ISSN 2515-8260 Volume 09, Issue 03, 2022

ORIGINAL RESEARCH

Evaluation of adverse drug reactions in patients of diabetes mellitus on 1st line Anti-tubercular treatment

Dr. Abhay Verma[1], Dr. D.K. Katiyar[2], Dr. Ajay Kumar Verma[3], Dr. Arpita Singh[4], Dr. Himanshu[5]

[1]Junior resident-3, Department of pharmacology KGMU Lucknow, Uttar Pradesh, India;
[2]Professor, Department of pharmacology KGMU Lucknow, Uttar Pradesh, India;
[3]Professor (JG), Department of pharmacology KGMU Lucknow, Uttar Pradesh, India;
[4]Associate Professor Dr RMLIMS Lucknow, Uttar Pradesh, India;
[5]Associate Professor Department of Medicine KGMU Lucknow, Uttar Pradesh, India;

Corresponding author:
Dr. Arpita Singh, Associate Professor Dr RMLIMS Lucknow, Uttar Pradesh, India;

ABSTRACT

Aim: Evaluation of adverse drug reactions in patients of diabetes mellitus on 1st line Anti-tubercular treatment.

Methods: Patients presenting to the Medicine OPD (Diabetic clinic), and Respiratory medicine OPD, KGMU, on specified days of the week diagnosed to be diabetes mellitus with tuberculosis was screened based on selection criteria. Written informed consent was taken from patients. Demographic details of the participants were recorded in semi-structured proforma. The overall description of the adverse drug effect was done for the selected patients. Seriousness of adverse drug effects were evaluated. Assessment of the severity of adverse drug effects were done. Causality assessment of ADRs was assessed by the WHO-UMC causality assessment system and Naranjo's causality assessment scale. The severity of ADRs was assessed by Hartwig's Severity Assessment and scale.

Results: In our study, incidence of Adverse Drug Reactions (ADRs) in diabetes mellitus patients receiving 1st line antitubercular treatment was 61.82% (68). Out of 110 patients, 68 patients developed a total 83 ADRs. Most common system involved was gastrointestinal system (24, 28.92%) followed by hepatobiliary system (21, 25.30%) and dermatological system (17, 20.48%). Least common system involvement was oto-vestibular, musculoskeletal and urinary system. Most common ADRs were Hepatitis/Jaundice (25.30%), Pruritis/rashes (20.48%) and Nausea/Vomiting (14.46%). Epigastric pain, Diarrhoea, Anemia/thrombocytopenia, Peripheral neuropathy and Headache was reported in 7.23%, 6.02%, 7.23%, 3.60% and 3.60% of the subjects respectively. According to WHO causality assessment scale, majority of ADRs were classified as probable (48, 57.83%). Possible ADRs were found in 33.74% of the subjects. Certain ADRs were found in 2.41% of the subjects. According to Naranjo's causality assessment scale, majority of ADRs were classified as Probable (54, 65.06%). Possible ADRs were found in 30.12% of the subjects. Definite and Doubtful ADRs were reported in 2.41% of the subjects

According to Hartwig's severity assessment level, mild, moderate and severe ADRs were reported in 80.72%, 15.67% and 3.61% of the subjects respectively. According to kappa analysis, the strength of association between Naranjo's causality assessment scale and WHO Causality Assessment scale to assess ADR is good (kappa value: 0.72, p value: 0.008).

Conclusion: Most of the ADRs belonged to mild category according to the Modified Hartwig and Siegel scale for severity assessment. ADRs induced by ATT are common, which can result in discontinuation of treatment and development of resistant bacilli.
Keywords: adverse drug reactions , diabetes mellitus, Anti-tubercular treatment

Introduction

The International Federation of Diabetes (IDF) estimates that globally 425 million people or 8.8% of adults in the age group of 20-79 years have DM and that 90% of these are Type 2 or T2DM.[1,2] The IDF report further estimates that India carries nearly 17% [72.9 million (CI: 55.5-90.2)] of the global burden of DM. It is estimated that US$ 1.7 trillion (US$ 900 billion for high-income countries and US$ 800 billion for low- and middle-income countries) will be required for diabetes care for the period 2011 to 2030.[3] DM affects the disease presentation and clinical outcome of TB and vice versa.[4] This comorbidity is known since the beginning of the 20th century. However, recent increase in the number of DM patients, attributed mainly to the modern lifestyle changes, created interest to further assess the association between both diseases.[5] The co-epidemic is emerging predominantly in resource poor countries where the burden of DM is increasing and also TB is highly endemic.

Active TB and reactivation of latent infection have long been known to be a risk of DM. A recent systematic review demonstrated approximately 3 times higher risk of developing TB in DM patients than non-DM patients[14]. TB infection also deteriorates the glycemic control and reduces the effectiveness of DM management.[6]Multiple studies from different countries reported 12–44% of TB cases linked with DM at the time of TB diagnosis. The patients of pulmonary TB with DM experienced poor rate of sputum conversion at the end of 2-month regimen along with higher rates of treatment failure and deaths at the end of treatment as compared to non-DM patients.[7] The currently recommended treatment for new cases of drug-susceptible TB is a regimen of four first-line drugs: isoniazid (H), rifampicin (R), ethambutol (E) and pyrazinamide (Z). In 1995, the World Health Organization (WHO) launched the Directly Observed Treatment Short course (DOTS). DOTS is a standard regimen which requires the TB patient to continually take weight-based drug combinations of H, R, E, Z and/or streptomycin (S) for a designated time period and it is currently practiced.[8]

Treatment of tuberculosis involves more than one drug which is consumed for a long duration. The anti-TB therapy includes a long-time, wide spectrum of drugs, which can predispose patients to develop adverse drug reactions. The emergence of adverse reaction depends on the patient's characteristics and also on concomitant medication during therapy. The use of anti-DM medication may lead to interactions with antitubercular drugs. A subjective assessment is therefore essential to elucidate the factors associated with anti-TB medication adverse reaction, which may determine adherence and, therefore, therapy success.[9]

According to WHO, an adverse drug reaction (ADR) is defined as "any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function." ADRs cause serious problems like morbidity, mortality and high cost of patient care. Based on a systematic review conducted by Singh et al., the overall prevalence of ADRs with first line anti-TB drugs varied from 8.4% to 83.5%. The use of multi-drug regimens in TB treatment has been associated with undesirable ADRs at varying degrees of severity, such as hepatotoxicity, skin rashes, gastrointestinal disturbances, neurological disorders and musculoskeletal disorders. ADRs were observed more commonly in the intensive phase of TB treatment and did not differ between intermittent or daily intake of anti-TB drugs.[8].

Material and methods

The prospective, observational study was conducted in the Department of Pharmacology & Therapeutics in collaboration with the Department of Respiratory Medicine and the Department of Medicine of King George's Medical University (KGMU), Lucknow. After taking ethical clearance from the institutional ethical committee of KGMU diabetic patients with tuberculosis was recruited from the Medicine OPD (Diabetic clinic) and Respiratory Medicine OPD. Their consent for the participation in the project was obtained and they were enrolled for the project study. 110 patients diagnostic with prediabetes and diabetes[10]and tuberculosis[11]were included in this study

Inclusion criteria

- Subjects age more than 18 years of either sex.
- Subjects who are willing to sign the informed consent form.
- Diabetes mellitus patients who are on 1st line anti-tubercular treatment.
- Subjects having no associated comorbidities except Diabetes Mellitus.
- Patients having normal baseline (pre-treatment) parameters like liver function test, kidney function test, thyroid function test, chest x-ray other than blood sugar.

Exclusion criteria

- Subjects less than 18 years of age.
- Subjects who were unwilling to participate and did not give consent in the study.
- Subjects having immune/autoimmune disorder.
- Subjects with chronic liver diseases - cirrhosis, chronic hepatitis, acute viral hepatitis.
- Pregnant and lactating females.
- Subjects with incomplete medical records.

Methodology

Patients presenting to the Medicine OPD (Diabetic clinic), and Respiratory medicine OPD, KGMU, on specified days of the week diagnosed to be diabetes mellitus with tuberculosis was screened based on selection criteria. Written informed consent was taken from patients. Demographic details of the participants were recorded in semi-structured proforma. The overall description of the adverse drug effect was done for the selected patients. Seriousness of adverse drug effects were evaluated. Assessment of the severity of adverse drug effects were done. Causality assessment of ADRs was assessed by the WHO-UMC causality assessment system and Naranjo's causality assessment scale. The severity of ADRs was assessed by Hartwig's Severity Assessment and scale.

Results

This was a prospective observational study conducted in the Department of Pharmacology in collaboration with the Department of Respiratory Medicine and the Department of Medicine of King George's Medical University (KGMU) among 110 diabetes mellitus patients who are on 1stline anti-tubercular treatment. The aim of the study was to analyse the Adverse Drug Reactions (ADRs) in patients of diabetes mellitus receiving 1st line antitubercular treatment and to describe the health and demographic characteristics of patients of diabetes receiving 1stline antitubercular treatment.

Table 1: Gender and age distribution among the study subjects

Gender	**N**	**%**
Male	71	64.55
Female	39	35.45
Age Group (in years)		
18-30	13	11.82
31-40	46	41.82
41-50	23	20.91
51-60	11	10.00
>60	17	15.45
Total	110	100

Out of 110 subjects, 71 (64.55%) were males and 39 (35.45%) were females. Maximum subjects were from the age group of 31-40 years (41.82%) followed by 41-50 years (20.91%). Minimum subjects from the age group of 51-60 years (10%) followed by >60 years as well as 41-50.(table 1.) 60.91% and 39.09% of the subjects were from rural and urban area respectively. Education viz. illiterate, primary, secondary, graduate and above was revealed in 19.09%, 7.27%, 49.09% and 24.55% of the subjects respectively. Hence maximum subjects had studied up to secondary level followed by graduate level. The occupation among the study subjects 37.27%, 30.91% and 22.73% of the subjects were businessman, housemaker and student respectively.

Table 2: Signs and symptoms among the study subjects

Signs and Symptoms	**N**	**%**
Cough	92	83.64
Weight Loss	90	81.82
Night Sweat	63	57.27
Body Malaise	67	60.91
Blood in Sputum	17	15.45
Decreased Appetite	6	5.45

Table 2, shows the signs and symptoms among the study subjects. Cough, weight loss, night sweat, body malaise, blood in sputum and decreased appetite was reported among 83.64%, 81.82%, 57.27%, 60.91%, 15.45% and 5.45% of the subjects respectively.

Table 3: Personal habits among the study subjects

Habits	**N**	**%**
Alcohol	37	33.64
Smoking	46	41.82

Alcohol and smoking habits were found in 33.64% and 41.82% of the subjects respectively (table 3).

Table 4: Incidence of Adverse Drug Reactions (ADRs) in diabetes mellitus patients receiving 1st line antitubercular treatment

ADRs	**N**	**%**
Absent	42	38.18
Present	68	61.82
Total	110	100

In our study, incidence of Adverse Drug Reactions (ADRs) in diabetes mellitus patients receiving 1st line antitubercular treatment was 61.82% (68) as shown in table 8.
Out of 110 patients, 68 patients developed a total 83 ADRs.

Table 5: Pattern of ADRs

System	**ADRs**	**No. of ADR**	**%**	**Total ADRs=83**	**%**
Gastrointestinal System (GIT)	Nausea and Vomiting	12	14.46	24	28.92
	Epigastric Pain	6	7.23		
	Diarrhoea	5	6.02		
	Constipation	1	1.20		
Hepatobiliary System (HB)	Hepatitis/Jaundice	21	25.30	21	25.30
Dermatological system (DS)	Pruritis and rashes	17	20.48	17	20.48
Hematological system (HS)	Anemia and thrombocytopenia	6	7.23	6	7.23
Nervous system (NS)	Headache	3	3.60	5	6.02
	Dizziness	1	1.20		
	Anxiety	1	1.20		
Metabolic Disorder (MD)	Hyperuricemia	2	2.40	4	4.82
	Hyperglycemia	2	2.40		
Peripheral Nervous system (PNS)	Peripheral neuropathy	3	3.60	3	3.61
Oto-vestibular System (OTS)	Impaired Hearing	1	1.20	1	1.20
Musculoskeletal System (MS)	Arthralgia	1	1.20	1	1.20
Urinary System (US)	Dysuria	1	1.20	1	1.20

Table 5, shows the pattern of ADRs. Most common system involved was gastrointestinal system (24, 28.92%) followed by hepatobiliary system (21, 25.30%) and dermatological system (17, 20.48%). Least common system involvement was oto-vestibular, musculoskeletal and urinary system. Most common ADRs were Hepatitis/Jaundice (25.30%), Pruritis/rashes (20.48%) and Nausea/Vomiting (14.46%). Epigastric pain, Diarrhoea, Anemia/thrombocytopenia, Peripheral neuropathy and Headache was reported in 7.23%, 6.02%, 7.23%, 3.60% and 3.60% of the subjects respectively.

Table 6: ADR according to WHO Causality Assessment Scale

Category	**N**	**%**
Certain	2	2.41
Probable	48	57.83
Possible	28	33.74
Unlikely	5	6.02
Unclassified	0	0
Unclassifiable	0	0
Total	83	100

According to WHO causality assessment scale, majority of ADRs were classified as probable (48, 57.83%). Possible ADRs were found in 33.74% of the subjects. Certain ADRs were found in 2.41% of the subjects (table 6, and table 7).

Table 7: Categorization of ADRs by using WHO Causality Assessment scale

ADRs	**No. of ADR**	**Certain**		**Probable**		**Possible**		**Unlikely**	
		N=2	**%**	**N=48**	**%**	**N=28**	**%**	**N=5**	**%**
Nausea and Vomiting	12	0	0	7	14.58	4	14.29	1	20
Epigastric Pain	6	0	0	4	8.33	2	7.14	0	0
Diarrhoea	5	0	0	3	6.25	2	7.14	0	0
Constipation	1	0	0	0	0.00	0	0.00	1	20
Hepatitis/Jaundice	21	2	100	11	22.92	5	17.86	3	60
Pruritis and rashes	17	0	0	10	20.83	7	25.00	0	0
Anemia and thrombocytopenia	6	0	0	3	6.25	3	10.71	0	0
Headache	3	0	0	2	4.17	1	3.57	0	0
Dizziness	1	0	0	1	2.08	0	0.00	0	0
Anxiety	1	0	0	0	0.00	1	3.57	0	0
Hyperuricemia	2	0	0	1	2.08	1	3.57	0	0
Hyperglycemia	2	0	0	1	2.08	1	3.57	0	0
Peripheral neuropathy	3	0	0	3	6.25	0	0.00	0	0
Impaired Hearing	1	0	0	0	0.00	1	3.57	0	0
Arthralgia	1	0	0	1	2.08	0	0.00	0	0
Dysuria	1	0	0	1	2.08	0	0.00	0	0

Table 8: ADRs by using Naranjo's causality assessment scale

Category	**N**	**%**
Definite	2	2.41
Probable	54	65.06
Possible	25	30.12
Doubtful	2	2.41
Total	83	100

According to Naranjo's causality assessment scale, majority of ADRs were classified as Probable (54, 65.06%). Possible ADRs were found in 30.12% of the subjects. Definite and Doubtful ADRs were reported in 2.41% of the subjects (table 8 and table 9).

Table 9: Categorization of ADRs by using Naranjo's causality assessment scale

ADRs	**No. of ADR**	**Definite**		**Probable**		**Possible**		**Doubtful**	
		N=2	**%**	**N=54**	**%**	**N=25**	**%**	**N=2**	**%**
Nausea and Vomiting	12	0	0	7	12.96	4	16	1	50
Epigastric Pain	6	0	0	4	7.41	2	8	0	0
Diarrhoea	5	0	0	3	5.56	2	8	0	0
Constipation	1	0	0	0	0.00	0	0	1	50
Hepatitis/Jaundice	21	2	100	11	20.37	8	32	0	0
Pruritis and rashes	17	0	0	11	20.37	6	24	0	0
Anemia and	6	0	0	4	7.41	2	8	0	0

thrombocytopenia									
Headache	3	0	0	3	5.56	0	0	0	0
Dizziness	1	0	0	1	1.85	0	0	0	0
Anxiety	1	0	0	1	1.85	0	0	0	0
Hyperuricemia	2	0	0	1	1.85	1	4	0	0
Hyperglycemia	2	0	0	2	3.70	0	0	0	0
Peripheral neuropathy	3	0	0	3	5.56	0	0	0	0
Impaired Hearing	1	0	0	1	1.85	0	0	0	0
Arthralgia	1	0	0	1	1.85	0	0	0	0
Dysuria	1	0	0	1	1.85	0	0	0	0

Table 10: Categorization of ADRs by using Hartwig's Severity Assessment Level

Category	**N**	**%**
Mild	67	80.72
Moderate	13	15.67
Severe	3	3.61
Total	83	100

According to Hartwig's severity assessment level, mild, moderate and severe ADRs were reported in 80.72%, 15.67% and 3.61% of the subjects respectively (table 10).

Table 11: Comparison of Naranjo's causality assessment scale and WHO Causality Assessment scale

WHO Causality Assessment scale			**Naranjo's causality assessment scale**		
Categories	**N**	**%**	**Category**	**N**	**%**
Certain	2	2.41	Definite	2	2.41
Probable	48	57.83	Probable	54	65.06
Possible	28	33.74	Possible	25	30.12
Unlikely	5	6.02	Doubtful	2	2.41
Unclassified	0	0			
Unclassifiable	0	0			
Total	83	100	Total	83	100
Kappa Value	0.72				
p value	0.008*				

*: statistically significant

Table 11, shows the comparison of Naranjo's causality assessment scale and WHO Causality Assessment scale. According to kappa analysis, the strength of association between Naranjo's causality assessment scale and WHO Causality Assessment scale to assess ADR is good (kappa value: 0.72, p value: 0.008).

Discussion

Out of 110 subjects, 71 (64.55%) were males and 39 (35.45%) were females in our study. Chaudhary A et al in their study showed that most of the patients were male (57.9%)[49]. Ali NasirSiddiqui et al[9] in their study found similar male dominancy. M. Kiran et al[13] in their study similarly found male preponderance.

Maximum subjects were from the age group of 31-40 years (41.82%) followed by 41-50 years (20.91%). Minimum subjects from the age group of 51-60 years (10%) followed by 18-

30 years as well as >60 years in our study. According to ChaudharyA et al12 [49], most of the patients were aged 21-40 years. Majority of ADRs belonged to age group 31-40 years (25.67%) as mentioned by M. Kiran et al[13] in their study. In a study by Ali NasirSiddiquiet al[9], mean age among the study subjects was 44.04 years.

Cough, weight loss, night sweat, body malaise, blood in sputum and decreased appetite was reported among 83.64%, 81.82%, 57.27%, 60.91%, 15.45% and 5.45% of the subjects respectively in our study. Ali NasirSiddiqui et al[9] in their study reported similar sign and symptoms too. Alisjahbana et al too revealed similar findings.14[18]. Fever (78.6%) was the most common sign at the time of diagnosis followed by cough (73.8%), weight loss (69.8%), night sweats (52.4%), malaise (50.8%) and blood in sputum (20.6%) as mentioned by Chaudhary A et al[12] in their study. Cough with expectoration was the most common presenting symptom as reported by Acharyaet al.[15]

Incidence of Adverse Drug Reactions (ADRs) in diabetes mellitus patients receiving 1st line antitubercular treatment was 61.82% (68). Most common system involved was gastrointestinal system (24, 28.92%) followed by hepatobiliary system (21, 25.30%) and dermatological system (17, 20.48%). Least common system involvement was oto-vestibular, musculoskeletal and urinary system. Most common ADRs were Hepatitis/Jaundice (25.30%), Pruritis/rashes (20.48%) and Nausea/Vomiting (14.46%). Epigastric pain, Diarrhoea, Anemia/thrombocytopenia, Peripheral neuropathy and Headache was reported in 7.23%, 6.02%, 7.23%, 3.60% and 3.60% of the subjects respectively. This increased incidence of ADRs may be due to the association of all the first line ATT drugs with gastrointestinal intolerance. Incidence of ADRs was 79.22% as mentioned by M. Kiranet al[13] in their study when compared to other regimens. Most common ADRs were from gastrointestinal (26.7%) and hepatobiliary (26.7%) system. ADRs under gastrointestinal system included nausea, epigastric pain and vomiting. A study by Sinha K et al showed that 64.71% of the subjects had ADRs.[16]

According to WHO causality assessment scale, majority of ADRs were classified as probable (48, 57.83%). Possible ADRs were found in 33.74% of the subjects. Certain ADRs were found in 2.41% of the patients. Unlikely ADRs were reported in 6.02% of subjects in our study. According to M. Kiranet al[13], majority of ADRs were classified as probable with WHO causality scale contributing to 59.45% of the subjects, which is similar to our study.

According to Naranjo's causality assessment scale, majority of ADRs were classified as probable (54, 65.06%). Possible ADRs were found in 30.12% of the subjects. Definite and Doubtful ADRs were reported in 2.41% each of the subjects in this study. According to M. Kiranet al[13], majority of ADRs were classified as probable with Naranjo's algorithm contributing to 78.37% of the subjects. ADRs classified as 'definite' constituted only 5.4% which can be explained as placebo effect was not studied and laboratory investigations were not done to determine the concentration of drug in body fluids.[13] According to kappa analysis, the strength of association between Naranjo's causality assessment scale and WHO Causality Assessment scale to assess ADR is good (kappa value: 0.72, p value: 0.008) in our study. However there was disagreement in causality assessment between two scales with respect to "probable" and "possible" criteria. This can occur due to differences in dechallenge pattern, timing of event and alternative etiological factors.[13]Naranjo's algorithm is simple, of high clarity and brief, in addition to less inter-rater disagreement when compared to the other scales. But validity of this scale is not consistent with pediatric population. Even though WHO-causality scale is convenient to use, it is non-probabilistic and generates unpredictability during evaluation. But both the methods are valuable in assessment of ADRs and to understand its scientific basis.

ADRs can result in discontinuation of drug or hospitalization or sometimes even death. To assess the severity of occurred reaction Modified Hartwig and Siegel scale was used.

According to Hartwig's severity assessment level, mild, moderate and severe ADRs were reported in 80.72%, 15.67% and 3.61% of the subjects respectively in our study. Out of 74 patients, 50 (67.56%) belonged to mild category which required no change in medication followed by 23 (31.08%) patients who belonged to moderate class as mentioned by M. Kiran et al[13] in their study. These findings were similar to Maqusood M et al that majority of ADRs were categorized as mild (75.94%).[17]

Conclusion

Gastrointestinal side effects and hepatotoxicity were the most frequently observed ADRs, followed by pruritus and rashes. As per WHO-causality scale and Naranjo's causality algorithm majority of ADRs were probable. Most of the ADRs belonged to mild category according to the Modified Hartwig and Siegel scale for severity assessment. ADRs induced by ATT are common, which can result in discontinuation of treatment and development of resistant bacilli. Hence counseling of patients regarding their life style with early detection and management will minimize the occurrence of ADRs and improve the adherence to treatment.

References

1. Chatterjee S, Khunti K, Davies MJ. Type 2 diabetes. The Lancet. 2017 3; 389(10085):2239-51.
2. International Diabetes Federation IDF Diabetes Atlas. 8th ed. Brussels, Belgium, Available at https://www.idf.org/elibrary/epidemiology-research/diabetes-atlas.html
3. Bloom DE, Cafiero ET, Jané-Llopis E, Abrahams-Gessel S, Bloom LR, Fathima S, et al. The global economic burden of non-communicable diseases (Working Paper Series). Geneva: Harvard School of Public Health and World Economic Forum; 2011.
4. Dooley KE, Chaisson RE. Tuberculosis and diabetes mellitus: convergence of two epidemics. Lancet Infect Dis. 2009;9(12):737-46.
5. Bukhary ZA. Rediscovering the association between tuberculosis and diabetes mellitus: a perspective. J TaibahUni Med Sci. 2008;3(1):1-6.
6. Diabetes TL. Diabetes and tuberculosis—a wake-up call. Lancet Diabetes Endocrinol. 2014;2(9):677.
7. MorsyAM, Zaher HH, Hassan MH, Shouman A. Predictors of treatment failure among tuberculosis patients under DOTS strategy in Egypt. EMHJ-Eastern Mediterr Health J.2003;9 (4);689-701.
8. Cheah MF, Zainal H, Hyder Ali IA. Evaluation of adverse reactions induced by anti-tuberculosis drugs in Hospital Pulau Pinang. Malays J Med Sci. 2018;25(5):103–114
9. Siddiqui AN, Khayyam KU, Sharma M. Effect of diabetes mellitus on tuberculosis treatment outcome and adverse reactions in patients receiving directly observed treatment strategy in India: a prospective study. BioMed Res Int 2016;2016
10. Care D, Suppl SS. Classification and diagnosis of diabetes: Standards of medical care in Diabetes 2018. Diabetes Care. 2018;41(January):S13–27.
11. Chaudhuri A. Recent changes in technical and operational guidelines for tuberculosis control programme in India - 2016: A paradigm shift in tuberculosis control. J Assoc Chest Physicians. 2017;5(1):1
12. Chaudhary A, Sarraf DP, Bhattarai NR, Chaudhary A, Rauniar GP. Clinical Profile, Drug Utilization Pattern and Adverse Drug Reactions of Anti-tubercular Drugs at DOTS Center in a Tertiary Hospital. Nepal Med Coll J. 2020;22(3):158-66
13. Kiran M, Nagabushan H. Adverse Drug Reactions Monitoring in Patients on Antitubercular Treatment in Tertiary Care Hospital, Mandya. Biomed Pharmacol J 2021;14(2).

ISSN 2515-8260 Volume 09, Issue 03, 2022

14. Alisjahbana B, Sahiratmadja E, Nelwan EJ, Purwa AM, Ahmad Y, Ottenhoff TH, Nelwan RH, Parwati I, Meer JW, Crevel RV. The effect of type 2 diabetes mellitus on the presentation and treatment response of pulmonary tuberculosis. Clin Infect Dis 2007;45(4):428-35.
15. D Acharya, JP Majra. A clinical-epidemiological study of tuberculosis among hospitalized cases in Dakshina Kannada district of Karataka. NTI Bulletin 2007; 43: 43-6.
16. Sinha K, Marak IR, Singh W A. Adverse drug reactions in tuberculosis patients due to directly observed treatment strategy therapy: Experience at an outpatient clinic of a teaching hospital in the city of Imphal, Manipur, India. J Assoc Chest Physicians.2013; 1:50-53.
17. Maqusood M, Khan F A, Swaroop A. A Study on Incidence of Adverse Drug Reaction of AntiTubercular Drugs in New Cases of Pulmonary Tuberculosis in a Tertiary Care Teaching Hospital. Int J Med Res Prof.2016; 2(3):53-56