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Original Research Article

Evaluation of cytokines during the loosening of prosthesis in knee and hip replacements

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ABSTRACT

Total hip and total knee joint arthoplasty has become a successful orthopaedic intervention for relieving joint pain and functions. However, over the time problems may occur due to implant wear and loosening as well as due to chronic inflammation induced by increased level of bone resorbing cytokine(s) level. This study was undertaken to evaluate the level of cytokines in patients with painful THA/TKA without any sign of lysis around the implant. These patients were further planned for revision arthoplasty. We did not observe any such significant change in hematological, biochemical parameter and signs of lysis among the groups. However, a storm of bone resorbing cytokine level was observed in patients with revision arthoplasty at baseline. Furthermore, this increased level of cytokines remained sustained for early time point of revision arthoplasty. Although, with time, the level of these cytokines decreased but was still observed to be on the higher side when compared with the accident arthoplasty group of patients. The bone resorbing cytokine(s) level remained stable in the accident arthoplasty group of patients throughout the study period. However, the arthoplasty group of patients were observed to take longer time for normalization of cytokine storms. Our results suggest that continuous monitoring of bone resorbing cytokine(s) level in patients with arthoplasty is essential for evaluation of successful implants.

1. Introduction

Total hip and total knee joint arthoplasty (THA and TKA) is essential to improve the quality of life in terms of regaining of compromised physical activity and reliving pain of affected individuals. It is one of the most successful and cost effective intervention in orthopaedic practice where there is chronic refractory joint pain association.[1–3] There are several conditions: osteoarthritis, inflammatory arthritis, fracture malignancy, dysplasia and other in which either/both TKA and THA are considered as a treatment option.[4,5] The prevalence of total replacement is higher in women than in men and also higher in increased aged group than the early age group individuals.[6,7] The successful outcome of total arthoplasty depends on disease condition, age, gender, body weight and race etc.

The main complications after total replacement includes: dislocation, fracture, infection, lysis and loosening of bones, etc. The need for late revision of implant is mostly due to mechanical wear and loosening of bone. However, the need for early revision is mostly due to prosthetic joint infection (PJI) and instability of implant at the local site.[8,9] In spite of all careful management to evade the possible source of infection, it is estimated that the occurrence of 1.7% PJI in primary hip arthoplasty and 2.5% in primary knee arthoplasty. The majority of PJI are associated with intraoperative contamination of implanted appliance that has been used. The contaminated implanted appliances in host body elicit the local innate host response that helps in facilitating the development of well-defined PJI.[10,11] Hence

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meticulous protective measures have been adopted in the clinical practice at the time of total arthoplasty to minimise or nullify the intraoperative microbial exposure at wound and implant along with antibiotics. [] In this study we have followed the patients after total THA/TKA joint arthoplasty after replacement and recruited only those patients who had severe pain as the sign of lysis. These patients were then further referred for revision therapy.

2. Materials and Methods

2.1. Ethical approval, enrolment of study subjects and conflict of interest

This study was done in compliance with institute's ethical standard and started after getting the institute ethical approval (Ref. No. IECPG-368/29.06.2016). The study subjects were enrolled after obtaining of signed consent form from the participant or their guardian. The study was supported by the departmental funds. There is no conflict of interest among the authors of the manuscript.

2.2. Study subjects

This was a prospective study: we followed 129 patients whose THA/TKA joint replacement was done in Department of Orthopaedics, in tertiary care hospital. Out of them we recruited 38 patients; those who had severe pain but no sign of lysis and loosening of prosthesis on clinical and radiological evaluation. 31 of these patients were for approved for THR and rest 7 for TKR. We thoroughly evaluated their previous and present surgical details: X-ray, MRI or CT scans and the type of prosthesis. The X-rays of study subjects were evaluated for grade of loosening (osteolysis). These 38 cases were planned for revision arthoplasty. As a comparison we also recruited 15 patients who were planned for first time arthoplasty due to accidental injuries.

2.3. Collection of specimens and their evaluation

The blood samples were collected from the study subjects and evaluated for acute phase of reactionant in terms of total leukocyte count (TLC count), Haemoglobin level (Hb) Erythrocyte sedimentation rate (ESR) and c-reactive protein (CRP level. Further, serum samples were collected and used for the evaluation of bone resorbing cytokines like IL-6, TNF-α and IL-1β in both pre operative and post operative period (after 13 days and 6-month post arthoplasty). Intra operative tissues (periprosthetic tissue) were also collected for culture/histopathology and immunohistochemistry (IHC). The tissue specimen was characterised, based on type of inflammatory responses, necrosis, no. of neutrophils (per ten HPFS), plasma cells, perivascular lymphocytic infiltration, macrophages with engulfed prosthetic debris, fibrosis, granulomatous reaction, any other foreign body materials.

2.4. Exclusion criteria

Patients having associated diseases like Rheumatoid Arthritis (RA), inflammatory arthritis, autoimmune diseases and those having on immunosuppressive therapy were excluded.

2.5. Statistical evaluation

Statistical analysis was performed using Graph Pad Prism 5 software including, Students t-test, Non-parametric Mann-Whitney Unpaired t-test, One-way ANOVA test. $P<0.05$ was considered as statistically significant.

3. Results

3.1. Characteristics of study subjects: revision arthoplasty and accidental arthoplasty

This was a prospective study, in which we have followed 129 patients whose THA/TKA joint replacement was done in Department of Orthopaedics, in tertiary care hospital All India Institute of Medical Sciences (AIIMS), New Delhi. Out of them, we recruited 38 patients (29.45%), who showed severe pain but no sign of lysis and loosening of prosthesis. The clinical details of previous surgery like: X-ray, MRI or CT scan, type of prosthesis was available at the time of enrolment for this study. The mean age of recruited cases was 53.03 years (SD $\pm$ 10.26 and the range was 41 to 80 years), 22 was male (57.89%) and 16 was female (42.1%). Out of 38, 31 were planned for total hip replacement (18.57%) and the remaining 7 was for total knee replacement (18.42%). The mean age of recruited control subjects (n=15) was 46.93 years (SD $\pm$ 11.59 and the range was 21 to 73 years), 10 was male (66.6%) and 05 was female (33.3%). Out of 15, 14 were planned for total hip replacement (93.3%) and the remaining 1 was for total knee replacement (6.7%) (Table 1). Majority of study subjects for revision therapy were above 60 year of age group (26 out of 38; that is 68% of total) (Table 1: Age wise distribution of study subjects). Histopathological findings showed: chronic inflammation in 28 patients (76.32%), Periprosthetic debris in 9 patients (23.68%), necrosis in 10 patients (26.32%), hemorrhage (with prosthetic debris) in 5 patients (13.16%), neutrophils infiltration in 2 patients (8-10/hpf) (5.27%), Foreign body giant cell reaction in 6 patients (15.79%), granuloma in 2 patients (5.27%) (Figure 1 and Table 1). Radiological data of 25 patients was showed: grade-1 severity in 15 (60%) and grade-2 severity in 10 (40%) (Table 2) of total recruited patients. In control group we enrolled 15 patients; those who were planned for arthoplasty due to accidental injury. Mean age was 46.93 years (SD $\pm$ 8.59 and the range was 37 to 55 years), 10 was male (66.66%) and 5 was female (33.33%). Out of 15,

14 were planned for total hip replacement (93.33%) and the remaining 1 was for total knee replacement (6.66%) (Table 1).

3.2. No significant change in hematological and biochemical parameters among the study subjects

Collected blood samples from the study subjects were used for the evaluation of hematological and biochemical changes among the study groups. The mean value of total leukocyte count (TLC) in revision arthoplasty group was 5.7 x10^9/L (SD ± 1.19 x10^9/L; range 5.4 x10^9/L to 5.9 x10^9/L) and in control group was 5.7 x10^9/L (SD ± 1.23 x10^9/L; range 5.45 x 10^9/L to 5.9 x10^9/L) (Figure 2A). The mean value of erythrocyte sedimentation rate (ESR) in revision arthoplasty group was 29.05mm/hr. (SD ± 7.18 mm/hr; range 12.0 mm/hr to 40.0 mm/hr.) and in control group was 28.27 mm/hr (SD ± 6.24 mm/hr; range 12.0 mm/hr to 40.0 mm/hr.) (Figure 2B). The mean value of C-reactive protein (CRP) in revision arthoplasty group was 24.08 mg/dl (SD ± 2.8 mg/dl; range 14.3 mg/dl to 24.7 mg/dl) and in control group was 22.70 mg/dl (SD ± 2.81 mg/dl; range 12.0 mg/dl to 40.0 mg/dl) (Figure 2C). The mean value of haemoglobin (Hb) in revision arthoplasty group was 11.79 g/dl (SD ± 0.76 g/dl; range 10.3 g/dl to 13.0 mg/dl) and in control group was 11.74 g/dl (SD ± 1.19 g/dl; range 8.1 g/dl to 13.0 mg/dl) (Figure 2D). The change in the values of these parameters among the study groups was not a significant (P values indicated in respective sub figures (A-D) of Figure 2).

Significantly increased level of bone resorbing cytokines (IL-6, IL-1β and TNF-α) in patients with revision arthoplasty compared with accidental arthoplasty group.

Sandwich ELISA was performed for the evaluation of soluble level of cytokines (IL-6, TNF-α and IL-1β) in the collected serum samples. At the time of recruitment (baseline), we observed a significantly raised level of IL-6 in revision arthoplasty group {N = 38; mean ± SD: 231.9 ± 9.9 pg/ml} compared with control group {N = 15; mean ± SD: 37.13 ± 3.1 pg/ml} (Figure 3Ai). The IL-6 level was decreased at the later time point (6-month follow-up) in revision arthoplasty group but remained consistently high as compared with control group (Figure 3 Aii and 3Aiii). Furthermore, in control group, the IL-6 level remained same during the study period (Figure 3Ai, 3Aii and 3Aiii). Moreover, we observed a significant change in soluble level of IL-6 during the follow up period in revision arthoplasty group of patients analysed with non-parametric Mann-Whitney Unpaired t-test.

Similarly, the TNF-α level was also significantly high in revision arthoplasty group at baseline {N = 38; mean ± SD: 234.5 ± 10.24 pg/ml} as compared with control group {N = 15; mean ± SD: 20.47 ± 1.7 pg/ml} (Figure 3Bi). At first follow up (13 days) the level of TNF-α in revision arthoplasty group was almost same as that of baseline (Figure 3Bii); however, the level decreased at 6 months' time points (Figure 3Biii). Nevertheless, the level of TNF-α was observed to be significantly high in revision arthoplasty group compared with control group. Further, in control group the TNF-α level was almost same during the study period (Figure 3Bi, 3Bii and 3Biii). Additionally, we also observed a significant change in soluble level of TNF-α during the follow up period in revision arthoplasty group of patients analysed with non-parametric Mann-Whitney Unpaired t-test.

Similar to the above mentioned cytokines, IL-1β was also significantly high in revision arthoplasty group at baseline {N = 38; mean ± SD: 485.2 ± 32.50 pg/ml} compared with control group {N = 15; mean ± SD: 46.87 ± 8.12 pg/ml} (Figure 3Ci). At the time of first follow up (13 days) the level of IL-1β in revision arthoplasty group was almost the same as at baseline (Figure 3C ii); however, the level decreased at 6 months' time points (Figure 3 Ciii). Similar to other measured cytokines, the level of IL-1β was significantly high in revision arthoplasty group compared with control group (Figure 3 Ci, 3Cii and 3Ciii) (P values indicated in respective sub figures (A-C) of Figure 3). Moreover, a significant change in soluble level of IL-1β during the follow up period in revision arthoplasty group of patients analysed with non-parametric Mann-Whitney Unpaired t-test.

Significantly decreased level of bone resorbing cytokines (IL-6, IL-1β and TNF-α) in patients with revision arthroplasty at 6 months' time point.

Longitudinal follow up was only possible in 14 revision arthoplasty group along with 10 accidental injury (control) group of study subjects. After successful arthoplasty most of study subjects did not come for follow up. In revision arthoplasty group, at early follow up (13 days) time point, we did not observe any significant change. However, at later time point of follow up (6 months) the cytokine levels were significantly decreased (Figure 4 Ai). Similarly, for TNF-α level we did not observe any significant change in follow up at early time point (13 days) from the baseline. However, at later time point of follow up (6 months) the cytokine levels were also observed to be significantly decreased (Figure 4 Aii). Similar to the above cytokines, IL-1β also showed similar trend (Figure 4Aiii). In accident injury (control) group; we did not observe any major significant change in the cytokine level especially IL-6 and TNF-α (Figure 4 Bi and 4Bii). However, at later follow up time point for IL-1β we observed a significant change (Figure 4 B iii). (P values indicated in respective sub figures (A-C) of Figure 3).

4. Discussion

Total joint replacements with implantation is permanently indwelling prosthetic components have been routinely done for the treatment of end stage joint problem since many decades. It is a cost effective treatment of degenerative joint disorders. There are many indications of hip/knee

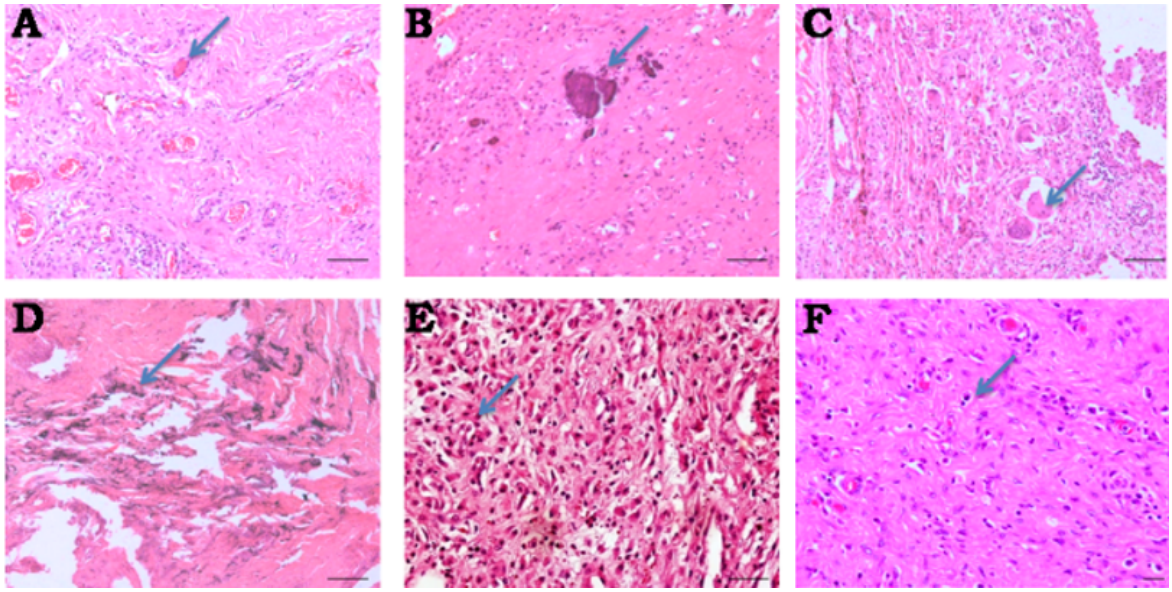

Fig. 1: Representative figures showing the histological findings seen in Hand E stain (HE stain) of tissue specimen in revision arthoplasty group of patient at the time of enrolment for this study: **A.** Fibrosis and chronic inflammation (100x) **B.** Calcification and hyalinization (100x) **C.** Foreign body/giant cells (100x) **D.** Wear particles (100x) **E.** Neutrophils (100x) **F.** Neutrophils (200X)

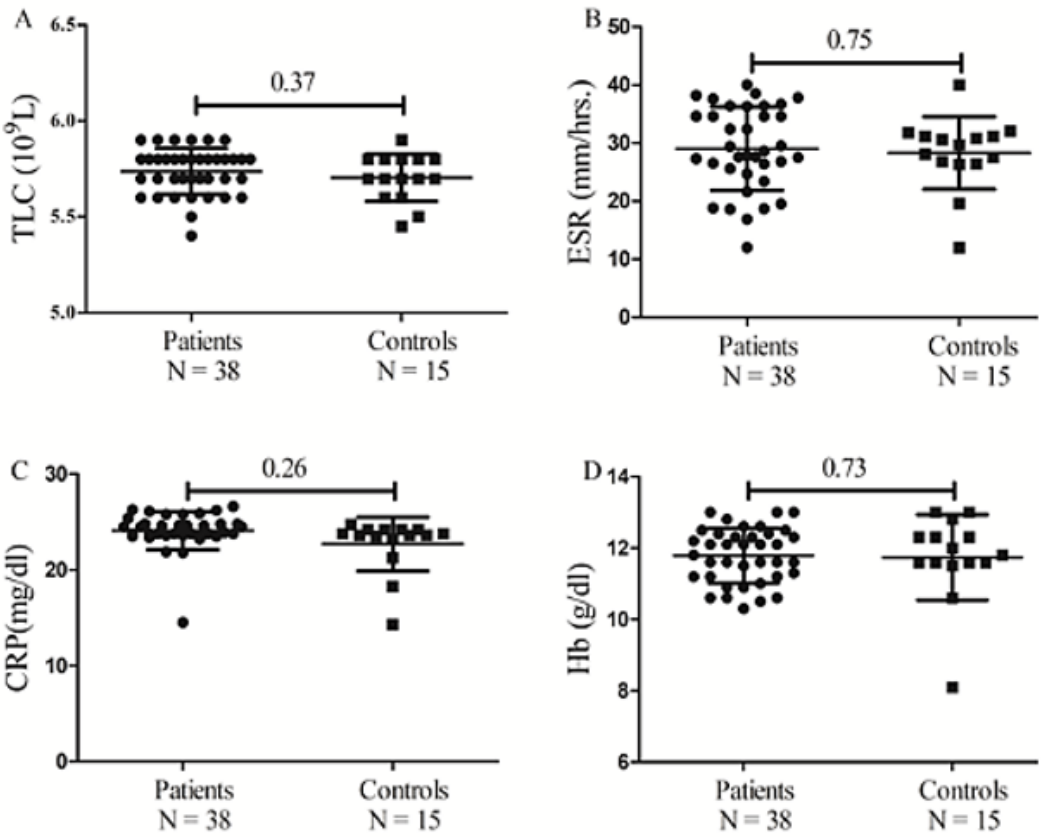

Fig. 2: Changes in hematological and biochemical parameters among the study groups: The separated serum from the study subjects were used for the evaluation of **A.** Total leukocyte count (TLC) **B.** Erythrocyte sedimentation rate (ESR) **C.** C-reactive proteins **D.** Haemoglobin (Hb)

Table 1: Demographic details study subjects involved in this study

Study subjects	**Patients**	**Controls**
Number of participants (N)	38	15
Age (Mean ± SD) years	53.03 ± 10.26	46.93 ± 8.59
Range (years)	41 - 80	37-55
Sex (Male/Female); ratio	22/16 ; 1.3:1	10/5 ; 2:1
Type of replacement		
Total hip replacement (THR); %	31; 81.57%	14; 93.33%
Total knee replacement (TKR); %	07; 18.42%	1; 6.66%
Age wise distribution of study subjects		
<30	0	0
30-40	1	2
41-50	4	3
51-60	7	3
61-70	**14**	**2**
71-80	**12**	**5**
Total	38	15
Haematological investigations		
TLC* (10^9/L)	5.7 ± 1.19	5.70 ± 1.23
ESR** (mm/hr.)	29.05 ± 7.18	28.27 ± 6.24
CRP# (mg/dl)	24.08 ± 1.96	22.70 ± 2.81
Hb## (g/dl)	11.79 ± 0.76	11.74 ± 1.19

* Total leukocyte count (TLC) ** Erythrocyte Sedimentation Rate (ESR)
# C-reactive protein (CRP) ## Haemoglobin (Hb)

Table 2: Histopathology and radiological findings of study subjects involved in this study

Histopathology N = 38		
	Present	**Absent**
Chronic inflammation	28 (73.6%)	10 (26.31%)
Periprosthetic debris	09 (23.68%)	29 (76.31%)
Necrosis	10 (26.31%)	28 (73.6%)
Radiological grade N = 25		
Grade-1	15 (60%)	
Grade-2	10 (40%)	

replacement such as osteoarthritis, rheumatoid arthritis, certain hip fracture etc. Today, total hip replacement (THR) and total knee replacement (TKR) are being performed worldwide with excellent results. In the past few decades, total hip replacement has become a frequently performed and the number of operations are increasing continuously. Worldwide, about 1.3 million hip replacements are performed annually. The total hip replacement is mainly due to accidents however; the total knee replacement is mainly due to osteoarthritis. We have followed 129 hip and knee transplanted patients in this study period. Overall the number of revision implantation was 38 (29%), which was very high. This may be due to most of followed study subjects (93%) were lies above the age of 60 years. 90-95% of hip replacements remain successful for 10-15 years but knee replacements are a little less successful than hip replacement in term of 10 years result. Due to small sample size (n=38) we have not segregated the study subjects in separate groups (Hip and knee replacement). In this study we have observed 81.57% (out of 38, 31) of our recruited cases were for total hip revision therapy and only 18.42% (out of 38, only 07) were for total knee revision therapy. The risk for revision therapy increases with the increase of age.[6,7] we observed these findings in our study group in which 88% of recruited cases were above the 60 age however only 32% were below the 60 years of age. Aging is accompanying with the increased basal level of inflammatory cytokines.[12] Further, the increased level of these cytokines are associated with the need of revision implantation.[13] Aging is also known for deteriorates of bone in terms of composition, structure and function that leads to osteoporosis and fragility of bones.[14] Additionally, we observed that the incidence of revision therapy was more in male than the female (1.3 vs. 1.0) in this study. In Indian population, the cases of TKR and THR are observed more in males than in females.[15,16] The loosening of prosthesis may start after few years of replacement. This phenomenon of loosening has been observed mainly in the western world. The failure rate, as observed in western literature, is 5-10% in the period of 10-15 years.[17] In our study, the mean time

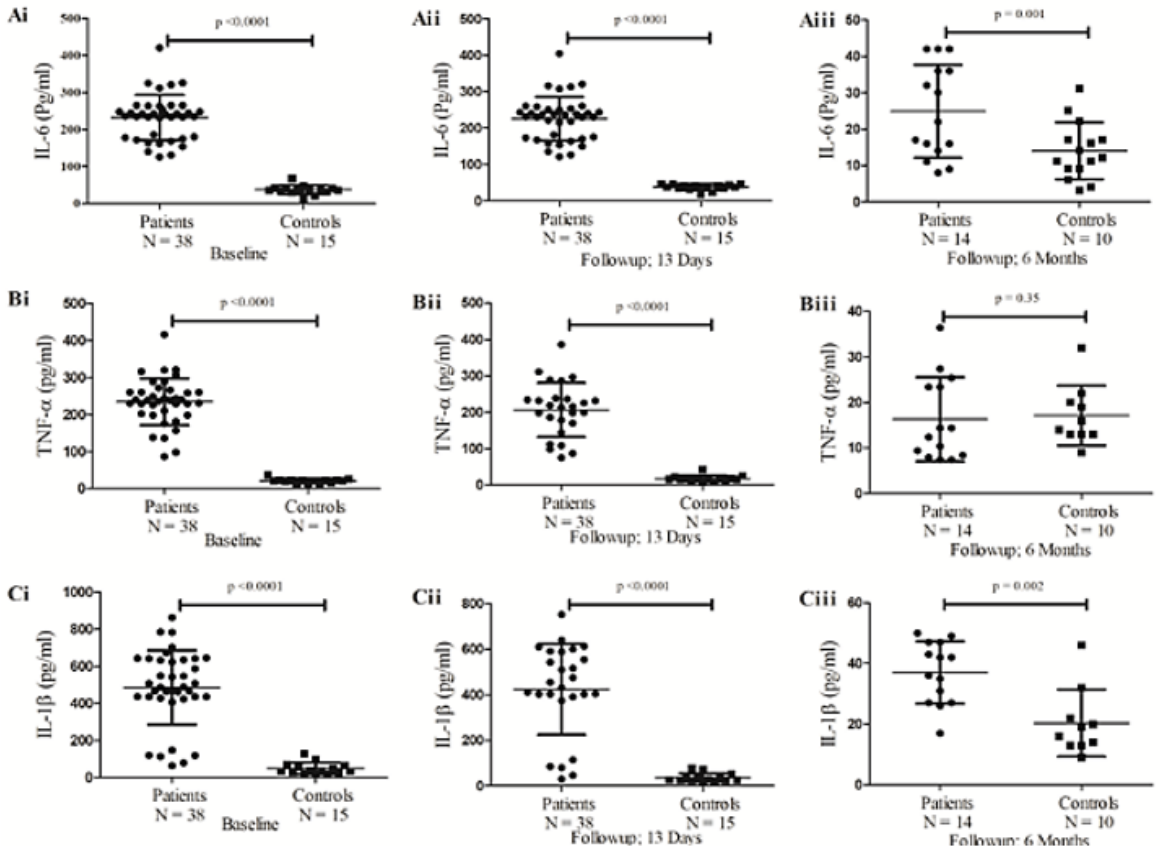

Fig. 3: Changes in immunological bone resorbing cytokines level among the study group: **A.** Interleukin-6 (IL-6) **B.** Tumor necrosis factor-alpha (TNF-α) **C.** Interleukin-1β (IL-1β)

of failure of prostheses came out to be 12.5 years.

Septic and aseptic loosening is the major cause for the failure of prosthesis. So far, several studies have been done on septic as well as aseptic loosening regarding their causes, features, symptoms etc.[2,3] Lars M et al., 2008 showed twenty-three neutrophils in ten high power fields is the best histopathological threshold to differentiate between aseptic and septic prosthesis loosening.[4] Likewise, Pandey et al., concluded that the presence of 2^+ or more (more than one neutrophil polymorph per high power field (X400) on average after examination of at least 10 high power fields) in periprosthetic tissues provides the most sensitive and accurate histopathological criterion for distinguishing between septic and aseptic loosening of hip arthroplasty.[5] This confirms that loosening in these two cases is due to infective etiology. Septic loosening is caused due to infection by various micro-organisms such as S. aureus, polymicrobial, gram-negative bacilli, Streptococci etc. Infection can be early postoperative, sub-acute or late infection. Time of onset of early postoperative infection is less than 2-4 weeks after the surgery. Symptoms related to this infection constitute persistent pain, fever, redness and swelling after surgery. Sub-acute infection may occur in less than 1 year. Late infection occurs after a period of 2 years. The related symptoms could be fever, pain, redness and swelling after a long period of wellness.[6] Aseptic loosening has multi-factorial etiology.[7] Several theories are attached to the causes of aseptic loosening such as particle disease.[7], stress shielding, shielded interface, endotoxin, micromotion, high fluid pressure.[7] In our study, presence of 8-10 neutrophils per high power fields (hpf) was found in 2 cases (5.6%) remaining 36 cases (94.4%) were of aseptic loosening. Out of 36 aseptic cases we observed wear particles in 5 cases which is an indicative of loosening in these cases due to particles generated from the prosthesis. The particles generated from prostheses migrate not only to the space within the hip capsule, but also to the entire area surrounding the joint into which particles can escape and still be in contact with bone. These particles are phagocytosed by macrophages. The number of macrophages present has a direct relationship to the degree of bone resorption. All the cases were found to have chronic inflammation among which, 29 (76.3%) cases had predominant chronic inflammation with the presence of comparatively more amount of lymphocytes and plasma cells. It was found that periproshtetic debris were present

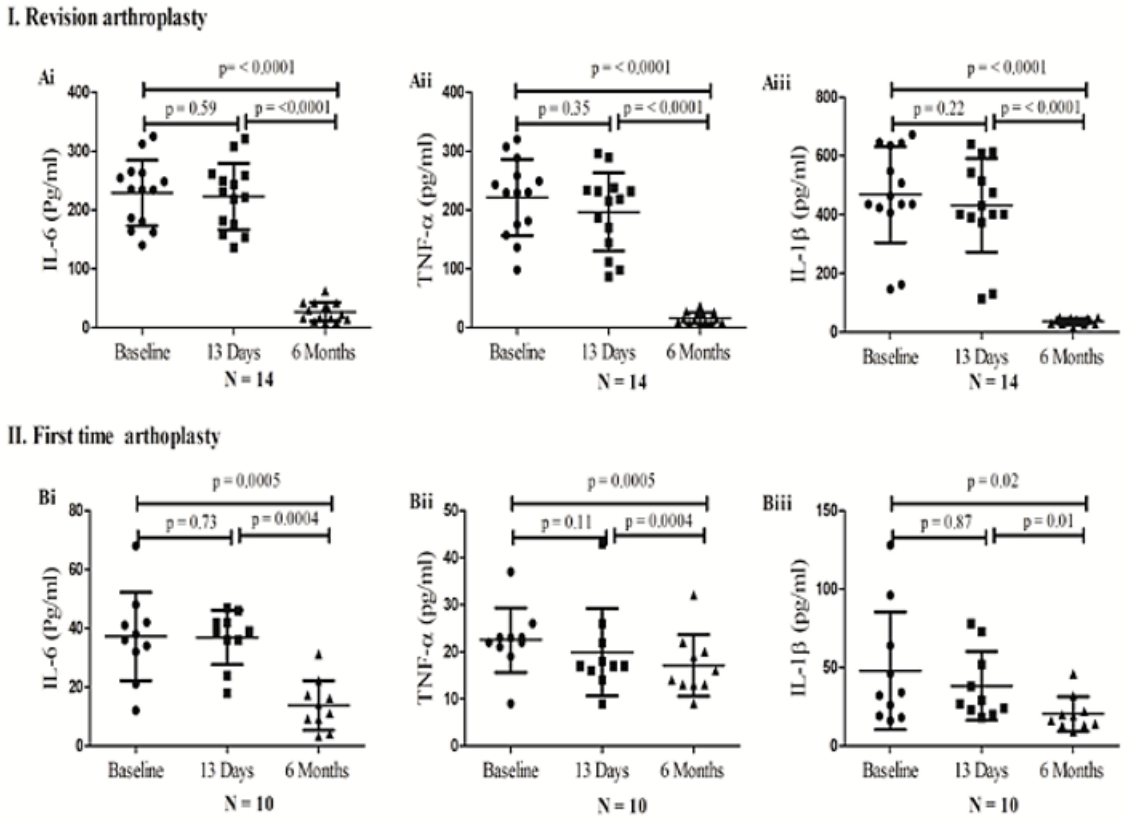

Fig. 4: Improved outcome at later time point in the level of bone resorbing cytokines level in revision arthoplasty group of study subject: I. Revision arthoplasty: **Ai.** Interleukin-6 (IL-6) **Aii.** Tumor necrosis factor-alpha (TNF-α) **Aiii.** Interleukin-1β (IL-1β) **II.** Accidental injury: **Bi.** Interleukin-6 (IL-6) **Bii.** Tumor necrosis factor-alpha (TNF-α) **Biii.** Interleukin-1β (IL-1β)

in 9 (23.7%) cases, necrosis in 10 (26.3%) cases, prosthetic debris with haemosediren-laden macrophages in 5 (13.15%) cases, foreign body giant cells reactions were observed in 6 (15.78%) cases, garnuloma formation was observed in 2 (5.26%) cases and 8-10 neutrophils per HPF in 2 (5.26%) cases which indicates infective etiology of loosening of prosthesis. Further, out of 38 cases 25 were taken for radiological grading of osteolysis.

The grading was performed according to Huddleston HD, 1988. It was found that 15 cases (60%) were of Grade-1 osteolysis and rest of 10 cases (40%) were of Grade-2 osteolysis. None of the cases were found to be of Grade-3 and Grade-4 osteolysis. This result indicates that Grade-1 and Grade-2 osteolysis are prominent in Indian population. Low grade infection is marked by chronic granulation. This lesion is characterised by activated fibroblasts, proliferation of small blood vessels, oedema, and inflammatory infiltrate of neutrophilic granulocytes. High grade infection can be identified by an excess of neutrophilic granulocytes within an oedematous connective tissue.

Osteolysis is a major cause of aseptic loosening in total joint arthroplasty (TJA). The release of bone-reasorbing cytokines (especially IL-6, IL-1β, TNF-α) has been associated with the development of osteolysis in patients with prostheses. These cytokines are mainly secreted by osteoblast and macrophages. The activated osteoblast cells cause the resorption of bone which may further result in loosening of implant. TNF-α and IL-1β have similar effects, despite having different receptors and different intracellular signaling pathways and activity.[18,19] TNF-α is synthesized primarily by macrophages. However, IL-6 is mainly secreted by monocytes and macrophages, neutrophils. We have evaluated the soluble level of these cytokines in study groups and observed at baseline all three cytokines was significantly high in revision orthoplasty group of cases compared with accidental group. Further at early time point (13 days' post revision surgery) there was no significant change in soluble level of these cytokines; eventually, at the later time point the level of these cytokines decreased. We have evaluated the soluble level of these cytokines in study groups and observed that at later time point the cytokines levels decreased but remained higher as compared with the accident group. Thus our study clearly suggests continuous monitoring of IL-6, TNF-α and IL-1β cytokines for the evaluation of a successful implant. The monitoring of these cytokines can serve as an early

predictor for the requirement of revision therapy. This study can be further undertaken in a larger cohort of patients to evaluate causal relationship of the inflammatory cytokines and failure of implants especially in older patients.

5. Source of Funding

None.

6. Conflict of Interest

The authors declare that there is no conflict of interest.

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