Diabetes and tuberculosis: a gathering storm?

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The number of cases of active tuberculosis (TB) continues to rise in the UK and in many other parts of the world.[1 2] In analysing the reasons behind this rise, it needs to be kept in mind that only a small proportion of those who become infected with TB will progress to become ill with active TB disease in the weeks and months after infection. They do, however, remain at risk of reactivation of their latent TB infection in the years (and indeed decades) to come. Clearly, a co-existing medical condition which impairs the immune response to the TB bacterium might increase the likelihood of direct progression to active disease shortly after infection, or increase the likelihood of latent TB infection in later life. Co-infection with HIV is a striking example; the relative risk of developing TB in HIV-positive individuals compared with HIV-negative individuals (the incidence rate ratio) is between about 20 and 35.[2]

In this issue of *Thorax*, Walker and Unwin (***see page 578***) consider the impact on numbers of TB cases in England of another increasingly common condition—namely, diabetes mellitus.[3] A link has long been suggested, the authors pointing out that combined clinics for those with diabetes and TB were being held more than half a century ago,[4] and recent analyses suggest that the association is indeed genuine.[5] Walker and Unwin focus their attention on pulmonary TB, choosing this because they consider the evidence for an association to be strongest for this type of TB. They constructed an epidemiological model using data on the incidence of TB, the prevalence of diabetes, the population structure and data on the age-specific relative risk of TB associated with diabetes from a cohort study. They acknowledge that there are limitations to their approach: the estimate of the total prevalence of diabetes in England is based on old and relatively small population-based studies and the age-specific relative risks for TB in those with diabetes are derived from a Korean study. The authors point out, however, that these appear to be the best tools available for the job they wished to do, and it is indeed arguable that a line of scientific enquiry should not be ignored simply because the available techniques for its investigation are as yet imperfect.

With the frank admission that 'given the nature of the data available, considerable uncertainty surrounds these estimates', the authors go on to suggest that the population attributable fraction (PAF) of diabetes for pulmonary TB in England is 19.6% for Asian men (95% CI 10.9% to 33.1%) and 14.2% for Asian women (95% CI 7.1% to 26.5%). The figures for white and black men are similar to each other at around 7%, and about 8.5% for white and black women. Expressed differently, the authors estimate that about 11% of the new cases of pulmonary TB which occurred in England in 2005 may be attributed to diabetes.

These figures are—or should be—of even greater concern than they may appear. It is pulmonary TB which is potentially infectious to others, and public health efforts to control TB have focused on the early identification and treatment of infectious pulmonary cases. Perhaps more importantly, we are confronted with an explosive and apparently inexorable rise in the prevalence of diabetes.[6 7] This rise in diabetes is, moreover, particularly marked in ethnic minority populations[8]—that is, those who are in any case most at risk of having pre-existing latent TB infection and of fresh exposure to other infectious cases. It is also associated with a sharp rise in the numbers of individuals with chronic renal failure, an independent risk factor for TB.[9] Even if the figures from Walker and Unwin are an overestimate, it seems likely that they soon won't be. If they are already an underestimate, then the interaction between diabetes and TB is rapidly becoming a major issue for TB control and one which, as the authors point out, appears to be receiving little attention. Diabetes does not achieve a mention in the 'TB Action Plan'[10] nor, indeed, in the 2009 Annual Report.[1]

What can be done? TB services in most countries—even wealthy ones—are hard pressed, and tackling the rising tide of obesity (the principal cause of the rise in diabetes) may be a task too far. This means dealing with the consequences while others struggle, probably unsuccessfully, with the underlying cause. Walker and Unwin suggest that, based on their figures, around one-third of Asians with newly diagnosed TB in England will have diabetes. There seems no reason to suspect that the figure would be markedly lower in other parts of the UK nor, probably, in other socioeconomically similar countries. In the UK there are probably around half a million undiagnosed diabetics[11] and, although their rates of TB may well be less than among diagnosed diabetics, we can at least ensure that newly diagnosed TB patients have a documented assessment of the presence or absence of diabetes. Active screening for evidence of latent TB in diabetics is part of US guidelines,[12] but not those from the National Institute for Health and Clinical Excellence (NICE).[13] Indeed, the NICE guidelines suggest that, although the relative risk of TB is increased in diabetics, the absolute risk of TB in diabetics is sufficiently low that there is no need to educate them about symptoms suggestive of disease (section 10.2.4 of the NICE guidelines).

Given the calculations set out in Walker and Unwin's paper in this issue of *Thorax*, these two issues—specific screening for latent TB in diabetics and health education regarding TB—are ones which should be reviewed by NICE or another expert group. Indeed, an expectation that those healthcare professionals who deal with diabetic patients should educate them about the symptoms suggestive of TB would mean that the professionals themselves would have to have the possibility of TB in mind, and this secondary effect may actually turn out to be of more importance than the apparent primary aim of such education. Whatever steps are taken, it seems highly likely that, at least for the foreseeable future, TB services will be managing increasing numbers of diabetics with tuberculosis.

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Treating latent tuberculosis with rifampin: is it the cheaper option?

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Treatment of latent tuberculosis infection (LTBI) is an important measure for tuberculosis control in the developed world. A recent study estimated that between 291 000 and 433 000 persons started LTBI treatment in the USA in 2002 and that between 4000 and 11 000 cases of active tuberculosis were prevented by this treatment.[1] However, many persons for whom LTBI treatment is recommended fail to initiate or complete treatment. Another recent cross-sectional survey of clinics in the USA and Canada showed that fewer than 50% of persons prescribed LTBI treatment completed the prescribed course.[2] Key barriers to successful completion of treatment include the length and suboptimal tolerability of the 9-month course of isoniazid that is most frequently used for LTBI treatment. Shorter better-tolerated regimens are clearly needed.

The study by Aspler *et al*[3] in this issue of *Thorax* (***see page 582***) examines one such regimen—namely, 4 months of daily rifampin. This regimen, while recommended as an alternative option for LTBI treatment by the Centers for Disease Control and Prevention,[4] has not been widely adopted in the USA. Major barriers to adoption include the possibility of inadvertent treatment of active tuberculosis with rifampin resulting in rifampin-monoresistant disease, concerns about effectiveness and the increased cost of rifampin compared with isoniazid. Aspler *et al* addressed the latter concern by prospectively examining health system costs in a randomised trial comparing 9 months of daily isoniazid with 4 months of daily rifampin for LTBI treatment. The study was conducted in centres in Canada, Brazil and Saudi Arabia, so health system costs in both high- and middle-income settings could be evaluated. Costs were all converted to 2007 Canadian dollars. The primary trial was designed to assess safety and tolerability, so the efficacy of rifampin was assumed to be equivalent to isoniazid in the base case scenario and varied widely. The average per patient cost for the isoniazid arm (N=427) was $C970 compared with $C854 for the rifampin arm (N=420), a statistically significant difference in favour of rifampin ($p<0.0001$). The difference in cost between the two regimens was primarily driven by the greater number of clinical visits required for the 9-month isoniazid regimen (average cost $C692 per patient for scheduled clinical visits vs $C481 for rifampin). Toxicity was a secondary driver of the cost differential, with $C113 per patient spent on non-scheduled care (ie, assessment or management of potential toxicity) in the isoniazid group and $C79 per patient in the rifampin group ($p=0.008$). Using these cost data, the authors deemed the rifampin regimen to be cost-saving while preventing more tuberculosis cases if the efficacy of the regimen in preventing tuberculosis reactivation was 75% or greater (assuming 9 months of isoniazid is 90% efficacious). This finding held when both Brazilian and Canadian health system costs were used, and over a range of assumptions regarding drug costs.

A growing body of evidence suggests that 4 months of daily rifampin may be an attractive regimen for the treatment of LTBI. A recent meta-analysis examined data from four studies (3336 subjects) and concluded that 4 months of treatment with rifampin was associated with about half the non-completion rate of 9 months of isoniazid treatment and 12% the risk of hepatotoxicity.[5] This meta-analysis estimated a cost saving of US$213 per patient by using rifampin instead of isoniazid for LTBI treatment, a value similar to the findings of Aspler *et al.* Similarly, another recently published decision analysis concluded that 4 months of rifampin treatment was cost-saving compared with 9 months of isoniazid, assuming that rifampin is no worse than 17% less efficacious than isoniazid.[6] However, cost determinations are certainly affected by local costs and monitoring practices; a retrospective cohort analysis from a public health clinic in Massachusetts found that, given local drug and provider visit costs, the treatment costs for 9 months of isoniazid were less than those for 4 months of rifampin.[7]

Of course, while treatment costs are certainly important, the overall cost-effectiveness of LTBI treatment is heavily influenced by the overall effectiveness of a given regimen in prevention of active tuberculosis. If 4 months of rifampin treatment prevented many more cases of active tuberculosis (due to higher

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