GENDER WISE CLINICAL RESPONSE OF ANTI-TUBERCULOSIS THERAPY (ATT): A PROSPECTIVE COHORT STUDY FROM LAHORE, PAKISTAN

[1]SALEEM Z, [1]SAEED H, [1]SALEEM N, [2]FAROOQ MS, [1]MASOOD A, [1]ASLAM S, [1]QAMAR M, [1]KHALID M, [1]ISLAM M, [1]HASHMI FK, [3]HASSALI MA

[1]Department of Clinical Pharmacy, Punjab University College of Pharmacy, University of the Punjab, AllamaIqbal Campus, 54000, Lahore, Pakistan

[2]Mayo Hospitals, 54000, Lahore, Pakistan

[3]School of Pharmaceutical Sciences, UniversitiSains Malaysia, Malaysia

*Corresponding Author: Email: Zikria Saleem: zikria.pharmacy@pu.edu.pk; Phone number: +92322-9801981

Place of work: Gulab Devi Chest Hospital Lahore and Punjab University College of Pharmacy Lahore, Pakistan

ABSTRACT

Objective: The aim of this study is to determine the gender wise adherence and clinical response to the DOT program in hospitalized patients. Several evidences collected by literature survey suggest that untimely diagnosis and non-adherence to therapy are main barriers to the management and completion of tuberculosis (TB) therapy. Directly observed therapy (DOT) was adopted to control TB pandemic–targeting treatment completion rates and drug resistance. However, there is lack of clinical DOT data on gender wise difference of response from Pakistan.

Design: This is a prospective study of TB DOT patients enrolled from tertiary care hospital.

Methods: The study was conducted by following a total of 302 patients enrolled under DOT program. Out of 302 patients enrolled in initial intensive DOT phase, only 51 subjects were followed till the end of a therapy.

Result: Patients on Anti TB therapy complained of fever (F; 75.94%, M; 79.86%), night sweat (F; 80.37%, M; 72.91%), cough with sputum (F; 81.64%, M; 86.1), loss of appetite (F; 84.17%, M; 85.41%), weight loss (F; 52.53%, M; 72.91%), shortness of breath (F; 75.31%, M; 72.91%), day and night cough (F; 62.65%, M; 73.61%) and weakness (F; 91.77%, M; 90.97%). The major adverse effects of the therapy, such as, itching problem (F; 34.17%, M; 29.86%), kidney stones (F; 25.94%, M; 43.05%), right quadrant discomfort (F; 39.87%, M; 29.17%) and minor side effects were more common in males. However, these complaints were resolved after completion of therapy. It was observed that cure rate (F; 31.37%, M; 54.90) and treatment completion (F; 33.33%, M; 58.82%) was more in males than females. However deaths (F; 2%, M; 0), treatment failure (F; 0, M; 2%) and defaulted/complaint (F; 2%, M; 9.80%) were more in females than in males.

Conclusion: Tuberculosis is still a major public health problem in remote areas having low educational background and lack of follow-up. Adherence and clinical response was more in males than females which demands further implementation of TB intervention and network participation of the patients and public health departments to ensure the achievement of minimum disease burden.

Keywords: Adherence, Center based DOT, Directly Observed Therapy, Self Administered Therapy, Tuberculosis,

Abbreviations: DOT (Directly observed therapy), SAT (Self administered therapy), TB (Tuberculosis), ATT (anti tuberculosis therapy), HTN (Hypertension), Hb (Hemoglobin)

1. INTRODUCTION:

Despite significant advancement in the treatment of tuberculosis (T.B), a chronic infectious condition caused by *Mycobacterium tuberculosis*, TB remains the leading cause of severe malady and mortality, particularly in developing countries, such as Pakistan [1]. According to a published report, 95% of TB cases and 98% of TB related deaths occur in developing countries. Moreover, TB is ranked as 8th leading cause of deaths in low and middle income countries [2, 3]. Pakistan is ranked among 22 countries that have high TB burden [4]. Despite development of DOT program to decrease the prevalence of TB, it still remains the most commonly reported disease – 374 out of 100,000 in 2009, in Pakistan. Despite improvements in the care and treatment practices, several issues, such as socioeconomic status of patients,

untrained practitioners and suboptimal or surcease detection still persist [4, 5]. One of the chief barriers in controlling TB is the duration of therapy – maximum six months, leading to discontinuation half way through the course and not even starting with the medication [6, 7]. In this context several studies have shown that non-adherence, discontinuation and inability to continue the TB medication resulted in increased TB burden, decreased chances of cure, higher risk of relapse and [8] Thus, direct observation of TB patients which was first opted in 1950s resulted in significant improvements in treatment completion rates and reduced drug resistance patterns; later adopted by WHO as its main tactic to combat growing TB menace [7, 9]. The success of DOT program has been documented by several literature reports, suggesting a significant rise in the proportion of cured patients [1, 7]. However, literature evidences also suggest that DOT program is questionable in certain settings such as those having higher TB burden/caseloads and constrained resources -particularly developing countries, coupled with dysfunctional politics affecting health official's capacity to implement DOT program [10].

However, in Pakistan, several social and cultural factors add to the complexities such as self professed conviction to abandon therapy after symptomatic relief sans realizing recommended duration, poor health literacy coupled with outmoded and deranged beliefs, influenced by culture leads, breeding wrong information regarding disease and therapy which affect over all cure rate [11, 12]. Biologically differences in genders impose more threat to the females than males particularly during reproductive stage. Furthermore, Tuberculosis fear and stigma has more impact on women than men effecting not only the treatment but also the family and society .[13]. Despite these factors women are more compliant to the treatment than males [14]. Previous studies conducted in Pakistan have pointed out factors affecting the implementation as well as practical aspects of universal DOT program which influence outcomes, yet none of them was of gender wise clinical response difference from Pakistan [1]. Thus, this study was aimed at examining the impact of Lahore based clinical DOTS program on gender wise TB cure rates; taking into account patient's socio-demographics variables, clinical characteristics and therapy related adverse effects.

2. SUBJECTS AND METHOD:

2.1 Ethical Approval:

The approval for study was taken from Ethical Committee, Punjab University College of Pharmacy, University of the Punjab and Gulab Devi chest hospital Lahore. Informed consent was obtained from the enrolled patients.

2.2 Study Population and Center:

A total 302 patients, 158 females and 144 males, were enrolled in this study and were directly observed for treatment. The study was conducted in Gulab Devi Chest Hospital Lahore, the largest cardiothoracic center in South Asia - specialized respiratory disease center, particularly tuberculosis.

2.3 Study Design:

It was a prospective study design to determine the gender wise adherence and clinical response to the DOT program in hospitalized patients and they were followed at particular intervals. An overview of the study is shown in **Figure 1.**

Inclusion criteria: Following was the inclusion criteria: patients under anti-tubercle treatment (ATT) for more than two weeks and registered under DOT program based on their clinical presentation, X-Ray examination and smear AFB test (either positive or negative).

Exclusion criteria: Patients were excluded based on the following criteria: under ATT for less than two weeks, vivid TB symptoms but not under ATT and patients on standby therapy.

2.4 Data Collection:

A review of the literature on the TB treatment was done and a questionnaire was designed based on the various variables such as demographics, clinical presentation, drug's adverse effects, laboratory values and co-morbidities related to TB treatment adherence. A prospective study was conducted in general wards of Gulab Devi Chest Hospital from February, 2015 to November, 2015. Patients of two categories i.e CAT 1 and CAT 2 were admitted in hospital. Newly diagnosed patients were categorized as CAT 1 whereas retreatment patients were under CAT 2 category. Different therapy strategies based on the clinical symptoms, age, weight and other co-morbidities were adopted by the physician. Different combinations of ATT drugs such as Rifampicin, Isoniazid, Pyrazinamide, Ethambutol and Streptomycin in different dosage forms and different strengths were administered to patients. Streptomycin was administered parentally while other ATT drugs were given orally. Patients suffering from other diseases were using medications

for the respective condition. Under DOT program, patients were registered in the hospitals and specific DOT numbers were issued to them to ensure compliance with treatment. After improvement in clinical condition or negative result of smear test, patients were referred on their discharge to anti TB centers in their home towns to complete their treatment. Patients were advised to visit assigned centers every month for check up. Under National TB control Program of Pakistan, Anti TB medicines were provided to patients in those centers.

2.5   Data Analysis:

Data was analyzed by SPSS (Statistical package for social sciences) version 21. Descriptive statistics was applied to compare different parameters gender wise. This gives the OR (odd ratio) and p-values of different parameters.
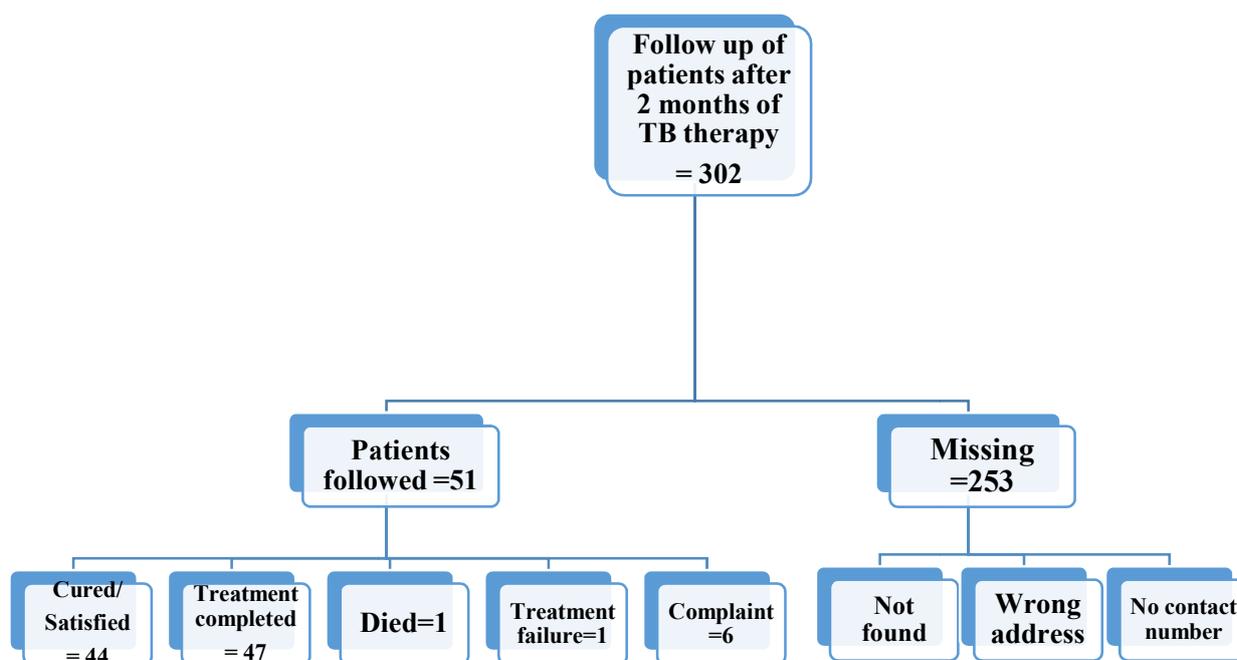

Figure 1: Overview of the study

3.   RESULTS:

3.1   Socio-Demographic data:

Table 1 shows the basic demographic and clinical presentation of the patient's gender-wise arms. The mean age of males was 44.77 ± 18.58420 and that of female was 32.8 ± 17.37792. However, mean age of followed male patients was 40.68 whereas of followed female was; 41.16 years). Percentage of females married was 60.75%. Percentage of married males was 81.25%). However, percentage of followed

married females was 67% whereas percentage of followed married male was 68%. Education was also a major contributing factor in prevalence of the disease as (F; 57%, M; 65.28%) were illiterate while (64%) of followed patients were also illiterate. Socio-economic status was also found to have a great impact on this disease as (F; 82.27%, M; 79.16%) were from a poor family having monthly income less than 20,000 rupees.   50 percent of the population belonged to rural area whereas 50 percent of the population belonged to urban area to while (F; 99.3%, M; 97.7%) were living with their families. Half of the total male population was smokers. Both newly diagnosed and relapsed cases were included in the study. Naïve (F; 82.2%, M; 76.3%) while (F; 17.8%, M; 23.7%) were of relapsed or CAT2 respectively.

3.2   Signs and Symptoms:

There were significant symptoms like Fever (F; 75.94%, M; 79.86%) with (OR;1.260, *p*; 0.414), Night sweat (F; 80.37%, M; 72.91%) (OR; O.66, *p*; 0.125), Cough with sputum (F; 81.64%, M; 86.1) (OR; 1.39, *p*; 0.293), Loss of appetite (F; 84.17%, M; 85.41%) (OR; 1.10, *p*; 0.766), Weight loss (F; 52.53%, M; 72.91%) (OR; 2.43), Shortness of breath (F; 75.31%, M; 72.91%) (OR; 0.88), Day and Night cough (F; 62.65%, M; 73.61%) with

(OR; 1.66, *p*; 0.042) and Weakness (F; 91.77%, M; 90.97%), with (OR; 0.90, *p*; 0.804). However, these symptoms were resolved with continued therapy and were present in a very low percentage in followed patients. Comparison of disease associated sign and symptoms in followed and DOT patients shown in **Figure 2. Figure 2** provides information both males and females. However, these symptoms were resolved within8 months of therapy. These symptoms vanished particularly in patients who were followed up as most of them had completed their therapy. Certain symptoms associated with TB such as Blood in sputum, Wheezing, Tightness in Chest, and failure to quick response to inhaler.

3.3   Concomitant diseases:

Some of the patients included in the study were suffering from co-morbidities. However, it was found that chronic obstructive disease, Diabetes mellitus and chronic heart disease were more prevalent in the study population. A comparison reflect that the percentage of people suffering from diabetes mellitus was greater (F; 17.08%, M; 19.44%) (OR; 1.17, *p*; 0.596) than those suffering from chronic obstructive disease (F; 10.12%, M; 22.22%)(OR; 2.54, p; 0.004) and heart disease (F; 12.02%, M; 8.33%) with (OR; 0.67, *p*; 0.291).

3.4   Side effects:

The adverse effects of the ATT (Anti tuberculosis therapy) are mentioned in **Table 3**.Itching problem was more prevalent in Females (F; 34.17%, M; 29.86%) (OR; 0.82, p; 0.422) whereas kidney stones (F; 25.94%, M; 43.05%) (OR; 2.16, p; 0.002) and Right quadrant discomfort is about (F; 39.87%, M; 29.17%) with (OR; 0.62, p; 0.051). However, flushing of skin, dizziness, sedation, hypertension during treatment, controlled HTN, paralysis attack; pain and swallowing in joints were found to be minor adverse effects. Minor adverse effects were also apparent in followed patients but the compliant resolved after completion of therapy. A comparison of adverse effects of therapy in DOT and followed patients – both males and females as shown in **Figures 3**.Adverse effects were absent in the study population which was followed under DOT program.

3.5   Clinical Outcome:

Table 4 shows the results of Lab values based on gender where the mean values for fasting blood sugar level (F; 77.6667g/dL$\pm$33.77, M; 77.1250g/dL$\pm$12.53) and Random Blood sugar level (F; 107.51g/dL$\pm$59.92, M; 112.59g/dL$\pm$58.56) respectively. Mean values for ESR level were measured as (F; 73.57$\pm$35.74, M; 66.35$\pm$34.59), Systolic B.P (F; 111.53 mmHg$\pm$16.50, M; 109.9 mmHg$\pm$9.13), Diastolic B.P (F; 75.61mmHg$\pm$8.45, M; 71.26 mmHg$\pm$7.27), Serum ALT (F; 34.55$\pm$17.13, M; 34.88$\pm$17.77), Serum AST (F; 28.18$\pm$13.00, M; 31.00 $\pm$15.64) and Bilirubin level (F; 0.82mg/dL$\pm$0.64, M; 0.82mg/dL$\pm$0.60397) respectively. **Table 5** represents the outcome of the study which shows cure rate (F; 31.37%, M; 54.90), treatment completed (F; 33.33%, M; 58.82%) more in males than females. However deaths (F; 2%, M; 0), treatment failure (F; 0, M; 2%) and defaulted/complaint (F; 2%, M; 9.80%) were more in females than in males. However, the cure rate of overall population could not be inferred due to unavailability of complete data of patients suffering from TB; unable to contact some patients after their discharge from hospital.

Table 1: Demographics and Diagnosis of TB DOT patients (CI= Confidence Interval) OR (Odd Ratio)

Parameters		Female (n=158)	Male (n=144)	OR (95%CI)	*P*-Value
Age (Mean +S.D)		32.87 +18.58	44.77+17.37	7.81-15.98	0.000
Education	Literate	68 (43.03)	50 (34.7)	1.24 (0.44-1.12)	0.139
	Illiterate	90 (57.00)	94 (65.28)	0.87 (0.73-1.05)	0.139
Residence	Rural	75 (47.5)	83 (57.6)	0.82 (0.67-1.02)	0.77
	Urban	83 (52.5)	61 (42.4)	1.24 (0.97-1.58)	0.77
Weight	<50 kg	101 (63.92)	76 (52.77)	0.75 (0.12-0.29)	<0.0001
	>50 kg	57 (36.07)	68 (47.22)	-	-
Marital status	Married	96 (60.75)	117 (81.25)	0.75 (0.65-0.87)	0.000
	Single	62 (39.2)	27 (18.8)	2.09 (1.42-3.10)	0.000
Social Living	Alone	1 (0.63)	3 (2.1)	0.30 (0.03-2.88)	0.271
	With Family	157 (99.36)	141 (97.91)	1.02 (0.99-1.04)	0.271
Smoking		3 (1.89)	72 (50)	51.67 (15.7-169.7)	0.000
Socioeconomic status	Average	28 (17.72)	30 (20.83)	0.85 (0.54-1.35)	0.493
	Poor	130 (82.27)	114 (79.16)	1.04 (0.93-1.16)	0.493
Clinical Presentation	Naïve	130 (82.27)	110 (76.38)	1.08 (0.96-1.21)	0.206
	Relapsed	28 (17.72)	34 (23.61)	0.76 (0.48-1.17)	0.206
Supervised	Centre Based DOT	158 (100)	144 (100)	-	-

Table 2: Symptoms and Concomitant diseases in TB DOT patients

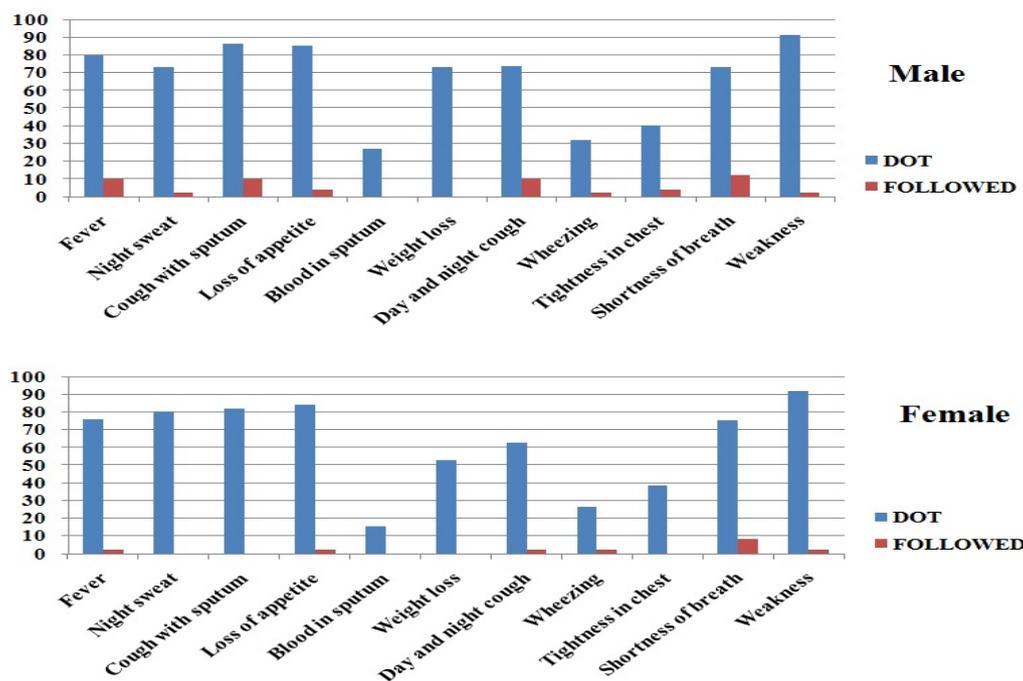| Parameters	Female (n=158)	Male (n=144)	OR (95%CI)	*P*-Value
Fever	120 (75.94)	115 (79.86)	1.26 (0.73-2.17)	0.414
Night sweats	127 (80.37)	105 (72.91)	0.66 (0.39-1.13)	0.125
Cough with sputum	129 (81.64)	124 (86.11)	1.39 (0.75-2.60)	0.293
Loss of appetite	133 (84.17)	123 (85.41)	1.10 (0.59-2.07)	0.766
Blood in sputum	24 (15.18)	39 (27.08)	2.07 (1.17-3.66)	0.011
Weight loss	83 (52.53)	105 (72.91)	2.43 (1.50-3.94)	0.000
Day and night cough	99 (62.65)	106 (73.61)	1.66 (1.02-2.72)	0.042
Wheezing	42 (26.58)	46 (31.94)	1.30 (0.79-2.13)	0.306
Chest Stiffness	61 (38.60)	58 (40.27)	1.07 (0.68-1.70)	0.767
Shortness of breath	119 (75.31)	105 (72.91)	0.88 (0.53-1.48)	0.634
Weakness	145 (91.77)	131 (90.97)	0.90 (0.40-2.02)	0.804
Concomitant Disease				
Asthma	4 (2.53)	8 (5.55)	2.27 (0.67-7.67)	0.179
Chronic obstructive pulmonarydisease	16 (10.12)	32 (22.22)	2.54 (1.33-4.86)	0.004
Heart diseases	19 (12.02)	12 (8.33)	0.67 (0.31-1.42)	0.291
Diabetes mellitus	27 (17.08)	28 (19.44)	1.17 (0.65-2.10)	0.596
Kidney disease	3 (1.89)	2 (1.38)	0.73 (0.12-4.42)	0.729
Hepatic disease	10 (6.32)	19 (13.19)	2.25 (1.01-5.01)	0.043
Allergy	6 (3.79)	7 (4.86)	1.29 (0.43-3.95	0.649

Figure 2: Comparison of TB symptoms in Males and Females of DOT (direct observed therapy) and Followed patients

Table 3: Side Effects in TB DOT patients

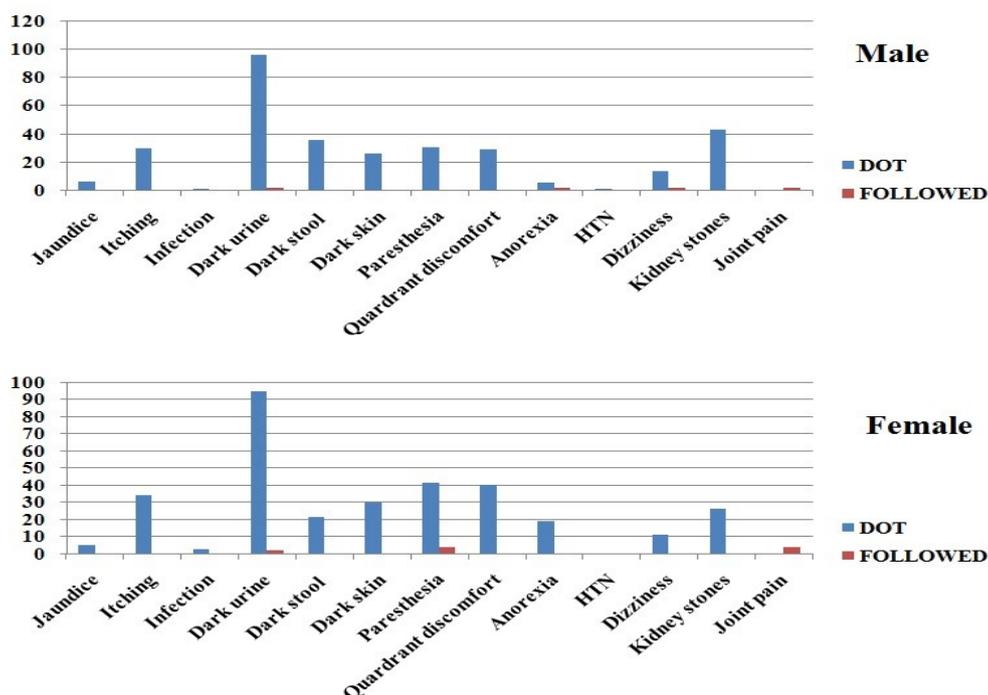| Parameters	Female (n=158)	Male (n=144)	OR (95%CI)	*P*-Value
Jaundice	8 (5.06)	9 (6.25)	1.25 (0.47-3.33)	0.655
Itching problem	54 (34.17)	43 (29.86)	0.82 (0.51-1.33)	0.422
Bacterial infection	4 (2.53)	2 (1.38)	0.54 (0.10-3.00)	0.477
Dark Urine	149 (94.3)	138 (95.8)	0.72 (0.25-2.08)	0.541
Dark Stool	34 (21.51)	51 (35.41)	0.49 (0.29-0.81)	0.005
Dark Skin	47 (29.7)	37 (25.7)	1.22 (.74-2.03)	0.432
Paresthesia in hands or feet	65 (41.14)	44 (30.55)	0.63 (0.40-1.01)	0.056
Right quadrant discomfort	63 (39.87)	42 (29.17)	0.62 (0.39-1.00)	0.051
Anorexia	30 (18.98)	8 (5.55)	0.25 (0.11-0.57)	0.000
HTN during treatment	0	1 (0.7)	0.48 (0.420.54)	0.294
Dizziness	17(10.76)	19(13.2)	1.27 (0.63-2.53)	0.514
Kidney stones	41(25.94)	62(43.05)	2.16 (1.33-3.50)	0.002

Figure 3: Side effects in Males Females of DOT (direct observed therapy) and Followed patients

Table 4: Lab values of TB DOT patients

Parameters			Follow up DOT After 2 months	
	Mean		**P-value**	**95% CI**
	Female (n=158)	**Male (n=144)**		
Sputum test (+)	82	78	-	-
Fasting Glucose level	77.6667+33.776	77.1250 +12.537	0.953	-19.34-18.25
Random Glucose level	107.51+59.921	112.259 +58.567	0.503	-9.85-20.02
ESR (before therapy)	73.5724+35.74092	66.3525 +34.595	0.085	-15.44-1.00
Creatinine level	0.5976 ±0.115	0.6444 +0.126	0.589	-2.543-2.90
Urea level	22.765 ±5.978	24.4841 +6.660	0.679	-178-198
Systolic B.P	111.533+16.501	109.901 +9.137	0.392	-5.36-2.11
Diastolic B.P	75.6140 +8.456	71.2613 +7.276	0.001	-6.83--1.88
Serum ALT	34.55+17.137	34.88 +17.772	0.968	-16.73-17.39
Serum AST	28.18+13.006	31.00 +15.648	0.674	-11.06-16.69
Bilirubin level	0.8265+0.643	0.8217 +0.604	0.948	-0.15-0.14
Hb level	11.192+2.255	21.342 +93.529	0.182	-4.78-25.08

Table 5: Outcome of the patients enrolled in study under TB DOT

Outcome	Female N (%)	Male N (%)
Cured	16 (31.37)	28 (54.90)
Treatment completed	17 (33.33)	30 (58.82)
Died	1 (2)	0 (0)
Treatment failure	0 (0)	1 (2)
Defaulted/Complaint	1 (2)	5 (9.80)

4. DISCUSSION:

This study was based on the patients who were enrolled under direct observed therapy (DOT) program for tuberculosis. The socio-economic status of people is found to be an important factor in the treatment course and onset of the disease. Literate people are more aware about the risk factors associated with the disease and they have good hygienic life style. In contrast, illiterate people having low financial status and living in densely populated areas were prone to infection caused by Mycobacterium. Therefore, it was found that life style plays a great role in the onset as well as in the treatment of Tuberculosis among the gender [15]. Congested environment is an important factor in transmission of the disease via air borne droplet.[16] Age and gender had no impact on adherence to the treatment and were found to be insignificant factors [17]. However, our study suggests that gender is a significant factor in the treatment of the disease and adherence to the therapy as it was more in males. Smoking was found to be a risk factor and Tobacco usage resulted in worsening of disease. All tobacco users were males, however, use of tobacoo provided symptomatic relief to patients suffering from COPD but it casted negative effects on patient's health. *Mycobacterium tuberculosis infection* causes the release of cytokines which subsequently result into pyrexia. Therefore ,before initiation of therapy patients complained about fever but the complaint was resolved after initiation of anti tubercle treatment [17]. Night sweat was observed in 80.37% in females and 72.91% in males of total study population. Before initiation of therapy, 56.8%of followed population complained about night sweats, the increase in production of TNF (tumor necrosis factor) by Helper T-cell 1 causes night sweating in TB patients. [18] Shortness of breath was also a predominant symptom of the TB which was found in patients undergoing treatment in their 1st or 2nd months of the therapy. The chronic infection caused by *Mycobacterium tuberculosis* resulted into destruction of pulmonary capillaries. Thus, dyspnea was caused by the destruction of pulmonary capillaries. [19] Coughing along with sputum was the presenting complaint in the patients - a defensive mechanism for the removal of entrapped bacilli, [20] these entrapped Bacilli further infected the mucus secreting cells present in the upper part of airway system. These mucus secreting cells, also known as goblet cells, produces mucus to trap these mycobacterium in sputum which is expelled out by the beating action of cilia [21].

Diabetic patients are more susceptible to infection caused by mycobacterium as compare to non-diabetic patients [22].High blood sugar causes immune system dysfunction and the underlying disease state [23] Concomitant diseases like diabetes affect compliance to the anti TB treatment .Poly pharmacy results into drug-drug interaction. For example, Rifampicin, an inducer of CYP450 enzyme, induces metabolism of oral anti-diabetics which leads to hyperglycemia. Therefore, oral anti diabetics are needed to be replaced with insulin.[24] Adverse effects of Anti TB drugs such as discoloration of urine (INH, Rifampicin),and darken stool color also causes patients to discontinue therapy in both male and female equally. However, it is due to excretion of unchanged drug in urine and therefore; counseling of patients can help to overcome challenges in the completion of treatment goals [25]. Pain and swelling of joints in patients undergoing ATT was due to infection of musculoskeletal system caused by mycobacterium . It was more prevalent in females than in males [26]. However, it may also be due to the decrease in urate crystal excretion from the body via kidneys. Decrease excretion causes the formation of renal stone and gouty arthritis [27]. Weight loss was another predominant symptom in

TB patients more in males. it might be due to decrease appetite that led to mal nourishment and weakness [28]. Long term use of steroids, Anti-tubercle (INH, Pyrazinamide) drugs and ATT induced Hepatotoxicity caused general discomfort, paresthesia and epigastric pain in some female patients who were followed to determine the effectiveness of DOT program. In addition to disease state, prolonged treatment with steroids causes liver vascular changes that are known as Peliosishepatis characterized by right quadrant discomfort and Hepato-megaly. This is due to formation of blood filled enlarged sinusitis cysts in liver. Metabolism of INH and Pyrazinamide by hepatic enzyme CYP-450 results into production of toxic metabolites and free radicals which cause liver toxicity [29]. Accumulation of bile salts in the skin causes mast cells to release cytokines (histamines) or proteases which cause pruritus (itching) [30]. The abdominal tenderness due to worsen underlying disease state along with failure of ATT drugs resulted into death of one patient [31]. Tenderness was due to obstruction of bowel caused by malignancy of abdominal area [32]. This study concludes that that the higher adherence and clinical response rate to ATT was achieved under TB DOT program in males as compare to the females to treat

Tuberculosis. There might be an increase in disease burden and chance of relapse due to negligence in the follow up of the female patients due to socioeconomic cultural factors which affect the early detection and progression of disease. This suggests that this programs and further likelihood investigations should be frequently carried out in Pakistan to eradicate the disease.

5. CONCLUSION:

Tuberculosis is still a major public health problem in remote areas and among illiterate population. Life style modification and maintenance of hygienic conditions can help to reduce the disease burden. Awareness among general population and counseling of patients particularly females can help to combat and prevent the spread of disease. Adherence and clinical response was more in males than females which demands further implementation of TB intervention and network participation of the patients and public health departments to ensure the achievement of minimum disease burden.

6. ACKNOWLEDGEMENT:

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