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STUDY THE PATTERN OF DRUG RESISTANCE IN PATIENTS OF PULMONARY TUBERCULOSIS HAVING DIABETES MELLITUS

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ABSTRACT

Introduction: As the pulmonary tuberculosis is still rampant in our country inspite of directly observed treatment short course(DOTS). Recently it has been observed that diabetic patients having pulmonary tuberculosis have more morbidity and mortality hence it gives us the impetus to know whether pulmonary tuberculosis is leading to development of diabetes**.** Hence we had undertaken this study to know the prevalence of diabetes in these early diagnosed pulmonary tuberculosis patients and assessing the pattern of drug resistance. Acute severe stress, fever, and malnutrition stimulate the stress hormones which is the cause of increased blood sugar level. **Material and Methods**: The study was done on 200 patients in the postgraduate department of Medicine and Tuberculosis and Chest Diseases, S.N. Medical College and Hospital, Agra. All newly diagnosed pulmonary tuberculosis patients who were non diabetics,nonsmokers and does not have any chronic disease were taken.These patients after detail clinical examination were adviced oral glucose tolerance test(OGTT) and sputum culture sensitivity and devided into group A,(euglycemic),B impaired glucose tolerance (IGT) and C(diabetic) on the basis of blood sugar level. **Results:** The prevalence of group B and C were 22.5% and 7.5% respectively.The development of multi drug resistance (MDR) tuberculosis accounted for nearly 37.5% in diabetics which is significantaly greater in comparison to IGT (33.3%) and nondiabetics (1.2%). **Conclusionl:** 1). The prevalence of frank diabetes and IGT in pulmonary tuberculosis is more than normal patients. 2). Response to therapy in the form of anti tuberculosis (ATT) has shown that some patients become euglycemic after 3 months of therapy. 3). MDR is more common in group C. 4). Group B and C patients have become acid fast bacilli (AFB) negative relatively later than group A.

KEYWORDS: Diabetes, Pulmonary Tuberculosis, IGT, MDR, AFB.

INTRODUCTION

Tuberculosis is one of the world's deadliest infectious diseases which infects one third of the world's population and kill 1.6 million[1] people each year. On the other hand global burden of diabetes mellitus is going to increase from estimated 180 million currently to 366 million by the year 2030[2]. Experts have raised concerns about the twin epidemics of DM and TB[3-5,] especially in low to middle income countries like India that are experiencing the fastest increase in DM prevalence[6] and have the highest burden of TB in the world.[7]

Diabetics are four to five times more prone to contact tuberculosis than the general population. Subclinical diabetes becomes manifest due to stress of prevailing infection, whereas status of glucose intolerance improves or normalizes following effective anti tubercular therapy.

Hadden (1967)[8] suggested malnutrition in tuberculosis as a possible cause. Acute severe stress, fever, inactivity and malnutrition stimulate the stress hormones epinephrine, glucagon and cortisol which raise the blood sugar level (Guptan et al, 2000)[9] Roychoudhary and Sen (1980)[10] suggested tuberculosis of pancreas as the possible cause.

Hence we have undertaken this study to know the prevalence of diabetes in these early diagnosed pulmonary tuberculosis patient and assessed the pattern of drug resistance in these diabetic patients.

Aims: To study the pattern of drug resistance in pulmonary tuberculosis in the diabetic study population.

Objectives

1 To study the blood sugar profile of patients suffering from pulmonary tuberculosis.

2 To study the effect of chemotherapy among the diabetic study subjects.

3 To find out the pattern of drug resistance in the patients having IGT or frank diabetics.

MATERIALS AND METHODS

Study Design: Hospital based prospective study.

Research Setting: Study was conducted on patients attending the outdoor patients and in wards of Department of medicine and Department of tuberculosis & Chest SN medical college Agra.

Study Duration: The study schedule was started from March 2014 to January 2015 with six month follow up.

Sampling Method:- Purposive sampling.

Sample Size: 200 Patients were taken who were admitted in the medicine and tuberculosis and Chest wards.

Test Applied: Chi Square Test (2015) and percentage.

Inclusion Criteria
• Patients who have symptoms suggestive of pulmonary tuberculosis e.g. fever,chronic cough, weight loss, haemoptosis, decrease appetite.
• Positive sputum smear for acid fast bacilli.
• Chest X ray with clinical features suggestive of pulmonary tuberculosis.

Exclusion Criteria
Previously diagnosed diabetic patients or any other severe co morbid illness.

• Those individuals who had refused to participate in the study.

Patients were selected according to inclusion-exclusion criteria and subjected to sputum microscopy. As soon as the positive sputum report came these patients were subjected to OGTT and the patients were classified as-
Group A-Pulmonary tuberculosis with normal blood sugar level
Group B - Pulmonary tuberculosis with IGT
Group C- Pulmonary tuberculosis with frank Diabetes
Sputum sampale for DST was send and ATT was started as per WHO guidelines. In IGT group life style modification and in diabetic group inj.Insulin were started and if they were converted in group B and group A patients were adviced exercise and life style modification.

Follow up: with sputum microscopy at every four week upto three months and with fasting and postprandial blood sugar weekly in the begining till 3 months. OGTT was repeated at every 12 weeks till the completion of therapy. Group C patients were treated with inj. Insulin. As soon as the report of drug sensitivity had come the ATT was modified as per WHO criteria.

RESULTS
We had conducted a hospital based prospective study in 200 sputum positive patients including 160 males and 40 females of primary pulmonary tuberculosis and subjected to blood sugar estimation by OGTT . Patients were devided into three different groups on the basis of blood sugar profile(A,B and C).
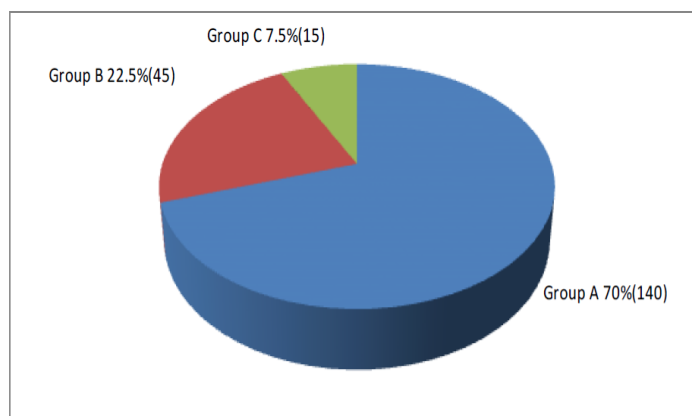

Figure.1; Pie chart showing distribution of patients according to the blood sugar profile in different groups

The age and sex distribution of the patients in group A,B and C are given below in table.1.

Serial No.	Group	Total	<40 years	≥40 years	Male	Female
1	A	140	80	60	110	30
2	%		57.1	42.9	78.6	21.4
3	B	45	19	26	37	8
4	%		42.2	57.8	82.2	17.8
5	C	15	5	10	13	2
6	%		33.3	66.7	86.7	13.3

Elderly population (≥40 years) in group B (57.8%) and group C (66.7%) were more than that of group A(42.9%). From the bar chart given below it is obvious that as the age increases the prevalence of IGT & diabeties also increases.

In all the three groups there were more males in comparison to females suggesting that probably males were more exposed to contacts due to out door works.

The group B having blood sugar in IGT were followed weekly with fasting and postprandial blood sugar and were shifted to inj. human insulin if they were found to be frank diabetes ie. converted in group C and group B patients were adviced life style modifications.

Culture sensitivity of all the patients were send before starting antitubercular treatment. Fasting and postprandial blood sugar were repeated weekly in group B upto 12 weeks and there was conversion of IGT patients to group A at every week (Table.2). After 12 weeks there was a significant improvement in 21 out of 45 IGT patients (46.7%)(Figure.2) and 24 out of 45 patients (53.3%) were remains in IGT range and none of the patient was reported of having frank diabetes.

Similarly in group C there were 2 patients were shifted to group A at the end of 9 week and 12 week(Table.2). showing 13.3% improvement in blood sugar and rest 86.7% remained in group C.

It was observed that in group C after start of ATT requirement of insulin decreased with therapy and few patients had develop frequent hypoglycemia and 2 patients even did not require insulin and were adviced life style modification and in due course of time converted to group A.

Table2. Showing distribution of patient in group B and group C responded after start of ATT weekly

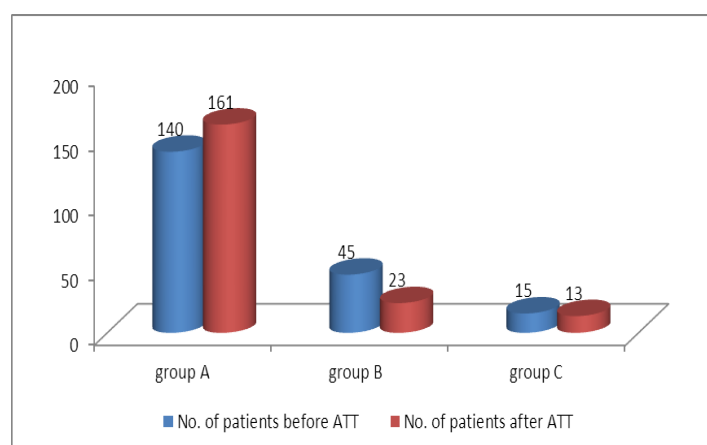| No.of weeks	1	2	3	4	5	6	7	8	9	10	11	12	Total
Group B (No.of patients)	0	0	1	2	2	0	1	3	5	4	2	1	21
Group C (No.of patients)	0	0	0	0	0	0	0	0	1	0	0	1	2

Figure.2 showing number of patients in group B and group C before & after 3 months of ATT therapy

Thus it was observed that after starting ATT there was significant decrease in patients blood sugar level in group B and group C indicating improvement in stress condition or other cytokines mediators.All the patients who had IGT (60 patients) and frank diabetes (15 patients) undergone drug sensitivity to know the resistance specially for category one by using solid culture/liquid culture DSTs/LPA.

As shown in table.3 in group A resistance was observed in 10.8% (18 patients out of 160) of which isoniazid 3.7% (6 patients), rifampicin 3.1% (4 patients), MDR 1.2% (2 patients), pyrazinamide 0.6% (1 patient) and streptomycin 1.2% (2 patients) and one patient has resistance to ethambutol (0.6%). In group B resistance observed were in MDR 30.8%(4 patients) followed by isoniazid in 23.1%(3 patients), rifampicin 15.4%(2), pyrazinamide 7.5%(1 patient) and streptomycin 15.4% (2 patients) and 6.7% (1 patient) against ethambutol resistant.

In group C resistance observed were in MDR 40%(2 patients) followed by isoniazid in 20% (1 patients), rifampicin 20% (1), and streptomycin 20% (1 patient) and no patient was found to have resistance to ethambutol and pyrazinamide.

Table:3 Showing patterns of drug resistance in patients of pulmonary tuberculosis in nondiabetic ,IGT and diabetic groups

S.N.	Patients	Total no.with resistance	MDR	H	R	Z	E	S
1	Group A (161)	18(10.8%)	2	6	5	2	1	2
2	%		1.2	3.7	3.1	1.2	0.6	1.2
3	Group B(15)	13(28.9%)	4	3	2	1	1	2
4	%	28.9	30.8	23.1	15.4	7.5	7.5	15.4
5	Group C(15)	5(33.3%)	2	1	1	0	0	1
6	%		40.0	20.0	20.0	-	-	20.0

MDR-multidrug resistant, H-isoniazid, R-rifampicin, Z-pyrazinamide, E-ethambutol, S-streptomycin

The figure.3 shown below clearly depicts that MDR is more common in diabetic patients than nondiabetic patients. Most common resistance was seen for isoniazid followed by rifampicin in both diabetic and nondiabetic and least resistance for ethambutol**.**
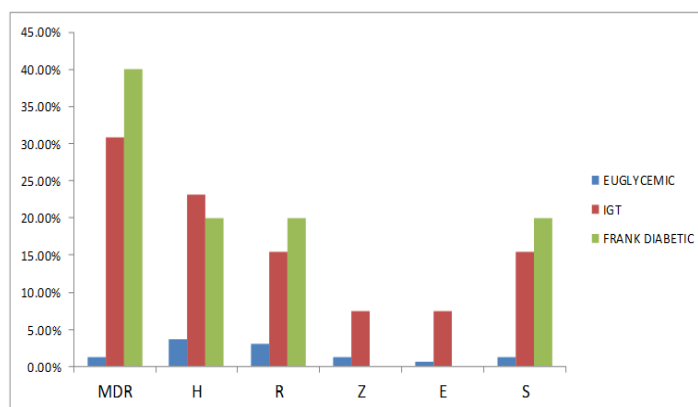
MDR-multidrug resistant, H-isoniazid, R-rifampicin, Z-pyrazinamide, E-ethambutol, S-streptomycin
Figure:3 Showing distribution of pattern of resistance of ATT in different groups

DISCUSSION

In our study, a total of 200 patients were enrolled out of which there were 160 males and 40 females. The prevalence of IGT and frank diabetes were 22.5% (45 patients) and 7.5%(15 patients) respectively.

Comparable results were also obtained for IGT by M.K. Jain et al (16.98%)[11], Kishore et al (1973)[12] 20.9%, Mugusi et al (1990)[13] 19% and Yamagishi et al (2000)[14] 14.1% .

In group B (57.8%) and group C (66.7%) there were more elderly population as compared to that of group A(42.9%).

The higher prevalence of impaired glucose tolerance in the elderly($\geq$ 40 years) were also observed by Kishore et al (1973)[12],Yamagishi et al (2000)[14] ,Roychoudhary and Sen (1980)[15] , and Basuglo et al (1999)[16]

The above discussion showed that as the age increases the number of patients in IGT and diabetic groups increases. These abnormalities were perhaps due to increase in incidence of diabetes in the elderly age group.

In this study IGT group shown that 22 out of 45(48.8%) patients becomes euglycemic without any antidiabetic medication but only on ATT and life style modifications, however 23out of 45(52.2%) patients remained in IGT and none of the patient developed frank diabetes.

Acute severe stress, fever, inactivity and malnutrition stimulate the stress hormones epinephrine, glucagon and cortisol which raise the blood sugar level (Guptan et al, 2000)[9] Roychoudhary and Sen (1980)[15] suggested tuberculosis of pancreas as the possible cause.

Group C patients were put on inj. insulin and lifestyle modification and were followed by strict blood sugar monitoring till the control of diabetes then these patients were followed up weekly till 3 months then monthly till completion of treatment. After 3 months of ATT and insulin therapy 2 patients out of 15 (13.3%) of group C were having their blood sugar level in euglycemic range even without insulin and developed frequent hypoglycaemia with insulin and hence were adviced lifestyle modifications. However the rest 13 patients (87.7%) were continued on insulin therapy.

It is obvious by the various observations that the patients were having drug resistance in group A , B and C were - 16 patiets out of 161(10.8%), 15 patiens out of 45(33.3%) and 8 patients out of 15 (53.3%) respectively.

Susan P. et al.[18] in 2010 June 18 showed in Mexican and Mexican American TB patients that MDR TB

associated with T2DM in Over 31% of patients ,compared with 27.8% of all TB patients.

The pattern of drug resistance among all the three groups were as follows-group A MDR, isoniazid(H), rifampicin(R), pyrazinamide(Z), ethambutol(E), and streptomycin (S) resistance were 2(1.2%),6(3.7%), 4(2.5%), 1(0.6%), 1(0.6%), 2(1.2%) patients respectively. In group B- MDR, isoniazid(H), rifampicin(R), pyrazinamide(Z), ethambutol(E), and streptomycin (S) resistance were in 5(33.3%), 3(20%), 3(20%), 1(6.7%), 1(6.7%), and 2(13.3%) patients respectively. In group C- MDR, isoniazid(H), rifampicin(R), pyrazinamide(Z), ethambutol (E), and streptomycin (S) resistance were in 3(37.5%), 2(25.0%), 1(12.5%), 1(12.5%), 0(0.0%), 1(12.5%) patients respectively.

So it is very obvious that group C have more cases of MDR as compareed to group B and group A.The pattern of drug resistance clearly reveals that overall resistance in diabetes is 38.3% comparable to other studies. One studies have shown that diabetic patients may be more than five times as likely to have infection with MDR-TB[17]than normal patients.

CONCLUSION
Hence our study concludes
1). The prevalence of frank diabetes and IGT in pulmonary tuberculosis is 7.5%(15 patients) and 22.5%(45 patients) respectively.
2). Responce to therapy in the form of ATT along with insulin has shown that some patients of group B had become euglycemic after three months of therapy. Two patients of group C were also become euglycemic after 3 month of therapy.
3). MDR is more common in group C (40.0%) as comparered to group B (30.8%) and group A(1.2%).
4). After achieving glycemic control in all the three groups, almost all patients became AFB negative at 3 months except in group C ,2 patients of MDR became AFB negative after 3 montshs of revised ATT regimen while 4 patients of MDR in group B became AFB negative at 2 months of revised ATT regimen.
5). It is obvious from this study that diabetic and IGT groups patients have become AFB negative relatively later than non diabetic groups.

Hence we suggest that each and every patient must be screened for diabetes before starting ATT because the control of resistance and blood sugar is very important not only to decrease morbidity but also helpful to prevent the propagation of resistant tuberculosis to society at large and these patients may be put on sensitive ATT regimen for complete cure from pulmonary tuberculosis especially resistant cases.

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