UNIVERSITI PUTRA MALAYSIA

RISK FACTORS OF TUBERCULOSIS AMONG DIABETES MELLITUS PATIENTS IN HOSPITAL SULTANAH BAHIYAH, ALOR SETAR 2015-2016

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By

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Dissertation Submitted to the Department of Community Health, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia in Fulfilment of the Requirements for the Degree of Master of Public Health

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August 2017

Chairperson : Associate Prof. Dr. Hejar Binti Abdul Rahman
Faculty : Medicine and Health Sciences

Introduction: Tuberculosis (TB) and diabetes mellitus (DM) is a double-burden disease where person with diabetes have triple risk of developing tuberculosis later in their life in view of their weak immune system. In view of both TB and DM is one of the major global health problem, combating both diseases will indirectly reduce its burden.

Objective: The aim of this study is to determine risk factors of tuberculosis (TB) among diabetes mellitus (DM) patients in Chest Clinic of Hospital Sultanah Bahiyah, Alor Setar.

Methodology: This study was conducted in Chest Clinic, Respiratory Unit of Medical Department, Hospital Sultanah Bahiyah, Alor Setar Kedah. It is an unmatched hospital based case-control study design where the study population consist of records of patients from the chest clinic HSB and diabetic clinic registry of primary care settings for both case and control. Simple random sampling method were used for this study. The case and control were randomly selected from the list of *e-Respiratory* registry of Hospital Sultanah Bahiyah.

Result: The final model has a good fit ($p>0.05$). Male patients who have diabetes mellitus (DM) were two times at risk of having tuberculosis as compared to female patients with DM (aOR=2.25, 95% CI=1.18, 4.30). Non-malays ethnicity who have diabetes mellitus (DM) were three times at risk of having tuberculosis as compared to Malay ethnic patients with DM (aOR=3.35, 95% CI=1.43, 7.86). Patients age of more than 50 years old at DM diagnosis two times more likely to have tuberculosis compared to patients age of less than 50 years old at DM diagnosis (aOR=2.21, 95% CI=1.18, 4.16). DM patients who smokes cigarette

were two times more likely to develop TB as compared to non-smokers DM patient (aOR=2.22, 95% CI=1.19, 4.14). DM patients who have history of contact with TB patients have 11 times odds of developing TB as compared with those who never have history of contact with TB patients (aOR=11.07, 95% CI=5.47, 22.40).

Conclusion: The important risk factors associated with tuberculosis among diabetics are gender, ethnicity, age at DM diagnosis, smoking status and history of contact with TB patient.

Keywords: tuberculosis, diabetes mellitus, tuberculosis-diabetes, risk factors

Abstrak disertasi yang dikemukakan kepada Jabatan Kesihatan Komuniti, Fakulti Perubatan dan Sains Kesihatan, Universiti Putra Malaysia sebagai memenuhi keperluan untuk Ijazah Sarjana Kesihatan Masyarakat.

FAKTOR RISIKO JANGKITAN TUBERKULOSIS DIKALANGAN PESAKIT DIABETES MELLITUS DI HOSPITAL SULTANAH BAHIYAH, ALOR SETAR 2015-2016

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Pendahuluan: Tuberkulosis (TB) dan diabetes mellitus (DM; kencing manis) merupakan dua penyakit yang memberi impak negatif antara satu sama lain. Pesakit yang mempunyai DM mengahadapi risiko tiga kali ganda untuk mendapat penyakit TB memandangkan sistem imunisasinya yang lemah. Oleh kerana kedua-dua penyakit ini merupakan penyakit yang sedang meningkat dikalangan rakyat Malaysia, dengan mengawal keduanya secara tidak langsung dapat menurunkan kadar beban penyakit tersebut.

Objektif: Menentukan faktor risiko jangkitan penyakit TB dikalangan pesakit DM di Klinik Dada, Unit Respiratori Hospital Sultanah Bahiyah Alor Setar bagi tahun 2015 hingga 2016.

Metodologi: Kajian ini adalah kajian *'unmatched case control'* yang dijalankan di Klinik Dada, Unit Respiratori, Hospital Sultanah Bahiyah dimana populasi kajian merupakan rekod pesakit dari senarai berdaftar di Klinik Dada Bagi kedua-dua *'case'* dan *'control'* dan juga rekod pesakit dari senarai berdaftar di Klinik Diabetes dari klinik kesihatan daerah Kota Setar. Persampelan secara rawak dilakukan bagi kajian ini. *'Case'* dan *'control'* dipilih secara rawak dari senarai *e-Respiratory* Hospital Sultanah Bahiyah.

Keputusan: Pesakit DM lelaki mempunyai risiko sebanyak dua kali ganda mendapat penyakit TB jika dibandingkan dengan pesakit DM wanita (aOR=2.25, 95% CI=1.18, 4.30). Pesakit DM dari etnik bukan Melayu mempunyai risiko sebanyak tiga kali ganda mendapat penyakit TB jika dibandingkan dengan pesakit DM etnik Melayu (aOR=3.35, 95% CI=1.43, 7.86). Pesakit DM yang

berumur lebih 50 tahun ketika diagnosis DM dilakukan mempunyai risiko dua kali ganda mendapat penyakit TB jika dibandingkan dengan pesakit DM berumur kurang 50 tahun semasa diagnosis DM dilakukan (aOR=2.21, 95% CI=1.18, 4.16). Pesakit DM yang merokok mempunyai risiko sebanyak dua kali ganda mendapat penyakit TB jika dibandingkan dengan pesakit DM bukan perokok (aOR=2.22, 95% CI=1.19, 4.14). Pesakit DM yang mempunyai sejarah kontak dengan pesakit TB mempunyai risiko sebanyak 11 kali ganda dalam mendapat penyakit TB jika dibandingkan dengan pesakit DM yang tidak mempunyai sejarah kontak dengan pesakit TB (aOR=11.07, 95% CI=5.47, 22.40).

Kesimpulan: Faktor risiko penting yang berkait rapat dalam jangkitan TB dikalangan pesakit DM adalah jantina, etnik, umur ketika diagnose DM dilakukan, merokok dan sejarah kontak dengan pesakit TB yang lain.

Kata kunci: tuberkulosis, diabetes mellitus, kencing manis, tuberkulosis-diabetes, faktor risiko

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I certify that a Dissertation Examination Committee has met on 1st August 2017 to conduct the final examination of Farah Fatin Binti Fauzi on her dissertation entitled "Risk Factors Of Tuberculosis Among Diabetes Mellitus Patients In Hospital Sultanah Bahiyah, Alor Setar 2015-2016" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Master of Public Health.

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Declaration by Members of Supervisory Committee

This is to confirm that:

- the research conducted and the writing of this dissertation was under our supervision;
- supervision responsibilities as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) are adhered to.

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LIST OF ABBREVIATIONS

TB	Tuberculosis
DM	Diabetes Mellitus
TB-DM	Tuberculosis-Diabetes Mellitus Comorbidities
T2DM	Type 2 Diabetes Mellitus
T1DM	Type 1 Diabetes Mellitus
FPG	Fasting Plasma Glucose
RPG	Random Plasma Glucose
OGTT	Oral Glucose Tolerance Test
IGT	Impaired Glucose Tolerance
IFG	Impaired Fasting Glucose
BMI	Body Mass Index
MOH	Ministry of Health, Malaysia
WHO	World Health Organization
<	Lesser than
≥	Greater than and equal to

CHAPTER 1

INTRODUCTION

1.1 Background

Tuberculosis (TB) is one of the contagious airborne disease and a major health problem globally. More than 9 million people diagnosed with tuberculosis with 1.5 million death in 2014 (Lewandowski, 2015). In the poor and vulnerable population, as high as one in three people is diagnose with tuberculosis (Lönnroth et al., 2010). Even though TB incidence has reduced by an average of 1.5% per year since 2000, however, this need to be further improved to achieve a 4–5% annual decline in order to reach the 2020 milestones of the "End TB Strategy" (WHO, 2016). According to Health Indicators 2014 published by Ministry of Health, Malaysia, incidence rate of tuberculosis in Malaysia was 82.10 per 100,000 population (MOH, 2015). As for Kedah state, it contributes around 5% of all cases in Malaysia with incidence rate of 63.58 per 100,000 population (Malaysia, 2015). Recent data published in the end of 2015 by Ministry of Health, Malaysia on tuberculosis mortality rate in Malaysia is 5.33/100,000 population. Kedah has exceeded this national limit with mortality rate of tuberculosis was as high as 6.65 per 100,000 population. Kedah is a state in Malaysia where it's neighbouring country is Thailand, and commuting between these two countries had always been easy via land transportation. Kedah carries a higher risk of TB as Thailand is listed as top 20 tuberculosis burden country with estimated about 120,000 of its population diagnosed with tuberculosis (WHO, 2016). Even though Malaysia was not listed in the top 30 of tuberculosis burden country, there are activities to actively find and detect new cases, regular and close monitoring of all tuberculosis cases through various tuberculosis prevention and control programme that are being conducted all over the country, headed by Ministry of Health, Malaysia.

On the other hand as of 2014 have about 422 million people living with DM worldwide while the global prevalence nearly doubled from 4.7% in 1980 to 8.5% in 2014 among adults aged 18 and above (World Health Organization, 2016). By 2030, WHO projects that diabetes will become the 7th leading cause of death. From recent Malaysia National Health Morbidity Survey (NHMS) conducted in 2015, the prevalence of diabetes mellitus in Malaysia among adults of 18 years and above was 17.5%. From the same survey, Kedah was the state with the highest prevalence of diabetes with 25.4%. Previously in 1980, prevalence of diabetes was highest among high-income countries, but now it is almost similar in both high- and low-income countries with the latter is catching up fast (Shaw, Sicree & Zimmet, 2010). This includes Malaysia as a developing country having struggle to reduce both diabetes and tuberculosis. With this may cause Kedah to be more susceptible to have increase tuberculosis prevalence too in the future.

Tuberculosis-diabetes is a deadly linkage where person with diabetes have triple risk of developing tuberculosis later in their life in view of their weak immune

system as a result of chronic disease that later will cause latent TB to progress into active TB (Lönnroth et al., 2010). In view of both TB and DM as major global health problem, combating both disease will indirectly reduce its burden. Some studies did not show any relation between DM and the outcome of TB treatment (Dooley & Chaisson, 2009; Ponce-de-Leon et al., 2004; Singla et al., 2006; Wang, Lee, & Hsueh, 2005). However, DM may have a negative impact on the outcome of TB treatment: higher failure rates (Chang et al., 2011; Mboussa et al., 2003; Morsy, Zaher, Hassan, & Shouman, 2003; Ponce-de-Leon et al., 2004) higher rates of all-cause mortality (Fielder et al., 2002; Oursler et al., 2002), and death specifically related to TB (Wang et al., 2009). In one study, after adjusting for other factors, the chance of death was over six times higher in patients with diabetes (Dooley, Tang, Golub, Dorman, & Cronin, 2009). Another study showed an adjusted odds ratio of 7.65 (95% CI 1.89 – 30.95) for treatment failure among DM in comparison to non DM tuberculosis patients after removing the effect of covariants such as non-compliance and drug resistance (Alisjahbana et al., 2007).

In Malaysia, the prevalence of diabetes among tuberculosis patients at tertiary centres range between 14-33% (Gnanasan et al., 2011; Sulaiman et al., 2013). Patients with diabetes mellitus (DM) were more likely to have pulmonary tuberculosis (OR=2.079, $p<0.001$) (Sulaiman et al., 2013). The evidence for this was seen in large scale studies done in South East Asia by Nissapatorn et al. in 2005. A greater percentage of pulmonary tuberculosis patients (91%, 1509/1651) were in the TB-DM group (Nissapatorn et al., 2005). Four smaller scale studies had conflicting evidence on this matter. A study supporting this view discovered 82% (107/131) of patients diagnosed with pulmonary tuberculosis suffering from either diabetes mellitus, hypertension, ischaemic heart disease or all three conditions (Ibrahim, Jetan, Jamaiah, Rohela, & Nissapatorn, 2010). Three other studies revealed the prevalence of tuberculosis among diabetics between the range of 18 and 30% (Ismail, 2004; Jamalludin, 2003).

1.2 Problem Statement

Diabetes is a chronic, non-communicable disease that weakens the immune system, making people with diabetes three times more likely to get active TB (Lönnroth et al., 2010). Diabetes is escalating, and has affected 382 million in 2013 projected to increase to 592 million by 2035. As diabetes increase, it will cause more and more people to develop TB (Diabetes, 2014).

TB is an infectious disease that spreads from person to person through the air. TB kills more people than any other infectious disease except HIV/AIDS: 1.5 million people worldwide died from TB in 2013. These cases of “active” TB disease emerge out of a massive pool of latent TB infection. One in three people around the world—two billion people—hold a latent TB infection somewhere in their body, where it can remain dormant through one’s whole life. Every person infected with TB faces about a 10 percent chance that the infection will activate and spread in the body, giving them the known symptoms of TB: gradual but

severe weight loss, night sweats, and the famously bloody cough. At this stage, the infection can spread to people nearby (Lewandowski et al., 2015).

Diabetes is fuelling the spread of TB. This is largely because diabetes rates are trending upwards around the world, and having diabetes increases the risk that a person will get infected with TB. Diabetes is also more difficult to manage in people who have TB. A person who have both diseases is likely to have complications that do not typically exist when either is present on its own.

Successfully addressing TB-DM therefore requires a coordinated response to both diseases at all levels of the health system—from the developing and implementation of national policies, to the management of disease control programs, to the delivery of services to individual patients (Dooley & Chaisson, 2009). Therefore it is important to determine the risk factors of tuberculosis-diabetes comorbidity. Knowing the link between this two serious illnesses will give us a better clearer view on where to act, how to prevent and who's responsibility on combating them.

1.3 Significance of Study

This study may give different perspective of how a medical practitioner typically have on a TB-DM patients. Associated factors that will be studied can lead the healthcare workers to different approaches on combating both diseases together. Being able to contain both disease at once, will have greater impact to the community by reducing the spread of tuberculosis among them especially in overcrowding housing area and low socio-economic community.

The risk factors on tuberculosis infection among diabetes mellitus patients is yet to be discovered as limited study on this relationship done in Kedah. While for Malaysia as a developing country, more comprehensive programme of prevention and control focusing concurrently on both TB-DM need to be done as there are more associated factors being known later on from this study. By knowing the risk factors it will also be helpful for future planning on having intervention programmes to both diabetes and tuberculosis together.

1.4 Research Questions

What are the risk factors associated with having tuberculosis among diabetes mellitus patients?

1.5 Objectives

The objectives of this study can be subdivided into general objective and specific objectives.

1.5.1 General Objective

To determine risk factors associated with risk of tuberculosis (TB) among diabetes mellitus (DM) patients in Chest Clinic of Hospital Sultanah Bahiyah, Alor Setar.

1.5.2 Specific Objectives

1.5.2.1 To describe the socio-demographic factors, diabetic characteristics, diabetic complications, other comorbidities and related factors among diabetes mellitus patients with tuberculosis and diabetes mellitus only patients in chest clinic, Hospital Sultanah Bahiyah, Alor Setar

1.5.2.2 To determine the association between sociodemographic factors (age, gender, ethnic and living house category) and TB among diabetes mellitus patients in chest clinic, Hospital Sultanah Bahiyah, Alor Setar.

1.5.2.3 To determine the association between diabetic characteristics (HbA1c level at TB diagnosis, duration of DM, type of DM treatment, HbA1c level at DM diagnosis and age at DM diagnosis) and TB among diabetes mellitus patients in chest clinic, Hospital Sultanah Bahiyah, Alor Setar.

1.5.2.4 To determine the association between diabetic complications (retinopathy, nephropathy, peripheral vascular disease, neuropathy and coronary heart disease) and TB among diabetes mellitus patients in chest clinic, Hospital Sultanah Bahiyah, Alor Setar.

1.5.2.5 To determine the association between having other comorbidities (Hypertension, Cancer and Dyslipidemia) and TB among diabetes mellitus patients in chest clinic, Hospital Sultanah Bahiyah, Alor Setar.

1.5.2.6 To determine the association between having other related factors (BMI level, smoking, history of contact with TB patient) and TB among diabetes mellitus patients in chest clinic, Hospital Sultanah Bahiyah, Alor Setar.

1.5.2.7 To determine the risk factors of developing tuberculosis among diabetes mellitus patients in chest clinic, Hospital Sultanah Bahiyah, Alor Setar.

1.6 Research Hypothesis

Null hypothesis

There is no association between socio-demographic factors, diabetic characteristics, diabetic complications, other comorbidities and other related factors and risk of developing tuberculosis among diabetes mellitus patients.

REFERENCES

Al-Attiyah, R. J., & Mustafa, A. S. (2009). Mycobacterial antigen-induced T helper type 1 (Th1) and Th2 reactivity of peripheral blood mononuclear cells from diabetic and non-diabetic tuberculosis patients and Mycobacterium bovis bacilli Calmette-Gu??rin (BCG)-vaccinated healthy subjects. *Clinical and Experimental Immunology*, *158*(1), 64–73. https://doi.org/10.1111/j.1365-2249.2009.04000.x

Alisjahbana, B., Sahiratmadja, E., Nelwan, E. J., Purwa, A. M., Ahmad, Y., Ottenhoff, T. H. M., … Crevel, R. v. (2007). The Effect of Type 2 Diabetes Mellitus on the Presentation and Treatment Response of Pulmonary Tuberculosis. *Clinical Infectious Diseases*, *45*(4), 428–435. https://doi.org/10.1086/519841

Alisjahbana, B., van Crevel, R., Sahiratmadja, E., den Heijer, M., Maya, A., Istriana, E., … van der Meer, J. W. M. (2006). Diabetes mellitus is strongly associated with tuberculosis in Indonesia.

Amare, H., Gelaw, A., Anagaw, B., & Gelaw, B. (2013). Smear positive pulmonary tuberculosis among diabetic patients at the Dessie referral hospital, Northeast Ethiopia. Infectious Diseases of poverty, 2(1), 6.

American Diabetes Association. (2012). Diagnosis and classification of diabetes mellitus. *Diabetes Care*, *35*(SUPPL. 1). https://doi.org/10.2337/dc12-s064

Argmann, C. A., Edwards, J. Y., Sawyez, C. G., O'Neil, C. H., Hegele, R. A., Pickering, J. G., & Huff, M. W. (2005). Regulation of Macrophage Cholesterol Efflux through Hydroxymethylglutaryl-CoA Reductase Inhibition A ROLE FOR RhoA IN ABCA1-MEDIATED CHOLESTEROL EFFLUX. Journal of Biological Chemistry, 280(23), 22212-22221.

Assembly, U. G. (2011). Political declaration of the high-level meeting of the general assembly on the prevention and control of non-communicable diseases. *New York: United Nations*.

Baker, M. A., Harries, A. D., Jeon, C. Y., Hart, J. E., Kapur, A., Lönnroth, K., ... & Murray, M. B. (2011). The impact of diabetes on tuberculosis treatment outcomes: a systematic review. *BMC medicine*, *9*(1), 81.

Balakrishnan, S., Vijayan, S., Nair, S., Subramoniapillai, J., Mrithyunjayan, S., Wilson, N., ... & Willis, M. (2012). High diabetes prevalence among tuberculosis cases in Kerala, India. PloS one, 7(10), e46502.

Bautista, L. E., Vera, L. M., Arenas, I. A., & Gamarra, G. (2005). Independent association between inflammatory markers (C-reactive protein, interleukin-6, and TNF-α) and essential hypertension. Journal of human hypertension, 19(2), 149-154.

Blas, E., & Kurup, A. S. (2010). *Equity, social determinants and public health programmes*. World Health Organization.

Centers for Disease Control and Prevention, C.D.C. (2016). Tuberculosis. Basic TB Facts. TB Risk Factors. Retrieved from https://www.cdc.gov/tb/topic/basics/risk.htm

Cegielski, J. P., & McMurray, D. N. (2004). The relationship between malnutrition and tuberculosis: evidence from studies in humans and experimental animals. *The international journal of tuberculosis and lung disease*, *8*(3), 286-298.

Chae, C. U., Lee, R. T., Rifai, N., & Ridker, P. M. (2001). Blood pressure and inflammation in apparently healthy men. Hypertension, 38(3), 399-403.

Chale, S. S., Swai, A. B., Mujinja, P. G., & McLarty, D. G. (1992). Must diabetes be a fatal disease in Africa? Study of costs of treatment. *BMJ*, *304*(6836), 1215-1218.

Chan, J. C., Gagliardino, J. J., Baik, S. H., Chantelot, J. M., Ferreira, S. R., Hancu, N., ... & Aschner, P. (2009). Multifaceted determinants for achieving glycemic control. Diabetes Care, 32(2), 227-233.

Chang, J.-T., Dou, H.-Y., Yen, C.-L., Wu, Y.-H., Huang, R.-M., Lin, H.-J., … Shieh, C.-C. (2011). Effect of Type 2 Diabetes Mellitus on the Clinical Severity and Treatment Outcome in Patients With Pulmonary Tuberculosis: A Potential Role in the Emergence of Multidrug-resistance. *Journal of the Formosan Medical Association*, *110*(6), 372–381. https://doi.org/10.1016/S0929-6646(11)60055-7

Chuang, L. M., Tsai, S. T., Huang, B. Y., & Tai, T. Y. (2002). The status of diabetes control in Asia—a cross-sectional survey of 24 317 patients with diabetes mellitus in 1998. Diabetic medicine, 19(12), 978-985.

Cliona Ni Mhurchu, Varsha Parag, Mieko Nakamura, Anushka Patel, Anthony Rodgers, Tai Hing Lam, Collaboration, A. P. C. S. (2006). Body mass index and risk of diabetes mellitus in the Asia-Pacific region. *Asia Pacific*, *15*(2), 127-33.

Davidson, M. B., Schriger, D. L., Peters, A. L., Lorber, B., H, K., WC, K., … C, R. (1999). Relationship Between Fasting Plasma Glucose and Glycosylated Hemoglobin. *JAMA*, *281*(13), 1203. https://doi.org/10.1001/jama.281.13.1203

Diabetes, F. W. (2014). the Looming Co-Epidemic of Tb-Diabetes : a Call To Action. *A Call to Action*, 24. Retrieved from http://www.theunion.org/what-we-do/publications/technical/english/EMBARGOED-DMTB-REPORT-Oct-22.pdf

Dony, J. F., Ahmad, J., & Khen Tiong, Y. (2004). Epidemiology of tuberculosis and leprosy, Sabah, Malaysia. *Tuberculosis (Edinburgh, Scotland)*, *84*(1–

2), 8–18. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/14670341

Dooley, K. E., & Chaisson, R. E. (2009). Tuberculosis and diabetes mellitus: convergence of two epidemics. *The Lancet Infectious Diseases*, *9*(12), 737–746. https://doi.org/10.1016/S1473-3099(09)70282-8

Dooley, K. E., Tang, T., Golub, J. E., Dorman, S. E., & Cronin, W. (2009). Impact of diabetes mellitus on treatment outcomes of patients with active tuberculosis. *The American Journal of Tropical Medicine and Hygiene*, *80*(4), 634–9. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/19346391

Elfatih, I. E; ABdul Razak, Muttalif; Mohamed Izham, M. I. . S. S. S. A. (2004). A Survey On Tuberculosis Cases In Penang Hospital : Preliminary Findings.

Feleke, Y., Abdulkadir, J., & Aderaye, G. (1999). Prevalence and clinical features of tuberculosis in Ethiopian diabetic patients. *East African Medical Journal*, *76*(7), 361–4. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10520361

Fielder, J. F., Chaulk, C. P., Dalvi, M., Gachuhi, R., Comstock, G. W., & Sterling, T. R. (2002). A high tuberculosis case-fatality rate in a setting of effective tuberculosis control: implications for acceptable treatment success rates. *The International Journal of Tuberculosis and Lung Disease : The Official Journal of the International Union against Tuberculosis and Lung Disease*, *6*(12), 1114–7. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12546121

Gnanasan, S., Ting, K. N., Wong, K. T., Mohd Ali, S., Muttalif, A. R., & Anderson, C. (2011). Convergence of tuberculosis and diabetes mellitus: time to individualise pharmaceutical care. *International Journal of Clinical Pharmacy*, *33*(1), 44–52. https://doi.org/10.1007/s11096-010-9452-3

Goldhaber-Fiebert, J. D., Jeon, C. Y., Cohen, T., & Murray, M. B. (2011). Diabetes mellitus and tuberculosis in countries with high tuberculosis burdens: individual risks and social determinants. *International journal of epidemiology*, dyq238.

Guptan, A., & Shah, A. (2000). Tuberculosis and diabetes: An appraisal. Indian Journal of Tuberculosis, 47(1), 3-8.

Hossain, P., Kawar, B., & El Nahas, M. (2007). Obesity and diabetes in the developing world—a growing challenge. *N Engl j med*, *2007*(356), 213-215.

Hu, Y., Liu, W., Chen, Y., Zhang, M., Wang, L., Zhou, H., … Jia, Y. (2010). Combined use of fasting plasma glucose and glycated hemoglobin A1c in the screening of diabetes and impaired glucose tolerance. *Acta Diabetologica*, *47*(3), 231–236. https://doi.org/10.1007/s00592-009-0143-2

Ibrahim, J., Jetan, C., Jamaiah, I., Rohela, M., & Nissapatorn, V. (2010). Tuberculosis : An Eight Year (2000-2007) Retrospective Study At The

University Of Malaya Medical Centre (Ummc), Kuala Lumpur, Malaysia. *Southeast Asian J Trop Med Public Health*, *378*(2).

Ismail, Y. (2004). Pulmonary tuberculosis--a review of clinical features and diagnosis in 232 cases. *The Medical Journal of Malaysia*, *59*(1), 56–64. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15535337

Jabbar, A., Hussain, S. F., & Khan, A. A. (2006). Clinical characteristics of pulmonary tuberculosis in adult Pakistani patients with co-existing diabetes mellitus.

Jamalludin, A. R. (2003). Review of pulmonary tuberculosis patients with positive culture in Kuala Terengganu, 1998-2001, *2*.

Jeon, C. Y., Harries, A. D., Baker, M. A., Hart, J. E., Kapur, A., Lönnroth, K., ... & Murray, M. B. (2010). Bi-directional screening for tuberculosis and diabetes: a systematic review. Tropical medicine & international health, 15(11), 1300-1314.

Ji, L. N., Lu, J. M., Guo, X. H., Yang, W. Y., Weng, J. P., Jia, W. P., ... & Shan, Z. Y. (2013). Glycemic control among patients in China with type 2 diabetes mellitus receiving oral drugs or injectables. BMC public health, 13(1), 602.

Kapur, A. (2007). Economic analysis of diabetes care. *Indian Journal of Medical Research*, *125*(3), 473.

Khattab, M., Khader, Y. S., Al-Khawaldeh, A., & Ajlouni, K. (2010). Factors associated with poor glycemic control among patients with type 2 diabetes. *Journal of diabetes and its complications*, *24*(2), 84-89.

Leung, C. C., Lam, T. H., Chan, W. M., Yew, W. W., Ho, K. S., Leung, G. M., … Chang, K. C. (2008). Diabetic Control and Risk of Tuberculosis: A Cohort Study. *American Journal of Epidemiology*, *167*(12), 1486–1494. https://doi.org/10.1093/aje/kwn075

Lewandowski, C. M., Co-investigator, N., & Lewandowski, C. M. (2015). WHO Global tuberculosis report 2015. *The Effects of Brief Mindfulness Intervention on Acute Pain Experience: An Examination of Individual Difference*, *1*, 1689–1699. https://doi.org/10.1017/CBO9781107415324.004

Liang, H. Y., Li, X. L., Yu, X. S., Guan, P., Yin, Z. H., He, Q. C., & Zhou, B. S. (2009). Facts and fiction of the relationship between preexisting tuberculosis and lung cancer risk: a systematic review. International journal of cancer, 125(12), 2936-2944.

Lienhardt, C., Fielding, K., Sillah, J. S., Bah, B., Gustafson, P., Warndorff, D., & Manneh, K. (2005). Investigation of the risk factors for tuberculosis: a case–control study in three countries in West Africa. International journal of epidemiology, 34(4), 914-923.

Lin, Y. H., Chen, C. P., Chen, P. Y., Huang, J. C., Ho, C., Weng, H. H., ... & Peng, Y. S. (2015). Screening for pulmonary tuberculosis in type 2 diabetes elderly: a cross-sectional study in a community hospital. BMC Public Health, 15(1), 3.

Liyanatul Najwa, Z., Nadiatul Ima, Z., Wan, M. K., Noor Haslinda, I., Intan Syafinaz, S., Hasneezah, H., … Rosliza, A. M. (2016). The concept of district health management in malaysia. *International Journal of Public Health and Clinical Sciences*, *3*(1), 1–16.

Loike, J. D., Shabtai, D. Y., Neuhut, R., Malitzky, S., Lu, E., Husemann, J., ... & Silverstein, S. C. (2004). Statin inhibition of Fc receptor–mediated phagocytosis by macrophages is modulated by cell activation and cholesterol. Arteriosclerosis, thrombosis, and vascular biology, 24(11), 2051-2056.

Lonnroth, K., Williams, B. G., Cegielski, P., & Dye, C. (2009). A consistent log-linear relationship between tuberculosis incidence and body mass index. *International journal of epidemiology*, *39*(1), 149-155.

Lonnroth, K., Castro, K. G., Chakaya, J. M., Chauhan, L. S., Floyd, K., Glaziou, P., & Raviglione, M. C. (2010). Tuberculosis control and elimination 2010-50: cure, care, and social development. *The Lancet*, *375*(9728), 1814–1829. https://doi.org/10.1016/S0140-6736(10)60483-7

Look AHEAD Research Group. (2010). Long term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes: four year results of the Look AHEAD trial. *Archives of internal medicine*, *170*(17), 1566.

Malaysia, M. of H. (2015). Petunjuk kesihatan. *Health Indicator 2014*, *12*. https://doi.org/ISSN 1511-4589

Malaysian Endocrine and Metabolic Society (MEMS). (2015). Clinical Practice Guidelines Management Of Type 2 Diabetes Mellitus (5th Edition).

Malik, V. S., Popkin, B. M., Bray, G. A., Després, J. P., Willett, W. C., & Hu, F. B. (2010). Sugar-sweetened beverages and risk of metabolic syndrome and type 2 diabetes. *Diabetes care*, *33*(11), 2477-2483.

Mboussa, J., Monabeka, H., Kombo, M., Yokolo, D., Yoka-Mbio, A., & Yala, F. (2003). [Course of pulmonary tuberculosis in diabetics]. *Revue de Pneumologie Clinique*, *59*(1), 39–44. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12717325

Ministry of Health Malaysia, Academy of Medicine Malaysia, & Malaysian Thoracic Society. (2012). *Management of Tuberculosis - Clinical Practice Guidelines (3rd Edition)* (Vol. 12).

Mohammad, Z., & Naing, N. N. (2004). Characteristics of HIV-infected tuberculosis patients in Kota Bharu Hospital, Kelantan from 1998 to 2001.

The Southeast Asian Journal of Tropical Medicine and Public Health, *35*(1), 140–3. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15272757

Morsy, A. M., Zaher, H. H., Hassan, M. H., & Shouman, A. (2003). Predictors of treatment failure among tuberculosis patients under DOTS strategy in Egypt. *Eastern Mediterranean Health Journal = La Revue de Sante de La Mediterranee Orientale = Al-Majallah Al-Sihhiyah Li-Sharq Al-Mutawassit*, *9*(4), 689–701. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15748066

Moxey, P. W., Gogalniceanu, P., Hinchliffe, R. J., Loftus, I. M., Jones, K. J., Thompson, M. M., & Holt, P. J. (2011). Lower extremity amputations—a review of global variability in incidence. *Diabetic Medicine*, *28*(10), 1144-1153.

Niazi, A. K., & Kalra, S. (2012). Diabetes and tuberculosis: a review of the role of optimal glycemic control. Journal of Diabetes & Metabolic Disorders, 11(1), 28.

Nissapatorn, V., Kuppusamy, I., Jamaiah, I., Fong, M. Y., Rohela, M., & Anuar, A. K. (2005). Tuberculosis in diabetic patients: a clinical perspective. *The Southeast Asian Journal of Tropical Medicine and Public Health*, *36 Suppl 4*, 213–20. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/16438212

Nnoaham, K. E., & Clarke, A. (2008). Low serum vitamin D levels and tuberculosis: a systematic review and meta-analysis. International journal of epidemiology, 37(1), 113-119.

Oursler, K. K., Moore, R. D., Bishai, W. R., Harrington, S. M., Pope, D. S., & Chaisson, R. E. (2002). Survival of Patients with Pulmonary Tuberculosis: Clinical and Molecular Epidemiologic Factors. *Clinical Infectious Diseases*, *34*(6), 752–759. https://doi.org/10.1086/338784

Pablos-Mendez, A., Blustein, J., & Knirsch, C. A. (1997). The Role of Diabetes Mellitus in the Higher Prevalence of Tuberculosis among Hispanics.

Padmalatha, P., & Hema, K. (2014). Study on prevalence of diabetes mellitus in tuberculosis patients attending a tertiary care hospital in Guntur, Andhra Pradesh. Indian Journal of Basic and Applied Medical Research, 4(1), 494-498.

Persaud, S. J., & Jones, P. M. (2016). A Wake-up Call for Type 2 Diabetes? *New England Journal of Medicine*, *375*(11), 1090–1092. https://doi.org/10.1056/NEJMcibr1607950

Philips, J. A., & Ernst, J. D. (2012). Tuberculosis Pathogenesis and Immunity. *Annual Review of Pathology: Mechanisms of Disease*, *7*(1), 353–384. https://doi.org/10.1146/annurev-pathol-011811-132458

Ponce-de-Leon, A., Garcia-Garcia, M. de L., Garcia-Sancho, M. C., Gomez-Perez, F. J., Valdespino-Gomez, J. L., Olaiz-Fernandez, G., … Sifuentes-

Osornio, J. (2004). Tuberculosis and Diabetes in Southern Mexico. *Diabetes Care*, *27*(7).

Qiu, G., & Hill, J. S. (2008). Atorvastatin inhibits ABCA1 expression and cholesterol efflux in THP-1 macrophages by an LXR-dependent pathway. Journal of cardiovascular pharmacology, 51(4), 388-395.

Rathmann, W., & Giani, G. (2004). Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes care*, *27*(10), 2568-2569.

Reis-Santos, B., Locatelli, R., Horta, B. L., Faerstein, E., Sanchez, M. N., Riley, L. W., & Maciel, E. L. (2013). Socio-demographic and clinical differences in subjects with tuberculosis with and without diabetes mellitus in Brazil–a multivariate analysis. *PloS one*, *8*(4), e62604.

Restrepo, B. I., Fisher-Hoch, S. P., Crespo, J. G., Whitney, E., Perez, A., Smith, B., & McCormick, J. B. (2007). Type 2 diabetes and tuberculosis in a dynamic bi-national border population. Epidemiology & Infection, 135(3), 483-491.

Ruslami, R., Aarnoutse, R. E., Alisjahbana, B., Van Der Ven, A. J. A. M., & Van Crevel, R. (2010). Implications of the global increase of diabetes for tuberculosis control and patient care. *Tropical Medicine & International Health*, *15*(11), 1289–1299. https://doi.org/10.1111/j.1365-3156.2010.02625.x

Shariff, N. M., & Safian, N. (2015). Diabetes mellitus and its influence on sputum smear positivity at the 2nd month of treatment among pulmonary tuberculosis patients in Kuala Lumpur, Malaysia: A case control study. International journal of mycobacteriology, 4(4), 323-329.

Shaw, J. E., Sicree, R. A., & Zimmet, P. Z. (2010). Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes research and clinical practice*, *87*(1), 4-14.

Singla, R., Khan, N., Al-Sharif, N., Al-Sayegh, M. O., Shaikh, M. A., & Osman, M. M. (2006). Influence of diabetes on manifestations and treatment outcome of pulmonary TB patients. *International Journal of Tuberculosis and Lung Disease*, *10*(1), 74–79.

Smith, I. (2003). *Mycobacterium tuberculosis* pathogenesis and molecular determinants of virulence. *Clinical Microbiology Reviews*, *16*(3), 463–496. https://doi.org/10.1128/CMR.16.3.463

Stalenhoef, J. E., Alisjahbana, B., Nelwan, E. J., Van Der Ven-Jongekrijg, J., Ottenhoff, T. H. M., Van Der Meer, J. W. M., … Van Crevel, R. (2008). The role of interferon-gamma in the increased tuberculosis risk in type 2 diabetes mellitus. *European Journal of Clinical Microbiology and Infectious Diseases*, *27*(2), 97–103. https://doi.org/10.1007/s10096-007-0395-0

Sulaiman, S. A. S., Khan, A. H., Muttalif, A. R., Hassali, M. A., Ahmad, N., & Iqubal, M. S. (2013). Impact of diabetes mellitus on treatment outcomes of tuberculosis patients in tertiary care setup. *The American Journal of the Medical Sciences*, *345*(4), 321–5. https://doi.org/10.1097/MAJ.0b013e318288f8f3

Suwanpimolkul, G., Grinsdale, J. A., Jarlsberg, L. G., Higashi, J., Osmond, D. H., Hopewell, P. C., & Kato-Maeda, M. (2014). Association between diabetes mellitus and tuberculosis in United States-born and foreign-born populations in San Francisco. PloS one, 9(12), e114442.

Swarna, N. Y. (2014). A review of tuberculosis research in malaysia. *Medical Journal of Malaysia*, *69*(August), 88–102.

Syed Suleiman, S. A., Ishaq Aweis, D. M., Mohamed, A. J., RazakMuttalif, A., & Moussa, M. A. A. (2012). Role of Diabetes in the Prognosis and Therapeutic Outcome of Tuberculosis. *International Journal of Endocrinology*, *2012*, 1–6. https://doi.org/10.1155/2012/645362

Thapa, B., Paudel, R., Thapa, P., Shrestha, A., & Poudyal, A. K. (2016). Prevalence of diabetes among tuberculosis patients and associated risk factors in Kathmandu valley. SAARC Journal of Tuberculosis, Lung Diseases and HIV/AIDS, 12(2), 20-27.

Tiroro, S. (2015). College Of Health Sciences School Of Public Health (Doctoral Dissertation, School Of Graduate Studies, College Of Health Science, School Of Public Health, Addis Ababa University).

Tuberculosis (TB) Disease: Symptoms & Risk Factors | Features | CDC. (2016). Retrieved November 11, 2016, from http://www.cdc.gov/features/tbsymptoms/

Venugopalan, B. (2004). An Evaluation of the Tuberculosis Control Programme of Selangor State, Malaysia for the Year 2001. *Med J Malaysia*, *59*(1).

Verdecchia, P., Staessen, J. A., Angeli, F., De Simone, G., Achilli, A., Ganau, A., ... & Reboldi, G. (2009). Usual versus tight control of systolic blood pressure in non-diabetic patients with hypertension (Cardio-Sis): an open-label randomised trial. The Lancet, 374(9689), 525-533.

Viswanathan, V., Kumpatla, S., Aravindalochanan, V., Rajan, R., Chinnasamy, C., Srinivasan, R., ... & Kapur, A. (2012). Prevalence of diabetes and pre-diabetes and associated risk factors among tuberculosis patients in India. *PloS one*, *7*(7), e41367.

Wang, C. S., Yang, C. J., Chen, H. C., Chuang, S. H., Chong, I. W., Hwang, J. J., & Huang, M. S. (2009). Impact of type 2 diabetes on manifestations and treatment outcome of pulmonary tuberculosis. *Epidemiology and Infection*, *137*(2), 203. https://doi.org/10.1017/S0950268808000782

Wang, J.-Y., Lee, L.-N., & Hsueh, P.-R. (2005). Factors changing the manifestation of pulmonary tuberculosis.

Wang, Q., Ma, A., Han, X., Zhao, S., Cai, J., Ma, Y., ... & Wei, L. (2013). Prevalence of type 2 diabetes among newly detected pulmonary tuberculosis patients in China: a community based cohort study. PloS one, 8(12), e82660.

WHO. (2016). The End TB Strategy is not a one size fits all; approach and its success depends on adaptation for diverse country settings. Adaptation of the strategy and targets at country level, with global collaboration.

Wolden-Kirk, H., Overbergh, L., Christesen, H. T., Brusgaard, K., & Mathieu, C. (2011). Vitamin D and diabetes: its importance for beta cell and immune function. Molecular and cellular endocrinology, 347(1), 106-120.

Workneh, M. H., Bjune, G. A., & Yimer, S. A. (2016). Prevalence and Associated Factors of Diabetes Mellitus among Tuberculosis Patients in South-Eastern Amhara Region, Ethiopia: A Cross Sectional Study. *PloS One*, *11*(1), e0147621. https://doi.org/10.1371/journal.pone.0147621

Workneh, M. H., Bjune, G. A., & Yimer, S. A. (2017). Prevalence and associated factors of tuberculosis and diabetes mellitus comorbidity: A systematic review. PloS one, 12(4), e0175925.

World Health Organization. (2016). Global Report on Diabetes. *Isbn*, *978*, 88. https://doi.org/ISBN 978 92 4 156525 7

World Health Organization. (2015). *Global status report on noncommunicable diseases 2015*. Geneva: World Health Organization.

Yu, Y. H., Liao, C. C., Hsu, W. H., Chen, H. J., Liao, W. C., Muo, C. H., ... & Chen, C. Y. (2011). Increased lung cancer risk among patients with pulmonary tuberculosis: a population cohort study. Journal of Thoracic Oncology, 6(1), 32-37.

Zumla, A., Atun, R., Maeurer, M., Mwaba, P., Ma, Z., O'Grady, J., … Grange, J. (2011). Viewpoint: Scientific dogmas, paradoxes and mysteries of latent Mycobacterium tuberculosis infection. *Tropical Medicine and International Health*, *16*(1), 79–83. https://doi.org/10.1111/j.1365-3156.2010.02665.x