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Effect of Diabetes on Tuberculosis and its' Treatment Outcomes: A Narrative Review from the Effect of Diabetes on Tuberculosis Severity (EDOTS) Cohort from Chennai, South India

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Highlights:

1. High prevalence of glycaemic disorders and observed heterogeneity within the people with TB DM co-morbidity
2. Persistent inflammation exists in TBDM group not only at baseline but throughout ATT
3. Low BMIs and low HbA1c levels were both associated with higher odds of bad TB treatment outcomes
4. High visceral adiposity index is correlated with adverse TB treatment outcomes despite its' correlation with HbA1c

India faces the dual burden of type 2 diabetes (DM) and also pulmonary tuberculosis (TB) [1,2]. Evidence suggest that coexistence of DM has adverse impact on TB in terms of disease progression and also treatment outcomes. Studies showed that the state of hyperglycaemia in person with diabetes makes more susceptible to infections mainly mycobacterium tuberculosis and further increases the severity and results in outcomes like death, resistance or recurrence of TB, delayed sputum conversion, severe radiographic manifestations such as multiple and large lung cavities and so on [3-5]. Longitudinal prospective studies are sparse in India on the interaction of TB and DM and the impact of DM on the severity of TB.

About the study on Effects of Diabetes on Tuberculosis Severity (EDOTS)

A comprehensive study was conducted to look into the several aspects of the impact of DM on TB presentation, progression and treatment outcomes. This was a prospective cohort study conducted by Prof M Viswanathan Diabetes Research Centre as a part of Regional Prospective Observational Research for Tuberculosis (RePORT) -India Consortium, enrolled study participants from 2014 to 2018. The individuals who were diagnosed with TB on the basis of mycobacterium tuberculosis culture reported in 10 government running TB units under Revised National Tuberculosis Control Programme (presently National Tuberculosis Elimination Programme) located in northern parts of Chennai were prospectively recruited into this study. They were aged between 25-60 years and those who had prior history of TB were excluded. The participants who received more than 7 days of anti-tuberculosis treatment, taken more than 7 doses of fluoroquinoline within a month duration, pregnant or lactating mothers, HIV positive or receiving any immunosuppressive therapy were also excluded. The individuals except who had known history of diabetes were screened for diabetes by oral glucose tolerance test and categorised into newly diagnosed diabetes and normoglycaemia using WHO criteria. The detailed methodology was given in one of our previous article [7]. This paper is attempted to narrate the presentation of TB with co-existence of DM, anthropometric and bio-chemical profile, glycaemic and radiological manifestations, mechanism of disease progression and immunological effects of diabetes on TB treatment outcomes from this EDOTS study.

Diabetes, Pre-diabetes and Normoglycaemia in people with TB

An interim analysis [7] of this cohort showed that out of 209 individuals screened, a total of 54.1% was having diabetes among whom 32.7% was newly diagnosed with diabetes. Around

21% was found to have impaired glucose tolerance and 24.9% was having normoglycaemia (NG) respectively. It was estimated that the infected community prevalence would be 22% as 54% of the patients in this cohort had DM and which exceeded the prevalence (10.4%) showed in a population based survey conducted in Tamil Nadu in 2011(8). The age of this cohort might provide partial explanation for the same as prevalence of DM used to be low in younger people and who were excluded. A previous study screened rural, urban and semi-urban population in 2011 found that 25% had DM (among whom 9.9% NDM) and 21% had prediabetes [9]. The burden of prediabetes was found to be similar as previous study. After complete enrolment of the study participants, it was found that 41.6% had KDM, 24.2% had NDM, 34.2% were with NG among the drug sensitive pulmonary TB patients (n = 329) from this cohort [10].

From the results, the investigators argued that some NDMs could have had prediabetes before developing TB and might proceeded to DM due to stress of infection. Further, two important questions were raised of interaction of pre-DM and TB due to high prevalence of pre-DM and NDM with new smear positive TB patients in this cohort. First, whether TB influences the progression from Pre-DM to DM and secondly, was it pre-DM that impairs protective immunity of the host and which increases the TB susceptibility? In order to support the first hypothesis, the authors further argued that decline of HbA1c in people with normoglycaemia and also NDMs who got treated for TB with non-use of antidiabetic drugs suggestive of supporting first hypothesis. An almost equal prevalence of DM and pre-DM in this cohort prior to incident TB indicates that pre-DM increases risk of TB as similar to DM and which supports second hypothesis.

Anthropometric and Biochemical profile of the study participants

An interim analysis showed that persons with KDM were found to have mean BMI of 20.8 kg/m^2, while NDM with BMI of 18.3Kg/m^2 and NG with 17.5 Kg/m^2 respectively ($p<0.001$)The mean waist circumference of people with KDM (79.1cm) and NDM (77.2) were markedly differed from people with NG (70.8 cm) [7]. The final analysis [10] of this cohort also showed that the median BMI of people with DM (both KDM and NDM) was significantly different from people with NG (19.9 kg/m^2 vs. 16.8 kg/m^2; $p<0.001$). It also showed that out of 329, 47.3% had a BMI <18.5 kg/mg^2. Within the low-BMI group, 46.2% had DM. It was also noted that 33.2%had BMI<18.5 kg/m^2 out of 256 individuals with DM [10]. The level of Hb was similar among the groups - KDM, NDM and NG respectively. But the level of total cholesterol, LDL, HDL, triglycerides were high in KDM compared to the other groups. But the level of 25-hydroxy vit-D was found to be significantly lesser in KDM compared to NDM and NG groups [7]. It was noted that the low albumin was associated with low BMI in this cohort and which might relate to under nutrition. This cohort also revealed a positive relationship between albumin and cure rate and a negative correlation between albumin and radiographic severity. But, no association was found among adverse TB outcomes and serum 25-hydroxyvitamin D or haemoglobin [10].

Glycaemic disorders at baseline and during anti-tubercular therapy in People with TB-DM and TB non-DM (NG)

At baseline, Haemoglobin A1c% was 10.49 among the individuals with KDM, while it was 6.8% in NDM and 5.7% in NG respectively [7]. The final analysis [10] after enrolment of all the study participants (n=389) showed that people with NG (n = 133) had median HbA1c of 5.7% and DM (n = 256) had median HbA1c of 10.5% respectively at baseline.

The interim analysis that included 129 study participants (93 with DM, 36 NG) who completed the first 3 months of TB treatment, at which point HbA1c determination was repeated. There was a significant reduction in HbA1c of about 1% in NDMs at month 3 from enrolment. But, there was 0.4% and 0.6% fall in HbA1c among NG patients and KDMs respectively and the statistical significance was marginal. Among 129 received TB treatment for at least 3 months)

showed that 24.9% of screened patients with TB were euglycemic and there was unanticipated heterogeneity in patients with TBDM [7].

Manifestations of Radiographic scores in TB-DM

From the preliminary results of the cohort [7], It was found that the median score of radiography among people with TB-DM and TB non-DM was similar at baseline. But, the TB-DM group showed greater residual lung after TB treatment completion compared to the TB non-DM group. There was a greater improvement in radiographic scores among people with TB non-DM (73.3% reduction) compared to DM (42.9% and 33.3% reduction in known and new cases of diabetes respectively).

When the radiographic scores were compared across BMI and HbA1c%, people with BMI<18.5kg/m²and HbA1c <8.0% [Mean(SD): 43.9(30)] had significantly higher scores compared to people with BMI<18.5% and HbA1c≥8% [Mean(SD):39.2(25.7)], BMI>18.5 kg/m² and HbA1c<8% [Mean(SD): 33.7(28.5)] and BMI>18.5 kg/m² and HbA1c>8% [Mean(SD): 31.0(25.4) (p=0.0002)]. The chest x-ray cavitation was also high in the group with BMI<18.5kg/m² and HbA1c<8%. The proportion of baseline bilateral disease was also higher in the group with BMI<18.5kg/m²and HbA1c<8% compared to the other groups (p<0.001). The adjusted regression models also showed that this group had greatest radiographic severity compared to other groups

Immunological aspects and Bio-markers in association of TB-DM co-morbid condition

Another important aspect of the study was to determine the bio-markers and immune response in the disease progression, during and after treatment in TB-DM co-morbidity. There are also number of markers identified using this cohort which are considered to have stronger impact in the treatment and response effect of Diabetes in Tuberculosis.

A sub study included 30 TBDM individuals and 27 TB non DM individuals to see the effect of ATT on the changes in dentritic cell (DC) and monocyte subset phenotype in TB-DM co-morbidity showed that coincident diabetes alters the frequencies of innate subset distribution of DC and monocytes in TB-DM co-morbidity. This is suggestive of these changes are reversible after ATT [11].

Another study that examined the frequency of different T-cell subsets in individuals with TBDM and TB non DM before, during and after completion of anti-tuberculosis chemotherapy revealed that TBDM is characterized by heightened frequencies of central memory $CD4^+$ and $CD8^+$ T cells and diminished frequencies of naive, effect or memory and/or effect or $CD4^+$ and $CD8^+$ T cells at baseline and after 2 months of treatment but not following treatment completion in comparison with PTB-NDM. Although this study is descriptive, it provides a probable mechanism for the differential effect of DM on memory versus regulatory T cells in TB [12].

Increased inflammation with elevated circulating levels of inflammatory cytokines has been observed in TBDM comorbidity. The systemic levels of VEGF-A, VEGF-C, VEGF-D, VEGF-R1, VEGF-R2, VEGF-R3 were examined to study the link between angiogenic factors with TBDM in individuals with either TB-DM (n = 44) or TB alone (n = 44) [13].

In a sub study of this cohort the authors tried to elucidate the systemic levels of RAGE ligands at baseline and at the end of intensive phase and also at the end of continuation phase of ATT, when TB treatment gets completed. They found markedly higher levels of AGE, sRAGE and S100A12 in TBDM and DM compared to TB and the healthy controls (HC). Similar pattern was observed during 2nd and 6th month of ATT. There was also increased levels of RAGE ligands found in individuals with TBDM and bilateral and cavitary diseases. There was a correlation found among sRAGE and S100A12 with HbA1c level. Hence this study demonstrated that DM distinctively moderates the circulating RAGE

ligands in people with TB before ATT, during and also after ATT. It also depicted that the levels of systemic RAGE ligands show the disease severity at baseline and extent in TBDM, further differentiate KDM from NDM and which are altered by ATT and metformin therapy [14].

In another sub study, the parameters interferon-γ (IFN-g), tumor necrosis factor-α (TNF-a), interleukin (IL) 1-β (IL-1b), IL-2, IL-4, IL-5, IL-6, IL-7, IL-8,IL-10, IL-12p70, IL-13, IL-17A), granulocyte colony-stimulating factor (G-CSF) and granulocyte macrophage colony-stimulating factor (GM-CSF) were analysed. In TBDM and TB non DM and found the heightened levels of pro-inflammatory cytokines only pre-ATT but also but also observed throughout the treatment in TBDM compared to TB non DM. At the end of one year after treatment, considerable convergence of mediator levels was observed between the groups [15].

Upon studying the association of TIMPs with TB -DM with or without metformin use, the authors showed that TIMPs - 1, 3 and 4 were elevated in TB-DM compared to TB non-DM significantly at baseline. It was also noted that ATT brought significant reduction in TIMPs - 2 and 3 and increase in TIMP-1 in both TB-DM and TB non-DM groups. It was also observed that KDM individuals who were on metformin treatment showed lower levels of TIMPs - 1,2 and 4 at baseline and of TIMP-4 at post-treatment. It was also correlated with HbA1c levels [16].

Effect of Diabetes in TB Treatment Outcomes

Earlier studies showed that adverse treatment outcomes were strongly associated with Interim analysis [7] showed that 62.1% of participants with KDM and 59.3% of participants with NDM had negative sputum culture results vs. 78.8% of participants with normoglycaemia showed negative sputum culture results at Month 1. But the culture conversion was negative among 92.3% in both KDM and NDM vs. 96.7% in persons with normoglycaemia and which is statistically not significant.

Further in-depth analysis was done after all the participants completed the follow up. This was a comparative analysis of treatment outcomes between people with normoglycaemia and DM stratified by low (<18 kg/m^2) or normal-high (≥18 kg/m^2) BMIs respectively and these were further stratified with low (<8%) or high HbA1c (≥8%) into four groups as low BMI and low HbA1c (BMIlo/A1clo), low BMI and high HbA1c (BMIlo/A1chi)

The median number of days taken for sputum conversion among people with low BMI (<18.5kg/m^2) and HbA1c<8% was 56.2 and which was significantly longer compared to other groups such as low BMI with HbA1c>8% (46.8 days), high BMI (≥18.5kg/m^2) with HbA1c <8%(47.7days) and HbA1c>8% (48.1 days) [10]. The adjusted regression models also showed that this group had longest time to sputum conversion among the 4 groups. It has been observed that DM has influenced poor treatment outcomes such as treatment failure and TB relapse. Surprisingly, this analysis showed people with TB and diabetes with low BMI with poor glycaemic control had better outcomes of TB treatment.

Low BMIs and low HbA1c levels were both associated with higher odds of bad outcomes. The individuals in BMIlo/A1chi group exhibited better treatment outcomes compared to those with BMIlo/A1clo, but they were not significantly different from the BMIhi/A1clo and BMIhi/A1chi groups. In adjusted models, the BMIhi/A1clo and BMIhi/A1chi groups did not differ from each other. These adverse TB outcomes has been correlated with a high visceral adiposity index despite its correlation with HbA1c and is found elevated in some individuals with low BMI and normal glucose tolerance [10].

Conclusion:

The elevated and persistent inflammation observed in TBDM comorbidity throughout ATT compared to individuals with TB gives an impression that co-existing DM alters and impairs immunity and also responsible for adverse outcomes. However, this cohort has shown that having a low BMI as the major risk factor for

adverse TB outcomes. This specific population might have had different interaction of TB-DM compared to others, where this co-morbid condition is commonly found to occur in overweight individuals. Understanding the effect of diabetes on TB is still remains as a complex and challenging process. This calls for a further exploration of the metabolic pathways and role of diabetes treatment on TB outcomes in understanding the same.

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