April 2019

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RESEARCH ARTICLE

Raised levels of IFN-gamma and IL-13 are associated with pre-diabetes amongst newly diagnosed patients with Tuberculosis

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Abstract

Objective: To investigate pre-diabetes and diabetes in newly-diagnosed tuberculosis patients and to assess the association of serum cytokine levels with diabetes status.

Methods: The cross-sectional study was conducted at Indus Hospital and The Aga Khan University Hospital, Karachi from May to November 2015, and included patients of either gender aged 18 years or more with a confirmed diagnosis of tuberculosis who were either newly diagnosed or had received up to 1 month of anti-tuberculosis therapy were included. Patients were enrolled from among those presenting to the clinics at Indus Hospital, Karachi, and the Department of Medicine, Aga Khan University Hospital (AKUH), Karachi. The patients were tested for glycosylated haemoglobin and random blood glucose. Diabetes was defined as HbA1c >6.5%; pre-diabetes as HbA1c=5.7-6.4%; and normoglycaemic as HbA1c <5.7%. Serum cytokines were investigated using the Bio-plex 27, Bio-Rad assay. SPSS version 19.0 was used for data analysis.

Results: Of the 211 subjects, 110(52%) were females and 101(48%) were males. The overall median age of the sample was 26 years, and 100(47.3%) subjects were underweight. Of the total, 24(11.4%) had diabetes and 45(21.3%) had pre-diabetes. Of the diabetics, only 7(29%) knew their status prior to screening. Interferon-gamma and interleukin-13 were significantly different among tuberculosis patients with diabetes, pre-diabetes and normoglycaemia ($p<0.05$). Glycosylated haemoglobin levels showed a significant correlation with interferon-gamma levels.

Conclusions: Raised interleukin-13 and interferon-gamma levels in newly-diagnosed tuberculosis patients with pre-diabetes.

Keywords: Pre-diabetes, Tuberculosis, Interleukin-13, Diabetes, Interferon-gamma.
(JPMA 69: 468 2019)

Introduction

Tuberculosis (TB) results in approximately 1.7 million deaths each year.[1] Pakistan ranks 5th amongst high TB-burden countries worldwide, with an incidence of 268/100,000 annually.[1] Pakistan has a diabetes prevalence of 6.9%, ranks 7th amongst high diabetes-burden countries and there are estimated to be 3.5 million undiagnosed diabetics in the country.[2] In TB with diabetes, there is an increased risk of death due to TB treatment and of TB relapse after treatment.[3] The World Health Organisation (WHO) recommends bidirectional screening of TB in patients with diabetes, and for diabetes in TB patients.[4] Unfortunately, both TB and diabetes are often not detected early and their public health burden is high. Mycobacterium tuberculosis (Mtb), the causative agent of TB, resides within macrophages and can be restricted by the appropriate activation of T cells and macrophages regulated by cytokines such as interferon-gamma (IFN), tumour necrosis factor alpha (TNF), interleukin (IL)-2 and IL-10. Impaired T cell mediated immune responses have been demonstrated in Mtb infected individuals with type 2 diabetes mellitus (T2DM).[5] Bacterial loads in macrophages from diabetic individuals with TB have been shown to be higher than in non-diabetics.[6] The mechanism responsible for immune deficiency in diabetes that leads to exacerbation of TB is as yet unclear.

TB remains common but many patients remain unaware

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of having diabetes. Overall, the data regarding rates of diabetes amongst TB patients in Pakistan ranges 11- 30%.[7,8]

Cytokines are shown to be immune markers for TB disease severity and outcome.[9] Raised levels of pro-inflammatory IFN , TNF and IL-10 have been associated with advanced TB.[10,11] In diabetes, T cell IFN responses are found to be defective.[12] In TB patients with DM and pre-DM, it has been shown that pro-inflammatory cytokines are raised, indicating heightened responsiveness to stimuli.[13,14] There is as yet limited understanding of the immune mechanisms responsible for poorer immune responses to Mtb in DM patients and also the identification of potential biomarkers of DM and TB. The current study was planned to screen newly-diagnosed TB patients for random blood glucose (RBG) and glycosylated haemoglobin (HbA1c) levels. Further, we determined serum levels of type 1 T helper (Th1) and Th2 cytokine levels in the patients to investigate the association between blood glucose levels and TB.

Patients and Methods

The cross-sectional study was conducted from May to November 2015 at Indus Hospital and The Aga Khan University Hospital (AKUH), Karachi after approval was obtained from the ethical review committees of Aga Khan University Hospital (AKUH), Karachi, and Indus Hospital, Karachi. Written informed consent was taken from each subject.

The sample size was calculated based on the prevalence of diabetes identified in Pakistan in 2015, 6.8%.[2] In TB patients there is a 2-3 time risk of diabetes,[15] thus the prevalence rate was estimated at 13-20%. The estimate of the expected proportion (p) rate was set at 13-20% by taking average proportion i.e. 16.5% with 5% desired level of absolute precision (d) for 95% confidence interval (CI) with 5% level of significance.

Those included were subjects from either gender aged 18 years or more with a confirmed TB diagnosis and who were either newly-diagnosed or had received up to 1 month of anti-tuberculous therapy (ATT). Those aged less than 18 years, and patients who had received more than one month of ATT were excluded.

Using consecutive sampling method, patients were enrolled from among those presenting to the TB clinics at the two hospitals. Diagnosis of TB was made according to the National TB Programme guidelines[16] on the basis of characteristic clinical features; chest X-rays/ a positive sputum smear and or / Xpert TB/RIF assay (Cepheid, USA). Sputum, when available for testing, was sent for both acid fast bacillus (AFB) smear microscopy and Xpert testing. In cases where sputum was not produced, patients were identified as pulmonary TB (PTB) cases based on strong radiological findings and clinical correlation.

Diagnosis of extrapulmonary TB (EPTB) was made on a positive Xpert test of site-specific specimen or histopathology confirming granulomatous inflammation, and co-incident with clinical history. Patients with EPTB had either pleural TB, tuberculous lymphadenopathy (LNTB), abdominal TB or other extrapulmonary site involvement. Detailed demographic information and information regarding clinical algorithm was logged by an attending medical officer on a pre-designed proforma.

Blood samples from each subject were screened for diabetes by testing for RBG and HbA1c.

Body mass index (BMI) was calculated for each patient based on their weight and height measurements at baseline. The categories were set at less than 18·5 kg/m^2 underweight; 18·5-22.9 kg/m^2 normal weight; 23-27·4 kg/m^2 overweight; and 27·5 kg/m^2 obese.[17]

Normal levels of HbA1c were less than 39 mmol/mol (5.7%). Diabetes was defined by HbA1c $\geq$ 48 mmol/mol (6.5%), and pre-diabetes at HbA1c 39-44 mmol/mol (5.7-6.4 %).[18]

Serum samples from study subjects were tested using the Bio-Plex Pro Human Cytokine (27-Plex Panel, Bio-Rad, USA) as per the manufacturer's instructions. The cytokines detected were IFNγ, IL-10, IL-12p70, IL-13, IL-2, IL-5, IP-10, MiP-1α, MiP-1β, IL-6, IL1-RA, GM-CSF, RANTES, IL-1β, Eotaxin, Basic FGF, VEGF, PDGF-β, MCP-1, IL-8, IL15, IL-17, G-CSF, IL-12p70, IL17A, IL-9 and TNF-α. Tests were performed on the Luminex 200 system (MERCK laboratories, USA).

Data analysis was done using SPSS version 19.0. Mann-Whitney U test was used to compare non-parametric variables. Significance of 95% CI was used to determine significant difference between variables which was set at $p \leq 0.05$.

Results

Of the 216 patients initially approached, 4(1.8%) refused to give a blood sample while 1(0.45%) was lost due to

Table-1: Description of study sample .

		Total n (%)
Age (years) (n=211)	≤ 25	100 (47.4)
	26-50	76 (36.0)
	>50	35 (16.6)
Gender (n=211)	Male	101 (47.9)
	Female	110 (52.1)
BMI kg/m^2 with Categories (n=167)	Underweight (<18.5)	100 (47.3)
	Normal (18.5-22.9)	44 (20.9)
	Overweight (23-27.4)	11 (5.7)
	Obese (≥27.5)	12 (5.7)
Site of TB	Pulmonary TB	172(81.5)
	Extra Pulmonary TB	39(18.5)
Category of Treatment (n=211)	New treatment	165 (78.2)
	Retreatment	46 (21.8)
Family History of TB (n=211)	Positive Family History	76 (36.0)
	No Family History	135 (64.0)

BMI=body mass index; TB=tuberculosis

Table-2: Microbiological and Radiological description of TB cases (n=211).

	n (% of total)	Result	n (%)
PTB cases	172 (81.5%)		
Sputum AFB Smear	150 (87%)	Positive	70 (46.7)
		Negative	80 (53.3)
Sputum Xpert MTB/RIF	144 (84%)	Positive	121 (84)
		Negative	23 (16)
Xpert MTB/RIF Result	121 (57.3%)	Not Detected	118 (97.5)
		Indeterminate	2 (1.7)
		Detected	1 (0.8)
Chest X-Ray	157 (74.4%)	Minimal	18(11.5)
		Moderate	85(54.1)
		Advanced	54(34.4)
EPTB cases	39 (18.5%)		
Category of TB		Pleural	16 (41)
		Abdominal	9 (23)
		Lymph node	7 (17.9)
		Bone and joint	2 (5.1)
		Others	5 (12.8)

PTB=pulmonary tuberculosis; EPTB=extrapulmonary tuberculosis; AFB=acid-fast bacillus; Xpert TB, Xpert MTB/RIF assay, Cepheid, USA.

haemolysis. After data collection 1(0.45%) patient had to be excluded due to old age which was identified later. The final sample, as such, stood at 211(97%). Of them, 110(52%) were females and 101(48%) were males. The overall median age of the sample was 26 years, and 100(47.3%) subjects were underweight (Table 1). The BMI values were available for 167(79%) subjects and, among them, median BMI was 17.78 kg/m^2. The median number of members in each household was 7, and 76(36%) cases had a family history / household contact with TB patients.

Overall, 165(78.2%) cases were new and 46 (21.8%) were re-treatment cases. At the time of recruitment, 135(63.5%) were newly-diagnosed and had not received ATT while 76 (36.5%) cases had received one month of ATT.

In terms of co-morbid conditions, 2(0.9%) patients had human immunodeficiency virus (HIV) infection, 3(1.3%) subjects had viral hepatitis B or C, 3(1.3%) were intravenous drug users (IDUs) and 1(0.45%) had an autoimmune disease. Besides, 7(3.3%) subjects were known diabetics and were on treatment for hyperglycaemia.

Further, there were 172(81%) cases of PTB and 39(19%) of EPTB (Table 2). Sputum was available for testing in 150 (87%) cases. Where sputum was not produced, patients were identified as PTB cases based on strong radiological findings and clinical correlation. On sputum testing, 70(46.7%) had a positive AFB smear. Of the 144(68%) cases in which sputum Xpert test was peformed, 121(84%) had a positive result; 118 (97.5%) had rifampicin-susceptible Mtb, 1 (0.8%) had rifampicin-resistant Mtb, and 2(1.6%) had indeterminate results.

Overall, 70 (41%) of 172 PTB patients were diagnosed on the basis of AFB smear being positive, and 121 (70%) were diagnosed via positive Xpert TB result.

Of the PTB cases, 85(54.1%) had moderate disease on chest radiograph followed by advanced disease 54(34.4%) and minimal disease in 18 (11.5%).

Table-3: Characteristics of study subjects as per diabetes status (n=211).

	Total n (%)	**Median** Age (Years)	**HbA1c** IQR=Median (Q_3 -Q_1) **IFCC (mmol/mol) NGSP HbA1c %**	**RBG** IQR=Median (Q_3 -Q_1)
Non-Diabetics	142 (67.30%)	23	34 mmol/mol (37-31) 5.30%(5.50-5.00)	95 (108-89)
Pre-Diabetics	45 (21.30%)	40	40 mmol/mol (42-39) 5.80%(6.00-5.70)	100 (122-93)
Diabetics	24 (11.40%)	50	92 mmol/mol (108-81) 10.6%(12.00-9.55)	281 (390-191)
Total	211 (100%)	26	37 mmol/mol (40-32) 5.50%(5.80-5.10)	98 (118-90)
p-value	----	$p<0.0001$*	$p<0.0001$*	$p<0.0001$*

RBG=random blood glucose, IQR=inter-quartile range, HbA1c=Glycosylated haemoglobin

Table-4: Comparison of TB patients as per glycaemic levels.

		Total n (%)	Non-Diabetics n (%)	Pre-Diabetics n (%)	Diabetics n (%)
Gender	Male	101 (47.9)	58 (57.4)	29 (28.7)	14 (13.9)
	Female	110 (52.1)	84 (76.4)	16 (15.5)	10 (9.1)
BMI (kg/m^2) with Categories (n=167)	Underweight (<18.5 (kg/m^2))	100 (60)	77 (77)	18 (18)	5 (5)
	Normal (18.5-22.9)	44 (26.3)	30 (68.2)	7 (16.2)	7 (16.2)
	Overweight (23-27.4)	11 (6.6)	4 (36.4)	4 (36.4)	3 (27.3)
	Obese (≥27.5)	12 (7.2)	4 (33.3)	6 (50)	2 (16.7)
Site of TB	Pulmonary TB	172 (81.5)	109 (63.4)	39 (22.7)	24 (14)
	Extra Pulmonary TB	39 (28.5)	33 (84.6)	6 (15.4)	0
Category of Treatment	New treatment	165 (78.2)	108 (65.5)	36 (21.8)	21 (12.7)
	Retreatment	46 (21.8)	34 (73.9)	9 (19.6)	3 (6.5)

BMI=body mass index are given in kg/m^2. All values represent the absolute number followed by the percentage in parentheses.
Non-diabetics or normoglycaemics with HbA1c <5.7%; Pre-diabetics with HbA1c 5.7-6.4% and Diabetics with HbA1c >6.4%

Table-5: Circulating cytokine values.

	n	IFN γ Mean±SD (pg/ml)	IL-10 Mean±SD (pg/ml)	IL-12p70 Mean±SD (pg/ml)	IL-13 Mean±SD (pg/ml)	IL-2 Mean±SD (pg/ml)	IL-5 Mean±SD (pg/ml)	TNF-α Mean±SD (pg/ml)
Normal	38	27.58 ±89.65	155.56 ± 490.18	117.66 ± 437.49	2.90±17.85	0.00	25.24 ±155.60	112.07±416.08
Pre-diabetic	24	444.11 ±1298.58	261.47 ± 747.79	362.00 ± 835.35	72.23 ±210.24	63.20 ± 220.39	102.63 ±263.72	730.74±2448.77
Diabetic	13	257.30 ±746.37	0.00	128.16 ± 462.07	68.00 ±245.19	64.34 ±231.98	76.84 ± 277.05	1700.78±5881.97
p-value		0.028*	NS	NS	0.003*	NS	NS	NS

IFNγ = interferon-gamma; IL, interleukin; TNFα=tumor necrosis factor-alpha.

Of the 39 EPTB cases, 32(82%) had a normal chest X-ray. The EPTB cases comprised pleural 16(41%), abdominal 9(23%), lymph-node TB 7(18%), bone and joint 2 (5%), and the remaining 5(13%) cases had additional sites involved.

Based on HbA1c and RBG test results, 142 (67.3%) patients had normal glycaemic levels, 45(21.3%) were pre-diabetics and 24(11.4%) were diabetics (Table 3). The median HbA1c levels of normoglycaemics was 5.3%, pre-diabetics 5.8% and diabetics 10.6%. Median RBG levels were 95 g/dl for normal, 100 g/dl for pre-diabetics and 281 g/dl for diabetics.

TB patients with diabetes were comparatively older than the rest (p<0.001). Of the diabetic patients, 17(71%) were newly-diagnosed while 7(29%) already knew they had diabetes.

Among the diabetics, 14(58%) were males and 10(42%) were females (Table 4). Among the pre-diabetics, 29(28.7%) were males compared to 16(15.5%) women ((p=0.026).

Among the 100(47.3%) underweight individuals, 77(77%) were non-diabetics, 18(18%) pre-diabetics and 5(5%) were diabetics. Amongst TB patients with normal weight, the corresponding values were 30(68%), 7(16%) and 7(16%). Among the overweight TB patients, the values were 4(36.4%) non-diabetics, 4(36.4%) pre-diabetics and 3(27%) diabetics. In the obese TB cases, there were 4(33.3%) non-diabetics, 6(50%) pre-diabetics and 2(16.7%) diabetics.

Circulating serum levels of cytokines were measured in 75 (35.5%). Of them, 13 (17.3%) had diabetes, 24 (32%) had pre-diabetes, and 38(51%) were non-diabetics. Significantly different levels of IFNγ (p=0.028) and IL-13 (p=0.003) were observed among normoglycaemic, diabetic and pre-diabetic cases. IFNγ levels in individuals with pre-DM were greater than those with DM (p=0.028) and normoglycaemic (p=0.007) TB patients. Also, IL-13 was raised in pre-DM compared to DM (p=0.003) and normoglycaemics (p=0.001).

Levels of IL-10, IL-12p70, IL-2 and IL-5 were comparable between normoglycaemic, diabetic and non-diabetic TB patients (Table 5).

HbA1c levels showed a weak but significant correlation with IFNγ (p=0.23, rho=0.262).

Discussion

This, to our knowledge, is the first study to identify rates

of pre-DM in a cohort of newly-diagnosed TB patients in Pakistan. Also, it identified IFNγ and IL-13 as biomarkers of individuals with TB and pre-DM. Pre-diabetes is a state which can often be managed with exercise and healthy eating. Identification of diabetes or pre-diabetes, defined also as intermediate diabetes, is important as uncontrolled blood glucose levels result in unfavourable outcomes in TB patients.[19]

A study in Karachi recently showed that diabetics were 10 times more likely to have TB than non-diabetics.[20] Previous studies have reported rates of diabetes amongst TB patients as 11-30% (7, 8). This has further varied to 6% of newly-diagnosed diabetics amongst TB patients[21] while another revealed that there were 39%[8] diabetics amongst TB patients.

The current study identified 11.4% cases of diabetes and 21.3% cases of pre-diabetes. The percentage of diabetics found here and in previous studies is higher than the prevalence of 6.9% shown nationwide.[2] These variations could be due to the cohort tested and also due to differences in methods used to assess diabetes, as there may be differences due to cut-offs by fasting blood glucose (FBG), HbA1c and oral glucose tolerance test (OGTT) methods.

The higher proportion of TB patients with pulmonary compared with EPTB matches the trends reported globally.

Most patients were under the age of 25 years, meaning TB occurs predominantly in young adults.[1] The trend of high household contacts for each individual was similar to those reported previously.[22] The rate of 36% amongst those with prior family history of TB suggests that the majority of TB cases were a result of new contact with TB patients. The age group of diabetics showed an older age distribution than those who didn't have diabetes, as shown previously.[8] The reduced BMI in TB patients with the majority of cases being underweight fits previous reports.[8] When patients were further differentiated as per BMI categories[17] and were correlated with their glycaemic status, it was apparent that amongst the overweight and obese TB patients there was a larger proportion of cases who were pre-diabetic and diabetic compared to the proportion of pre-diabetic and diabetic cases found in the underweight and normal weight groups. This correlates with previous reports that showed an increased association of diabetes with raised BMI in TB patients.[7]

An impaired T cell mediated immune response has been demonstrated.[5] Bacterial loads in macrophages from diabetic individuals with TB are higher than in non-diabetics.[6] This leads to less favourable outcomes in TB patients who have diabetes.

Pre-diabetes is a state which can often be managed with exercise and healthy eating. We found that 21% of newly-diagnosed TB patients were pre-diabetic. Further, it was apparent that IFNγ and IL-13 levels were significantly higher in those with pre-DM compared with DM and normoglycaemic TB patients.

A recent study showed there was a diminished inflammatory response to Mtb in individuals who had latent TB coincident with pre-diabetes.[23] Separately, certain inflammatory markers such as immunoglobulin E (IgE), IL-4, IL-10, and tryptase have been positively associated with pre-diabetes or T2DM.[24] Our data indicating an increase in IFNγ levels in pre-DM TB patients confers with previous reports.[13] However, a study observed an increase in additional cytokines Type 1 and Type 2.[13] Another difference from this study was that we observed a weak but significant correlation between IFNγ levels and HbA1c levels in TB patients, which was in contrast to that observed by a previous study.[13]

It is of note that IL-13 was found to be raised in TB patients with pre-DM. Our observation that IL-13 levels are reduced in DM is in line with reduced glycaemic control. IL-13 is a Th2 cytokine known to mediate macrophage alternate activation. IL-13 knockout mice have been shown to display hyperglycaemia resulting in hepatic insulin resistance and systemic metabolic dysfunction.[25] Therefore, IL-13 is important for the regulation of glucose metabolism. During TB treatment there is a transient state of hyperglycaemia.[26] This is likely to be further raised in those with previously raised blood glucose levels. Uncontrolled hyperglycaemia leads to chronic inflammation. Therefore, in the absence of a homeostatic balance of cytokines immune responses to Mtb infection will be defective.

Conclusions

IL-13 and IFNγ were identified as biomarkers of pre-diabetes in TB patients. There is a need for early identification and management of diabetes and pre-diabetes in TB.

Disclaimer: None.
Conflict of Interest: None.
Source of Funding: The study received technical and

financial support from the World Health Organisation (WHO) Special Programme for Research and Training in Tropical Diseases (TDR): The EMRO/TDR Small Grant Scheme for Operational Research in Communicable Diseases.

References

1. WHO. Global Tuberculosis Report. Geneva, Switzerland; 2017.
2. IDF. IDF Atlas. International Diabetes Federation; 2014
3. Sullivan T, Ben Amor Y. The co-management of tuberculosis and diabetes: challenges and opportunities in the developing world. PLoS Med 2012; 9: e1001269.
4. WHO. Collaborative framework for care and control of Tuberculosis and Diabetes. Geneva, Switzerland; 2011.
5. Mendoza-Aguilar M, Garcia-Elorriaga G, rce-Paredes P, Gonzalez-Bonilla C, Del Rey-Pineda G, Rojas-Espinosa O. Functional state analysis of phagocytic cells of patients with type 2 diabetes and pulmonary tuberculosis. Clin Lab 2012; 58: 299-305.
6. Hodgson K, Morris J, Bridson T, Govan B, Rush C, Ketheesan N. Immunological mechanisms contributing to the double burden of diabetes and intracellular bacterial infections. Immunology 2015; 144: 171-85.
7. Mukhtar F, Butt ZA. Cohort profile: the diabetes-tuberculosis treatment outcome (DITTO) study in Pakistan. BMJ Open 2016; 6: e012970.
8. Aftab H, Ambreen A, Jamil M, Garred P, Petersen JH, Nielsen SD, et al. High prevalence of diabetes and anthropometric heterogeneity among tuberculosis patients in Pakistan. Trop Med Int Health 2017; 22: 465-73.
9. Jamil B, Shahid F, Hasan Z, Nasir N, Razzaki T, Dawood G, et al. Interferon g:IL10 ratio defines the severity of disease in pulmonary and extra-pulmonary tuberculosis. Tuberculosis 2007; 87: 279-87.
10. Hasan Z, Jamil B, Khan J, Ali R, Khan MA, Nasir N, et al. Relationship between Circulating Levels of IFNg, IL10, CXCL9 and CCL2 in Pulmonary and Extrapulmonary Tuberculosis is Dependent on Disease Severity. Scan J Immunol 2009; 69: 259-67.
11. Doherty M, Wallis RS, Zumla A. Biomarkers for tuberculosis disease status and diagnosis. Curr Opin Pulm Med 2009; 15: 181-7.
12. Stalenhoef JE, Alisjahbana B, Nelwan EJ, van der Ven-Jongekrijg J, Ottenhoff TH, van der Meer JW, et al. The role of interferon-gamma in the increased tuberculosis risk in type 2 diabetes mellitus. Eur J Clin Microbiol Infect Dis 2008; 27: 97-103.
13. Kumar NP, Banurekha VV, Nair D, Sridhar R, Kornfeld H, Nutman TB, et al. Coincident pre-diabetes is associated with dysregulated cytokine responses in pulmonary tuberculosis. PLoS One 2014; 9: e112108.
14. Kumar NP, Sridhar R, Banurekha VV, Jawahar MS, Fay MP, Nutman TB, et al. Type 2 diabetes mellitus coincident with pulmonary tuberculosis is associated with heightened systemic type 1, type 17, and other proinflammatory cytokines. Ann Am Thorac Soc 2013; 10: 441-9.
15. WHO. Tuberculosis & Diabetes. Geneva, Switzerland; 2011.
16. National Tuberculosis Control Program. Desk Guide for doctors on Management of Tuberculosis. Ministry of National Health Services, Regulation & Coordination, Government of Pakistan; 2015
17. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004; 363: 157-63.
18. American Diabetes A. 2. Classification and Diagnosis of Diabetes. Diabetes Care 2017; 40(Suppl 1): S11-S24.
19. Baker MA, Harries AD, Jeon CY, Hart JE, Kapur A, Lonnroth K, et al. The impact of diabetes on tuberculosis treatment outcomes: a systematic review. BMC Med 2011; 9: 81.
20. Jabbar A, Hussain SF, Khan AA. Clinical characteristics of pulmonary tuberculosis in adult Pakistani patients with co-existing diabetes mellitus. East Mediterr Health J 2006; 12: 522-7.
21. Usmani RA, Nasir MI, Wazir S, Pervaiz Z, Zahra T, Akhtar M. Diabetes mellitus among tuberculosis patients in a tertiary care hospital of Lahore. J Ayub Med Coll Abbottabad 2014; 26: 61-3.
22. Ayaz A, Hasan Z, Jafri S, Inayat R, Mangi R, Channa AA, et al. Characterizing Mycobacterium tuberculosis isolates from Karachi, Pakistan: drug resistance and genotypes. Int J Infect Dis 2012; 16: e303-e9.
23. Kumar NP, Moideen K, Dolla C, Kumaran P, Babu S. Prediabetes is associated with the modulation of antigen-specific Th1/Tc1 and Th17/Tc17 responses in latent Mycobacterium tuberculosis infection. PLoS One 2017; 12: e0178000.
24. Wang Z, Shen XH, Feng WM, Ye GF, Qiu W, Li B. Analysis of Inflammatory Mediators in Prediabetes and Newly Diagnosed Type 2 Diabetes Patients. J Diabetes Res 2016; 2016: 7965317.
25. Stanya KJ, Jacobi D, Liu S, Bhargava P, Dai L, Gangl MR, et al. Direct control of hepatic glucose production by interleukin-13 in mice. J Clin Invest 2013; 123: 261-71.
26. Niazi AK, Kalra S. Diabetes and tuberculosis: a review of the role of optimal glycemic control. J Diabetes Metab Disord 2012; 11: 28.