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Role of micronutrients in uptake of sequestrum in paediatric chronic diaphyseal osteomyelitis: An analysis of 15 cases

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Abstract
Background: The socioeconomic status and the healthcare delivery system in developing countries has made chronic osteomyelitis as one of the pressing concerns. The main issue is the ability of microorganism to persist in minute quantity even after adequate antibiotic therapy for adequate time period. It is advised to remove the sequestrum early and let the bone heal faster but it is associated with risk pf growth plate injury as well as pathological fracture.
Materials and methods: A prospective observational study was done at All India Institute of Medical Sciences from October 2015 to October 2016. The inclusion criteria were (1) age less than 14 years (2) type 3/4 Cierny Mader chronic osteomyelitis (3) albumin level less than 4gm/dl (4) those giving informed consent. The exclusion criteria were (1) any surgical intervention prior to presentation (2) any surgical intervention in due course of treatment. Supportive treatment of vitamin C, vitamin D, Iron and Calcium supplementation was given. Serial monthly follow up was done clinically and radiologically and outcome in terms of ambulatory status was noted.
Results: 15 patients of which 10 (66.6%) were in the age group 10-14 years. Femur and humerus were commonly involved. Culture was positive in 4 cases with Staph aureus and E coli growth of2 cases each. 8 cases had discharging sinus whereas 4 of the cases had associated pathological fracture. All the patients at the end of follow up were mobilized with or without brace.
Discussion: Paediatric chronic osteomyelitis is frequently associated with diaphyseal sequestrum, which when removed, compromises mechanical stability of the bone which would entail further surgical procedure as well as a financial burden for the family. Studies show post sequestrectomy, the regenerate is formed slowly as well as of poor quality. Hence a non-aggressive conservative treatment is advised. Vitamin C, Vitamin D, Iron and calcium supplementation in malnourished children boosts up immunity as well as tissue healing through various mechanisms including effect on T and L lymphocytes, macrophages, monocytes and fibroblasts.

Keywords: Paediatric, osteomyelitis, micronutrients

1. Introduction
Chronic osteomyelitis in paediatric age group is one of the commonest presenting complaints in outpatient department in developing countries. The lack of development of socioeconomic status and health care delivery system has led to it being still being common than in developed countries [1]. It's usually a sequalae of acute osteomyelitis [2]. The usual presentation is with features of local skin changes long with draining sinuses and typical radiological features of osteolysis with or without bony destruction. The main problem in chronic osteomyelitis is the ability of microorganism to persist for long periods of time even with appropriate antibiotic therapy [3].
Most of the patients of chronic osteomyelitis have a surgical management which entails debridement of necrotic tissue along with soft tissue coverage and bony stabilization [4]. Antibiotics do not have a role in chronic osteomyelitis [4]. It is usually advised to remove the sequestrum as early as possible to make the bone heal faster [5]. It is also associated with increased risk of growth plate injury as well as risk for pathological fracture during operative procedure [6].

There is a strong suggestion that these children might be having low immunity due to malnourishment as the main cause. Innate host immunity decides the response to acute osteomyelitis. Hence the role of immunity in chronic osteomyelitis can't be too underrated.

Our hypothesis is that in patients having sub-clinical under-nutrition, the uptake of sequestrum is better when the deficiency is eliminated. The purpose of this study is to share our experience regarding conservative management of Type 3/4 Cierny Mader chronic osteomyelitis in paediatric age group.

2. Materials and methods

This was a prospective observational study set at All India Institute of Medical Sciences, Rishikesh. All the cases of paediatric chronic osteomyelitis presenting from Oct 2015 to Oct 2016 were screened initially at presentation.

The inclusion criteria were:

(1) age less than 14 years
(2) type 3/4 Cierny Mader chronic osteomyelitis anatomically
(3) albumin level less than 4gm/dl
(4) Those giving informed consent.

The exclusion criteria were:

(1) any surgical intervention prior to presentation
(2) Any surgical intervention in due course of treatment.

Data with reference to the following were collected in a questionnaire. The following were recorded: age, sex, socioeconomic status [7], bone involved, part of bone involved, total leucocyte count, erythrocyte sedimentation rate [ESR], c reactive protein [CRP], serum albumin, history of discharging sinus, history of pathological fracture, pathogen isolated, antibiotics, duration of antibiotic, supportive treatment and healing status.

Outcome measures were assessed by the following factors:

(1) reduction of discharge
(2) healing of draining sinus and
(3) Weight bearing mobilization.

Antibiotics were given according to sensitivity report. Supportive treatment in terms of Vitamin C (Vitamin C 100mg + Sodium Ascorbate 450mg daily), Vitamin D (Cholecalciferol 60000 units weekly), Iron (folic acid 0.5mg + Cyanocobalamin 7.5mg + Ferric Ammonium Citrate 160mg daily) and calcium (Calcium Carbonate 1250mg + Vitamin D3 250 units daily) were given. The dosing was titrated according to the child's age. High calorie and high protein diet was advised. Patients who had or were seen to be progressing towards pathological fracture were given splintage. Regular monthly follow up was done. Serial radiographs were used to chart the progression of healing. Patients were ambulated with support when at least two cortices on two radiological views showed signs of continuity. A minimum of 1 year follow up was done. Descriptive analysis of the data collected was done.

3. Results

A total of 15 patients were followed up which 66.6% (n=10) were in the age group 10-14 years. The youngest child followed up was 2.5 years old.

Table 1: shows distribution of the patients according to their age and location of osteomyelitis.

	Male	Female	Femur	Tibia	Humerus	Others
0-5 years	1	0	0	0	1	0
5-10 years	4	1	3	1	1	0
10-14 years	6	3	7	0	1	1

Femur (n=10) followed by humerus (n=3) were commonly involved. There was one case of tibia chronic osteomyelitis and an uncommon case of cuboid involvement. Isolated diaphysis (n=6) and metaphysis (n=4) were commonly involved. Multiple anatomical parts of bone were involved in 4 and whole of cuboid was involved in 1 case. ESR and CRP was elevated in 14 and 12 patients respectively at presentation. There was significant improvement of ESR, CRP and serum albumin. Total leucocyte count didn't show any statistical significance in improvement. They normalised in 57.1% (n=8) and 66.6% (n=8) of patients in whom they were raised respectively.

	At presentation (mean)	At end of follow up (mean)	p-value
Total leucocyte count	11544.67	6600	0.9
ESR	40.4	15.4	0.0001
CRP	31.1	5.2	0.01
Serum albumin	3.5	4.1	0.002

Culture was positive in 4 (1 humerus and 3 femur) cases with 2 cases each of E coli and Staph aureus. These 4 patients were given sensitive antibiotics till the sinus healed up. 8 (2 humerus and 6 femur) cases were having discharging sinus and 4 (4 femur) cases were having a pathological fracture either at the outset or during the course of treatment. 7 sinuses had healed at an average time of 5.6 months and 1 (1 humerus) patient still had on and off discharging sinus at the end of 14 months. All the 4 cases of pathological fracture patients showed improvement radio logically over the period of follow-up and gradually all patients were mobilized under protection once the x-rays showed at least two intact cortices in two perpendicular views. An average of 9.3 months was required before they could be mobilized. The remaining patients 8 patients were ambulant from the initial period with protection provided. At the end of last follow up, all patients were mobilised with or without brace.

4. Discussion

One of the most common modes of treatment employed for chronic osteomyelitis is sequestrectomy which comes with its own pros and cons. Depending on the size of sequestrum, mechanical stability of remaining bone is determined [6]. Diaphyseal sequestrums are frequent in the paediatric age group which may be difficult to tackle following its removal needing further surgical procedure increasing the morbidity as well as financial implication for the family. Hence, while deciding for

conservative versus operative treatment, systemic signs of sepsis, amount of pus collection, possible differential on the basis of clinical and radiological features like tuberculosis, fungal or neoplastic condition and a highly virulent bacterium on culture report may warrant operative treatment. Studies have showed removal of sequestrum results in slower regeneration of bone as well as the regenerate formed is of poor quality [8, 9]. Hence a non-aggressive conservative treatment involving immunomodulation is being gradually advocated considering the above-mentioned causes.

Calcitriol influences the function of immune cells like T lymphocytes, B lymphocytes, macrophages, monocytes and dendritic cells [10]. Its action is known to be mediated by differentiation of monocytes to macrophages, increased secretion of lysosomal enzymes and induction of cathelicidin synthesis [11]. Further, sufficient Vitamin D levels in plasma reduce the oxidative stress in ill patients by titrating the concentration of glutathione, cysteine and its respective disulphide [12]. Vitamin D is known to promote tissue healing further by helping in glucose homeostasis, stabilizing the lipid profile and also lowering proinflammatory markers like ESR and CRP [13].

Vitamin C is intricately involved in the synthesis of collagen. It catalyses hydroxylation of proline in procollagen and stabilises the triple helical structure of collagen. It is involved in all phases of tissue healing starting from inflammation to remodelling [14]. It helps in neutrophil clearance and apoptosis during inflammatory phase and synthesis, maturation and secretion of collagen during proliferative phase. Chondrogenic and osteogenic cells, both alike are helped in their differentiation and proliferation by Vitamin C [15, 16]. Its antioxidant activity reduces the osteoclastic activity and osteoblastic activity is increased by expression of Transforming growth factor-β, osteopontin and oestrogen receptor-α.

Adequate amount of iron in human body influences immune system by differentiation and proliferation of T lymphocytes, NK cells, monocytes and macrophages. Deficiency leads to reduced phagocytic activity of T lymphocytes as well as immunoglobulin levels. Activity of neutrophils get impaired by reducing the concentration of myeloperoxidases in them leading to impaired chemotaxis and phagocytosis [17]. It also reduces the activity of reactive oxygen species which help in reducing inflammation. Iron deficiency is related with increased bone resorption as noticed by assay of iron biomarkers as well as markers of bone resorption [18]. Also, deficiency of vitamin D and iron seems related, with higher proportion of iron deficiency in patients of vitamin D deficiency [19].

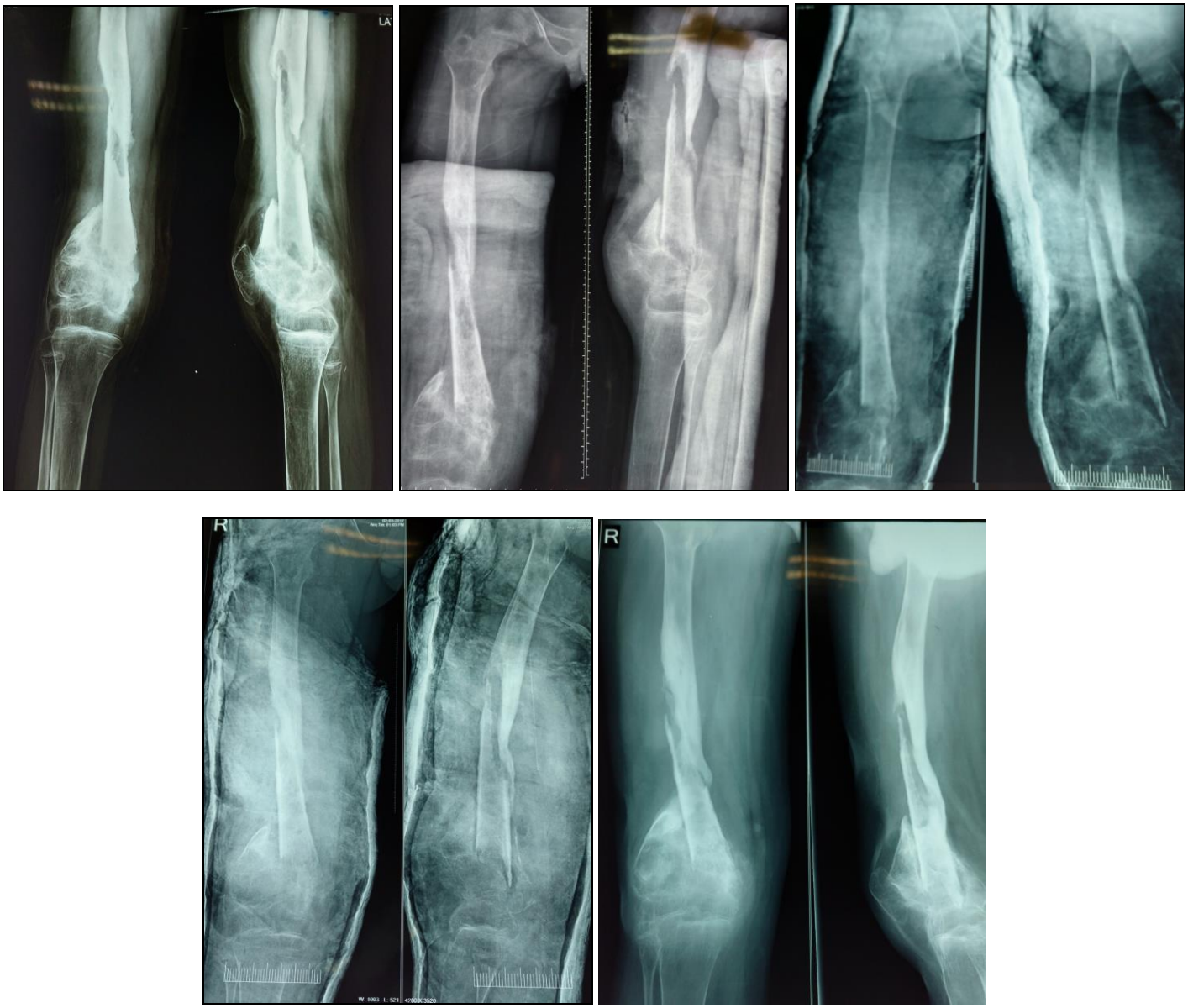
There are very few studies which have highlighted the role of immunity modulators in the treatment of chronic osteomyelitis in children and adolescents. Mantero *et al.* in his study of 96 paediatric chronic osteomyelitis intervened surgically by sequestrectomy and with mean follow up of 12 months had a relapse rate of 12.2% with particular focus on antibiotic therapy [20]. Matzkin followed up 55 patients with chronic osteomyelitis in whom 87% required debridement and 44% required sequestrectomy [21]. All the patients (n=27) in the study by Wirbel underwent an average of 4 surgical procedures including debridement in all and sequestrectomy in a selected few [22].

Jain *et al.* noticed incorporation of diaphyseal sequestrum up to 60% in 16 of 17 patients of chronic osteomyelitis in their follow up [5]. Only 1 patient had less than 30% incorporation. The percentage of patients requiring surgical removal of sequestrum is not known.

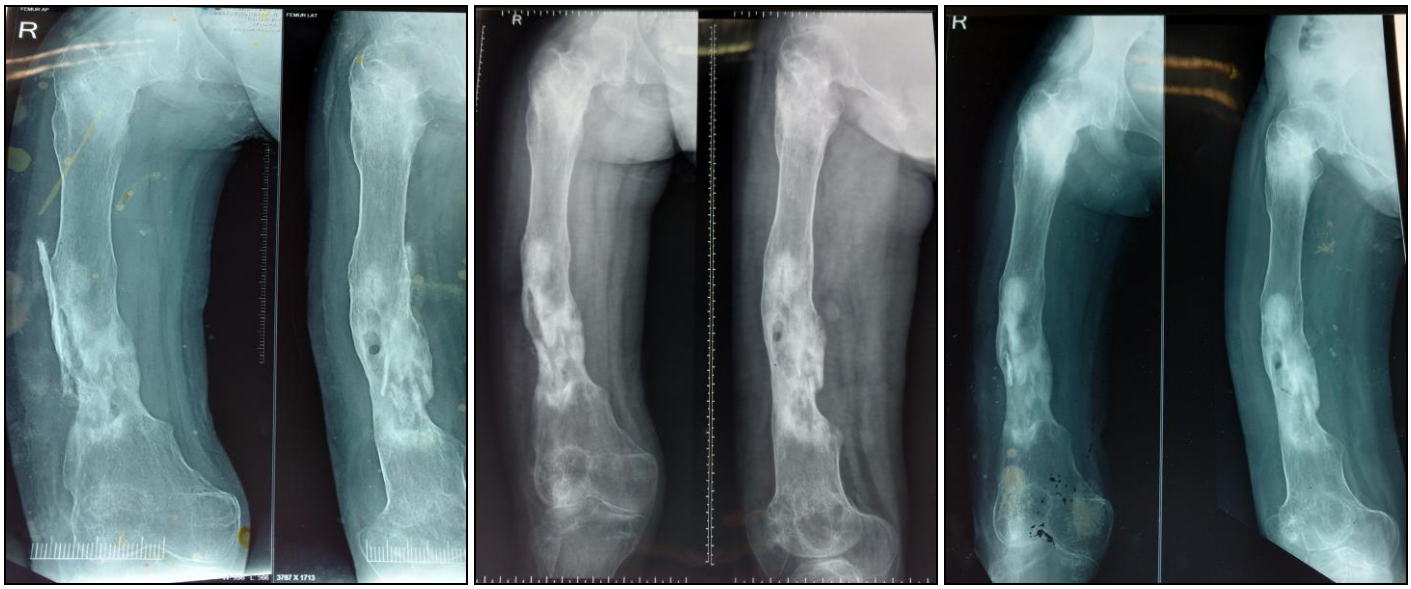
The limitations of this study are the small sample size and short follow up. Further studies with a standardized protocol for immunomodulation in paediatric chronic osteomyelitis with a bigger study group followed up for a longer period of time along with studies at the molecular level in such pathology will help in imparting further knowledge.

In conclusion, surgery shouldn't be considered as the first line of management in paediatric chronic osteomyelitis. A non-aggressive conservative treatment seems more prudent in this setting.

Serial radiograph of 10 year old showing chronic osteomyelitis of tibial diaphysis showing gradual reduction of sclerosis as well as improved corticomedullary differentiation gradually.



Serial radiograph of 12 year old showing severe bony destruction along with well demarcated sequestrum formation in a case of diaphysio-metaphyseal chronic osteomyelitis femur. Patient sustained pathological fracture during the course and was managed conservatively by immobilisation. At follow up of 10 months, patient was gradually mobilised supported by a thigh corset.



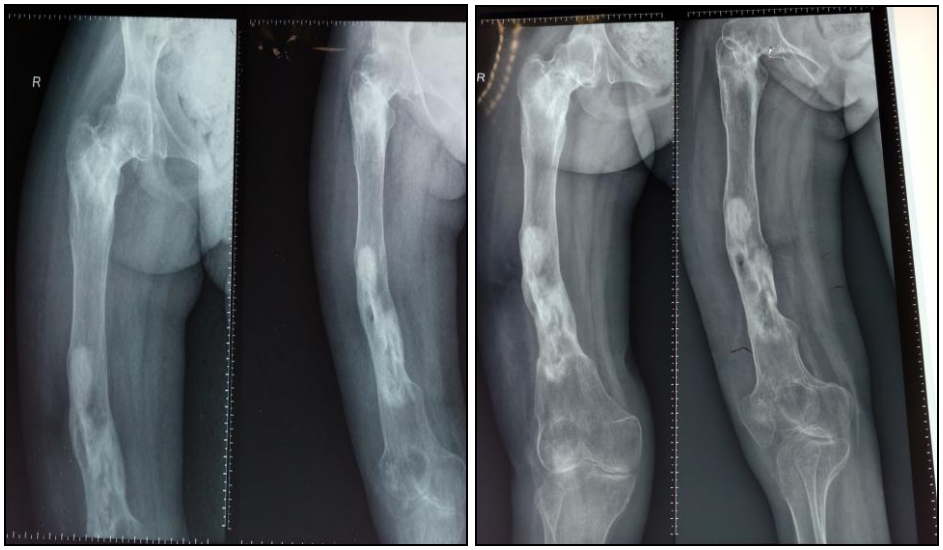


Fig 3: Serial radiographs of a 12-year-old showing diaphyseal chronic osteomyelitis of femur with increased sclerosis and cloaca formation which gradually progressed to reduce sclerosis as well as healing of the cloaca gradually with no evidence of any pathological fracture.

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