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Is Glycemic Control the Secret to Tuberculosis Control?

The deleterious impact of diabetes mellitus (DM) on people with tuberculosis (TB) is well established. Globally, 15% of people with active TB also have DM (1) and suffer from worse TB treatment outcomes, including elevated odds of relapse and fatality (2).

In this issue of the *Journal*, Liu and colleagues (pp. 347–356) have added additional nuance to the relationship between DM and TB (3). The authors measured fasting plasma glucose (FPG) serially among 405 patients with newly diagnosed TB in China at the time of diagnosis, the third and sixth month of treatment, and at 2 and 4 months after treatment completion. The resulting glycemic trajectories were used to categorize patients into groups corresponding to normal glycemic values ($n = 172/405$, 43%), transient hyperglycemia ($n = 97/405$, 24%), erratic glycemic instability ($n = 48/405$, 12%), known or newly diagnosed DM ($n = 65/405$, 16%), and consistently hyperglycemic but not diabetic ($n = 25/405$, 6%) based on clinical definitions.

The glycemic trajectories revealed that nearly half (49.7%) of patients who did not meet diagnostic criteria for DM still exhibited glycemic elevations before, during, and/or after TB treatment. As expected, compared with patients with a consistently normal glycemic trajectory, patients with known or newly diagnosed DM were more likely to experience treatment failure (adjusted odds ratio, 6.56; 95% confidence interval [CI], 2.22–19.35). More surprisingly, patients with transient hyperglycemia and erratic glycemic instability also had increased odds of treatment failure (adjusted odds ratio, 4.20; 95% CI, 1.57–11.25; and 5.98; 95% CI, 2.00–17.87, respectively). The transient hyperglycemia and erratic glycemic instability groups, despite not meeting diagnostic criteria for DM, accounted for nearly half ($n = 23/48$,

49%) of the observed treatment failures in the cohort. When including the DM group, the proportion of all treatment failures increased to 80% ($n = 38/48$), meaning the vast majority of patients who failed TB treatment had abnormal glycemic control.

Liu and colleagues demonstrate the power of analyzing dynamic trajectories rather than relying on a single or summary measure when evaluating risk factors in longitudinal studies. A baseline FPG measure or an average of FPG measures throughout treatment would not have identified different patterns of dynamic changes in FPG, obfuscating their unique risks of treatment failure. Similarly, it has been shown in other fields, such as hypertension research (4), that using full patient trajectories can improve prediction of patient outcomes. In addition to FPG, there are a multitude of other clinical characteristics (e.g., TB drug pharmacokinetics or biomarkers) and patient behaviors (e.g., medication adherence) that evolve throughout TB treatment and that may impact treatment outcome. For some of these measures, clinical classification schemes may not be available to define groups a priori as they are for FPG trajectories. In these instances, pharmacodynamic nonlinear mixed effect modeling (5) or statistical classification methods such as group-based trajectory modeling (6, 7) can identify groups of patients with similar trajectories using a data-driven approach.

The findings of this study, if confirmed in other cohorts, have important implications for TB care and research. First, glycemic changes during treatment may become a critical factor to assess in all patients with TB, not just those with DM. Further research is needed to define the optimal frequency and methods for assessing glycemic control and to understand mechanistic factors driving abnormally increased FPG levels. Second, after identifying patients at increased risk for poor treatment outcomes, further research is needed on how to mitigate the risk conferred by poor or unstable glycemic control. There has been considerable interest in the oral hypoglycemic agent metformin as a host-directed therapy adjunct to standard TB treatment (8). In this study, patients with DM with normal glycemic testing and patients with DM who were taking metformin did not have an elevated risk of treatment failure compared with patients without DM. The findings

reported here suggest that patients with abnormal glycemic trajectories should also be prioritized or targeted for further research in this area. Lastly, the relationship between glycemic control and the duration of anti-TB treatment requires further investigation. In particular, it remains unknown if glycemic control can be incorporated as a novel on-treatment risk factor to help identify "easy-to-treat" patients who may qualify for a shortened duration of anti-TB treatment versus "hard-to-treat" patients who require an extended duration of treatment (9).

Liu and colleagues have nicely demonstrated the value of using FPG trajectories to capture the nuances in the relationship between glycemic control and treatment outcomes. By moving beyond the standard dichotomous classification of DM status, this study revealed additional groups of patients with an elevated risk of treatment failure, opening pathways to further study on the role of glycemic control in TB treatment outcomes. ∎

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