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'The tubercular diabetic': the impact of diabetes mellitus on tuberculosis and its threat to global tuberculosis control

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ABSTRACT – The incidence and prevalence of diabetes mellitus (DM) is rapidly increasing across the globe. Tuberculosis (TB), meanwhile, remains a significant problem in low and middle income countries fuelled by high rates of HIV/AIDS. This article explores the long recognised but underappreciated connection between the two, revealing that DM makes a substantial contribution to the burden of incident TB around the world and may also worsen TB severity and treatment outcome. The dual management of the diseases may be challenging but must be addressed, both in low and high income settings, because the rising worldwide diabetes burden poses a threat to global TB control.

KEY WORDS: AIDS, diabetes mellitus, DOTS, global health, HIV, tuberculosis

Introduction

It is well known that tuberculosis (TB) is associated with HIV, smoking, malnutrition and underlying lung disease, though presently the association between TB and diabetes mellitus (DM) is less familiar. In recent history, clinicians were accustomed to this connection: 'during the latter half of the nineteenth century, the diabetic patient appeared doomed to die of pulmonary tuberculosis if he succeeded in escaping coma'.[1] Before the introduction of insulin and indeed for many years thereafter, TB was a major cause of mortality in the diabetic population.[1] In the 21st century, at a time of unprecedented integration and interdependence of economies, environments, societies and cultures, the relationship between these two diseases is once again significant.

Over two billion people in the world are infected with *M. tuberculosis*, of whom more than 11 million have active TB, and the total number of yearly incident cases and attributable deaths is rising globally.[2] TB remains predominantly a disease of low and middle income countries, but with increasing international travel and migration the disease persists in high income countries. The impact of an increasingly globalised world on disease burden goes beyond infections to non-communicable diseases (NCDs), which are rising in prevalence in middle and low income countries due to ageing populations and changing lifestyles and diets. Diabetes exemplifies this process. In the year 2000, developing countries were estimated to share 67% of the global burden of DM, a proportion which is predicted to rise to 78% by 2030.[3] Therefore, as a plague of the developing world meets a disease of the affluent West, knowledge of the interaction between these two diseases becomes essential for the health of all citizens of this interconnected world.

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The DM–TB association

Diabetes increases the incidence of TB

Diabetes is a risk factor for developing active TB. There is strong evidence for this association, with studies examining the incidence of TB showing it to be two to five times higher in diabetic patients than in non-diabetic patients.[4–6] Calculations from an epidemiological model in India suggest that DM accounts for 14.8% of pulmonary TB and 20.2% of smear-positive TB.[7] It is estimated that an increased prevalence of DM in urban areas is associated with a 15.2% increased incidence of smear-positive pulmonary TB in urban, compared to rural, populations.[7]

The only study to be published on the direct interaction between TB and DM in sub-Saharan Africa was performed in Tanzania in 1990 and found DM to be at least four times as common in patients with TB compared to the general population (in the TB population, 4% had DM compared to 0.9% in the general population).[8]

The connection between DM and TB has even been reported to be more significant than the well recognised connection between HIV/AIDS and TB, though this has not been consistently reproduced in different populations. Retrospective analysis of TB control programme data in 5,049 TB patients on the South Texas–Mexico border showed self-reported DM co-morbidity substantially exceeded that of HIV/AIDS.[9] A study in São Paulo reported DM as a co-morbidity in 16% of TB deaths and HIV infection as a co-morbidity in 11%.[10] A case-control study in California involving 5,290 hospital discharges who had a diagnosis of TB found that the risk of TB attributable to DM among middle-aged Hispanics (25.2%) was similar to that attributable to HIV infection (25.5%), whereas among the middle-aged White population the risk of TB attributable to DM (2.4%) was far lower than the risk attributable to HIV (45.7%).[11]

DM may be a serious co-morbidity of TB

DM has been found to be independently associated with an unfavourable outcome of pulmonary TB.[12] TB in diabetic

patients has been reported to have more cavitatory lesions, less sputum positivity and a paucity of symptoms and signs compared to TB in non-diabetic patients.[4] DM has been found to be a risk factor for death in TB patients: one study showed the risk to be twofold higher than in those without DM;[13] and another, after adjusting for HIV, age, weight and foreign birth, showed the risk of death to be 6.5 times greater in diabetics compared to non-diabetics.[13]

However, there does remain some controversy around these effects of DM on the treatment and outcome of TB infection. One study found that the final outcome did not differ between patients with or without DM.[14] Another showed that smear and culture conversion rates at the end of the intensive phase of TB treatment were similar in both diabetic and non-diabetic groups.[15]

Evidence concerning radiological appearances in TB patient groups with and without concurrent DM is conflicting. Some studies suggest that TB patients with DM are more likely to present with atypical images,[12] whereas others suggest there are no differences in the radiological findings.[16]

Two studies have shown a significant association between diabetes and multidrug-resistant TB (MDR-TB), suggesting that diabetic patients may be more than five times as likely to have infection with MDR-TB.[5,17] However, contrasting results from other studies suggest that there is no association,[18,19] others even show a lower prevalence of drug resistance to antituberculous therapy compared to patients without DM.[14]

Though existing evidence is inconclusive, the data does raise concern about the effect of DM on the clinical picture, disease severity and outcome of TB infection. Clarification of this uncertainty is important, because the presence of clinical differences in TB between patients with or without DM may indicate underlying differences in response to TB infection once infected, separate to or in keeping with that of infection risk. Understanding of this could help to target management and prevention of the dual pathologies.

Uncertain causality

There has been a paucity of research into the underlying cause for the association between DM and incident TB. Existing studies strongly support the hypothesis that DM impairs the innate and adaptive immune responses necessary to prevent the proliferation of tuberculosis.[6] The findings from one study showed diabetic patients without TB to have strongly reduced non-specific interferon gamma production which is essential for the initial growth of *M. tuberculosis* and so suggests a defective, non-specific immune response in DM may contribute to the increased susceptibility to active TB disease.[20]

The implications for TB control

The global burden of DM is predicted to rise from an estimated prevalence of 171 million in 2000 to 366 million in 2030.[3] The clear evidence showing diabetics to be at greater risk of developing active TB than non-diabetics suggests that there is potential for these rising DM trends to provoke a surge in incident TB, particularly in TB endemic and urban areas, with knock-on consequences for TB control in the non-diabetic population. This carries serious implications for global TB control and the achievement of the United Nations Millennium Development Goal 6c, to halt and begin to reverse the incidence of diseases such as TB by the year 2015.[2]

Of additional concern is the potential impact on MDR-, and extensively drug-resistant (XDR-), TB, either directly, or indirectly through a rise in total TB cases. Of the 10 countries with the highest numbers of estimated cases of DM in both 2000 and 2030, six are also among the 10 countries currently estimated to have the highest numbers of MDR-TB (India, China, Russia, Bangladesh, Pakistan and Indonesia in 2000; India, China, Bangladesh, Pakistan, Indonesia and Philippines in 2030).[2,3] The top two countries are India and China, where there has been an explosion in diabetes cases. India, with an estimated diabetic population of 31.7 million in 2000 had a total number of 131,000 MDR-TB cases in 2007.[2,3] China had populations numbering 20.8 million and 112,000 respectively.[2,3] By 2030 the number of people with DM in India is predicted to rise to 79.4 million and in China to 42.3 million.[2,3] The global extent of XDR-TB is currently unknown, but by November 2009, 57 countries and territories had reported at least one case.[2] The potential but currently uncertain impact of the rise of DM to both MDR- and XDR-TB is of global concern.

Dual management

No evidence exists to guide the management of the dual pathologies in low, middle or high income countries. Should all TB patients be screened for DM? Should DM patients be screened for TB? The American Thoracic Society and the US Centers for Disease Control and Prevention explicitly state DM as a risk factor that should prompt consideration for targeted TB testing. While the British Thoracic Society and the National Institute for Health and Clinical Excellence recognise diabetics to be at increased relative risk of TB, this has not translated to screening recommendations due to the low absolute risk of TB.

The dual treatment of the diseases may be challenging. Rifampicin can have hyperglycaemic effects, directly or indirectly through interaction with oral hypoglycaemics,[21,22] and diabetes may affect the pharmacokinetics of antituberculous medication. Plasma concentrations of rifampicin have been found to be twofold lower in TB patients with DM compared to those without.[23] Integration of the management of these two conditions when co-existent would clearly be beneficial to optimise outcomes.

The structured directly observed treatment, short course (DOTS) approach has enabled large-scale administration, monitoring and planning of TB treatment in low income countries, but no comparable systematic service exists for the management of chronic diseases such as diabetes. Could lessons be taken from TB management? It has been suggested that the DOTS approach

may be suitable for extrapolating to the management of NCDs such as DM in an attempt to provide regulated, monitored management in a means which is affordable and sustainable.[24] The organisational components of the DOTS framework – which includes an effective drug supply and management system, a monitoring and evaluation system as well as political commitment – could feasibly be adapted with minimal change to function well for diabetes. However, the elements of case detection and standardised treatment need careful consideration to be adapted successfully for DM. Of central importance for this is the availability of accurate and affordable diabetes diagnostics, suitable for low income populations and settings. With recent recommendations for the use of glycated haemoglobin (HbA_{1c}) for DM diagnosis,[25] along with advances in point-of-care HbA_{1c} devices,[26] the development of a DOTS DM management framework in the foreseeable future is promising.

Conclusions

The impact of diabetes on TB is underappreciated. It makes a substantial contribution to the burden of incident TB around the world; consequently the rising global diabetes epidemic poses a threat to global TB control. However, detailed questions relating to the interaction and co-existent management of the two pathologies remain unanswered and lack rigorous evidence. Basic epidemiology is unknown: are there subgroups within the diabetic population who are more or less at risk of TB infection (does it relate to severity or chronicity of diabetes)? The evidence for the impact of DM on TB severity and MDR-TB is inconclusive and requires further research. More comprehensive causality explanations, including detail on the immunological changes seen in DM and how this relates to the increased risk of TB infection, may help to identify targets for the prevention or management of the dual pathologies. Concern for appropriate management leads to the question: does optimal DM control reduce the risk of TB infection and improve the outcome for those with co-existent TB? This in turn begs the question of how diabetes can best be managed in resource-poor settings.

Our ongoing understanding of the global impact of these dual pathologies requires accurate surveillance systems to monitor and record outcomes and patterns. This is particularly crucial for low and middle income countries which hold the greatest burden of both diseases, yet where such systems are largely non-existent for NCDs. Adaptation of the DOTS model may prove to be successful. Ultimately, in order to formulate management guidelines for co-existent TB-DM disease in high and low income settings, this increasingly important issue demands attention from academics and clinicians in all corners of the world.

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