to the risk of developing Mtb infection in LTBI.[2,3] The risk of developing active PTB can be significantly reduced if prophylaxis is given to LTBI patients. Treatment of LTBI is an important component of the elimination of active PTB with several treatment regimens, namely isoniazid daily or twice a week for 9 months, isoniazid and rifapentine weekly for 3 months, or rifampicin daily for 4 months.[2,13]

Systematic screening and early diagnosis of PTB involve the identification of groups at risk of PTB. Systematic screening can yield better results in risk groups and thus increase the potential for a higher cure.[13] The groups included in PTB screening include those with a history of home contact with PTB patients, people with HIV, prisoners or jails and patients who have PTB.[2,14]

Vaccination is the most effective intervention in infectious disease control. The BCG (Bacillus Calmmette-Guerin) vaccine was introduced in 1921. This vaccine is used globally to prevent PTB in infants and children. This is proven by its effectiveness in preventing PTB disease. Vaccination can prevent secondary infections, including Mtb infection, in risk groups of patients with DM. Genetic factors in DM patients are recommended for early BCG vaccination.[15,16] Some of the above strategies can be considered to prevent MTB infection in patients who have a history of DM or are on DM treatment.

CONCLUSION

Infectious diseases are more prevalent in individuals with DM. The main pathogenic mechanisms are hyperglycemia, increasing virulence of some pathogens, decreased interleukin production in response to infection, reduced chemotaxis and phagocytosis activity, immobilization of polymorphonuclear leukocytes, glycosuria, and gastrointestinal and urinary dysmotility. PTB and DM have significant comorbidities. One of the risk factors for PTB with impaired immunity is DM. The increased risk of PTB in patients with DM is multifactorial and consists of several immunologic mechanisms. Prevention strategies that can be carried out in patients include controlling blood sugar levels, conducting PTB diagnosis and screening, LTBI treatment and vaccination. Further research is needed to clarify the immunopathogenesis mechanisms linking DM and PTB so as to develop strategies to increase vaccination coverage for DM patients.

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