West African Journal of Pharmacy (2016) 27 (2) 111-119

Short Communication

Treatment outcomes of tuberculosis patients with diabetes mellitus in a secondary health facility in Lagos Nigeria.

Foluke Ayeni[1], Bolajoko Aina[1], Olubukola Oyetunde[1], Olusola Adejumo[2].

[1]Department of Clinical Pharmacy and Biopharmacy, Faculty of Pharmacy, University of Lagos, Idi Araba Campus, Lagos State, Nigeria.

[2]Department of Community Health and Primary Health Care, Lagos State University Teaching Hospital, Ikeja, Lagos, Nigeria

Corresponding Author: Foluke Ayeni
E-mail address: folukeayeni@live.com Phone : +234-8075614126

ABSTRACT

Background: The presence of diabetes mellitus (DM) has been shown by a growing body of evidence to be a risk factor for tuberculosis (TB) and co-infected patients may show poor response to TB treatment as both diseases interact negatively.

Objectives: This study is aimed at determining associated factors and comparing the treatment outcomes of TB patients living with and without DM in a secondary care TB treatment facility in Lagos state, Nigeria.

Methods: A retrospective review of patients records above 18 years' enrolled between 1st January 2011 and 31st December 2012 in a secondary care TB treatment facility in Lagos state was carried out.

Results: A total of 424 records of TB patients were reviewed, out of which 36 (8.5%) had DM. Mean age of TBDM patients (50.0±12.8) was higher than for TB-only patients (34.1±13.8). Male: Female ratio of TBDM and TB only patients was comparable. All TBDM patients had pulmonary TB. Of these, proportion of smear negativity (72.2%) was significantly higher than TB only patients (34.9%, $p < 0.001$). More TBDM patients (38.9%) compared to TB only patients (20.6%) had poor treatment outcomes ($p = 0.012$).

Conclusion: The prevalence of TBDM was substantial and it was associated with advanced age, smear negative sputum result and poor treatment outcomes. Concurrent management of both diseases should be considered to improve treatment outcomes.

Key Words: Tuberculosis, Diabetes Mellitus, Treatment outcomes, Lagos, Nigeria

Résultats de traitement des patients tuberculeux atteints de diabète sucré dans un établissement de santé secondaire à Lagos au Nigeria

Auteur de correspondance: Foluke Ayeni
E-mail: folukeayeni@live.com Téléphone : +234-8075614126

RESUME

Contexte: La présence de diabète sucré (DM) a été démontrée par un nombre croissant de preuves comme un facteur de risque de tuberculose (TB) et les patients co-infectés peuvent montrer une mauvaise réponse au traitement de la tuberculose, car les deux maladies interagissent négativement.

Objectifs: Cette étude vise à déterminer les à comparer les Résultats de traitement des patients tuberculeux vivant avec ou sans diabète dans un établissement de soins secondaires pour le traitement de la tuberculose dans l'État de Lagos, au Nigeria.

Méthodes: Un examen rétrospectif des dossiers des patients âgés de plus de 18 ans inscrits entre le 1er janvier 2011 et le 31 décembre 2012 dans un établissement de traitement secondaire de la tuberculose dans l'état de Lagos a été effectué.

Résultats: Un total de 424 dossiers de patients tuberculeux ont été examinés, parmi lesquels 36 (8,5%) avaient le diabète. L'âge moyen des patients tuberculeux et diabétiques (50,0 ± 12,8) était supérieur à celui des patients atteints uniquement de la tuberculose (34,1 ± 13,8). Le rapport hommes/femmes des patients atteints deux maladies (tuberculose et diabète) et ceux atteints de la tuberculose seulement était comparable. Tous les patients tuberculeux et diabétiques avaient une tuberculose pulmonaire. Parmi ceux-ci, la proportion de négativité de frottis (72,2%) était significativement plus élevée que celle de patients atteints de tuberculose seulement (34,9%, p <0,001). Plus de patients tuberculeux et diabétiques (38,9%) que de patients tuberculeux seulement (20,6%) avaient des Résultats médiocres (p = 0,012).

Conclusion: La prévalence de la tuberculose et du diabète était importante et elle était associée à l'âge avancé, au frottis négatif du crachat et à des Résultats médiocres du traitement. La prise en charge simultanée des deux maladies devrait être envisagée pour améliorer les Résultats du traitement.

Mots-clés: Tuberculose, Diabète sucré, Résultats du traitement, Lagos, Nigéria

INTRODUCTION

Tuberculosis (TB) is considered the leading killer among bacterial diseases worldwide and approximately one-third of the world's population are infected with Mycobacterium tuberculosis.[1.] In 2012, almost 9 million new cases were diagnosed globally and 1.3 million people died from the disease.[2.]

Much has been documented about the association between tuberculosis and diabetes mellitus (DM), from the early reports by Avicenna over one thousand years ago[3] to more recent epidemiological studies including a systematic review which investigated the relationship between TB and DM, and showed that the risk of developing TB among people living with DM was three times higher than in people living without DM.[4] Other studies also reported the association between DM and TB, showing the proportion of TB cases attributable to DM to be between 5% and 30% depending on the prevalence of DM in the region.[5-10]

The highest burden of TB, (about 80% of global TB cases), are borne by 22 high TB burden countries (HBCs), mostly in low and middle income countries in Asia and Africa, and over 95% of TB deaths occur in these countries. These are developing countries where about 80% of diabetic patients also live.[1,7] Nigeria is currently ranked 4th among the 22 highest-burdened TB countries in the world with an estimated incidence of 590 cases per 100 000 population.[11] The prevalence of DM among TB patients Nigeria has been recently reported to be 5.7%.[12]

The International Diabetes Federation (IDF) has predicted that the global prevalence of DM will increase to about 552 million by the year 2030, from 382 million in 2013. It also predicted that the number of individuals with DM in Nigeria will increase from about 3 million in 2011 to over 6 million people by 2030.[1,13] This anticipated increase may increase the prevalence of TB infections.

Both diseases interact at multiple levels, each exacerbating and worsening the outcomes of the other.[8,14] Diabetes mellitus has been associated with higher risks of TB treatment failure or relapse, poor culture conversion rates and death.[15-19] A decrease in both cell mediated immunity and activation of alveolar macrophages are thought to play a key role in the occurrence of TB, especially the development of pulmonary TB as against extra-pulmonary TB, in patients with diabetes mellitus.[4,15,20]

Studies have shown that tuberculosis patients living with diabetes (TBDM patients) may show poor response to TB treatment and are more likely to develop MDR-TB.[17,20] They are also prone to poly-pharmacy, poor treatment adherence and poor treatment outcomes.[8]

In Nigeria, the management of TB is carried out under directly observed treatment, short course (DOTS) treatment, which is largely under the care of physicians, nurses and community health workers. Pharmacists are not directly involved in TB patient's care. The roles of pharmacists however has evolved from product oriented, dispensing of medications to more patient focused services. These services include the provision of pharmaceutical care, which in turn includes the identification, prevention and resolution of drug-related problems (DRPs) in patients, as well as educating the patient about their disease to encourage compliance and monitoring patient medications throughout their treatment.[21] Pharmaceutical care (PC) programs developed and implemented by pharmacists have been found to be useful in improving treatment outcomes and the quality of care of both ambulatory and hospitalized patients, and can produce improved treatment outcomes for patients with chronic and acute diseases.

The link between TB and DM, and the effect of DM on TB treatment outcomes in Nigeria has not been extensively studied. Two studies have reported the prevalence of diabetes mellitus among tuberculosis patients in Lagos state, but to our knowledge, no study has reported the prevalence of prediabetes or the effect of DM on TB treatment outcomes, or the role pharmacists can play in the interdisciplinary care of TB patients with co-morbidities.[21] It can be hypothesized that developing collaborative care and management of both the TB and DM patients might resolve some of the adverse treatment outcomes currently being experienced by TBDM patients, leading to better treatment outcomes.

This study therefore retrospectively compared the treatment outcomes of TB patients living with and without DM in a secondary care TB treatment facility in Lagos state, Nigeria.

METHODS

Study design

A retrospective review of records of 424 patients above 18 years' enrolled between 1st January 2011 and 31st December 2012 in a secondary care TB treatment facility in Lagos state was carried out using random sampling. Patients with TB and human immunodeficiency virus (HIV), hepatitis B, C or both, cancer and patients with incomplete medical record were excluded from the study. This study is part of an ongoing study to determine the impact of concurrent DM management on TB treatment outcomes.

Study setting

This study was carried out at the directly observed treatment short course (DOTS) clinic of a secondary chest care clinic in Lagos state. Lagos state is located in the South western part of Nigeria and has a population of about 21 million people with a total of 20 local government areas (LGAs) and 37 local council development areas established in the state. TB control in Lagos State is coordinated by the Lagos State TB and Leprosy Control Programme (LSTBLCP).

The study facility serves as a TB referral centre for individuals suspected to be infected with TB, multi drug resistant TB and human immune deficiency virus (HIV) infection. In Nigeria, Lagos State where this study is located, accounts for 8.4% of Nigeria's TB burden and consistently has been responsible for about 11% of the cases of TB registered in Nigeria.[22]

TB control in Lagos state

The DOTS management of TB started in Lagos State in 2003. At the end of 2011, The LSTBLCP had 317 DOTS facilities. There were 214 public and 103 private health care facilities {89 Private for Profit (PFP) and 14 Private Not for Profit (PNFP)}DOTs facilities. Treatment of TB is free in the state; however patients managed at the private DOTS facilities are charged for consultation and laboratory tests. Those managed at the public DOTS facilities were also required to pay for any other laboratory tests apart from sputum AFB and Gene-Xpert tests. Treatment duration is six months and the treatment regimen consists of two months intensive phase of Rifampicin, Isoniazid, Pyrazinamide and Ethambutol as fixed dose combination and four months continuation phase of Rifampicin and Isoniazid as fixed dose combination.

Definition of outcome variables:

Cure: This is the proportion of patients among smear positive patients who complete treatment and had at least two negative smears with an interval of at least one month, one of which should be obtained at the end of treatment.

Treatment completed: This is the proportion of patients that completed treatment but whose sputum examination results were not available.

Died: The proportion of patients that died before completion of treatment.

Default: This is the proportion of patients that did not take drugs for two consecutive months or more.

Treatment failure: This is the proportion of patients who are still sputum smear positive at five months or more after the commencement of chemotherapy, or who stopped treatment for more than 2 months after completing one month of chemotherapy, thereafter returned to treatment and wre found to be smear positive

Transferred out: This is the proportion recorded that moved out of the health facility catchment area.

Treatment success: Defined as the sum of the cases that were cured and that completed treatment.

Classification of diabetes

Patients were classified as diabetic either on self-report or documented result of a fasting blood sugar above 126mg/dl or both

Data analysis

Data obtained were analysed using IBM Statistical Package for Social Sciences (SPSS) version 20.0. Descriptive statistics such as percentages and proportions were used for categorical variables. Chi square and Fishers exact test were used to compare categorical variables as the case may be. The confidence interval was set at 95% for all statistical tests.

Ethical approval

The study was approved by the health research ethics committee of the Lagos University Teaching Hospital (ADM/DCST/HREC/APP/665)

RESULTS

A total of 424 records of TB patients were reviewed in this study, out of which 36 (8.5%) had DM.

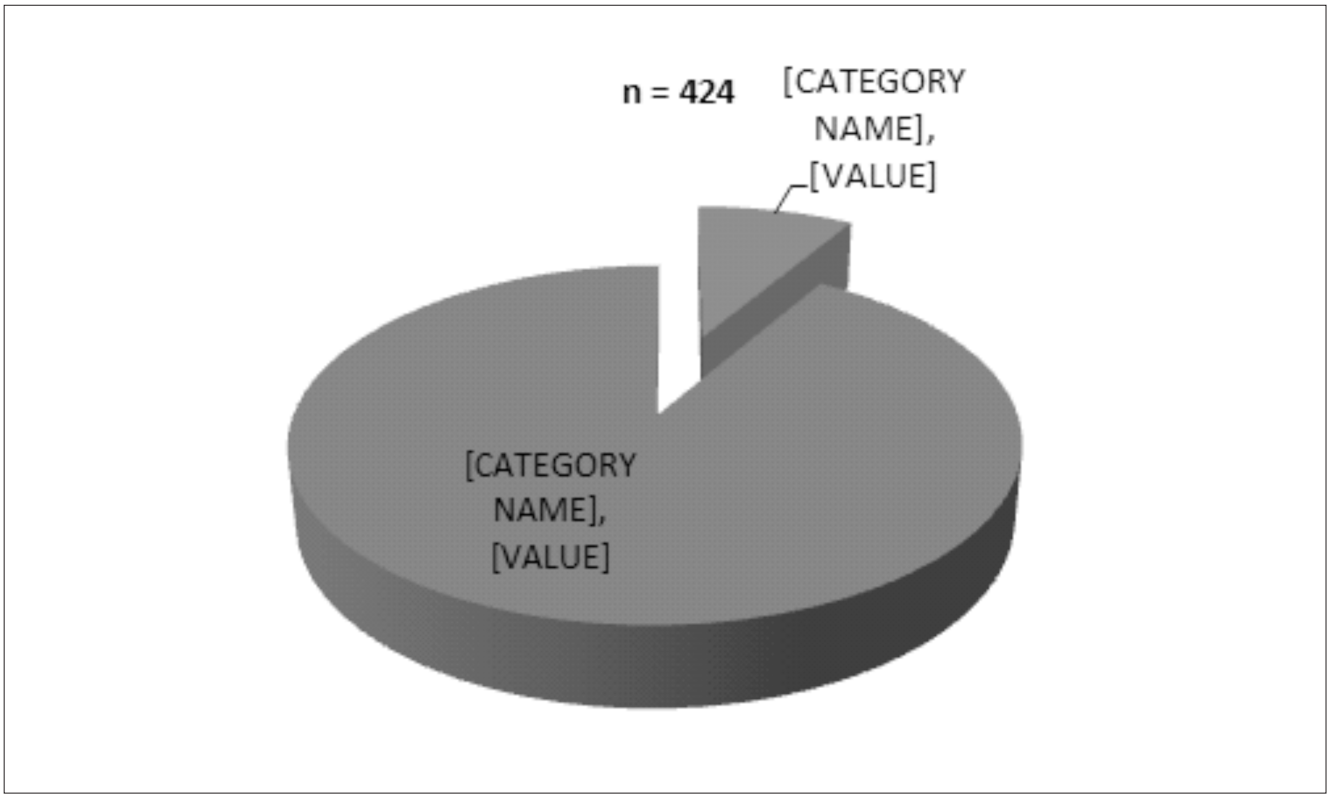

Fig I: Prevalence of TB/DM

The mean age of TBDM patients (50.0±12.8) was higher than that of TB-only patients (34.1±13.8), $p < 0.001$. Male: Female ratio of TBDM and TB only patients was comparable. A significantly higher proportion of TBDM patients (100%) as against 76.8% of TB only patients were new cases ($p <0.001$). In addition, more (100%) of the TBDM patients compared to the TB only patients (97.4%) had pulmonary TB. Of those that had pulmonary TB, the proportion of TBDM patients that were smear negative (72.2%) at treatment initiation was significantly higher than TB only patients (34.9%, $p <0.001$). More TBDM patients (38.9%) compared to TB only patients (20.6%) had poor treatment outcomes ($p = 0.012$) as shown in Table I.

Table 1: Socio demographic characteristics & clinical details of TB/DM and TB patients

Variables	TB/DM n = 36 (%)	TB n = 388 (%)	x2	p
Age group (years)				
< 30	4 (11.1)	176 (45.4)	15.818	<0.001
>30	32 (88.9)	212 (54.6)		
Mean±SD	50.0±12.8	34.1±13.8		
Gender				
Male	22 (61.1)	250 (64.4)	0.158	0.691
Female	14 (38.9)	138 (35.6)		
Treatment category				
New	36 (100.0)	298 (76.8)	10.601	<0.001
Retreatment cases	0 (0.0)	90 (23.2)		
Disease location				
Pulmonary	36 (100.0)	378 (97.4)	0.950	0.330
Extra-pulmonary	0 (0.0)	10 (2.6)		
Treatment success				
No	14 (38.9)	80 (20.6)	6.373	0.012
Yes	22 (61.1)	308 (79.4)		
Smear results	n = 36	n = 378		
Positive	10 (27.8)	246 (65.1)	19.38	<0.001
Negative	26 (72.2)	132 (34.9)		

Table 2 compares the treatment outcomes of TBDM and TB only patients. A total of 330 patients had good treatment outcomes, while 94 had poor outcomes. Of those that had poor treatment outcomes a higher proportion of TB patients defaulted compared to TBDM patients, while a higher proportion of TBDM patients died compared to TB only patients. There were no treatment failure and transfers among TBDM patients.

Table 2: Treatment outcomes of TBDM and TB patients

Treatment outcomes	TBDM n = 36(%)	TB n = 388 (%)	p
Good treatment outcome			
Cured	6 (16.7)	164 (42.3)	0.003
Treatment completed	26 (72.2)	134 (34.5)	<0.001
Poor treatment outcome			
Defaulted	2 (5.6)	72 (18.6)	0.049
Died	2 (5.6)	6 (1.5)	0.142*
Treatment failure	0 (0.0)	10 (2.6)	
Transferred out	0 (0.0)	2 (0.5)	

NB * = Fishers exact test

DISCUSSION

Prevalence of TBDM

DM is increasing globally, especially in developing countries.[4] The prevalence of DM in TB patients in this study was 8.5%. This is higher than that reported in a study from a tertiary hospital in Lagos Nigeria[12] but lower than 12.3% reported in a population based study in the state.[23] The reason for this finding is unknown but the prevalence of DM in TB patients in this study was within the predicted range of 5%-30% reported in a systematic review based on the prevalence of DM in any region.[8]

Association between TBDM and treatment outcomes

TBDM patients have been reported to be associated with poorer treatment outcomes compared to those with TB only.[18] No study in Nigeria has compared the treatment outcomes of TBDM and TB patients before now. In this study, the treatment success of TBDM patients was significantly lower than for TB patients only (p = 0.012). Also, the treatment success rates in both groups were far lower than WHO targets for TB control.[24] Poor treatment outcomes can increase the rate of transmission of TB in the community. Similar findings were obtained in studies from Taiwan, Maryland and Indonesia[14, 15 & 17] where DM was associated with poorer treatment outcomes. However, studies from Saudi Arabia, Thailand and Malaysia reported comparable treatment outcomes between patients with TBDM and TB only.[9, 12 & 26.]

Other associated factors with TBDM

This study shows that TBDM patients were significantly older than TB only patients. Similar association between older age and presence of TB-DM has been observed in studies from Saudi Arabia and Malaysia.[9, 24 & 26] This may be because there is an increased risk of developing DM in older age.[27] In addition, compromised hosts have increased susceptibility due to aging, or changes in the dietary life and social life.[26]

DM also plays an important role in the development of TB.[28] The risk of developing TB in DM patients ranged between 5 – 26 times higher than the general population depending on whether it is non-insulin dependent diabetes mellitus (NIDDM) or insulin dependent diabetes mellitus (IDDM).[29, 30] In this study, a higher proportion of TBDM patients had pulmonary TB than patients with TB alone, which is supported by findings in other studies.[26, 28] This finding is similar to what was reported in a study from Malaysia where pulmonary TB was twice as prevalent in TBDM patients than extra-pulmonary TB.[25] Other studies from Nepal and India also reported an association between DM and pulmonary TB.[31, 32] However, no such association was reported in a study from Turkey.[33] The association between DM and pulmonary TB may be because of increased susceptibility of DM patients to certain respiratory tract infections.[34]

In this study, a higher proportion of TBDM patients were sputum smear negative at treatment initiation. The reason for this is not clear. This is contrary to previous studies which reported the association of TB patients with DM and higher smear positivity than patients with TB only[8, 15] and also to another study where sputum smear results showed that DM was an independent risk factor associated with numerous AFB on sputum smear examinations.[9] It was also suggested that immune

suppression induced by DM may increase the bacillary load in TB patients with DM.[9]

CONCLUSION

The prevalence of TBDM in this study was high and it was associated with advanced age, smear negative sputum result and poor treatment outcomes. The need to institute public health measures to reduce the incidence of TB and DM in Lagos Nigeria and also institute concurrent management for TB patients with DM cannot be overemphasized.

This study was a retrospective review of patient record and might be limited in not considering other factors that could be associated with patient's clinical parameters and treatment Success, risks factors for TB and DM, time to sputum conversion and adverse drug reactions as these were not consistently recorded. These factors are possible confounders for our result. The study was also a one-centre study, so it might not be representative of what obtains in the general population.

ACKNOWLEDGMENTS

The authors wish to acknowledge all medical personnel of the facility where this study was carried out for their support. The research was self-funded and the authors declare no conflict of interest.

REFERENCES

1. Tuberculosis & Diabetes Factsheet. The growing threat of the double burden of diabetes and tuberculosis.*http://www.worlddiabetesfoundation.org/sites/default/files/TB-diabetes%20coepidemic%20fact%20sheet_March2014%20update.pdf* 2014 (accessed 16.03.02).
2. World Health Organization, Global Tuberculosis Report, (2013) 1–98. doi:978 92 4 156450 2.
3. Baghaei, P., Marjani, M., Javanmard, P., Tabarsi, P., & Masjedi, MR. (2013). Diabetes mellitus and tuberculosis facts and controversies. *Journal of Diabetes & Metabolic Disorders*, *12*(1), 1.
4. Jeon CY, Murray MB (2008) Diabetes mellitus increases the risk of active tuberculosis: A systematic review of 13 observational studies. *PLOS Medicine* 5(7): e152. doi:10.1371
5. Alisjahbana B, Van Crevel R, Sahiratmadja E, Den Heijer M, Maya A, Istriana E, Danusantoso H, Ottenhoff TH, Nelwan RH, van der Meer JW (2006): Diabetes mellitus is strongly associated with tuberculosis in Indonesia. *International Journal of Tuberculosis and Lung Disease*, 10(6):696–700.
6. Pablos-Mendez A, Blustein J, Knirsch CA (1997): The role of diabetes mellitus in the higher prevalence of tuberculosis among Hispanics. *American Journal of Public Health*, 87(4):574–579.
7. Stevenson CR, Forouhi NG, Roglic G, Williams BG, Lauer JA, Dye C, Unwin N (2007). Diabetes and tuberculosis: the impact of the diabetes epidemic on tuberculosis incidence. *BioMed Central Public Health*. 7, 234. doi:10.1186/1471-2458-7-234.
8. Ruslami R, Aarnoutse RE, Alisjahbana B, van der Ven AJ, Van Crevel R (2010): Implications of the global increase of diabetes for tuberculosis control and patient care. *Tropical Medicine & International Health* 2010,15(11):1289–1299.
9. Singla R, Khan N, Al-Sharif N, Ai-Sayegh MO, Shaikh MA, Osman MM (2006): Influence of diabetes on manifestations and treatment outcome of pulmonary TB patients. *International Journal of Tuberculosis and Lung Disease*, 10(1):74–79
10. Restrepo BI, Camerlin AJ, Rahbar MH, Wang W, Restrepo MA, Zarate I, Mora-Guzman F, Crespo-Solis JG, Briggs J, McCormick JB, Fisher-Hoch SP(2011). Cross-sectional assessment reveals high diabetes prevalence among newly-diagnosed tuberculosis cases, *Bulletin of the World Health Organization*. 89:352–359. doi:10.2471/BLT.10.085738.
11. World Health Organization, Global Tuberculosis Report, (2015) 1-204. doi: 978 92 4 156505 9
12. Olayinka AO, Anthonia O, Yetunde K. (2013) Prevalence of diabetes mellitus in persons with tuberculosis in a tertiary health centre in Lagos Nigeria. *Indian Journal of Endocrinology and Metabolism;*17:486−9
13. Whiting DR, Guariguata L, Weil C, Shaw J (2011). IDF Diabetes Atlas: Global estimates of the prevalence of diabetes for 2011 and 2030, *Diabetes research and clinical practice* 94, 311-321.
14. Niazi AK, Kalra S (2012). Diabetes and tuberculosis: a review of the role of optimal glycemic control, *Journal of Diabetes & Metabolic Disorders*. 11: 28. doi:10.1186/2251-6581-11-28.
15. Duangrithi D, Thanachartwet V, Desakorn V, Jitruckthai P, Phojanamongkolkij K, Rienthong S, Chuchottaworn C, Pitisuttithum P (2013). Impact of diabetes mellitus on clinical parameters and treatment outcomes of newly diagnosed pulmonary tuberculosis patients in Thailand. *International Journal of Clinical Practice*67:

1199–1209. doi:10.1111/ijcp.12215.
16. Wang CS, Yang CJ, Chen HC, Chuang SH, Chong IW, Hwang and Huang MS (2009). Impact of type 2 diabetes on manifestations and treatment outcome of pulmonary tuberculosis. *Epidemiology and Infection,* 137, pp 203-210. doi:10.1017/S0950268808000782.
17. Dooley KE, Tang T, Golub JE, Dorman SE, Cronin W (2009). Impact of diabetes mellitus on treatment outcomes of patients with active tuberculosis. *American Journal of Tropical Medicine and Hygiene.* 80:634–9. doi:19346391.
18. Baker MA, Harries AD, Jeon CY, Hart JE, Kapur A, Lönnroth K, Ottmani SE, Goonesekera SD, Murray MB (2011). The impact of diabetes on tuberculosis treatment outcomes: a systematic review*. BioMed Central Medicine.* 9: 81. doi:10.1186/1741-7015-9-81.
19. Alisjahbana B, Sahiratmadja E, Nelwan EJ, Purwa AM, Ahmad Y, Ottenhoff THM, Nelwan RHH, Parwati I, Van der Meer JWM, Van Crevel R (2007). The effect of type 2 diabetes mellitus on the presentation and treatment response of pulmonary tuberculosis. *Clinical Infectious Diseases* 45 428–35. doi:10.1086/519841.
20. Dooley KE, Chaisson RE (2009). Tuberculosis and diabetes mellitus: convergence of two epidemics. *The Lancet Infectious Diseases* 9:737–746.
21. Chua SS, Kok LC, Yusof FAM, Tang GH, Huey Lee, Efendie B, Paraidathathu T (2012). Pharmaceutical care issues identified by pharmacists in patients with diabetes, hypertension or hyperlipidaemia in primary care settings. *BioMed Central Health Services Research* 12:388
22. World Health Organization, Tuberculosis: Fact sheet N°104. http://www.who.int/mediacentre/factsheets/fs104/en/#, (2010) (accessed 16.05.01).
23. Ogbera AO, Kapur A, Chinenye S, Fasanmade 0, Uloko A, Odeyemi K (2014). Undiagnosed diabetes mellitus in tuberculosis: A Lagos report. *Indian Journal of Endocrinology and Metabolism*. 18:475–9. doi:10.4103/2230-8210.137488.
24. WHO. 44th World Health Assembly: resolutions and decisions—resolution WHA 44.8 (WHA44/1991/REC/1). World Health Organization, Geneva; 1991.
25. Sulaiman SAS, Khan AH, Ahmad N, Iqubal MS, Muttalif AR, & Hassali MA (2013). Impact of diabetes mellitus on treatment outcomes of tuberculosis patients in tertiary care setup. *American Journal of the Medical Sciences.* 345(4), 321-325. doi:10.1097/MAJ.0b013e318288f8f3.
26. Nissapatorn V1, Kuppusamy I, Jamaiah I, Fong MY, Rohela M, Anuar AK (2005). Tuberculosis in diabetic patients: a clinical perspective. *Southeast Asian Journal of Tropical Medicine and Public Health*. 36 Suppl 4 (2005) 213–220.
27. Morley JE (1998). The elderly type 2 diabetic patient: special considerations. *Diabetic Medicine* 15:41–46.
28. Yamagishi F, Sasaki Y, Yagi T, Yamatani H, Kuroda F, Shoda H (2000). Frequency of complication of diabetes mellitus in pulmonary tuberculosis. *Kekkaku* 75:435-7
29. Kim SJ, Hong YP, Lew WJ, Yang SC, Lee EG (1995). Incidence of pulmonary tuberculosis among diabetics. *Tubercle and Lung Disease 76:* 529-533.
30. Feleke Y, Abdulkadir J, Aderaye G (1999). Prevalence and clinical features of tuberculosis in Ethiopian diabetic patients. *East African medical journal 76:* 361-364.
31. Sreeramareddy CT, Panduru KV, Verma SC, Joshi HS, Bates MN (2008). Comparison of pulmonary and extrapulmonary tuberculosis in Nepal- a hospital-based retrospective study. *BioMed Central Infectious Diseases* 7: 1–7. doi:10.1186/1471-2334-8-8.
32. Shetty N, Shemko M, Vaz M, D'Souza G (2006). An epidemiological evaluation of risk factors for tuberculosis in South India: a matched case control study. *International Journal of Tuberculosis and Lung Disease.* 10:80–86. doi:16466042.
33. Musellim B, Erturan S, Duman ES, Ongen G (2005). Comparison of extra-pulmonary and pulmonary tuberculosis cases: Factors influencing the site of reactivation. *International Journal of Tuberculosis and Lung Disease* 9:1220–1223.
34. Joshi N, Caputo GM, Weitekamp MR, Karchmer AW (1999). Infections in patients with diabetes mellitus. *New England Journal of Medicine.* 341: 1906-1912.