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Convergence of the tuberculosis and diabetes epidemics: renewal of old acquaintances

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The current pandemic of type 2 diabetes mellitus is accelerating[1,2] in a world where approximately one third of the population is latently infected with *Mycobacterium tuberculosis* [3]. Diabetes affects 230 million worldwide, anticipated to reach 366 million by 2030 at which time 80% of those affected will be living in low- and middle-income countries where active tuberculosis is widespread [4,5]. Eight of the ten countries with the highest incidence of diabetes worldwide[5] are also classified as high burden countries for tuberculosis by the World Heath Organization [6]. The consequences of these converging epidemics are likely to be substantial.

The association between diabetes and tuberculosis was documented by Avicenna (980–1027). In the early 20th century it was said that the patient who did not die in a diabetic coma was likely to do so from tuberculosis, particularly if they were poor[7,8]. The discovery of insulin in the 1920s and the later discovery of effective antibiotics led to the eclipse of the combination of these life-threatening diseases. Nevertheless, large surveys prior to the 1960s indicated tuberculosis was 2–4 times more prevalent in individuals with diabetes than those without diabetes [7–10]. The patients' characteristics (onset at young age, insulin use) suggested at least half had type 1 diabetes [7,9]. Today with type 2 now accounting for 90 to 95% of all diabetes we are "re-discovering" this association [11–21].

The current literature on tuberculosis and diabetes is sometimes contradictory and difficult to interpret. Most reports have limitations inherent in retrospective studies, lack confirmation of diabetes, or provide no measures of blood glucose control. Many contain data only on hospitalized patients, with bias towards the most seriously ill. Nevertheless, in the aggregate they point to a significant impact of diabetes on tuberculosis and these reports cannot be ignored. For example, data consistently shows that the odds ratio of having type 2 diabetes in patients with active tuberculosis ranges from 1.3 to 7.8-fold [14,16,18,22–24], indicating that diabetes clearly increases the risk for tuberculosis. Though the risk of tuberculosis is less at the individual level for diabetes compared with that of AIDS (113 to 170-fold)[25,26], the sheer numbers of patients with diabetes are likely to have an equal or greater effect at the population and public health level. In at least one region of the United States the number of excess cases of tuberculosis attributable to diabetes has already reached that attributable to HIV infection [14]. What is more difficult to interpret from the current literature is the effect

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of type 2 diabetes on the clinical presentation and treatment response during tuberculosis. Though results are sometimes conflicting, several studies, including our own, indicate that tuberculosis patients with diabetes present higher bacillary load in sputum[17,27], delayed mycobacterial clearance [27,28] and higher rates of multi-drug resistance[12]. These results imply that tuberculosis patients with diabetes may be more seriously ill and pose higher risk for spread of (drug-resistant) mycobacteria in the community. Thus, these issues require urgent attention.

On page XX of this journal[29], Alisjahbana and collaborators present prospective data from a cohort of tuberculosis patients in Indonesia where prevalence of confirmed diabetes among tuberculosis patients is 14.8%, compared with 3.2% in the general population[18]. Their study contrasts with the mostly retrospective reports cited above by providing detailed prospective data (including HIV documentation and exclusion), clinical manifestations, diabetes classification and microbiological findings at diagnosis, two and six months of DOT treatment on at least 543 patients. Their most significant conclusion was that after six months of treatment, diabetes patients were 7.65-fold more likely to have positive cultures in a multivariate model which controlled for age, gender, study site, body-mass index, chest x-ray and culture conversion at eight weeks.

This careful and complete prospective study provides strong evidence of the deleterious effect of diabetes on tuberculosis treatment, and its potential impact on control. Will similar findings be observed in other areas where diabetes and tuberculosis are prevalent? We can only know this when we have more prospective studies. In the meantime we can speculate on why we might see variations between reports. For instance, in contrast to other publications [17,27], Alisjahbana and collaborators were not able to detect differences between the prevalence of positive smears at the start of treatment between tuberculosis patients with and without diabetes. Sputum smears are highly insensitive, and since a positive smear is the defining criteria for tuberculosis diagnosis in Indonesia, as in many developing countries, differences in smear positivity can only be reported in programs where diagnosis is based on clinical criteria, cultures and smears.

The detectable impact of diabetes on tuberculosis in a given population will depend on the characteristics of those with tuberculosis but not diabetes. In places where AIDS is highly prevalent, the immunosuppression induced by this infection is likely to be so strong that it will probably “mask” the impact of diabetes. A similar scenario but to a lesser degree may be encountered with other risk factors for tuberculosis, such as incarceration, alcohol or drug abuse. Thus, a critical component of data analysis is proper modeling based on understanding the role of risk factors for tuberculosis as possible confounders or effect modifiers. In the study by Alisjahbana et al, the effect of diabetes on tuberculosis was detected in a population where less than 1% of the tuberculosis patients were HIV-positive (and were excluded) and none reported a history of incarceration, alcohol or substance-abuse.

Notably, by the end of DOTS there were still 38/322 tuberculosis patients with diabetes who remained culture positive in the study from Indonesia. This delayed clearance may be related to drug resistance. The authors report no association between multi-drug resistant tuberculosis and diabetes at diagnosis, but no further evaluation of drug resistance was conducted during the course of treatment. This is an important consideration since multi-drug resistant tuberculosis may be more frequent among tuberculosis-diabetes patients from certain populations, including ours [12], but whether this is due to primary or acquired resistance remains unknown. Studies in Indonesia by the same research team have in fact indicated that plasma levels of rifampin were 53% lower in tuberculosis-diabetes patients in contrast to tuberculosis patients without diabetes [19]. It may well be that the metabolism of rifampin is

affected by diabetes rendering it less effective and predisposing patients to acquisition of resistance to rifampin during treatment.

In summary, the findings by Alisjahbana and collaborators highlight the need for further research aimed at understanding how the current global epidemic of type 2 diabetes is affecting tuberculosis control and prevention. Many questions are yet unanswered: What is the magnitude and impact of these converging epidemics worldwide? Should every patient with diabetes be screened for latent tuberculosis infection, and if positive, how should tuberculosis progression be monitored or prevented? Should patients with tuberculosis and diabetes be treated with a different drug regimen compared to those with tuberculosis alone? What is the biological basis of the association between tuberculosis and diabetes? What is the most cost-effective measure to assess diabetes among tuberculosis patients? In the meantime, simple and economically-realistic approaches can be immediately implemented at every tuberculosis clinic worldwide. This includes documenting self-reported diabetes in every new tuberculosis patient, and where feasible, performing a finger stick glucometer assay for a random blood sugar. In any patient with diabetes and active tuberculosis, readings will likely be very high. These patients can then be flagged for potential treatment failure, and be accorded special attention.

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