

Influence of Diabetes Mellitus and Risk Factors in Activating Latent Tuberculosis Infection: A Case for Targeted Screening in Malaysia

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SUMMARY

A review of the epidemiology of tuberculosis, its contributing risk factors (excluding HIV) and the role of screening latent tuberculosis infection in Malaysia was done. Despite the global and domestic decrease in prevalence rates of tuberculosis in the past decade, there is an alarming increase in the trend of non communicable diseases in the country. High prevalence rates of major risk factors leading to reactivation of tuberculosis were seen within the population, with diabetes mellitus being in the forefront. The rising numbers in the ageing population of Malaysia poses a further threat of re-emergence of tuberculosis in the years to come. Economically, screening of diabetic patients with comorbidities for latent tuberculosis infection (LTBI) using two major techniques, namely tuberculin sensitivity (TST) and Interferon gamma release assay tests (IGRA) could be a viable option. The role of future research in the detection of LTBI in the Malaysian setting might be necessary to gauge the disease reservoir before implementing prophylactic measures for high risk groups involved.

KEY WORDS:

Latent tuberculosis infection, Non communicable diseases, TST, IGRA, Prophylactic treatment, Risk factors

INTRODUCTION

This article reviews the prevailing trends in risk factors related to tuberculosis in Malaysia and the latest developments in screening LTBI. With the increase in risk factors relevant to LTBI, mainly diabetes mellitus in the country, the feasibility of a screening LTBI in high risk groups (excluding HIV infection) becomes even more crucial. The aim of this article is to highlight the possibility of devising a targeted latent tuberculosis screening model amongst diabetic patients who have compounding risk factors (ageing population, chronic renal failure, smoking and dyslipidaemia). Data obtained from the review of articles were utilized to point out the significance of screening latent tuberculosis in view of the rising trends in the related risk factors in Malaysia.

MATERIALS AND METHODS

A search was made on the relationship between tuberculosis and its relevant risk factors (mainly non communicable diseases). Extensive research was done on analyzing the

viability of IGRA instead of TST as a screening tool. Journals plus abstracts were obtained from PubMed (for indexed publications) and Google Scholar searches (for non indexed publications). A total of 87 journal articles/abstracts were reviewed with references from the guidelines on latent tuberculosis management of CDC and WHO.

EPIDEMIOLOGY

Global And Regional Epidemiology Of Tuberculosis

The escalation of non communicable diseases and the rapid demographic shift towards population senescence poses a threat to global health scenario by influencing the resurgence of tuberculosis throughout the world. In a recent survey, an estimated 8.8 million incident cases of tuberculosis were reported worldwide in 2010 with 59% of cases occurring in Asia (regions in declining disease burden order - India, China, Africa and Indonesia)¹. 1.1 million deaths occurred among HIV-negative cases of tuberculosis¹. In 2002, tuberculosis was classified as the eight leading cause of death and is projected to fall to twenty third by 2030². However, tuberculosis is projected to cause the loss of 21.8 million disability life years in 2015 and is second to only HIV in this category³.

Regionally (classified according to WHO regions of disease burden), tuberculosis has the highest prevalence in the South East Asian region (5.0 million which includes India) followed by the Western Pacific region (3.8 million which includes Malaysia and China). Both regions contribute to 63.3% of the global prevalence of the disease⁴. Tuberculosis, childhood cluster diseases, HIV, AIDS and meningitis are classified as the 4 other major causes of mortality from the infectious disease category in South East Asian region, only to be superseded by diarrhoeal diseases as the leading cause of death⁵.

Local Epidemiology Of Tuberculosis

There has been a steady decreasing trend in terms of prevalence, incidence and deaths in tuberculosis cases in Malaysia from year 2001 to 2009⁶. Despite the cautious optimism, there has been an increase in the prevalence of risk factors (smoking, diabetes mellitus, chronic/end stage renal failure, dyslipidaemia and aging population)⁷⁻¹¹. This is likely to impair the innate immunity of a patient with latent tuberculosis and hence accelerate the progression towards reactivation of tuberculosis.

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The burden of the disease in Malaysia is increasing due to the influx of migrants workers from neighbouring nations. Hence tuberculosis is being recognized as 'a disease without borders' in Malaysia. Close to 10% of reported cases were immigrants from neighbouring high burden tuberculosis nations¹². This is more apparent in Sabah, East Malaysia, where new cases of tuberculosis that are attributed to immigrants hovers at 24%¹³.

RISK FACTORS AND ITS IMPLICATIONS ON RE-ACTIVATION OF TUBERCULOSIS

Diabetes Mellitus

Research suggests that diabetes is a potential risk factor in the development of tuberculosis¹⁴. More vigilant screening and prevention of diabetes is mandatory as diabetic patients with concurrent tuberculosis infection have poorer treatment outcomes¹⁵.

It was reported that there has been a continuous surge in the prevalence of diabetes in Malaysia, with figures almost double in magnitude over a span of just a decade⁸. In fact, Malaysia has already reached its projected prevalence of diabetes for the year 2025¹⁶.

With the rise of non communicable disease in mostly middle income nations¹⁷ and with an intermediate tuberculosis disease burden within the country¹, diabetic patients in a tuberculosis endemic region such as Malaysia should be considered a high risk population prone to tuberculosis reactivation. In a review of 232 patients diagnosed with tuberculosis at a medical facility in Malaysia, 17.7% of the patients were discovered to have underlying diabetes mellitus - the percentage for this risk factor was the highest in contrast to all other associated risk factors¹⁸. Pulmonary tuberculosis was more common amongst diabetic patients when compared to non diabetic patients¹⁹.

It is also evident that the prevalence of diabetes in Malaysia is above average when compared with all regions around the world²⁰. Diabetics with HbA1c level more or equal to 7.0% were found to be susceptible to the reactivation of tuberculosis²¹. Thus, such high risk population would warrant latent tuberculosis screening and prophylactic treatment as a pre-emptive measure to reduce incident cases of tuberculosis²².

Chronic/End Stage Renal Failure

Diabetes was the single most important cause of primary renal disease leading to eventual hemodialysis in chronic renal failure patients in Malaysia⁹. This is synchronous with the significant rise in the prevalence of diabetes in the country. Several studies have confirmed that uremia weakens immune defenses and renders the body incapable to combat the attack of infectious diseases^{23,24}.

Clinical studies based on this premise confirmed that chronic renal failure predisposes any patient to tuberculosis infection (extrapulmonary form predominates the pulmonary form) with an incidence rate of 4% in a recent study, but most patients tested negative for tuberculin skin test²⁵. The prevalence of tuberculosis is also increased in end stage renal failure patients on dialysis^{26,27}.

Smoking

Malaysia is ranked as the country with the highest number of smokers in South East Asia'. Scientific research has shown that mucociliary clearance is crucial as a primary innate defense in the airways²⁸. Smoking therefore leads to impaired mucociliary clearance that impedes the ability of the lungs to combat attacks against *Mycobacterium tuberculosis* and other infections²⁹.

This evidence is consistent with clinical studies that have demonstrated higher prevalence of tuberculosis amongst smokers in comparison to non smokers³⁰⁻³². Smokers also have 30-50% chance greater to contract the disease than non smokers³³. The risk of reactivation of latent tuberculosis in a smoking adult is two fold that of a non smoker³⁴.

Ageing

Over a duration of just 5 years (2000 – 2005), the elderly population (aged above 60) grew from 1.4 million to 1.7 million in Malaysia¹¹. At present, Malaysia is in the 'Window Of Opportunity' phase, where there is a large working age population (aged 25 to 64) and the decline of young aged persons (aged 15 to 24)³⁵. This trend will persist up to the year 2020 and thereafter, the country will inherit a generation of increasing old age burden which is likely to have an average life expectancy up to the age of 72³⁶. Projections made by the United Nations reveal that there will be a rise of 22% in the older generation of the population in 2050¹¹.

Ageing results in a decline in T-cell mediated immunity that hampers the ability to combat tuberculosis infection effectively³⁷⁻³⁹. This increases the host susceptibility to the illness. In tandem with this evidence, surveys have shown that tuberculosis is predominant in the ageing population in comparison to their younger counterparts^{40,41}. In one study, mortality was higher in elderly patients at 20% when compared to younger subjects (3%)⁴².

A high index of suspicion is required to detect prevailing tuberculosis cases in the elderly as they present with atypical presentation and symptoms maybe be masked by underlying age related comorbidities⁴²⁻⁴⁵. A more vigilant and targeted screening of tuberculosis in this age group could be viable option.

Dyslipidaemia

The role of dyslipidaemia as a risk factor in tuberculosis remains controversial and further investigative studies in this field is ongoing. A landmark finding in a recent study implies that hypercholesterolemia leads to a defectively inefficient innate adaptive mechanism which reduces resistance against tuberculosis⁴⁶.

Several studies, however, dispute the role of hypercholesterolemia as a risk factor in tuberculosis. Patients with higher cholesterol levels seem to possess better radiological signs of tuberculosis and faster sputum sterilization after chemotherapy^{47,48}. But these findings were misinterpreted as these studies seem to indicate that low cholesterol levels are the consequence and not the cause of the disease⁴⁹.

Summary Of Incidence/Relative Risk/Odds Ratio Of Major Risk Factors In Tuberculosis

Table I: Incidence/Relative Risk/Odds Ratio of Major Risk Factors Contributing to The Reactivation of Tuberculosis

Risk Factor	Risk	Studies
HIV	26.7 (RR*)	17
Diabetes Mellitus	3.1 (RR)	14, 20
CRF†/ESRF‡	6.9 – 52.5 (RR in CRF and ESRF on dialysis)	25, 27
Smoking	2.0 (RR)	6, 34
Aging	1.61 – 27.02 (OR§ as an independent risk factor)	21
	2-3 (RR, in nursing home residents)	57, 58
Dyslipidaemia	No data	No studies

* Relative risk

† Chronic renal failure

‡ End stage renal failure

§ Odds ratio

Malaysia ranks as the country with the fourth highest prevalence of raised cholesterol levels in the South East Asian region⁵⁰. It is widely understood that dyslipidaemia plays a central role as a risk factor for coronary heart disease⁵¹. In the NHMS III study, the fourth most common chronic illnesses in Malaysia were cardiovascular diseases⁵². This fact seems to be linked to the statistic that out of the 55.9% of patients with acute coronary syndrome in the country were previously diagnosed with dyslipidaemia prior to the incident⁵³.

The practice of widespread use of statins amongst diabetic patients due to assumption of an inherent rise in cardiovascular risk has to be observed with caution. Several experiments document that statins increase CD4/CD25 regulatory T cells (Tregs)⁵⁴. Tregs are responsible for hyporesponsiveness to chronic infections⁵⁵ by suppressing Th1 immune response that predisposes patients to the reactivation of latent tuberculosis⁵⁶.

In view of the pervasiveness of dyslipidaemia in the Malaysian population, the influence of dyslipidaemia in reactivation of tuberculosis infection needs to be re-evaluated once corroborative evidence on this link has been established by future research in this field.

LATENT TUBERCULOSIS IN HIGH RISK POPULATION (PREVALENCE AND THE IMPORTANCE OF INTERVENTION)

Worldwide it is predicted that 2 billion individuals are likely to be latently infected and will serve as hosts for dissemination of the disease unless reactivation can be halted⁵⁹. It is thus imperative that active screening amongst high risk groups be considered as it could increase the yield of new cases⁵⁹.

Few studies have been done to evaluate the prevalence of latent tuberculosis in high risk population in Malaysia^{12,60,61}. To date, there are no studies done on the prevalence of LTBI in the general population in the country⁶⁰. With the gradual rise in the number of immigrants from high tuberculosis burden nations, the disease has become a major public health issue globally^{62,63}. It is not surprising that tuberculosis is more common in older locals¹² who are prone to reactivation secondary to age related risk factors/comorbidities⁶³.

An early intervention in high risk groups seems to decrease cavitating disease in tuberculosis and have the advantage of reducing transmission in the community⁶⁴. This is a feasible

proposition in the Malaysian context since there is an increase in aging population and the prevalence of non-communicable diseases, namely diabetes. Studies have shown that adequate chemoprophylaxis is not only cost-effective but prevents risk of tuberculosis reactivation by almost 70%⁶⁵.

The treatment and control of tuberculosis should focus on both primary and secondary prevention methods (treating LTBI) rather than paying emphasis on just one area of tuberculosis elimination⁶⁶. Over-reliance has been placed on BCG vaccination to provide the community with primary and secondary prevention of tuberculosis. Studies have shown that BCG conferred very poor overall protection in adults and a low level of protection in children⁶⁷.

A two-pronged approach involving the coupling of primary with secondary control should be employed as treatment efficacy of both LTBI and the active disease work in synergy⁶⁶. Calculations based on this approach have revealed that these interventions retard the progression from latent to active disease and when this combined approach is implemented, it has the potential to reduce tuberculosis incidence rate below the elimination threshold by 2050⁶⁶.

EFFECTIVE SCREENING TOOL FOR LATENT TUBERCULOSIS INFECTION

Various studies have been conducted in Malaysia to evaluate LTBI using the IGRA and tuberculin sensitivity testing method^{60,68}. At the beginning and the middle of the 1990s, TST was declared the only test available to identify LTBI in patients who do not have primary progressive tuberculosis⁶⁹. As research progressed, TST is being increasingly supplanted by IGRA which has been proven to be much superior to TST^{70,71}.

Two in vitro tests have been discovered (Quantiferon and T-Spot TB tests) that detect sensitized interferon gamma produced by T lymphocytes that are sensitized to specific antigens of *Mycobacterium tuberculosis*⁷². These tests seem to provide better sensitivity and specificity than TST amongst immunocompromised subjects^{72,73-75}. IGRA tests are not influenced by prior BCG vaccination, booster effect or contact with non-tuberculous mycobacterium^{71,76}.

In screening patients with immunosuppressed conditions (which includes diabetes, chronic renal failure and aging), IGRA was found to be positive in 35.5% of test subjects when compared to TST (17.3%)⁷⁴.

TST is known to be fraught with many false negative and false positive results⁷⁷ which could conceal the true prevalence of LTBI. The sensitivity of TST is also lowered in immunosuppressed patient in comparison to healthy individuals^{74,78}. TST also poses other weaknesses that might lead to research limitations in evaluating LTBI. TST is poorly reproducible (due to booster effect), brings about inconvenience to patients as it requires two visits to assess its performance and it is also subject to observer error⁷². The designated cut off point for a positive TST (indicative of LTBI) is not standardized and varies between countries or recommended guidelines⁷².

Most importantly, identifiable risk factors that cause immunosuppression could bring down host defenses⁷⁹ which would ultimately weaken the innate immunological response (delayed type hypersensitivity) to PPD (pure protein derivative), thus a less sensitive TST^{80,81}. The typical anergy in this population group could yield more negative results which could be either interpreted as the absence of LTBI or anergy – there are no clear techniques to distinguish between the two outcomes⁷⁴. On the other hand, IGRA has a higher positivity rate amongst immunocompromised patients in comparison to TST⁷⁴. However, in severely immunocompromised patients, there is a greater degree of indeterminate results arising from anergy when IGRA was used⁸².

The use of TST, though it performed better in regions with low endemicity⁸³, has to be interpreted carefully (except in non vaccinated individuals) and should not be the criterion to commence preventive treatment⁸⁴. In areas of intermediate to higher endemicity such as the Western Pacific region (which includes Malaysia) and where there has been pervasive vaccination of BCG, commercial IGRA seems to be a better method of assessment for high risk individuals / immunosuppressed individuals⁸⁵.

DISCUSSION

To fulfill the objective of achieving the status of a developed nation, the struggle to prevent the re-emergence of tuberculosis due to the continuous increase in its compounding risk factors (excluding HIV), remains a crucial challenge in the public health sector in Malaysia.

The rising rates in diabetic patients (subsequently chronic kidney disease as a result of long standing diabetes), gradual increase in aging population and escalating numbers in smokers (regardless of gender) in the country could pose a hidden threat by raising the number of patients in the latent tuberculosis reservoir (mostly undetected but primed for re-activation) despite reassuring trends in the prevalence of tuberculosis.

Though commendable efforts have been made to eradicate tuberculosis by aggressively screening high risk population

groups who are prone to contracting the disease (screening of foreign workers and establishing non-communicable disease programs at health clinics), a formal assessment of latent tuberculosis burden in this vulnerable population has not been undertaken at a community level. Instead, tuberculosis screening methods of asymptomatic patients have been reliant on chest x-rays and sputum microscopy, which only detects the stage of primary progressive tuberculosis, not LTBI or smear negative cases.

CONCLUSION (AVENUE FOR FUTURE RESEARCH AND SCREENING OF LTBI IN MALAYSIA)

The compulsory prophylactic treatment of tuberculosis in confirmed HIV patients in Malaysia seems to be a step in the right direction towards containing latent tuberculosis from transforming into a full blown contagious form of tuberculosis. In line with the same intention, due consideration should be made to perform targeted screening on patients with other equally important medical risk factors²², namely diabetes, to facilitate prophylactic treatment of tuberculosis.

In deciding the confirmation of LTBI before preventive treatment could be started, several studies have concluded that it is financially prudent if the disease is first detected by a positive TST (with reference local cut off margins) and then confirmed by IGRA before commencement⁸⁵⁻⁸⁷. In only countries with high proportion of negative tuberculin test, IGRA is preferred over TST as a more cost effective screening tool for close contacts and high risk patients⁸².

A paradigm shift should take place in the approach towards eradicating tuberculosis in Malaysia – both primary prevention (detection and prophylactic treatment of LTBI to reduce incidence rates) and secondary prevention (elimination of tuberculosis amongst symptomatic patients) should be employed in unison.

Future avenues for research in the light of the information depicted in this review include

1. *Meaningful health initiatives to gauge the burden of the LTBI in the community preferably by using a combination of TST and IGRA*

The outcome of the study might help determine the classification of high risk groups who need screening and the decision to commence early intervention through prophylaxis in this population. The results could also unveil of a hidden reservoir of latent tuberculosis infection. Ultimately, this could pre-empt health authorities to aggressively address the issue by focusing on primary/secondary prevention of tuberculosis and not relying entirely on eradication symptomatic tuberculosis patients alone.

2. *A cost-effective analysis to be conducted on best method to test for LTBI in patients with risk factors*

The results obtained from this analysis could serve as a guideline for clinicians in deciding a practical and economical way of screening LTBI amongst patients with risk factors.

3. *Comparative studies by performing targeted screening of LTBI in vulnerable population diabetes mellitus with compounding risk factors and a control group consisting of diabetic patients without comorbidities using IGRA*

A positive outcome of the study above could help health authorities decide on targeted screening of tuberculosis patients, especially amongst diabetic patients with other comorbidities in the country. It can help formulate a more economical screening strategy of diabetic patients for latent tuberculosis infection by stratifying diabetic patients with underlying comorbidities for IGRA testing. The program can be integrated into the pre-existing non communicable disease programs in the primary health care setting.

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