Original Research Article

A study of correlation between tuberculosis and gall bladder pathology

Ushma K. Butala^{1*}, Geeta S. Ghag¹, Vinayak V. Dewoolkar², Prachi S. Ghag³, Mihir R. Patel⁴

¹Department of Surgery, H. B.T Medical College and Dr. R. N. Cooper Municipal General Hospital, Mumbai, India

²Department of Surgery, K. J. Somaiya Medical College, Mumbai, India

³Medical and research student, RCSI Government Medical College, Kolhapur, Maharashtra, India

⁴Department of Orthopedic Surgery, K. B. Bhabha municipal general hospital, Mumbai, India

Received: 22 July 2016

Revised: 26 July 2016

Accepted: 29 July 2016

*Correspondence:

Dr. Ushma K. Butala,

E-mail: ushmabutala@yahoo.in

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ABSTRACT

Background: Tuberculosis is a re-emergent problem in many industrialized countries. Tuberculosis occurring at any site may produce symptoms and findings that are not specifically related to the organ or tissues involved but, rather, are systemic in nature. The objective of the study was to study correlation between gall bladder pathology and tuberculosis.

Methods: A prospective study of 100 patients was conducted in a tertiary medical college and hospital. 50 patients suffering from active tuberculosis were selected with dietary and socio-economic status. They were subjected to biochemical and radiological investigations and evaluated for existence of any gall bladder pathology. 50 patients were selected from OPD with dietary and socio-economic status similar to previous group and analyzed for gall bladder pathology. The results thus obtained were compared and a correlation was sought based on statistical tests.

Results: Results of all patients were tabulated and incidence of gall bladder disease in both the groups was calculated. Statistical tests for significance were applied. It was found that the difference in the incidence of gall bladder disease between both the groups is significant. Chi-Square test was performed and it was found that significant correlation between gall bladder disease and tuberculosis exists.

Conclusions: Significant correlation between gall bladder pathology and tuberculosis exists. Patients suffering from tuberculosis are at a higher risk for developing gall bladder disease as compared to general population.

Keywords: Gall bladder disease, Tuberculosis, Correlation

INTRODUCTION

Today, as it has been for centuries, tuberculosis remains one of the leading causes of death in the world from infectious disease. Approximately one third of world's population has been infected with *Mycobacterium tuberculosis* and is at risk for developing disease.¹ Tuberculosis is a re-emergent problem in many industrialized countries.^{2,3} Tuberculosis occurring at any site may produce symptoms and findings that are not specifically related to the organ or tissues involved but, rather, are systemic in nature. This may alter normal

physiological function of other systems leading to pathological variations in other organ systems.

In the study, pathological variations in gall bladder due to tuberculosis were assessed.

Gall bladder diseases are common in western and Indian population. They are among the most common gastrointestinal illness requiring hospitalization. Availability of improved, simple modalities has made diagnosis of gall bladder diseases more feasible and easy.

Gall bladder stones may occur due to various pathological conditions like sickle cell disease, thalassemia, hereditary spherocytosis, ileal damage, hypercholesterolemia, obesity, cirrhosis, Crohn's disease.

Alterations in gall bladder in tuberculosis patients and assessed for existence of any correlation between tuberculosis and gall bladder stones were studied.

METHODS

The study was conducted in a tertiary medical college and hospital. The study was approved by the hospital ethics committee. Study comprised of 100 patients, 50 patients were selected under case group. Criteria for eligibility:

- Patients suffering from active tuberculous infection.
- Patients having mixed diet (vegetarian and non-vegetarian).

These patients were admitted in our hospital and detailed history and various blood and serological investigations were carried out (complete blood count, ESR, liver function tests, transcutaneous ultrasonography). Diagnosis of tuberculosis was established on the basis of relevant investigations done as per the pathological type of tuberculosis. Patients were categorized on basis of pathological type of tuberculosis as

- Pulmonary
- Abdominal
- Tuberculous lymphadenitis
- Tuberculosis of bone
- Others

Patients were followed up at serial intervals with these investigations after starting antituberculous treatment. Ultrasonography findings of gall bladder considered as pathological were categorized as

- Calculous gall bladder
- Acalculous gall bladder
- Sludge
- Psuedo thickening of gall bladder wall.

Control group comprised of 50 patients who presented with symptoms of abdominal pain and discomfort, increased flatulence, fullness of abdomen in surgery OPD but not suffering from active tuberculosis or had no history of tuberculosis in past. These patients had socioeconomic history and dietary habit similar to case group. Detailed history and investigations i.e. complete blood count, liver function test, ultrasonography of abdomen were carried out to diagnose gall bladder pathology in these patients.

Statistical analysis was conducted by applying null hypothesis. Standard error of difference of proportion was calculated. Chi-square test was applied. Comparison

between study and control groups for incidence of gall bladder pathology was done and level of significance calculated. The significance in difference in incidence of gall bladder pathology between the two sample groups was assessed by calculating standard error of difference.

Null hypothesis is that difference in incidence of gall bladder pathology in Tuberculosis and non-tuberculosis patient is not significant.

Standard error of difference =

$$\sqrt{\frac{(S.E.P_1)^2 + (S.E.P_2)^2}{\frac{P_1 q_1}{n_1} + \frac{P_2 q_2}{n_2}}}$$

$$= \frac{8.88}{2.93}$$

Standard error of difference between 2 sample proportions = Z = $\frac{d}{S.E.P.} = 2.93$

Since 2.93 > 1.96 (critical value), null hypothesis rejected, i.e. there exists significant difference in incidence of gall bladder pathology between patients suffering from tuberculosis and non-tuberculosis. Correlation between gall bladder pathology and tuberculosis was further analyzed by chi-square test.

$$\text{Chi-square } X^2 = \frac{[1ad - bc - \frac{1}{2}V]^2 \cdot X \cdot V}{(a+d)(b+c)(a+c)(b+d)}$$

$$X^2_{\text{Cal}} = 6.73$$

$$X^2_{\text{tab}} = 6.63$$

(At degree of freedom = 1) ('p' < 0.01)

$X^2_{\text{cal}} > X^2_{\text{tab}}$

RESULTS

In this study, 100 patients were studied out of which 50 patients were suffering from active tuberculosis and undergoing treatment for the same, while remaining 50 patients were of similar nature, lifestyle and dietary habit with no history of tuberculosis in past and not suffering from active tuberculosis. The observations and results of our study were tabulated and analyzed. Patients suffering from tuberculosis were analyzed as per the site of pathology (Table 1).

Out of 50 patients, 36 were suffering from pulmonary tuberculosis. There were 3 patients with TB spine and 3 patients with tuberculous cervical lymphadenopathy.

Table 1: Sitewise distribution of patients suffering from active tuberculosis.

Site of tuberculosis	Number of patients
Pulmonary	36
Abdominal	6
Combined	2
Lymph node	3
Skeletal	3

Incidence of gall bladder pathology in patients suffering from active tuberculosis and those with no tuberculosis was studied (Table 2). Out of 50 patients with active tuberculosis, 22 cases had gall bladder pathology. While in other group only 9 patients had gall bladder pathology. Thus, in our study of 100 patients there were 31 patients with gall bladder pathology.

Table 2: Incidence of gall bladder pathology.

	Gall Bladder Disease			Total
		Present	Absent	
Active tuberculosis	Present	22	28	50
	Absent	9	41	50
	Total	31	69	100

In our study of 100 patients, there were 19 females with gall bladder pathology (Table 3). It shows that incidence of gall bladder disease is more in females. Ultrasonographic findings in patients with gall bladder pathology were analyzed (Table 4). In both the groups, maximum number of patients with gall bladder pathology had calculous type of presentation on ultrasonography.

Table 3: Sex-wise distribution of gall bladder disease.

Sex	Number of patients
Male	12
Female	19

Table 4: Distribution of gall bladder pathology as per USG findings.

Type of gall bladder pathology	Active TB	Non TB patients
Calculous	11	9
Acalculous	1	0
Sludge	5	0
Pseudothickening of gall bladder	5	0

Analysis of liver enzymes in patients with active tuberculosis was done (Table 5). Liver function tests in these patients were within normal range except for serum alkaline phosphatase levels. Of 50 patients with active tuberculosis, 26 patients had raised alkaline phosphatase levels (4-5 times) and 21 patients from this did not have any gall bladder pathology. Most of these patients were

newly diagnosed cases of tuberculosis. After starting antituberculous treatment all of these patients were regularly followed up at serial intervals with the same investigations. It was observed that alkaline phosphatase levels had started declining and in 3-4 months reached normal range.

Table 5: Analysis of serum alkaline phosphatase in patients with active tuberculosis.

Serum alkaline phosphatase	Patients with gall bladder pathology	Patients with no gall bladder pathology	Total
Normal	17	7	24
Raised	5	21	26
Total	22	28	50

In control group, patients with gall bladder pathology had normal liver enzymes except for 1 patient where alkaline phosphatase was mildly raised.

DISCUSSION

Tuberculosis continues to be an important cause of illness and death world-wide, despite the fact that the causative organism was discovered more than 100 years ago. In spite of existence of effective drug treatments and vaccine, 2.5 to 3 million people die of this disease every year.

The global incidence of tuberculosis (per capita) is growing at approximately 1.1 percent per year and the number of new cases at 2.4 percent per year.^{2,3} About 1/3rd of the current global population is infected with tuberculosis asymptotically, of whom 5-10 percent will develop clinical disease sometime during their lifetime.¹ The rise of tuberculosis is directly linked to the spread of AIDS and the evolution of new multi-drug resistant strains. India accounts for nearly 1/3rd of global burden of tuberculosis. Every year approximately 1.8 million people develop tuberculosis, of which about 0.8 million are new smear positive and highly infectious cases.^{4,5} The burden of suffering caused by tuberculosis in India is enormous. It is one of the biggest health problems in India. In present study it has been observed that pulmonary tuberculosis is more common as compared to other sites (Table 1). Out of 50, 36 patients had lungs as site of tuberculous infection.

On the other hand, gall bladder disease constitutes one of the most important indications of abdominal surgery. After the routine use of ultrasonography, the diagnosis of gall bladder (stone) disease has become far more simple and definite.

Gall bladder disease is multifactorial and depends on various host and environmental factors which play an important role. It is believed that gall bladder diseases

occur when bile contains excess of cholesterol or bilirubin, but not enough bile salts; or when the gall bladder does not empty completely.⁶ Whether tuberculosis does cause these alterations, and at which level, is a matter of discussion. There are various factors that contribute to the development of gall bladder disease. These include sex, weight, diet, age, rapid weight loss, diabetes and consumption of cholesterol lowering drugs.

Incidence of gall bladder disease is more common in females as compared to males.⁷ In present study, the incidence of gall bladder disease is common in females which is 19% (Table 3).

Gall bladder diseases are more commonly seen in people having red meat diet i.e. Food containing haem iron, such as meat and sea food. These people are at a higher risk as compared to people eating non haem iron diet.^{8,9}

Thus, diet is a strong factor influencing predisposition to gall bladder stones. In our study, all the 100 patients selected for study were non-vegetarians with similar type of dietary pattern, so as to remove diet as a confounding factor. There has been an established correlation between gall bladder disease and abdominal tuberculosis. Abdominal tuberculosis involving terminal ileum and ileo-cecal junction affects the absorption of bile flow from the intestine in blood circulation. Interruption of entero-hepatic circulation, in turn is accompanied by decrease in concentration of bile salts and phospholipids, thus reducing the solubility of cholesterol. This leads to precipitation of cholesterol causing gall stone formation. This is also seen with other abdominal conditions like Crohn's disease, follows right hemicolectomy, coloplasty.¹⁰⁻¹³

However, there is no such correlation established for study between the gall stone disease and tuberculosis per se (irrespective of site of pathology). Hence, we undertook a study of existence of any such correlation between tuberculosis and gall bladder disease.

Our study was one comparing the incidence of gall bladder stones in tuberculosis and non-tuberculosis patients and to evaluate the existence of correlation between tuberculosis and gall bladder disease. In any study, of this type, statistical analysis is important since it gives an objective way of comparing the incidence. In our study, 50 patients suffering from active tuberculosis and 50 patients with no past or present history of tuberculosis infection were investigated for gall bladder disease.

It was observed that the incidence of gall bladder disease in tuberculosis patients (Igb/tb) is 44% as compared to incidence of gall bladder disease in patients not suffering from tuberculosis is (Igb/ntb) 18% (Table2). In our study, relative risk of gall bladder disease in TB patients was 2.44. Relative risk greater than 1 suggests "positive" association between exposure and disease under study.

Thus, in our study positive association between TB and gall bladder disease was established.

From our study we also calculated the attributable risk which indicates to what extent the disease under study can be attributed to the exposure. This suggests the amount of disease that might be eliminated if the factor under study could be controlled or eliminated. In our study, attributable risk was 26%. In our study, proportion of gall bladder diseases in both the sample groups was estimated. The significance in difference in incidence of gall bladder pathology between two sample groups was assessed by calculating standard error of difference (S.E.).

Standard error of difference between two sample proportions in our study is 2.93. Since, $2.93 > 1.96$ (critical value), the difference in incidence of gall bladder disease in both sample groups is significant and not by chance.

Significance in correlation between gall bladder disease and tuberculosis was further analyzed by chi square test.¹⁴

$$\begin{aligned}\text{Chi square } X^2 &= \\ X^2_{\text{cal}} &= 6.73 \\ X^2_{\text{tab}} & \text{ (at d.f. = 1, } P < 0.01); \\ X^2_{\text{tab}} &= 6.63 \\ X^2_{\text{cal}} &> X^2_{\text{tab}}\end{aligned}$$

Thus, there exists significant correlation between gall bladder pathology and tuberculosis. Our data was also verified by SPSS system of statistical analysis, similar results were achieved.

Our study shows that 42% of cases with active tuberculosis were newly diagnosed cases and were not started on antituberculous treatment (Table 5). These patients had highly raised serum alkaline phosphatase level; while other liver enzymes mainly SGOT and SGPT were within normal range. These indicators suggest minimal or no liver cell damage due to tuberculosis. These patients did not have any gall bladder disease. However raised alkaline phosphatase levels indicated that there may be obstruction of biliary canaliculi and or irritation of biliary tree, which may be due to under utilization of secreted bile.

The underutilization of bile may be due to low nutrition intake, mainly of fat, which needs bile for its emulsification. Decreased nutrition intake may be attributed to anorexia and cachexia associated with immunopathogenesis of tuberculosis.¹⁵ As a part of immune response to *Mycobacterium tuberculosis*, there is release of tumor necrosis factor alpha (TNF- α), which releases toxins like cachexins.^{16,17} These toxins are responsible for significant loss of weight and anorexia in tuberculosis. This results in decreased nutritional intake leading to biliary stasis. Thus, excessive accumulation of bile, with subsequent dehydration, causes the formation of biliary sludge and gall stones.¹³ These cases with raised

serum alkaline phosphatase may have been in a transitional phase, preliminary to formation of biliary sludge. However, time duration required for the formation of sludge and gall stones cannot be evaluated. Duration of exposure to bacilli and delay in onset of treatment of tuberculosis might be influencing development of sludge and gall stones in these patients. These patients with raised serum alkaline phosphatase when started with anti-tuberculous treatment showed gradual fall in enzyme (serum alkaline phosphatase) to normal range in 3-4 months with clinical improvement of symptoms. This shows that cholestasis observed in these cases is not likely to be due to anti-tubercular drugs.¹⁸ However, changes occurred in gall bladder do not revert. Hence, formation of sludge occurs over a period of time. Our study shows rise in serum alkaline phosphatase in significant proportion of cases and hence this enzyme needs to be elaborated in detail.

Alkaline phosphatase is a hydrolase enzyme responsible for removing phosphate groups from many type of molecules, including nucleotides, proteins and alkaloids. The process of removing the phosphate group is called dephosphorylation. In humans, alkaline phosphatase is present in all the tissues of the entire body, but it is particularly concentrated in liver, bile duct, kidney, bone and the placenta. Exact site of pathology causing a rise in serum alkaline phosphatase can be evaluated by determining the type of isoenzyme in serum.

In our study, the cases with raised serum alkaline phosphatase were evaluated for other pathological sites. However, with no other detectable organic pathology, the rise in alkaline phosphatase is possibly due to involvement of hepatobiliary system, as with other liver enzymes being normal, source of raised serum alkaline phosphatase is most likely to be from the biliary system.

Gall bladder stones occur due to disturbance in cholesterol metabolism, decreased bile salt synthesis and altered gall bladder motility. It has been studied in past that the three key enzymes involved in cholesterol metabolism are regulated by phosphorylation and dephosphorylation.¹⁹ These enzymes are HMG CO-A reductase (3-Hydroxy-3-Methyl glutaryl-coenzyme A); Acyl CO-A cholesterol O-acyl transferase (ACTase) and cholesterol 7- α hydroxylase. These 3 key enzymes involved in cholesterol metabolism are regulated by phosphorylation/dephosphorylation which provides a short mechanism for intracellular unesterified cholesterol. HMG CO-A reductase is activated by dephosphorylation and this result in increased cholesterol formation. ACATase and cholesterol 7- α hydroxylase are responsible for cholesterol utilization and bile acid synthesis. However, these enzymes are inhibited by dephosphorylation.¹⁹

It was observed that incubation of rat liver microsomes with *E.coli* alkaline phosphatase produced a loss of cholesterol 7- α hydroxylase activity. Raised serum

alkaline phosphatase, as evidenced in our study, might be associated with increased dephosphorylation activity of these enzymes. This result in increased cholesterol synthesis, decreased cholesterol utilization and decreased bile acid synthesis. The above hypothesis is put forward on the basis of our observation and biochemical studies established in past. However, further evaluation and confirmation by analyzing activity of these enzymes and level of cholesterol and bile acids in patients suffering from tuberculosis, is indicated.

In past, there have been studies in which blood lipoids were evaluated in TB patients.²⁰⁻²¹ In tuberculosis, there is toxemia with resulting emaciation.²¹⁻²³ There is formation of characteristic tubercles, which contain much lipid material. It was observed that the blood plasma in TB showed presence of relatively large amount of an unknown substance which is probably closely related to cholesterol.²¹

Mycobacterium tuberculosis persists in dormant state for many years in infected persons without causing disease. *In-vivo*, it persists within macrophages by storing triacylglycerols in inclusion bodies.²⁴ Similar process occurs *in-vitro* when these bacilli infect adipose tissue. In dormant state, *Mycobacterium tuberculosis* accumulates lipids for their survival which are hydrolysed during reactivation phase. These lipids include triacylglycerols and phospholipids mainly produced from host cell membrane and de novo synthesis. Thus, these bacilli can interfere with host lipid metabolism for its survival.

All these factors may be hypothetical at present. But the significant correlation between tuberculosis and gall bladder disease, as evidenced in our study, do demand a detailed laboratorial and biochemical study of various enzymes, in TB patients.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the institutional ethics committee

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Cite this article as: Butala UK, Ghag GS, Dewoolkar VV, Ghag PS, Patel MR. A study of correlation between tuberculosis and gall bladder pathology. *Int Surg J* 2016;3:1806-11.