

## Observational Study

# Insulin use in patients with diabetes and tuberculosis

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Current estimates from the World Health Organisation (WHO) suggests that 15% of patients of with tuberculosis infection have the additional double burden of diabetes mellitus. Control of hyperglycaemia among these patients is as important as anti-tubercular therapy. Though there are currently no randomised studies to suggest insulin therapy has better outcomes in comparison to oral anti-diabetic therapy among these patients, there are plenty of historical and clinical data to suggest that insulin therapy is a superior choice. Historically within a year of the availability of insulin commercially in 1923, physicians in Europe and America started using insulin among patients with tuberculosis and normal glucose tolerance. This was primarily for its benefits in improving appetite, augmenting weight gain and improving strength. Though this is currently not indicated the historical advantages of insulin continue to serve patients with co-existing diabetes mellitus and tuberculosis. Insulin therapy has no drug interactions with the currently used first and second line anti-tubercular agents unlike oral anti-diabetic drugs. In patients with liver and renal dysfunction, insulins remain the drug of choice. Patients with significant hyperosmolar symptoms, weight loss, HbA1c >9%, fasting plasma glucose >250mg/dl and those who are catabolic with poor appetite insulin is absolutely indicated as the therapy of choice for their diabetes.

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**Key words :** Insulin, Diabetes Mellitus, Tuberculosis.

The International Diabetes Federation (IDF) estimates for 2017 revealed that 9.3% of the world's population had diabetes mellitus (DM). With 74 million people or 16% of world's population with diabetes mellitus currently living in India, our country was ranked second in the world<sup>1</sup>. Globally, 10.4 million new cases of tuberculosis (TB) were estimated to have occurred in 2015 with India harbouring a good many of them<sup>2</sup>. Tuberculosis has for time immemorial been a formidable foe in our battle against infectious diseases. This time around it has united with another menacing adversary: diabetes mellitus. Chronic hyperglycaemia increases the susceptibility of patients to infections by suppression of both the innate and adaptive immunity. The synergy between these communicable and non-communicable diseases is a worrying fact. The duo has been responsible for a significant amount of morbidity, mortality and medical expenditure.

A good control of blood glucose in a patient with diabetes mellitus and tuberculosis is just as important to the outcome of tuberculosis as the primary anti-tubercular therapy itself. There is a bidirectional relationship between these two disorders which has been clearly demonstrated by a vast epidemiological evidence base<sup>3-8</sup>. According to the data put forward by the World Health Organisation (WHO), 15% of patients infected with tuberculosis world-

- Insulin is superior to OAD in TB patients with DM.
- It increases appetite, weight gain and strength.
- No drug interactions with ATD unlike OAD.
- Insulin is the choice of therapy in hepatic and renal dysfunction, hyperosmolar state, HbA1c >9.0%, FPG > 250 mg%.

wide have either diagnosed or undiagnosed diabetes mellitus. The Research Society for Study of Diabetes in India (RSSDI) recently published an exhaustive recommendation for diagnosis, treatment and control of this double burden of diabetes mellitus with tuberculosis<sup>9</sup>.

### *Glycemic Control and Outcomes in Tuberculosis:*

Diabetes mellitus increases the risk of developing tuberculosis especially when the blood glucose levels are uncontrolled. Worse treatment outcomes, death during treatment, increased risk of disease relapse, delayed sputum conversion and an increased incidence of drug resistance are all associated with tuberculosis infection in patients with diabetes mellitus<sup>10</sup>. Better glycaemic control improves the outcomes in patients with tuberculosis. But, many of the commonly used oral anti-diabetic agents have multiple drug interactions with standard anti-tubercular therapy leading to a decline in drug adherence and effectiveness. Besides the conventional drug treatments, other modalities such as education and lifestyle modifications may be needed, especially for patients with newly diagnosed diabetes mellitus<sup>11</sup>. According to the meta-analysis of eight cohort studies that addressed the question of

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glycaemic control and treatment outcomes in patients with tuberculosis by Shewade et al found that unfavourable outcomes and non-conversion of sputum was associated with poor glycaemic control<sup>12</sup>.

**Type of Anti-diabetic Therapy and Outcomes:**

An aggressive approach to blood glucose management should be equated against the potential risks and the supplementary efforts required for its implementation. Personalised, tailored glycemic targets should be made for each patient accounting for the age, co-morbidities, level of work and activity, severity of the tuberculosis infection, risk of hypoglycaemia and availability of resources. Periodic monitoring is required to provide an adequate glycemic control. In a study of patients with diabetes and tuberculosis, Magee MJ et al from Peru revealed that when compared to those receiving 'OHA only', those receiving 'Insulin only' had significantly higher risk of unfavourable end treatment outcomes while those receiving 'insulin and OHA' did not have significantly different unfavourable end of treatment outcomes<sup>13</sup>.

**Historical Use of Insulin among Patients with Tuberculosis without Diabetes :**

The first reported trial of use of Insulin in patient with non diabetic tuberculosis patients was by Nyiri in 1923<sup>14</sup>. Subsequently insulin was used extensively in Europe for "fattening cures" in small doses in patients with tuberculosis related wasting. An extensive review by Fredrick Allen suggested that larger doses of insulin could be administered in patients with tuberculosis without diabetes by combining insulin use with frequent use of dextrose concomitantly. The author claimed "striking gains in appetite, weight, strength and spirits" with this combination. Weight gain in the author series of 45 patients ranged from 1.4 kg to 13.2 kg in females and 2.3 kg to 24.5 kg in men with an average weight gain of 11.3 kg<sup>15</sup>.

**Advantages of Insulin in Tuberculosis :**

It should be clear at the outset that there is limited evidence-based scientific support available with regards to preference of diabetes therapy. Before choosing an oral hypoglycaemic agent (OHA), we should be well aware of the propensity of drug interactions, especially when rifampicin is used. Rifampicin increases the hepatic metabolism of all conventional diabetic drugs especially sulphonylurea group of drugs. Dipeptidyl peptidase- 4 (DPP-4) inhibitors theoretically can lower immunocompetence<sup>16</sup>. This repercussion could alter the outcome of tuberculosis infection. Limited information is available about the newer anti-diabetic drug classes. Its use in tuberculosis endemic areas are hampered by high costs and unavailability.

Insulin on the other hand is not metabolised in the liver and hence has no pharmacokinetic interactions with Rifampicin or any other anti-tubercular therapy. The stress related hyperglycaemia associated active tuberculosis with worsens the glycemic status and hence insulin will be a superior choice in view of straightforward modification protocols<sup>17</sup>. Insulin use at the start of TB treatment has been suggested by many even though there is limited evidence to back that claim<sup>18</sup>.

Insulin requirements are higher than usual due to the ongoing stress hyperglycaemia, increased appetite with start of treatment of tuberculosis and the concurrent use of corticosteroids. Few studies have also found an association between TB and insulin resistance development in TB patients<sup>19</sup>. The debate with regard to the choice of insulins to be used cannot be dwelled upon since there is no scientific evidence as of now to guide therapy. The factors that affect glycemic control in diabetic patients with tuberculosis are listed in Fig 1. Some have also suggested insulin use as an aid in non-diabetic patients with tuberculosis for the purpose of weight gain<sup>20</sup>. The advantages of insulin use in patients with diabetes and co-existing tuberculosis are summarised in Table 1.

**Absolute Indications for Use of Insulin in Tuberculosis<sup>9,22,23</sup> :**

1. Oral anti-diabetic drugs fail to reach HBA1c targets
2. Oral anti-diabetic drugs contraindicated due to liver or kidney dysfunction
3. Patients with diabetes who are in a catabolic state
4. New patients with diabetes with ketonuria or those who have hyperosmolar symptoms
5. New patients with diabetes with HBA1c > 9%
6. New patients with diabetes whose fasting blood glucose is > 250 mg/dL



Fig 1 — Factors that affect glycemic control for patients with DM during TB treatment

Table 1 — Advantages of insulin use in diabetic patients with tuberculosis<sup>19</sup>

1. **Chronic and severe TB infection**
  - a) Increased susceptibility in diabetes
  - b) Reactivation of old focus of infection
  - c) More cavitation, smear or culture positivity
  - d) Deceptively mild or absent toxic symptoms and signs
  - e) Ineffective chemotherapy in hyperglycemia
2. **Loss of tissue and function of pancreas**
  - a) Pancreatic endocrine deficiency
  - b) Tuberculous pancreatitis
  - c) Tuberculin toxicity on pancreas
3. **Requirement of high calorie, high protein diet**
  - a) Counter negative nitrogen balance
  - b) Facilitate tuberculosis therapy
  - c) Prevent further infection, reactivation
4. **Interactions and adverse effects of anti-tuberculous drugs**
  - a) Rifampicin accelerates the metabolism of antidiabetic drugs
  - b) Rifampicin per se may increase insulin requirements
  - c) Isoniazid antagonizes sulphonylureas
  - d) Isoniazid may rarely cause pancreatitis
  - e) Interference with intestinal absorption of carbohydrates
5. **Associated hepatic disease**
  - a) With tuberculosis and/or diabetes
  - b) Induced by anti-tuberculous therapy
6. **Contraindications for oral antidiabetic drugs**
  - a) For sulphonylureas
    - i) Tuberculosis, a serious intercurrent illness
    - ii) Pancreatic disease
    - iii) Hepatic disease
  - b) for biguanides
    - i) Loss of appetite
    - ii) Loss of weight
    - iii) Glucose malabsorption
7. **Aging**
  - a) Augments susceptibility to tuberculosis
  - b) Masks tuberculous infection
  - c) More severe  $\beta$ -cell dysfunction
  - d) Long duration of diabetes
  - e) Labile diabetic control
8. **Other factors in diabetes-tuberculosis association**
  - a) Anti-insulin stress hormones induced by infection
  - b) Requirement for thyroid or glucocorticoid supplementation
  - c) Supranormal concentrations of insulin antagonists
  - d) Possible improvement of immune deficits by insulin
  - e) Defective lung defence mechanisms, laryngeal injury
  - f) Concurrent corticosteroid intake

### Conclusions :

Insulins are a good choice of glucose-lowering agents in patients with diabetes and tuberculosis especially in the setting of drug-interactions, insulin resistance, weight and behaviour alterations, stress hyperglycaemia, chronic inflammation and concurrent corticosteroid use. Its mal-leability and effortless adaptivity makes it a prime choice in the above setting.

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