Latent Mycobacterium tuberculosis infection among Type 2 Diabetes Mellitus Patients

O.O. Adewole[1], O, Kayode[1], O. Abe[1], H.A Oshokoya [3], B.A. Kolawole[1], R.T. Ikem[1], T.O. Adewole[4], G. E. Erhabor[1]

1. Department of Medicine, Obafemi Awolowo University/Teaching Hospitals, Ile Ife
2. Department of Medicine, Specialist Hospital ,Akure,
3. Department of Microbiology, Obafemi Awolowo University, Ile Ife.
4. Department of Family Medicine, Obafemi Awolowo University Teaching Hospitals, Ile Ife

Background: There is dearth of data on the prevalence of latent tuberculosis infection among diabetic patients.
Objective: To determine prevalence and predictors of latent tuberculosis infection among diabetic patients .
Methods: Type 2 diabetic patients attending medical outpatient clinic in a Specialist Hospital in Nigeria and apparently healthy controls matched for age and sex were recruited. Socio demographic and clinical data were obtained through a pro forma. Blood specimen collected into the QuantiFERON tubes for measurement of interferon gamma were processed , analysed and read according to the manufacturers' instruction. Glycosylated haemoglobin and total cholesterol done within the preceding month were recorded.
Results: Sixty type 2 diabetic patients and 60 controls similar in age , sex and social class distribution were recruited. Mean interferon gamma was significantly higher among diabetic patients compared with control,(0.36+ 0.24IU/ml and 0.19+ 0.02IU/ml, p value < 0.05). Twenty two(37%) and 11(20%) type 2 diabetic patients and control had positive QuantiFERON results respectively ,p value =0.002. Latent tuberculosis infection in DM patients was associated with degree of glyceamic control and smoking, p value was less than 0.05 each .
Conclusion: The prevalence of latent tuberculosis infection is high among type 2 diabetic patients.

Corresponding author: Dr. O.O Adewole , Department of Medicine, Obafemi Awolowo University/Teaching Hospital, Ile Ife, Nigeria. E mail: adewolef@yahoo.co.uk
Running title: Latent TB T2DM in Nigeria

INTRODUCTION

Tuberculosis (TB) continues to be a public health problem worldwide . It is one of the most important causes of death from infectious diseases. [1] In 2012, an estimated 8.6 million people developed TB and 1.3 million died from the disease.1 Nigeria ranks eleventh among the 22 high –burden TB countries in the world with about 108,000 to 186,000 incident cases in 2012.[1] Transmission occurs by inhalation of droplets containing the bacilli from infectious individuals, usually those with pulmonary diseases. Only 5%–10% of infected individuals develop active TB, while the remaining individuals may harbour the tubercle bacilli in a non infectious and dormant state termed latent tuberculosis infection (LTBI).TB is fuelled by several social and economic factors, such as poverty or malnutrition as well as other infectious diseases, such as HIV and non communicable diseases like diabetes.

In recent years, there has been a increased interest between TB and diabetes mellitus. That link had been suspected for centuries.[3] Many studies now show that diabetes may be associated with an increased risk of developing active TB. [4,5] Several recent publications have described the association between diabetes and TB, specifically the increased prevalence of active TB among patients with diabetes and the poorer treatment outcomes in these patients when compared with those without diabetes.[6,7] A recent systematic review of 13 studies reported that diabetic patients had about 3-fold increased risk of developing TB when compared to those without diabetes. [9]

Others studies have reported poorer treatment outcomes in patients with diabetes and TB, including a higher risk of death and treatment failure [7,8] One prospective study examined sputum cultures at the completion of 6 months of TB treatment, finding positive cultures in 22.2% of patients with diabetes and 6.9% of those without diabetes.[6] Another systematic review of treatment outcomes by Baker et al described a relative risk of

death of 1.89 among TB patients with diabetes when compared to non-diabetic patients.8 After controlling for potential confounders, the pooled risk of death among TB patients with diabetes was nearly five times greater than in those without diabetes.[8] Diabetics therefore constitute an important target group in whom the detection of LTBI and its treatment may potentially be an important strategy for tuberculosis control and elimination.

However, the development of active TB is preceded by LTBI. Despite the data available on interaction between DM and active TB, there has been scarcity of data on the LTBI rate among DM patients. Until recently the most common test to detect LTBI is the tuberculin skin test (TST). [10]The test consists of measuring the delayed-type hypersensitivity reaction to purified protein derivate (PPD). However, this test has a low specificity due to the possibility of cross-reactivity to Bacillus Calmette-Guérin (BCG) or exposure to non-tuberculous mycobacterial strains from the environment . [10,11] Detection of surrogate markers that allow the diagnosis of infection has been pursued and now a new sensitive and more specific test for LTBI known as interferon-gamma release assay (IGRA) is available . [12,13]
There are two main forms of IGRAs, QuantiFERON-TB Gold in-tube (QFT-IT)(Cellestis Ltd, Victoria, Australia) and T-SPOT.TB (Oxford Immunotec, Oxfordshire, United Kingdom). Both tests evaluate the T-cell response to MTB antigens, including ESAT-6, CFP-10, and TB7.7. QFT-IT uses whole-blood for detection of IFN-γ by enzyme-linked immunosorbent assay, while T-SPOT.TB uses an enzyme- linked immunospot (ELISPOT) assay to detect IFN-γ by peripheral blood mononuclear cells. The performance of QFT-IT have been previously studied among TB cases in Nigeria.[14]

The aim of this current study is to determine the prevalence of latent tuberculosis in patients with type 2 diabetes mellitus with QuantiFERON TB-Gold in tube test.

The study was done at the Medical Outpatient Patient Clinic , State Specialist Hospital , Akure, Nigeria. Sixty previously diagnosed type 2 DM patients who were attending the medical outpatients clinic and apparently healthy individuals who do not have DM, or active TB were consecutively recruited. The controls were matched in age, sex and other socio-demographic parameters with the cases. The controls were individuals working in the hospital or around the hospital who responded to calls for volunteer for the study, who wanted to know their tuberculosis status. Both the controls and patients with DM who had chronic cough, haemoptysis and positive sputum smear for acid fast bacilli were excluded from the study. In addition, controls must not have used steroid or any other immunosuppressive drugs and fasting blood sugar must be within normal limit. Diagnosis of DM was based on a fasting blood glucose of > 7mmol/L or 2hrpostpandrial ¬ > 11.1 mmol/L.[15]
All subjects were evaluated with a questionnaire including items on socio-demographics like social class, occupation, risk factors for TB, previous treatment for TB, drug history, contacts with persons with chronic cough or TB. Socio-economic classification proposed by Oyedeji was used.[16] Simply subjects are classified as follows :1 Highly skilled professionals like doctors, engineers etc , II Semi Professionals, senior teachers, III Medium grade traders, IV Junior public servants, and V Petty traders , artisans. Classes I and II were regarded as high socioeconomic class while III to IV was regarded as low.

Physical examination with measurement of the blood pressure, weight and height were done and body mass index was calculated. Blood was collected from patients and control and assayed for IFN-γ and blood glucose. Values of lipid profile and HB1AC done within the preceding 4 weeks of recruitment were noted for the DM cases. Informed consent was obtained from each subject and ethical clearance was obtained from the hospital ethical committee.

Cell Culture and IFN-Γ Levels

Whole blood Interferon-gamma release assay (IGRA) -the QuantiFERON-TB Gold In-Tube kit (QuantiFERON-TB Gold In-Tube, Cellestis Ltd., Carnegie, Australia)was used. The assay was performed according to the manufacturer's recommendations and as previously described.[14,17] Peripheral blood samples were collected into three different tubes and cultured in vitro: the first containing no antigen (negative control or Nil), the second tube impregnated with TB-specific

antigens (ESAT-6, CFP-10, and TB7.7) and the third tube containing phytohemagglutinin (positive control or Mitogen. Samples were incubated for 16–24 h at 37 °C , centrifuged and serum was harvested and stored at minus 300 C till analysed. An enzyme-linked immunosorbent assay (ELISA) sandwich test for IFN-gamma detection was performed; absorbance readings were obtained at 450 nm.[17]

Results were considered positive, negative, or indeterminate according to the criteria established by the manufacturer.[17] Briefly, the results of the QFT assay were considered positive if the IFN-gamma level was =0.35 IU/mL in the antigen-stimulated well after subtracting the IFN-gamma value of the Nil well. The QFT was considered indeterminate if the Nil result was >8.00 IU/mL or if the Mitogen, after subtracting the Nil value, was <0.50 IU/mL.

Statistical analysis . Results were analysed using SPSS version 18. Categorical variables were presented in frequencies and percentages while association between them was tested using chi square and fischer test when the number was less than five. Comparison between mean levels of interferon gamma was done with Student¡s T test. Level of significance was set at $p<0.05$

RESULTS

I. Characteristics of subjects

Sixty DM patients and 60 controls were recruited. The mean age of both groups were similar 57+29.5 years for the DM patients and 54+34.6 years for the control, p value = 0.2. Twenty one (35%) and 22(40%) of the cases and controls were males respectively, this was not statistically significant. p value = 0.06.

All subjects in both groups were married. Social class distribution in the two groups were similar with subjects in the social class 4 constituting the majority in the two groups. Only one patient(1.7%) with DM had history of past treatment for TB. Ten (16.7%) DM subjects were ex smokers while none of the controls were .None of the subjects were HIV positive and hypertension was the commonest comorbid state among the two groups.

II. QFT Results

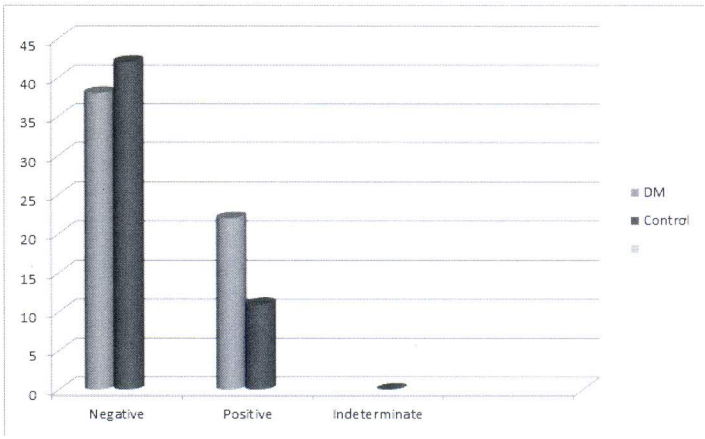

Fig. 1. QuantiFERON results among DM patients and controls

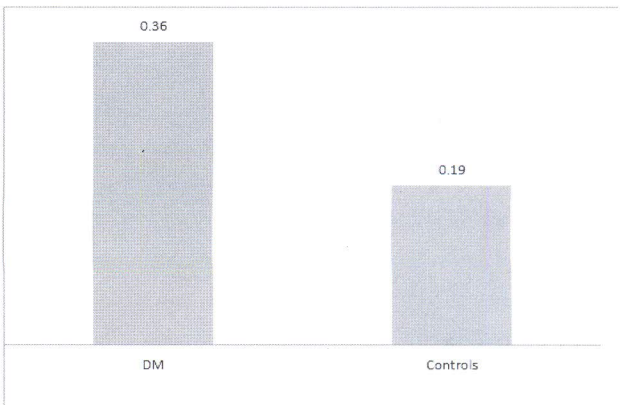

Figure 2.
Mean level of IFN gamma response in DM patients and controls

Figure 2 shows the mean level of IFN-γ among DM patients and controls As shown, the mean IFN-γ level in controls was 0.19 + 0.02 IU/ml which was lower than 0.36 + 0.24 IU/ml obtained among T2DM patients. This was statistically significant, p value =0.001

III. Factors associated with QFT-IT results among DM patients

Table 2 shows some factors associated with a positive or negative QFT-IT response among the

patients with DM.. As shown there was no significant difference in the sex distribution of those with a positive or negative QFT-IT result. The mean(median) age in those with positive and negative QFT-IT result, were 58.4+13.6(55.5) and 57.7+12.9(54.7) years respectively, this was not statistically significant p value =0.8. The mean duration of DM was 5.2+1.3years ,median of 4.7 years among those with a positive QFT-IT result and 4.4 + 1.5 years with a median of 4.4years among DM patients with a negative result, p value= 0.5. Mean BMI and fasting blood glucose levels were similar among those with positive and negative QFT-IT result, p value > than 0.05 in each case.

Table 2 also shows the association between HB1AC and TC level and QFT-IT result. As shown, the mean HBIAC level among those with a positive result was 8.9+0.7 % , median of 9.5% compared with 7.3+0.4% and a median of 6.9% among those with negative result, p value =0.001.
Similarly, the mean TC was lower in those with a negative result, 3.8+0.34mmol/l(median 4.6mmol/l) compared with those with a positive result, 4.4+0.23mmol/l(median 4.2mmol/l)., p value =0.002.

DISCUSSION

Many studies have reported the prevalence of active TB among DM patients [5,6,9] but very few if any have documented this association ,especially in developing countries facing the double trouble of TB and DM epidemic. Since MTB infection precede development of actual disease, it is important that attention should be paid to the control of MTB infection to prevent active TB in DM patients because managing TB in DM patients could be quite challenging.[7,8,9]

This study showed a higher MTB infection rate among DM patients (37%) compared with apparently healthy controls (20%) . Mycobacterium tuberculosis infection in type 2 diabetic patients is associated with elevated HB1AC, hypercholesterolemia and history of tobacco smoking.

Other studies that have determined MTB infection rate among DM patients reported rates varying from 29.3% to 42.2%. [18,19] However , our method eliminated the draw backs of studies that used TST and our results may be a truer reflection of the burden of MTB infection among the study population. QuantiFERON is more specific for diagnosing MTB infection compared with TST. [14,20]

There was no association between the duration of DM and MTB infection. Rather we found a significant association between glyceamic control measured by the HB1AC and MTB infection . Exposure to ETS and TC were other factors that influenced MTB infection rate. These findings have important implications and provide viable strategies for the control of MTB infection and TB disease.

Chronic hyperglycaemia has strong immune suppressing effects. [21] It weakens the cell mediated immune response necessary for controlling TB infection. Although the biological basis for the increased susceptibility of diabetic patients to tuberculosis remains unclear. Given the critical role of mononuclear phagocytes in mycobacterium tuberculosis containment, chronic hyperglycemia leads to an immunocompromised state with functional defects in mononuclear phagocytes, thereby facilitating progression to active tuberculosis. [22]

Achieving and sustaining long term optimal control of blood glucose could minimise , the risk of TB infection in T2DM as shown by our finding of lower rate of MTB infection in those with lower HB1AC. As shown, the contribution of hyperglycaemia to LTBI among T2DM patients was the strongest. Strategies aimed at ensuring adequate glycaemic control should be adopted or intensified.

The impact of smoking on TB is well documented. [23,24] Both active and passive smoking were significantly associated with LTBI. The adjusted odds ratio (AOR) of active smoking being AOR?=?2.56 (95% CI 1.20-5.45) and passive smoking AOR?=?2.27 95% CI 1.09-4.72). 24,25 Even though, none of the patients were currently smoking, reported exposure to second hand smoke and the high rate of MTB infection corroborate previous observation that a dose-response relationship exists between tobacco smoke exposure and M. tuberculosis infection. [25] Cigarette smoke amongst other mechanisms attenuates effector cytokine responses and impairs

mycobacterial containment within infected human macrophages derived from the peripheral blood and alveolar compartments, thus supporting the hypothesis that cigarette smoke subverts mycobacteria-related immunity. [26]

Targeted smoking prevention and cessation programs should therefore be included in comprehensive national TB control efforts.

Many studies have shown the association between active TB and serum cholesterol .[27,28] Low levels of cholesterol have been reported in active TB and the level correlates well with severity. [28] However, findings have been different in LTBI. [29] In this study, we found that higher mean total cholesterol level was associated with MTB infection among patients with type 2 DM. This may be reflective of the general dyslipedimic state DM patients have. Host hypercholesterolemia is known to play an important pathogenetic role in tuberculosis.[29] The baccili is able to utilise the lipid rich environment to switch on to dormancy, slowed growth and possibly development of drug tolerance. This way the organism is able to establish a long-lasting highly prevalent infection inside the human body . [29] It has been demonstrated in apolipoprotein E -deficient (ApoE-/-) mice that hypercholesterolemia is associated with high susceptibility to tuberculosis and that this susceptibility depends on the severity of hypercholesterolemia. Hypercholesterolemia cause delayed expression of adaptive immunity to tuberculosis caused by defective priming of the adaptive immune response. [30] Pariah et al in their study found that peripheral blood mononuclear cells and monocyte-derived macrophages from patients with familial hypercholesterolamia receiving statin therapy were more resistant to M. tuberculosis infection, with reduced bacterial burdens, compared with those of healthy donors. [31] Moreover, statin treatment in experimental murine M. tuberculosis infection studies increased host protection, with reduced lung burdens and improved histopathologic findings, suggesting that statin therapy in DM may have the potential of preventing TB. [31,32] Therefore it seems that statin therapy in diabetes mellitus may have the potential to attenuate the predisposition to tuberculosis in diabetic patients and may be useful for multiple positive outcomes. More studies will be needed to determine the strength of the association between LTBI and serum cholesterol.

This study is limited by sample size hence large scale studies with higher sample size will be needed to determine the relative or independent predictor of LTBI

Prospectively following up DM patients with LTBI to determine predictor of active TB is another research priority in this group.

As most parts of the world, especially developing countries , that are plagued with a TB infection resurgence, are also undergoing a type 2 diabetes pandemic, a collaborative framework for control of TB in diabetic patients is necessary. Such efforts will include screening of diabetes patients for latent TB and screening TB patients for DM. This effort will help in stemming the tide and reduce DM related morbidity and mortality.

Acknowledgement

The authors acknowledge the support QIAGEN,GmbH, Hilden, Germany for providing the QuantiFERON test kit used for this study, and the support and cooperation of the medical and nursing staff of State Specialist Hospital during the study.

TABLE 4. Correlation of total score with years of practice and CME

Characteristics	DM Cases n= 60(%)	Control n=60(%)	Total	P-Value
Mean age	57+29.5	54+34.6		0.2
Sex				
M	21(35%)	23(38%)	44	
F	39(65%)	37(62%)	76	
Marital Status				
Married	60(100%)	60(100%)		0.06
Social Class				
I	-	-		
II	9(15%)	8(13.3%)	17	
III	19(31.6%)	19(31.6%)	38	
IV	22(36.7%)	23(38.3%)	45	0.06
V	10(16.7%)	10(16.7%)	20	
Smoking History				
Ex smoker	10(16.7%)	0	10	
Past history of TB	1(1.7%)	0	1	
QFT Result				
Negative	38(63%)	45 (75%)	85	
Positive	22(37%)	12(20%)	33	
Indeterminate	0	3(5%)	3	0.000

Table 2:
Factors associated with QFT results among DM patients

Characteristics	Positive n=22(%)	Negative n=38(%)	P-Value
Sex			
M	8(36.3%)	13(34%)	0.1
F	14(63.7%)	25(66%)	
Ex smokers			
Yes	5(22.7%)	2(5.2%)	
No	1(4.5%)	2(5.2%)	0.002**
Mean Age	58.4+ 13.6	57.7+ 12.9	0.8
Mean Duration of diagnosis of DM	5.2+ 1.3	4.4+ 1.5	0.5*
Mean BMI	27.6+4.7	26.2+ 5.5	0.7*
Mean Fasting Blood glucose	8.9+ 6.4	8.8+ 6.5	0.9*
Mean HB1AC (Glycosylated hemoglobin)	8.9+0.7	7.3+ 0.4	0.001*
Mean Total Cholesterol	4.4+0.23	3.8+0.34	0.002*

* Independent t - test was done.
** Fischer test was done

References

1. WHO, Global Tuberculosis Control: WHO Report 2013, WHO/HTM/TB/2013.11.WHO, Geneva, Switzerland. Accessed at www.who.int/tb

2. Lonnroth K, Jaramillo E, Williams BG, Dye C, Raviglione M Drivers of tuberculosis epidemics: the role of risk factors and social determinants. Soc Sci Med. 2009; 68: 2240–2246

3. Root HF The association of diabetes and tuberculosis. N Eng J Med. 1934; 210: 1–13

4. Restrepo BI, Camerlin AJ, Rahbar MH, Wang W, Restrepo MA Zarate I. Cross-sectional assessment reveals high diabetes prevalence among newly-diagnosed tuberculosis cases. Bull World Health Organ. 2011; 89: 352–59

5. Stevenson CR, Forouhi NG, Roglic G, Williams BG, Lauer JA, et al. Diabetes and tuberculosis: the impact of the diabetes epidemic on tuberculosis incidence. BMC Public Health. 2007; 7: 234.

6. Dooley KE, Tang T, Golub JE, Dorman SE, Cronin W Impact of diabetes mellitus on treatment outcomes of patients with active tuberculosis. Am J Trop Med Hyg 2009;80: 634–639

7. Baker MA, Harries AD, Jeon CY, Hart JE, Kapur A, et al. The impact of diabetes on tuberculosis treatment outcomes: a systematic review. BMC Med 2011;9 :81 -85

8. Alisjahbana B, Sahiratmadja E, Nelwan EJ, Purwa AM, Ahmad Y, , et al. The effect of type 2 diabetes mellitus on the presentation and treatment response of pulmonary tuberculosis. Clin Infect Dis 2007;45: 428–35

9. Jeon CY, Murray MB Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. PLoS Med 2008; 5: e152.

10. Cardoso, F. L. L., P. R. Z. Antas, A. S. Milagres, A. Geluk, K. L. M. C. Franken,et al. T-cell responses to the Mycobacterium tuberculosis-specific antigen ESAT-6 in Brazilian tuberculosis patients. Infect. Immun. 2002; 70:6707-6714.

11. Al-Orainey , Ibrahim O. Diagnosis of latent tuberculosis: Can we do better? Annals of Thoracic Medicine. 2009;4: 5-9.

12. H. Kunst, "Diagnosis of latent tuberculosis infection: the potential role of new technologies," Respiratory Medicine, 2006;12: 2098–2106,

13. Painter JA, Graviss EA, Hai HH, Nhung DTC, Nga TTT, et al. Tuberculosis Screening by Tuberculosis Skin Test or QuantiFERON®-TB Gold In-Tube Assay among an Immigrant Population with a High Prevalence of Tuberculosis and BCG Vaccination. PLoS ONE .2013 8: e82727. doi: 10.1371/journal.pone.0082727,

14. Adewole O.O. ,Erhabor G. E., Sogaolu M.O , Onipede A.O. , Owiafe P.K et al. Diagnostic Utility of QuantiFERON-TB Gold In-Tube in Active Pulmonary Tuberculosis in Nigeria. WAJM 2013; 3: 180–185.

15. WHO Defination,diagnosis and classification of diabetes mellitus and its complication: Part 1: Diagnosis and classification of diabetes mellitus. Department of Non-communicable Diseases Surveillance.Geneva.1999

16. Oyedeji GA. Socioeconomic and cultural background of hospitalised children in Ilesa. Nig J Paediatr 1995; 12: 111-7.

17. QuantiFERON-TB Gold In-Tube assay (package insert). Valencia: Cellestis Inc.; 2009

18. Webb EA, Hesseling AC, Schaaf HS, Gie RP, Lombard CJ, et al. High prevalence of Mycobacterium tuberculosis infection and disease in children and adolescents with type 1 diabetes mellitus. Int J Tuberc Lung Dis. 2009 ;13:868-74

19. Bermejo MJ, Gil MJ, Velasco MP, Prado A A, García JJ, et al. Tuberculin test in diabetic patients in a health center. Aten Primaria. 1995;16:154-7

20. Diel R, Goletti D, Ferrara G, Bothamley G, Cirillo D, et al . Interferon-release assays for the diagnosis of latent Mycobacterium tuberculosis infection: a systematic review and meta-analysis. Eur Respir J. 2011 37:88-99.

21. Restrepo BI, Fisher-Hoch SP, Pino PA, Salinas A, Rahbar MH, et al Tuberculosis in poorly controlled type 2 diabetes: altered cytokine expression in peripheral white blood cells. .Clin Infect Dis. 2008 5:634-41.

22. Restrepo BI, Twahirwa M, Rahbar MH, Schlesinger LS. Phagocytosis via complement or Fc-gamma receptors is compromised in monocytes from type 2 diabetes patients with chronic hyperglycemia. PLoS One. 2014 ;9 e92977

23. Van Zyl Smit RN, Pai M, Yew WW, Leung CC, Zumla A, , et al. Global lung health: the colliding epidemics of tuberculosis, tobacco smoking, HIV and COPD. Eur Respir J. 2010; 35:27-33

24. Lindsay RP, Shin SS, Garfein RS, Rusch ML, Novotny TE. The Association between active and passive smoking and latent tuberculosis infection in adults and children in the united states: results from NHANES. PLoS One. 2014;9:e93137.

25. Shin SS, Laniado-Laborin R, Moreno PG, Novotny TE, Strathdee SA, et alDose-response association between salivary cotinine levels and Mycobacterium tuberculosis infection. Int J Tuberc Lung Dis. 2013;17:1452-8

26. Van Zyl-Smit RN, Binder A, Meldau R, Semple PL, Evans A, Smith P, et al..Cigarette smoke impairs cytokine responses and BCG containment in alveolar macrophages Thorax. 2014 ;69:363-70.

27. Sahin F, Yıldız P. Distinctive biochemical changes in pulmonary tuberculosis and pneumonia. Arch Med Sci. 2013 ;9:656-61

28. Deniz O, Gumus S, Yaman H, Ciftci F, Or F, et al.. Serum total cholesterol, HDL-C and LDL-C concentrations significantly correlate with the radiological extent of disease and the degree of smear positivity in patients with pulmonary tuberculosis. Clin Biochem. 2007 ;40:162-6.

29. Rodríguez JG, Hernández AC, Helguera-Repetto C, Aguilar Ayala D, Guadarrama-Medina R, et al. Global Adaptation to a Lipid Environment Triggers the Dormancy-Related Phenotype of Mycobacterium tuberculosis. MBio. 2014 ; 20;5(3).

30. Martens GW, Arikan MC, Lee J, Ren F, Vallerskog T, Kornfeld H. Hypercholesterolemia Impairs Immunity to Tuberculosis. Infect Immun. Aug 2008; 76: 3464–3472

31. Parihar SP, Guler R, Khutlang R, Lang DM, Hurdayal R, et al. Statin therapy reduces the mycobacterium tuberculosis burden in human macrophages and in mice by enhancing autophagy and phagosome maturation. J Infect Dis. 2014;5:754-63

32. Banerjee D, Bhattacharyya R. Statin therapy may prevent development of tuberculosis in diabetic state. Med Hypotheses. 2014 ;1:88-91.