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DIABETES AND TUBERCULOSIS: TACKLING THE DUO, TRANSLATING RESEARCH TO MANAGEMENT AND POLICY

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ABSTRACT

When combined with other poor treatment results from tuberculosis, diabetes mellitus (DM) triples the likelihood of developing in TB patients and doubles their risk of dying during treatment. Additionally, DM may put a person at risk for latent tuberculosis infection (LTBI). While there has been a lot of attention paid to this combo of diseases, the majority of the works focused on screening TB patients for undiagnosed diabetes or following up on TB treatment outcomes in DM subjects through observation. Targeted immunization campaigns, LTBI screening, preventative treatment for those with pre- diabetes and diabetes, and enhanced diabetes management with newer anti-hyperglycaemic medications and early insulin introduction are all important and effective ways to stop the spread of tuberculosis. Prevention of diabetes needs to be considered by propagation of awareness about diabetes and importance lifestyle changes. Recent extensive research on diabetes management has prompted clinicians to undertake timely management of DM but the situation may not same in case of TB and still many gaps are to filled up from research to management to policy. **Keywords:** diabetes; latent tuberculosis; tuberculosis

INTRODUCTION

Relationship between diabetes (DM) and tuberculosis (TB) was noticed a century ago by some clinicians. Before insulin was identified and used in 1922, TB was thought to be the cause of death for type 1 diabetics who did not pass away from a diabetic coma. American physician Howard Root conducted autopsy on patients who died of juvenile diabetes and came to the conclusion in 1934 that type 1 diabetes was linked to a 10-fold higher incidence of tuberculosis.

This association was somewhat disregarded due to the decrease in TB occurrence and mortality as well as the development of anti-tuberculous medications. Then, when type 2 diabetes became more common in several middle-class and low-income nations where tuberculosis was still rampant in the 1990s, several epidemiological studies "rediscovered" diabetes as a potential concern for the disease.[1]

The association between diabetes and tuberculosis has been the reason of several studies; the focus will be on research findings that are applicable to policy and clinical care of both diseases. The epidemiological consequences of diabetes on TB, screening techniques for combination diseases, combined treatment of diabetes and TB, and potential population-level controls for diabetes- associated tuberculosis are all important subjects to be covered in this article.

DIABETES'S EPIDEMIOLOGICAL IMPACT ON TUBERCULOSIS

Significant medical and societal repercussions have resulted from the global DM epidemic, which affected about 570 million people in 2019 and is expected to touch 629 million by 2045. Over 80% of cases of type 2 DM, in this article, are found in countries with low and moderate incomes as well as in regions where TB is still common. The prevalence of both diseases has increased in India and other countries in the Southeast.[2][3]

Diabetes is often undiagnosed (upto 50%) in India as recently reported by ICMR and known to cause cardiovascular, renal, and other micro and macro vascular complications leading to heart failure and end stage renal disease.

In many situations, a serious infection may be the initial sign of diabetes, and diabetes increases the risk of numerous infections and their sequelae considerably. People without diabetes hardly ever get infections, mostly in developed countries. In fact, some infections—known as "signal infections"—are so closely linked to diabetes that they are extremely uncommon in healthy individuals[13]. The recent COVID-19 pandemic has highlighted the higher risk of serious infections in those with DM [9]; nevertheless, new research indicates that type 1 diabetes increases requirement for medical care in the event of any illness by almost four times, while type 2 diabetes increases hospital treatment needs by approximately two times. There is a dearth of information on the potential impact of type 1 DM on TB in low- and middle-income countries (LMICs), as the majority of studies on TB and diabetes focus on type 2 diabetes.[2]

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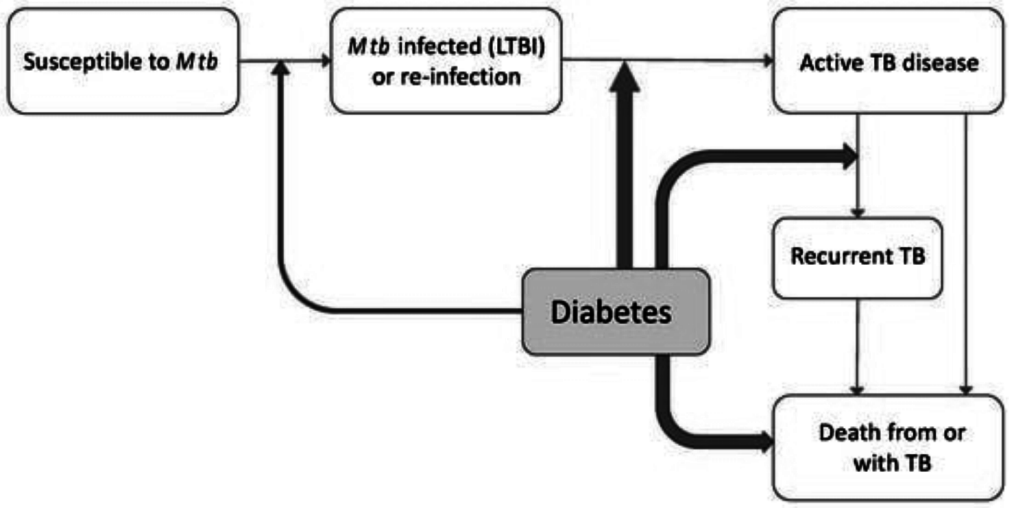

DIABETES AND THE TB NATURAL HISTORY

Diabetes may increase the risk of tuberculosis at several points or stages of the disease's route due to the complex natural history of tuberculosis (see Figure 1). Due to their own immunity or medical interventions, many persons who are initially exposed to M. tuberculosis become clear of the infection; nonetheless, many will have latent infections, which put them at risk of developing tuberculosis in the future. Latent TB infection (LTBI) is thought to affect about 25% of people globally,with a substantially greater prevalence in India. 10% of infected individuals are predicted to experience active tuberculosis disease at some point in their lives; around half of these cases are predicted to proceed rapidly, occurring 1-2 years after infection.

Typically, cohort studies are unable to differentiate between the presence of hyperglycaemia as a risk factor for TB and the possibility of preexisting LTBI contributing to a higher risk of tuberculosis disease in diabetics.

Most people agree that the rise in TB illness among LTBI patients may be more significant than their notably higher risk of contracting *M. tuberculosis* in the first place.

Only those diagnosed with diabetes more than three years ago had a higher risk of developing tuberculosis in industrialized nations; long-term patients do not have this increased risk. Some have suggested that this could indicate a role for diabetes, especially initial hyperglycaemia, in the transition from lethal treatable brain injury to active disease; however, this could also be a result of diagnostic bias. Whole genome sequencing research and extensive longitudinal studies that could contribute to a clearer understanding of the mechanisms involved are currently lacking [5].

DIABETES AND THE CHANCE OF CONTRACTING M. TUBERCULOSIS

Diabetes patients may be more susceptible to infection or have a higher exposure to M. tuberculosis. This might happen because diabetics' immune systems are altered. The majority of the research that made up this review had serious limitations and had a cross-sectional design. Glycated haemoglobin (HbA1C) was used in a recently published US cross-sectional study to test all immigrants for diabetes. This revealed a graded response and higher infection risk, with an elevated risk of LTBI in those who were considered "pre-diabetes." [6]

DIABETES'S IMPACT ON THE RISK, PRESENTATION, AND TREATMENT RESULTS OF TUBERCULOSIS

Diabetes also affects how TB presents itself, as seen by increased cavitation, higher severity TB ratings, and a greater frequency of pulmonary TB with a positive culture or smear, according to numerous research. It suggests that diabetes patients have a lower incidence of extra-pulmonary tuberculosis. Patients who also have HIV co-infection, however, may exhibit a different pattern, which unquestionably raises the likelihood of disseminated and extrapulmonary tuberculosis presentations. Diabetes can also somewhat raise the bacterial burden of M. tuberculosis and postpone the time until a smear or culture is negative.

Individuals with diabetes with TB remain culture positive in months 2-3 at a rate about twice that of individuals with TB alone. Diabetes now doubles the chance of dying while receiving treatment for tuberculosis, one of the many researches and evaluations that show how the disease impairs the results of TB treatment. The exact cause of death in patients with both diabetes and tuberculosis is not always known, but both conditions are linked to a higher risk of cardiovascular problems, including myocardial infarction and stroke.[4]

DIAGNOSIS AND TESTING FOR CO-OCCURRING DIABETES AND TUBERCULOSIS

WHO recommendations and other national organizations recommend screening for diabetes in newly registered tuberculosis patients, even if this may not always be done well in practice. This has been added to the DOTS management for tuberculosis in a number of nations, including India. International guidelines recommend that a basic blood glucose or HbA1c test be used for screening; nevertheless, it is estimated that around half of TB clinics worldwide lack access to laboratoryfacilities, even for blood glucose testing. Because point-of-care tests are less reliable and therefore require careful interpretation. [21]

TREATMENT FOR TUBERCULOSIS IN PATIENTS WITH CO-MORBID DIABETES

Patients with diabetes and tuberculosis should receive similar prescribed TB treatment as those with tuberculosis alone. Diabetes is linked to TB medication resistance, a delayed response to therapy, and increased rates of toxicity, failure, and recurrent TB, therefore this may need to be reevaluated.

In addition to treatment duration, greater doses of TB medication may also contribute to better treatment outcomes.

Treating patients who have both diabetes and tuberculosis requires taking into account a number of additional factors. For example, the interactions between drugs are more likely to occur. Rifampicin accelerates the metabolism of numerous medications that diabetics frequently take, such as calcium-channel blockers, warfarin, ACE inhibitors, metformin, and statins. In addition, drug toxicity may be severe; INH can worsen diabetic neuropathy; and those who have diabetes who suffer from tuberculosis are more likely to experience damage to the kidneys and liver. This is critical for the treatment of multidrug-resistant tuberculosis (MDR-TB), since individuals with diabetes may be more vulnerable to aminoglycoside-induced kidney impairment and linezolid-induced neuropathy. Moreover, a high pill load in patients receiving therapy for two conditions may result in missed doses, improper medication administration, treatment discontinuations, or default.[23]

IMPROVING DIABETES CONTROL IN PATIENTS WITH CO-OCCURRING TUBERCULOSIS

Reducing both short- and long-term consequences including cardio-renal and other micro- and macrovascular events is the goal of managing diabetes. The treatment of diabetes involves by lifestyle modifications for diet, exercises and by quitting smoking, and consuming less alcohol.

Medications like OHAs, anti-hypertensives, and statins should be undertaken.

GLYCAEMIC CONTROL

An acknowledged goal for glucose control in diabetes is a HbA1c < 7% (53 mmol/mol), according to the American Diabetes Association (ADA). Drug interactions with rifampicin as well as changes in appetite and digestion and energy use over the course of TB illness and its recovery, this may be challenging with concomitant ATT.

It's also critical to understand that inflammation linked to tuberculosis can cause transient hyperglycaemia, which frequently resolves on its own when anti-tuberculosis medication is taken.

Three pharmacological families are available for selecting glucose-lowering medications: insulin, sulphonyl urea derivatives, and biguanides. While DPP-4 inhibitors, SGLT2 inhibitors, thiazolidinediones (TZD), and GLP-1 receptor agonists are among the numerous pharmacological classes that can be used to treat diabetes, there is evidence that these medications are more successful and effective.

Metformin serves as the first-choice glucose-lowering drug that is recommended

for people with type 2 diabetes; there is no explanation why this should be distinct for those who are actively TB positive. Metformin's benefits include a minimal risk of hypoglycaemia, a long history of use, low cost, efficacy, positive effects on CVD, absence of a meaningful clinical interaction between rifampicin and other drugs.If metformin is not working or is contraindicated, sulphonyl urea derivatives can be used as an add on or single oral glucose-lowering medication. Gliclazide, glimepiride, and glipizide are the sulphonyl urea derivatives that are most frequently utilized. The possibility of hypoglycaemia and significant medication interactions with rifampicin, which exhibit significant inter-individual variance but limit their efficacy by 30–80%, are the two main drawbacks.

In programmatic terms, insulin is an important option in patients who are ill and admitted to the hospital or those who were on insulin before being diagnosed with tuberculosis. When there is severe hyperglycaemia (e.g., blood glucose > 18 mmol/L or a HbA1c > 10%), insulin should be administered. According to recent guidelines, it is possible to achieve normoglycemia by using newer medicines like as DPP4 inhibitors, SGLT2 inhibitors, and GLP-1 RA in combination of other glucose lowering agents.[12][13][14]

EVALUATION AND MANAGEMENT OF CARDIOVASCULAR RISK

For those with diabetes, atherosclerotic cardiovascular disease (ASCVD)—which includes peripheral artery disease, MI, and stroke—is the main cause of morbidity and death.[15] Any level of heart failure is a significant factor to take into account. The interventions that are the main emphasis of cardiovascular risk assessment are weight loss, hypertension medication, lipid-lowering therapy (statins), and lifestyle counselling. For individuals with diabetes and newly diagnosed TB, starting TB treatment successfully is far more crucial than managing cardiovascular risk. Patients may receive counselling regarding alternative healthy lifestyle options and antihypertensive medication following the completion of the first rigorous phase of anti-TB treatment.[16]

MANAGEMENT OF DIABETES-RELATED TUBERCULOSIS IN THE GENERAL PUBLIC

The majority of early efforts to address the TB–diabetes combo has focused on screening, especially for diabetes that may go untreated in TB patients. This is significant since, worldwide, diabetes affects 15% of newly diagnosed TB patients, the majority of whom go undetected. Improving diabetes management and screening during tuberculosis therapy may lead to improved results for the duration of the illness and long-term health of those who have the condition. Several observational research has indicated that improved diabetes control may lower the incidence of tuberculosis and enhance the results of tuberculosis treatment. Randomized controlled trial data are scarce, and selection biases may have an impact on these investigations. Therefore, for the person who has just received a TB diagnosis, screening for diabetes may be clinically significant. [17][18][19]

SUMMARY

Diabetes may have a variety of effects on the natural history of tuberculosis, including elevated risks of tuberculosis infection and disease, worse treatment outcomes, and greater mortality rates during and after therapy. Health systems can improve outcomes at many points along this pathway, but from a population viewpoint, the most effective treatments may be those that are implemented earlier to prevent tuberculosis in this patient group that is at-risk. Using HbA1c or glucose blood tests, the yield of testing TB patients for undiagnosed diabetes is very high and must be performed in all elder patients. In highly endemic countries, screening individuals with diabetes for tuberculosis (TB) may be contemplated. This might be directed towards people having a higher risk of developing tuberculosis. A chest X-ray exam can also be a useful tool for screening. When it comes to treatment, managing diabetes and TB together, as well as diabetes, TB, and HIV together, presents a number of difficulties and significant evidence gaps. In cases where medication resistance is more prevalent, TB treatment may need to be escalated. It is still necessary to identify and adjust optimal objectives and therapeutic algorithms for the managing of diabetes in TB patients.

In order to prevent needless infections in diabetes clinics, we also need to determine what is required for the best possible delivery of health services. This involves figuring out where to send people for specialist diabetic care and how to continue getting care for chronic diabetes after TB treatment is completed. [5][14] [16]

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