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Review Article
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Role of Diabetes in prevalence of Tuberculosis

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Abstract

Tuberculosis is a lethal disease caused by *Mycobacterium tuberculosis*. The Mycobacterium initially infects lungs. If the infection spreads beyond the lungs, the symptoms will depend upon the individual organs. Diabetes is a type of metabolic disease in which a person has increased blood sugar level. It's because the body does not produce enough insulin or the cells inside the body do not respond to the insulin that is produced. Diabetics have a three to five time's higher risk of developing tuberculosis (TB) than those without diabetes disease. Diabetes mellitus is an important risk factor for tuberculosis and may affect disease treatment and also the response. Additionally tuberculosis may induce glucose intolerance and worsen the glycaemic control in people with diabetes. The main aim of this Review is to evaluate the epidemiology of diabetes mellitus and tuberculosis disease, the effect of diabetes mellitus on tuberculosis and vice versa.

Keywords: Tuberculosis; Diabetes mellitus; Insulin; Glucose intolerance; Blood sugar level

Introduction

Tuberculosis (TB) is a common, lethal and an infectious disease caused by various strains of mycobacterium, usually *Mycobacterium tuberculosis* [1]. "Robert Koch", a German physician first isolated it in 1882 and received the Nobel Prize for this discovery [2]. TB most commonly affects the lungs but also can affect almost any organ of the body. *Mycobacterium tuberculosis* is a small aerobic non-motile bacillus. This Pathogen has high lipid content which accounts for its unique clinical characteristics [3]. Mycobacterium divides every 16 to 20 hours, an extremely slow rate comparing to other bacteria, which usually divide in less than an hour. It is classified as a Gram-positive bacterium which lacks cell wall, has a phospholipid outer membrane [4]. On performing gram stain, it stains very weakly Gram-positive or does not retain dye as a result of the high lipid and mycolic acid content of its cell wall. It can survive in a dry state for weeks and can withstand weak disinfectants. Usually the bacterium can grow within the cells of a host organism, but *M. tuberculosis* can be cultured and grown *in vitro* [5]. A person gets infected with tuberculosis bacteria when he or she inhales small minute particles of infected phlegm or sputum from the air. The bacteria spread in air when someone who has a tuberculosis lung infection coughs, sneezes, shouts, or spits or otherwise transmit their saliva through the air [6]. People who are nearby can possibly breathe the bacteria into their lungs. Normally people don't get TB by just touching the clothes or shaking the hands of someone who is infected with it. Tuberculosis is spread (transmitted) primarily from person to person by breathing infected air during close contact.

Signs and Symptoms of Tuberculosis

TB infection initially occurs in the upper part of the lungs. The body's immune system, possess the capacity, to stop the bacteria to reproduce continually. Thus, the immune system can make the lung infection inactive (dormant state) [7]. On the other hand, if the body's immune system is not strong enough and cannot contain the TB bacteria, then the bacteria will reproduce (become active or reactivate) in the lungs and spread elsewhere in the body. It may take many months from the time the infection initially gets into the lungs until symptoms develop. The symptoms that occur with an active TB infection are:

- Tiredness or weakness,
- Weight loss,
- Fever,
- Night sweats.

If the infection in the lung worsens, then further symptoms can include:

- Coughing,
- Chest pain,
- Coughing up of sputum (material from the lungs) and/or blood,
- Shortness of breath.

If the infection spreads beyond the lungs, the symptoms will depend upon the organs involved. Diagnosis relies on radiology (commonly chest X-rays), a tuberculin skin test, blood tests, as well as microscopic examination and microbiological culture of bodily fluids [8]. Treatment is difficult and requires long courses of multiple antibiotics [9]. Prevention relies on screening programs and vaccination, usually with "Bacillus Calmette-Guérin" (BCG) vaccine [10].

Facts about tuberculosis

- ✓ Tuberculosis (TB) is an infection, primarily in the lungs a "pneumonia" caused by bacteria called *Mycobacterium tuberculosis*. It usually spread from person to person by breathing infected air during close contact [11].
- ✓ TB can remain in an inactive (dormant) state for years without causing any symptoms or spreading to other people.

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- ✓ When the immune system of a patient with dormant TB is weakened, the TB can become active (reactivate) and cause infection in lungs or any other parts of the body.
- ✓ The risk factors for acquiring TB include close-contact situations, alcohol, drug abuse and certain diseases (examples include diabetes, cancer, and HIV) and occupations (for example, health-care workers).
- ✓ The common signs and symptoms of TB include fatigue, fever, weight loss, coughing, and night sweats.
- ✓ The diagnosis of TB involves skin tests, chest X-rays, sputum analysis (smear and culture), and PCR tests to detect the genetic material of the causative bacteria or causative agent [12].
- ✓ Inactive tuberculosis may be treated with an isoniazid (INH), antibiotic, in order to prevent the TB infection from becoming active.
- ✓ Active TB is usually treated, successfully, with INH in combination with one or more of several drugs, including rifampin (Rifadin), ethambutol (Myambutol), pyrazinamide, and streptomycin [13].

Immune response against TB

Primary TB: When the inhaled tuberculosis bacteria enter the lungs, they can multiply and cause a local lung infection called (pneumonia). The local lymph nodes associated with the lungs may also become involved with the infection and usually enlarges in size [14]. The hilar lymph nodes (the lymph nodes adjacent to the heart in the central part of the chest) are often involved. Additionally, TB may also spread to other parts of the body [15]. The body's immune (defense) system is as strong as such it can fight off the infection and stop the bacteria from spreading [16]. The immune system forms a scar tissue around the TB bacteria which isolate it from rest of the body. Tuberculosis that occurs after initial exposure to the bacteria is often referred to as primary TB [17]. If the person's body is able to form a scar tissue (fibrosis) around the TB bacteria, inside the body then the infection is contained in an inactive state. Such an individual has no symptoms and cannot spread TB to other people. Due to the process of calcification of the scars (deposition of calcium from the bloodstream in the scar tissue) the scar tissue and lymph nodes may eventually become hardened, like stone. These scars often appear as round marbles in X-rays and imaging studies and are referred to as a granuloma [18]. If these scars do not show any evidence of calcium on X-ray, they can be difficult to distinguish from cancer.

Secondary TB: Sometimes, the body's immune system becomes weakened, and the TB bacteria break through the scar tissue and can cause active disease, referred to as reactivation tuberculosis or secondary TB [19]. For example, the immune system can be weakened by old age, or with the development of any infection or cancer, or certain medications used such as cortisone, anticancer drugs, or certain medications used to treat arthritis or inflammatory bowel disease [20]. The breakthrough of bacteria can result in a recurrence of the pneumonia and a spread of TB to other locations in the body. The kidneys, bone, and lining of the brain and spinal cord (meninges) are the most common sites affected by the spread of TB beyond the lungs [21].

Risk factors associated with TB

- ➢ In some cases people suffering with various diseases are at higher risk for developing TB which includes:
- ➢ People with silicosis have an approximately 30-fold greater risk for developing TB.
- ➢ Persons with chronic renal failure and also persons on hemodialysis have an increased risk for TB [22].
- ➢ Persons with diabetes mellitus have a risk for developing active TB that is two to four times greater than persons without diabetes mellitus, and this risk is likely to be greater in persons with insulin-dependent or poorly controlled diabetes [23].
- ➢ HIV is a major risk factor for tuberculosis [24]. The risk of developing TB is estimated to be between 20-37 times greater in people living with HIV than among people those who are without HIV infection. TB is a leading cause of morbidity and mortality among people living with HIV [25].
- ➢ Diabetes increases the risk of TB three-fold. The correlation between diabetes mellitus and TB shows a distinct connection between a contagious disease and a chronic disease. TB is a highly contagious air-borne bacterium. Therefore, contracting tuberculosis depends on whether or not a person comes into contact with the bacteria. People with diabetes mellitus are more likely to move from a latent form of TB to an active form of TB. This is where the public concern comes from, because when TB is active it is contagious and potentially fatal

Mechanism of Transmission and Pathogenesis

Transmission: People suffering from active pulmonary TB When cough, sneeze, speak, sing, or spit, expel or blow infectious aerosol droplets of size 0.5 to 5 μm in diameter [26]. A single sneeze can release up to 40,000 infectious aerosol droplets. Each one of these droplets may transmit the disease, since the infectious dose of tuberculosis is very low and inhaling fewer than ten bacteria may cause an infection [27]. People with prolonged, frequent, or intense contact with TB patients are at particularly high risk of becoming infected. A person with active but untreated tuberculosis can infect 10 to15 other people annually [28]. The probability of transmission from one person to another depends upon the number of infectious droplets expelled by a carrier, the duration of exposure, the effectiveness of ventilation, and the virulence of the *M. tuberculosis* strain. The chain of transmission of TB can be broken by isolating people with active disease and treating them with effective anti-tuberculous therapy [29]. After two weeks of such treatment, people with non-resistant active TB generally cease to be contagious. If someone does get infected, then it will take three to four weeks before the newly infected person can transmit the disease to others.

Pathogenesis: TB infection begins when the mycobacteria reach the pulmonary alveoli, where they invade and replicate within the endosomes of alveolar macrophages [30]. "Ghon focus", is the primary site of infection in the lungs and is generally located in either the upper part of the lower lobe, or the lower part of the upper lobe.

Bacteria are picked up by dendritic cells, which do not allow the replication of bacteria, but can transport the bacilli to local (mediastinal) lymph nodes [31]. Further spread of the bacilli is through the bloodstream to other tissues and organs where secondary TB lesions can develop in other parts of the lung (particularly the apex of the upper lobes), peripheral lymph nodes, kidneys, brain, and bone [32]. All parts of the body can be affected by the disease, but it rarely affects the heart, skeletal muscles, pancreas and thyroid. "Miliary tuberculosis" is the TB disease, most common in infants and the elderly people.

If untreated, infection with *Mycobacterium tuberculosis* can cause lobar pneumonia. About 90% of those infected with *Mycobacterium tuberculosis* have asymptomatic, latent TB infection (sometimes called LTBI), with only a 10% lifetime chance that a latent infection will progress to TB disease [33]. However, if untreated, the death rate for these active TB cases is more than 50% [34].

Diabetes

Diabetes, is a group of metabolic diseases in which a person has increased or high blood sugar [35,36]. It's either because the body does not produce enough insulin or because cells do not respond to the insulin that is produced [37, 38]. Diabetes mellitus is increasing at an alarming rate [39]. Over 200 million people are affected with diabetes mellitus worldwide [40,41]. Diabetes is one of the most important public health challenges for the 21st century [42]. Diabetes mellitus is associated with an increased risk for a number of serious and sometimes life-threatening diseases like cardiovascular disease [43,44], peripheral vascular disease, and cerebrovascular disease [45,46]. The high blood sugar level produces some of the symptoms of polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger) [47]. The diseases which are listed under Diabetes are many with the most common being Type-1 and Type-2 diabetes [48]. These are the diseases of the metabolic system and involve the body's ability in metabolizing sugar using the hormone insulin [49]. Usually insulin uses the simple sugar glucose which is needed for repair, growth and energy of cells.

Diabetes mellitus is caused either if insulin in the body is not produced or is being produced but is unable to be used by the cells in the body. Within the class of diabetes mellitus are several types of diabetes but overall diabetes mellitus is the most common form of diabetes [50]. Gestational Diabetes mellitus (GDM) is defined as glucose intolerance of varying degrees, which appears, or is first diagnosed, during pregnancy and may or may not persist after delivery [51, 52]. Diabetes Insipidus is the amount of fluid or water which is retained in the system and overall is very rare.

Type-1 Diabetes: In Type-1 Diabetes, the body produces little or no insulin so those with this type of diabetes need to be on insulin therapy for their entire lives [53]. Type-1 diabetes mellitus is characterized by loss of the insulin-producing beta cells of the islets [54] of Langerhans in the pancreas leading to insulin deficiency [55]. In early days people suffering from Type-1 Diabetes usually ended with death, but with the advent of insulin now people are able to manage this disease [56]. Type-1 diabetes is also known as "Juvenile diabetes" because it represents a majority of the diabetes cases in children [57].

Type-2 Diabetes: In Type-2 Diabetes, the body produces plenty of insulin but cells are unable to use it. Type-2 diabetes is most common form of diabetes and normally develops in older people, but now it is developing in all age group of people [58, 59]. The main causes of Type-2 diabetes are unhealthy diets, obese or being overweight or lack of exercise, sedentary life styles revolving around the computers, television, video games and also the fast food or junk food [60].

The complications of diabetes include problems with nerves as well as the blood flow through the blood vessels that supply energy for every organ [61]. The complications can be with the eyes, heart, kidneys, the feet and many other areas of the body [62]. It may affect the bones also [63]. Because of the restricted blood flow when there is a problem or complication, the body is extremely slow to heal.

Diabetics at higher risk of tuberculosis

Tuberculosis occurs with a high frequency in diabetics or people suffering with diabetes and causes a significantly greater mortality [64]. Reactivation of tuberculosis lesions with increased rates has also been recorded in diabetics. At the same time, tuberculosis appears to make diabetes more worsen, with patients requiring higher doses of insulin than before [65]. As compared to the general population, the incidence of diabetes appears to be higher among tuberculosis patients than the normal and general population [66].

Tuberculosis and its complications with Diabetes Mellitus

The association between diabetes and tuberculosis has some of the following observations:

- Tuberculosis development occurs ten times more frequently in juvenile diabetics.
- In most of the cases, tuberculosis develops after the onset of diabetes.
- The pulmonary tuberculosis occurrence increases with the duration of diabetes.

It means that diabetic patients tend to contract tuberculosis but the reverse would be rare.

Immune dysfunction in diabetics

Host defense and immune cell functions could get defected with the increased incidence of pulmonary tuberculosis in diabetics [67]. The immune disorganization involves the cell-mediated arm of the immune system [68]. There is a distinct influence of hyperglycemia on the microbicidal function of macrophages, with even brief exposures to blood sugar level of 200 mg% significantly depressing the respiratory burst of these cells [69]. This is observed in poorly controlled diabetics, with high levels of glycated haemoglobin, tuberculosis follows a more destructive course and is associated with higher mortality rate [70]. Multiple pulmonary physiologic abnormalities have also been documented in diabetics that contribute to delayed clearance of infection and spread of infection in the host [71]. Alterations in cytokines, monocyte-macrophages and CD4/CD8 T cell populations are due to infection with tubercle bacilli [72]. CD4 and CD8, subsets of the T lymphocyte plays a main role in the modulation of host defenses against mycobacteria and has a profound influence on the rate of regression of active pulmonary tuberculosis [73].

Glucose intolerance in tuberculosis

"Tuberculous patients do not develop diabetes with any greater frequency than the non-tuberculous". This view was changed by various studies conducted in different countries like India, Africa and Tanzania etc [74]. Impaired glucose tolerance (IGT) in tuberculosis is much higher than overt diabetes [75]. With effective chemotherapy, IGT reverts to normal in a large number of cases and there is higher percentage with IGT because, according to the National Diabetes Data Group of NIH, one to five per cent of patients with IGT may progress to overt diabetes, per year.

Causes of glucose intolerance in tuberculosis

Important cause of the development of impaired glucose tolerance is acute severe stress. Stress hormones like epinephrine, glucagon, cortisol and growth hormone are stimulated by Fever, protracted inactivity and malnutrition which raise the blood sugar level in excess amounts

[76]. Plasma levels of Tumor Necrosis Factor alpha (TNF alpha) and Interleukin-1 (IL-1) are also raised in severe illness which can stimulate the anti-insulin hormones [77]. Serum levels of adrenocortico-tropin hormone, cortisol and T_3 have been found to be decreased in patients with tuberculosis [78]. All these abnormalities make the patient's ability for a doubtful stress response [79]. In severe tuberculosis, endocrine function of Pancreas has also been found to be adversely affected. In patients with concomitant diabetes and tuberculosis, a higher incidence of chronic calcific pancreatitis occurs, leading to an absolute or relative insulin deficiency state [80]. Dysregulation of energy homeostasis in the TB disease may cause by a family of fatty-acid-transporter proteins in the tubercle bacillus. Hepatocytes increase preferentially the uptake of long chain fatty acids (LCFAs). For most organisms LCFAs are an important source of energy and also function as blood hormones regulating key functions such as hepatic glucose metabolism. Disorganization of lipid metabolism has been described in patients with tuberculosis [81].

Anti-tuberculosis drugs on blood sugar level

Rifampicin is a powerful inducer of the hepatic microsomal enzyme which lowers the serum levels of sulphonyl ureas and biguanides [82]. Rifabutin, another inducer which induces hepatic metabolism but is not as potent as Rifampicin. Other drug like anti-tuberculosis interferes very rarely with blood sugar level [83]. An overdose of Isoniazid or Isonicotinylhydrazine (INH) may cause hyperglycemia while in some cases or circumstances [84]; it is difficult to control diabetes in patients on Pyrazinamide [85].

Conclusion

Diabetics or people with diabetes face a higher risk of tuberculosis (TB) than non-diabetics. Diabetics who have had recent contact with TB patients were the prime candidates for preventive treatment. Most of the countries are missing their opportunities to prevent TB in diabetes patients. Clinicians diagnose diabetes in people with TB and also TB in Diabetes patients. Diabetes depresses or let down the immune response, which in turn facilitates infection with *Mycobacterium tuberculosis* and/or progression to symptomatic disease. The studies and the researchers recommend that screening the TB contacts for diabetes in order to improve the detection and management of both TB and Diabetes diseases. There are implications for these studies in particular for countries with high prevalence of both the Tb and Diabetes diseases, such as India, Indonesia, China, Bangladesh, Brazil, Pakistan etc.

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