THE INCIDENCE OF AUTO-ANTIBODIES IN OSTEOARTICULAR TUBERCULOSIS

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BACKGROUND: Tuberculosis is found everywhere in the world but it occupies a dominant position in underdeveloped countries. India has a large population of tubercular cases, both pulmonary and extra-pulmonary. Apart from the chronic nature of the disease, the waxy layer present on the bacteria is known to modulate the immune response of the host. In osteo-articular tuberculosis also these possibilities hold good. In addition, certain antigenic components released due to destruction of cartilages, synovial membrane and bony tissues in a host infected with Mycobacterium tuberculosis may lead to autoimmune antibody formation. To the best of our knowledge association of any form of tuberculosis with autoimmunity has not been looked in by workers so far. The present work was planned with an idea to elicit some data in osteoarticular tuberculosis, to find out whether tuberculosis may lead to any autoimmune disorder? Can rheumatoid arthritis be a result of tuberculosis infection? **AIMS AND OBJECTIVES:** The present study was undertaken to evaluate the autoimmune status in different groups of patients of osteoarticular tuberculosis and compare it with control subjects. **MATERIAL AND METHODS:** The study was conducted in Department of Orthopaedics, Pathology and Micro at Hind Institute of Medical Sciences, Barabanki, extending from 2010 to 2012. A total of 130 patients of osteoarticular tuberculosis attending the OPD of department and those admitted in ortho wards of hospital, were taken on random basis. Thirty healthy individuals were taken as controls, in which systemic infection and parasitic infestations were excluded.

Patients were divided in two groups' viz. Group A (with active disease) and Group B (with healed disease). Each group was further divided into two sub-groups of synovial and non-synovial joint involvement. Thus there were four sub-groups which are as follows:

- Active disease of synovial joints (FS) : 36 patients
- Active disease of Non-synovial joints (FNS) : 31 patients
- Healed cases of synovial joint disease (HS) : 30 patients
- Healed cases of non-synovial joint disease (HNS) : 33 Patients

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130 Patients

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Control cases : 30

Thus a total of 160 individuals were investigated.

Routine haematological investigations, radiological investigations like Fluoroscopy chest/ x-ray Chest, X-ray of the affected parts were done.

IMMUNOLOGICAL STUDIES: In all the cases and controls tissue non-specific and tissue specific autoantibodies were examined. The findings were recorded and data were analysed using suitable statistical techniques. Following auto antibodies were studied:

A) Tissue Non-specific auto antibodies:
   a) Rheumatoid factor-Rose-Waaler test.
   b) Antinuclear antibody.
B) Tissue specific auto-antibodies:
   a) Thyroid-Antithyroglobulin antibody.
   b) R.B.C.-Cold haem-agglutinating antibody.
   c) In addition as a parameter of in vivo immune reaction complement component 3 (C^3) level in serum was estimated.

RESULTS AND DISSCUSSION: Sixty seven cases of active osteoarticular tuberculosis and 63 cases of healed osteoarticular tuberculosis and 30 healthy control subjects were examined in the present work for the prevalence of four types of auto-antibodies and level of complement 3 in their sera. The cases of active tuberculosis were divided into two groups depending on joints affected i.e. (i) Synovial and (ii) non-synovial. Similarly healed cases were also divided into two groups. Whereas, male patients were found in higher number with affection of synovial joints, female patients outnumbered the males in case of non-synovial joints (similar preponderance) of female patients in tuberculosis cases affecting non-synovial joints. In active disease affecting non-synovial joints 25.81% of patients were positive, whereas 30.30% of the healed cases of this category gave positive reaction to Rose-Waaler test. Healed patients were recalled after the mean period of 18.53 months of successful treatment. There was one patient who came 36 months after being healed and another patient came 16 months later both giving positive Rose-Waaler reaction. It appears that little percentage of cases of tuberculosis affecting non-synovial joints remained Rose-Waaler positive in 60 months after being healed.

All the sera from control cases were negative but nine (25%) active synovial joint involvement and seven (22.58%) non-synovial joint cases were positive for anti-nuclear antibody. Amongst the healed patients ten cases (33.33%) of synovial joint involvement and six cases (18.18%) of non-synovial joint affection were also positive for anti-nuclear factor. Thus, the results of anti-nuclear antibody test not only showed its presence in patients with active osteoarticular tuberculosis but it was found even in cases that have been successfully treated and declared to be healed. It appears that the autoimmune antibody against nuclear antigen that is triggered by M. tuberculosis persists even after clinical cure.

Serum of the same groups of patients and control subjects were examined for antibody to thyroglobulin. The control subjects six (20%) showed presence of antibody. Nine (25%), ten (33.33%), 13 (41.94%) and seven (21.21%) cases revealed antibody reactive to thyroglobulin amongst fresh synovial, healed synovial, fresh non-synovial and healed non-synovial cases, respectively. The prevalence of the antibody was significantly higher in fresh non-synovial cases only. In rest of the groups of the patients the prevalence of antibody was not significantly different from control subjects. But, while looking in the titre of positive cases it was found that amongst normal subjects four had a titre of 1:8 and two reacted at 1:16 dilution of the sera. In the study

patients in active tuberculosis of synovial joints there was one patient who had anti-thyroglobulin antibody to attire of 1:256, rest of the patients in this group reacted at titre of 1:16 or below. In healed synovial group there were two cases positive at 1:64 and another case at 1:128. In fresh non-synovial, the anti-thyroglobulin antibody was either 1:8 or 1:16. Some range was also found in healed non-synovial cases.

Cold haem-agglutinin in their sera, 08.33%, 10.0%, 6.45% and 24.24% cases in fresh synovial, healed non-synovial patients were positive, respectively. It appears that in certain percentage of active cases of tuberculosis of bones and joints cold haem-agglutinin appear in the blood which persists in a few cases even after healing. In all the study groups the mean levels of complement C3 were found to be significantly lower compared to that in the control subjects. Further, the mean complement levels in synovial or non-synovial cases were significantly lower corresponding to their healed groups. From the above results it appears that during the active phase of osteoarticular tuberculosis apart from autoimmune antibody, anti-mycobacterial antibody might also be involved in raising complement consumption in vivo, but in healed cases of tuberculosis the lower level of C3 found in study can only be explained by postulating continuation of autoimmune antibody formation leading to Ag-Ab reaction in vivo.**CONCLUSION:** Osteoarticular tuberculosis not only triggers formation of auto-antibodies, but once these auto-antibodies are formed, they appear to persist even when the patients, are healed of tuberculosis.

As the present study is not a prospective one, definite conclusion on the responsibility of osteoarticular tuberculosis for autoimmune diseases cannot be drawn. Although there is very strong evidence available in results obtained in the present work, but perhaps a sustained examination with a long follow-up study with big number of patients will be necessary to clinch definitely the strong possibility of osteoarticular tuberculosis leads to autoimmune disorder.

KEYWORDS: Osteoarticular Tuberculosis, Autoimmunity, Antinuclear Antibody, Rose-Waller test.

INTRODUCTION: Tuberculosis is found everywhere in the world but it occupies a dominant position in underdeveloped countries. India has a large population of tubercular cases, both pulmonary and extra-pulmonary[1]. Although the fright associated with this disease has abated with advancement of antibiotics and chemotherapeutic agents but the chronic course and its high prevalence in a country like ours prove a real problem not only for the patient and hospital, but also for the health planners[2]. Apart from the chronic nature of the disease, the waxy layer present on the bacteria is known to modulate the immune response of the host[3]. In osteo-articular tuberculosis also these possibilities hold good. In addition, certain antigenic components released due to destruction of cartilages, synovial membrane and bony tissues in a host infected with Mycobacterium tuberculosis may lead to autoimmune antibody formation[4]. To the best of our knowledge association of any form of tuberculosis with autoimmunity has not been looked in by workers so far. Apart from the theoretical possibilities of stimulating auto-reacting antibody in tuberculosis, in clinical practice often healed cases of osteoarticular tuberculosis come back with symptoms and signs leading to the diagnosis of rheumatoid arthritis[5].

The questions that remain to be answered with the given background above are:

- Whether tuberculosis may lead to any autoimmune disorder?[6]
- Can rheumatoid arthritis be a result of tuberculosis infection? [3]

The present work was planned with an idea to elicit some data in osteoarticular tuberculosis, to find out an answer to the questions.

The study was done with a group of fresh cases of tuberculosis affecting either synovial or non-synovial joints or another group of patients with healed osteoarticular tuberculosis. A control group of healthy subjects also was included keeping in view the nutritional status and family background of the study patients. Four types of autoantibodies were looked for in the patients and the controls. These were Antinuclear antibody (ANA)[7], Antithyroglobulin antibody(ATA)[8], Cold haemagglutinin and Rheumatoid factor[9]. In addition to assess if an antigen-antibody reaction is taking place in the host the level of complement 3 (C'3) in serum was also assessed[10].

AIMS AND OBJECTIVES: The present study was undertaken to evaluate the autoimmune status in different groups of patients of osteoarticular tuberculosis and compare it with control subjects.

MATERIAL AND METHODS: The study was conducted in Department of Orthopaedics and Microbiology at Hind Institute of Medical Sciences, Barabanki, extending from 2010 to 2012. A total of 130 patients of osteoarticular tuberculosis attending the OPD of department and those admitted in ortho wards of hospital, were taken on random basis. Thirty healthy individuals were taken as controls, in whom systemic infection and parasitic infestations were excluded.

Patients were divided in two groups' viz. Group A (with active disease) and Group B (with healed disease). Each group was further divided into two sub-groups of synovial and non-synovial joint involvement. Thus there were four sub-groups which are as follows:

- Active disease of synovial joints (FS) : 36 patients
- Active disease of Non-synovial joints (FNS) : 31 patients
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130 Patients

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Control cases : 30

Thus a total of 160 individuals were investigated.
Routine haematological investigations, radiological investigations were done.

IMMUNOLOGICAL STUDIES:

In all the cases and controls tissue non-specific and tissue specific autoantibodies were examined. The findings were recorded and data were analysed using suitable statistical techniques (Rao, 1978). Following autoantibodies were studied:

A) Tissue Non-specific autoantibodies:
   a) Rheumatoid factor-Rose-Waaler test.
   b) Antinuclear antibody.

B) Tissue specific autoantibodies:

a) Thyroid-Antithyroglobulin antibody.

b) R.B.C -Cold haemagglutinating antibody.

c) In addition as a parameter of in vivo immune reaction complement component 3 (C^3) level in serum was estimated.

OBSERVATION:

In this study to find out auto-immune phenomenon, if any, in osteoarticular tuberculosis, a total of 130 cases of fresh and healed tuberculosis affecting synovial and non-synovial joints were examined. 30 non-tubercular subjects were also studied as control subjects. The distribution of fresh and healed tubercular cass according to age and sex vis a vis control subjects is shown in table - 1 and 2.

TABLE – 1

Showing sex distribution in study and control cases

	CONTROL	FRESH SYNOVIAL	HEALED SYNOVIAL	FRESH NON-SYNOVIAL	HEALED NON-SYNOVIAL
MALE	24	21	25	13	14
FEMALE	6	15	5	18	19
TOTAL	30	36	30	31	33

TABLE – 2

Showing age distribution in control and study cases

AGE IN YEARS	NUMBER OF CASES				
	CONTROL	FRESH SYNOVIAL	HEALED SYNOVIAL	FRESH NON-SYNOVIAL	HEALED NON-SYNOVIAL
0 - 10	-	5	4	5	4
11 – 20	8	11	12	6	5
21 – 30	10	8	6	10	17
31 - 40	6	6	2	4	4
41 - 50	5	4	3	4	3
>50	1	2	3	2	-
TOTAL	30	36	30	31	33

Sera from all the cases under study and controls were subjected to Rose-Waaler (RWT), Anti-Nuclear Antibody (ANA), Anti-Thyroglobulin Antibody (ATA), Complement C3 level and cold Haemagglutination test (CHA). All the sera were separated at room temperature after keeping clotted blood at 37°C for two hours. The separated sera were kept at -20°C till they were tested. All the sera were examined within three months of collection.

ROSE-WAALER TEST: (Differential sheep-cell agglutination test – DAT)

The results of RWT are shown in Table – 3. The test was considered to be positive when agglutination titre with sensitized sheep RBCs was eight fold or higher than that with unsensitized

cells. All the control subjects were negative by this criterion. Of the 36 fresh tubercular cases affecting synovial joints (FS), ten (27.78%) gave positive rose-waaler test. This was definitely significantly higher compared to control cases (P<0.01). There were 30 cases of healed tuberculosis of synovial joints (HS), of which 14 (46.67%) reacted positively to RWT. This also was statistically significant (P<0.01). There were 31 fresh cases of tuberculosis affecting non-synovial joints (FNS), of these cases RWT was positive eight (25.81%), showing a significant difference compared to the control subjects (p<0.01). Of the 33 healed cases of tuberculosis affecting non-synovial joints (HNS), ten were Rose-Waaler positive (30.30%). the Rose-Waaler positivity in this group was significantly higher compared to control (P<0.01). The four groups of fresh and healed patient's viz. FS, HS, FNS and HNS, when compared with each other regarding RWT positivity, did not differ significantly.

TABLE – 3
Showing Incidence of Rose-Waaler Test In Controls and Study Subjects

NO. OF CASES	CONTROL	FS*	HS**	FNS***	HNS****
POSITIVE	-	10 (27.78)	14 (46.67)	8 (25.81)	10 (30.30)
NEGATIVE	30 (100)	26 (72.22)	16 (53.33)	23 (74.19)	23 (69.70)
TOTAL	30	36	30	31	33

C : FS	X^2 : 9.82	P <0.01
C : HS	X^2 : 18.260	P <0.01
C : FNS	X^2 : 8.910	P <0.01
C : HNS	X^2 : 10.806	P <0.01
FS : HS	X^2 : 2.532	P >0.05
FNS : HNS	X^2 : 0.1598	P >0.05
F : H	X^2 : 1.8722	P >0.05
FS : FNS	X^2 : 0.0329	P >0.05
HS : HNS	X^2 : 1.784	P >0.05

Figures in parenthesis indicate percentage.
FS = Fresh Synovial
HS = Healed synovial
FNS = Fresh non-synovial
HNS = Healed non-synovial

ANTI-NUCLEAR ANTIBODY TEST (ANA):

All the cases and controls that were submitted to RWT were also examined for the presence of ANA in their sera. The ANA was tested in the sera only qualitatively. The results of the test are shown in table – 4.

TABLE – 4
Showing incidence of Anti-Nuclear Antibody in controls and study subjects

NO. OF CASES	CONTROL	FS*	HS**	FNS***	HNS****
Positive	-	9 (25)	10 (33.33)	7 (22.58)	6 (18.18)
Negative	30 (100)	27 (75)	20 (66.67)	24 (77.42)	27 (81.82)
Total	30	36	30	31	33

C : FS	X^2 : 8.684	P <0.01
C : HS	X^2 : 12.00	P <0.01
C : FNS	X^2 : 7.651	P <0.01
C : HNS	X^2 : 6.028	P <0.05
FS : HS	X^2 : 0.554	P >0.05
FNS : HNS	X^2 : 0.1910	P >0.05
F : H	X^2 : 0.0402	P >0.05
FS : FNS	X^2 : 0.0536	P >0.05
HS : HNS	X^2 : 1.904	P >0.05

Figures in parenthesis indicate percentage.

Whereas all the control subjects were negative for anti-nuclear antibody (ANA), nine, ten, seven and six were positive in FS, HS, FNS and HNS respectively. On statistical analysis, the incidence of ANA was significantly different amongst the fresh and healed tubercular patients compared with each other.

ANTI-THYROGLOBULIN ANTIBODY (ATA):

Sera from 30 non-tubercular controls and 130 subjects belonging to four different categories of osteoarticular tuberculosis were examined for ATA by complement fixation test. Positively upto 1:4 dilution of sera was considered as within normal level and those which gave positive reaction at 1:8 or above dilutions were recorded as positive.

On the basis of these criteria 6 out of 30 controls were positive for ATA. Of the study population 25% in FS, 33.33% of HS, 41.94% of FNS and 21.21% of HNS cases reacted positively. On comparison with control cases only in FNS group the incidence of ATA was found to be significantly higher. Further, the individual groups of study population did not differ significantly when compared with each other in respect of prevalence of ATA.

TABLE - 5
Showing incidence of Anti-Thyroglobulin antibody in controls and study subjects

NO. OF CASES	CONTROL	FS*	HS**	FNS***	HNS****
POSITIVE	6 (20)	9 (25)	10 (33.33)	13 (41.94)	7 (21.21)
NEGATIVE	24 (80)	27 (75)	20 (66.67)	18 (58.06)	26 (78.79)
TOTAL	30	36	30	31	33

C : FS	X^2 : 0.2329	P >0.05
C : HS	X^2 : 1.363	P >0.05
C : FNS	X^2 : 15.339	P <0.01
C : HNS	X^2 : 0.0140	P >0.05
FS : HS	X^2 : 0.554	P >0.05
FNS : HNS	X^2 : 3.195	P >0.05
F : H	X^2 : 0.5224	P >0.05
FS : FNS	X^2 : 2.1662	P >0.05
HS : HNS	X^2 : 1.1718	P >0.05

Figures in parenthesis indicate percentage.

SERUM COMPLEMENT C^3 LEVEL:

As a criterion of autoimmune activity, estimation of C^3 was done in the sera of 30 controls and 130 tubercular cases belonging to different clinical groupings. The C^3 level in serum was significantly depressed in all the four groups of the study population, compared to controls. When the level in FS group was compared with HS group the difference was significant, similarly the C^3 level was different significantly in FNS and HNS. The results of serum complement C^3 level are given in Table – 6.

TABLE – 6
Showing concentration of serum complement C3 in controls and study subjects

	CONTROL	FS*	HS**	FNS***	HNS****
Mean ±S.D.	0.789 ± 0.0047	0.224 ± 0.0009	0.244 ± 0.0028	0.225 ± 0.001	0.340 ± 0.0019
Total	30	36	30	31	33

C : FS	t : 226 x 10^3	P <0.01	DF : 64
C : HS	t : 778.57	P <0.01	DF : 58
C : FNS	t : 6.795	P <0.01	DF : 59
C : HNS	t : 6.067	P <0.01	DF : 61
FS : HS	t : 45.450	P <0.01	DF : 64
FNS : HNS	t : 396.55	P <0.01	DF : 62

COLD – HAEMAGGLUTINATION TEST (CHA):

Cold – haemagglutination test (CHA) was performed in all the study cases and controls (Table – 7). None of the control cases was found to have cold – haemagglutination in the serum at 1:10 dilution. In the FS group three cases had positive CHA, of which one case gave positive reaction at 1:2560 dilution of serum. Other two cases were positive at 1:10 dilution. In HS group there were three positive cases, two of which at 1:10 and one at 1:20 dilution of serum. In FNS cases only two gave positive reaction, one at 1:10 and the other at 1:80 serum dilutions. In the HNS group a total of

eight cases were found to be positive by HA test. The titre of positively varied between 1:10 and 1:1280.

TABLE – 7
Showing incidence of COLD – HAEMAGGLUTINATION TEST in controls and study subjects

	CONTROL	FS*	HS**	FNS***	HNS****
POSITIVE	-	3 (8.33)	3 (10)	2 (6.45)	8 (24.24)
NEGATIVE	30 (100)	33 (91.66)	27 (90)	29 (93.54)	25 (75.75)
TOTAL	30	36	30	31	33

DISCUSSION:

It is known that many chronic infections due to bacteria, viruses, fungi and parasites can lead to production of auto antibodies[11] .Tuberculosis being a chronic infection has also adjuvant action of M. tuberculosis, may lead to autoimmune reaction in patients. It had been an experience of the senior orthopaedic surgeon that a few cases of osteoarticular tuberculosis after they were successfully treated returned later with the signs and symptoms of rheumatoid arthritis. This has brought the question whether auto-antibodies produced during the active phase of osteoarticular tuberculosis may lead to a diseased condition later. The autoantibody formed associated with chronic infections disappears after the eradication of the infection[11]. In the present work mainly two points were examined viz.

1) Incidence of autoimmune antibodies in active cases of osteoarticular tuberculosis and the ability of the antibodies to activate complement.
2) Whether the auto antibodies persists in healed cases of osteoarticular tuberculosis.

Sixty seven cases of active osteoarticular tuberculosis and 63 cases of healed osteoarticular tuberculosis and 30 healthy control subjects were examined in the present work for the prevalence of four types of auto-antibodies and level of complement 3 in their sera.

The cases of active tuberculosis were divided into two groups depending on joints affected i.e. (i) Synovial and (ii) non-synovial. Similarly healed cases were also divided into two groups.

Whereas, male patients were found in higher number with affection of synovial joints, female patients outnumbered the males in case of non-synovial joints (similar preponderance) of female patients in tuberculosis cases affecting non-synovial joints[12].

ROSE-WAALER TEST: The Rose-Waaler test was taken to be positive when the agglutination titre with the sensitized cells was at least eight fold higher than that with non-sensitized sheep cells. All the 30 control cases were negative by this criterion. Ten (27.78%) of the patients with active infection affecting synovial joints and eight patients (25.81%) of cases of active tuberculosis of non-synovial joints were Rose-Waaler test positive. Eight percent patients with tuberculosis to give positive response for rheumatoid factor by latex agglutination test[13]. 13.1% cases to be positive by sensitized sheep cell test and 7.3% positive by sensitized sheep cell test in cases of chronic pulmonary tuberculosis[14]. These workers looked for rheumatoid factor in cases of pulmonary tuberculosis, whereas the present work has studied in osteoarticular tuberculosis patients. This might explain the much higher percentage of Rose-Waaler positivity in present study.

In healed tuberculosis cases of synovial joints 14 (46.67%) and 10 (30.30%) of the healed cases of non-synovial joints were found to give positive Rose-Waaler reaction. We did not find any report in literature of similar work in healed osteoarticular tuberculosis patients. Apparently Rose-Waaler positivity was higher in healed cases compared to patients with active disease. But, on statistical analysis these difference were not found to be significant.

It appears that the auto-antibodies detected by Rose-Waaler test are triggered by tubercular infection of the joints and bones, but this antibody instead of declining following successful treatment persists. In case of healed disease of synovial joints the mean time that elapsed since they were declared completely healed was 14.98 months. There were patients who were recalled for the study after more than 12 years of getting cured. Rose-Waaler positivity in healed cases of synovial joints was found in patients maximum 12 years after completion of treatment and minimum one month after healing. In four cases that were recalled after a minimum period of 17 months he Rose-Waaler test was found to be positive. It is difficult to say how many of patients who become Rose-Waaler positive at active stage of disease remain positive for years, as the study was not conducted with the same patients.

In active disease affecting non-synovial joints 25.81% of patients were positive, whereas 30.30% of the healed cases of this category gave positive reaction to Rose-Waaler test. Healed patients were recalled after the mean period of 18.53 months of successful treatment. There was one patient who came 36 months after being healed and another patient came 16 months later both giving positive Rose-Waaler reaction. It appears that little percentage of cases of tuberculosis affecting non-synovial joints remained Rose-Waaler positive in 60 months after being healed.

The results obtained with Rose-Waaler test don't confirm the opinion that the auto antibodies found during the active phase of infection disappear after successful treatment[11].

ANTI-NUCLEAR ANTIBODY: Like Rose-Waaler Test, anti-nuclear antibody is also detected in every patient suffering from chronic infectious disease like tuberculosis[11]. The sera of the same subjects that were examined by Rose-Waaler test examined for the presence of anti-nuclear factor by immunoperoxidase technique. Only qualitative test was performed. All the sera from control cases were negative but nine (25%) active synovial joint involvement and seven (22.58%) non-synovial joint cases were positive for anti-nuclear antibody. Amongst the healed patients ten cases (33.33%) of synovial joint involvement and six cases (18.18%) of non-synovial joint affection were also positive for anti-nuclear factor. Thus, the results of anti-nuclear antibody test not only showed its presence in patients with active osteoarticular tuberculosis but it was found even in cases that have been successfully treated and declared to be healed. It appears that the autoimmune antibody against nuclear antigen that is triggered by M. tuberculosis persists even after clinical cure. What would be the mechanism operating in persistence of anti-nuclear antibody in healed cases is not clear.

ANTI-THYROGLOBULIN ANTIBODY: Serum of the same groups of patients and control subjects were examined for antibody to thyroglobulin. The control subjects six (20%) showed presence of antibody. Nine (25%), ten (33.33%), 13 (41.94%) and seven (21.21%) cases revealed antibody reactive to thyroglobulin amongst fresh synovial, healed synovial, fresh non-synovial and healed non-synovial cases, respectively. The prevalence of the antibody was significantly higher in fresh

non-synovial cases only. In rest of the groups of the patients the prevalence of antibody was not significantly different from control subjects. But, while looking in the titre of positive cases it was found that amongst normal subjects four had a titre of 1:8 and two reacted at 1:16 dilution of the sera. In the study patients in active tuberculosis of synovial joints there was one patient who had anti-thyroglobulin antibody to attire of 1:256, rest of the patients in this group reacted at titre of 1:16 or below. In healed synovial group there were two cases positive at 1:64 and another case at 1:128. In fresh non-synovial, the anti-thyroglobulin antibody was either 1:8 or 1:16. Some range was also found in healed non-synovial cases.

The results obtained of anti thyroglobulin antibody are not sufficient to draw any dependable conclusion. But, two points need attention viz:

(i) Significantly higher prevalence of anti thyroglobulin antibody in fresh non-synovial cases.
(ii) Higher titre of positivity in cases of healed synovial. Perhaps examination of a larger series of different groups of osteoarticular tuberculosis needed to be undertaken to verify whether the above indications are correct or not.

COLD HAEMAGGLUTINATION ANTIBODY: Although all the control subjects were negative when tested for cold haemagglutinin in their sera, 08.33%, 10.0%, 6.45% and 24.24% cases in fresh synovial, healed non-synovial patients were positive, respectively. The number of positive cases in each of the study groups is rather low; hence no statistical analysis could be done. It appears that in certain percentage of active cases of tuberculosis of bones and joints cold haemagglutinin appear in the blood which persists in a few cases even after healing. It may be interesting that in one case of fresh synovial group the titre was as high as 1:2560.

COMPLEMENT C^3 LEVEL : The complement C3 level in serum was estimated in all groups of study cases and the control subjects. In autoimmunity, antibodies to self antigens have produced and if antibodies belong to IgG or IgM class then reaction with corresponding antigens will lead to complement activation. Such a consequence will lower the levels of all components of the complement system. The level of C3 was estimated as an indicator of the above autoimmune antigen-antibody reaction in vivo.

In all the study groups the mean levels of complement C3 were found to be significantly lower compared to that in the control subjects. Further, the mean complement levels in synovial or non-synovial cases were significantly lower corresponding to their healed groups. From the above results it appears that during the active phase of osteoarticular tuberculosis apart from autoimmune antibody, anti-mycobacterial antibody might also be involved in raising complement consumption in vivo, but in healed cases of tuberculosis the lower level of C3 found in study can only be explained by postulating continuation of autoimmune antibody formation leading to Ag-Ab reaction in vivo.

Certain bacterial infections are known to accentuate autoimmune phenomenon in patients. Particularly infections with M. tuberculosis are known for their adjuvant effect[15]. Thus normal or relatively low level of autoimmune antibody may be amplified by the infectious agent itself.

Certain auto-antibodies are known to occur in older people. But, the auto-antibody detected in the present work was found not to be affected by the age of the subjects. Thyroid antibodies are said to be more prevalent in female subjects, but in the present study thyroid antibody did not show any sex dependent deviation in prevalence.

Very little work is available on autoimmunity in tuberculosis in general and osteoarticular tuberculosis in particular. As such results obtained in present study could not be compared with finding of any other worker. The conclusion that is available is that there is strong possibility of perpetuation of autoimmune phenomenon triggered by osteoarticular tuberculosis even long after patient are cured. It remains to be seen whether auto-antibody detected gives rise to autoimmune diseases in patients in long run or not. Perhaps a sustained examination with a long follow-up using a large number of patients might be able to answer this question.

CONCLUSION: The incidence of auto-antibodies viz. Rose-Waaler, anti-nuclear and cold haemagglutinin were significantly higher in all cases of active tuberculosis of bones and joints irrespective of synovial or non-synovial joint involvement. In addition, the prevalence of anti-thyroglobulin antibody was found to be significantly higher in fresh non-synovial joint involvement. Although anti-thyroglobulin antibody was found in comparable number of control and in patients belonging to other groups, the titre of antibody was found to be much higher in cases of non-synovial joint tuberculosis.

The lower levels of C3 in all groups of study cases whether with healed or active tuberculosis may indicate complete activation in vivo due to reaction between auto-antibodies with corresponding antigen.

Osteoarticular tuberculosis not only triggers formation of auto-antibodies, but once these auto-antibodies are formed, they appear to persist even when the patients, are healed of tuberculosis.

As the present study is not a prospective one, definite conclusion on the responsibility of osteoarticular tuberculosis for autoimmune diseases cannot be drawn. Although there is very strong evidence available in results obtained in the present work, but perhaps a sustained examination with a long follow-up study with big number of patients will be necessary to clinch definitely the strong possibility of osteoarticular tuberculosis leads to autoimmune disorder.

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