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Calcium Crisis in the Shadows of Miliary Tuberculosis: A Prospective Study

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Abstract: ***Miliary tuberculosis may be associated with hypercalcemia because activated macrophages produce excess 1,25-dihydroxyvitamin D, leading to increased calcium absorption and suppression of parathyroid hormone. This prospective observational study evaluated the incidence, clinical profile, and treatment correlation of hypercalcemia in 40 adults with confirmed miliary tuberculosis treated at a tertiary care hospital over 18 months. Patients with other known causes of hypercalcemia were excluded. Clinical assessment, biochemical investigations, and imaging were performed, with hypercalcemia defined as a serum calcium level above 10.5 mg/dL. Hypercalcemia was identified in 22.5% of the patients, and all affected individuals had suppressed parathyroid hormone levels, supporting a non-parathyroid origin. Most cases were mild, while severe cases improved with anti-tuberculosis therapy and supportive management. Calcium levels returned to normal during treatment, showing that the condition was temporary and closely linked to active disease. Early monitoring of serum calcium may help reduce complications and improve patient care in miliary tuberculosis.***

Keywords: Miliary tuberculosis, Hypercalcemia, Vitamin D metabolism, Parathyroid hormone, Anti-tuberculosis therapy

1. Introduction and Aim

Tuberculosis (TB) continues to be one of the leading infectious causes of morbidity and mortality worldwide despite remarkable advances in diagnostic techniques and therapeutic interventions. According to the World Health Organization (WHO), millions of new cases are diagnosed annually, with India contributing the largest share of the global TB burden. While pulmonary tuberculosis accounts for the majority of cases, disseminated forms such as miliary tuberculosis remain clinically challenging because of their multisystem involvement, atypical presentation, and higher mortality.

Miliary tuberculosis is characterized by hematogenous dissemination of *Mycobacterium tuberculosis*, resulting in widespread formation of tiny granulomas throughout multiple organs. The lungs, liver, spleen, bone marrow, kidneys, meninges, and adrenal glands are frequently affected. Patients commonly present with prolonged fever, weight loss, anorexia, night sweats, generalized weakness, and constitutional symptoms, often making early diagnosis difficult.

Apart from organ involvement, tuberculosis may produce several metabolic disturbances. Hypercalcemia is one of the most clinically significant yet under-recognized complications. Unlike primary hyperparathyroidism, hypercalcemia in tuberculosis results from dysregulated vitamin D metabolism. Activated macrophages within granulomatous tissue express extrarenal 1-α-hydroxylase, which converts 25-hydroxyvitamin D to its biologically active metabolite, 1,25-dihydroxyvitamin D (calcitriol). This process occurs independently of parathyroid hormone (PTH), resulting in increased intestinal calcium absorption and suppression of endogenous PTH secretion.

Clinical manifestations range from asymptomatic biochemical abnormalities to severe metabolic emergencies. Patients may develop nausea, vomiting, constipation, dehydration, polyuria, muscle weakness, altered mental status, nephrocalcinosis, acute kidney injury, cardiac arrhythmias, pancreatitis, and, in severe cases, hypercalcemic crisis. Because many of these symptoms overlap with the manifestations of disseminated tuberculosis, hypercalcemia may remain undiagnosed unless clinicians actively monitor serum calcium levels.

The reported prevalence of hypercalcemia in tuberculosis varies widely due to differences in geographic location, nutritional status, vitamin D levels, sunlight exposure, dietary calcium intake, disease severity, and laboratory criteria. Although several case reports and observational studies have described this association, prospective studies focusing specifically on miliary tuberculosis remain limited, particularly in the Indian setting.

Early recognition of hypercalcemia is important because it is generally reversible following effective anti-tubercular therapy and appropriate supportive care. Routine biochemical monitoring may therefore prevent significant complications and improve patient outcomes.

The present prospective observational study was undertaken to determine the incidence of hypercalcemia in patients with miliary tuberculosis, describe the associated biochemical profile, and evaluate treatment-related outcomes.

Aim

To evaluate incidence and profile of hypercalcemia in miliary TB and treatment correlation.

2. Methods and Criteria

Study Design

This was a **prospective observational study** conducted over a period of **18 months** at a tertiary care hospital.

Study Population

A total of **40 consecutive adult patients** with confirmed miliary tuberculosis were included in the study after fulfilling the eligibility criteria.

Inclusion Criteria

Patients fulfilling all of the following criteria were included:

- Age ≥18 years.

- Clinically diagnosed miliary tuberculosis.
- Radiological evidence suggestive of miliary tuberculosis.
- Microbiological confirmation wherever feasible.
- Patients willing to provide informed consent.

Exclusion Criteria

Patients were excluded if they had:

- Primary hyperparathyroidism.
- Chronic kidney disease.
- Sarcoidosis.
- Malignancy associated with hypercalcemia.
- Current vitamin D or calcium supplementation.
- Other established causes of hypercalcemia.

Data Collection

After enrolment, demographic details, clinical presentation, laboratory investigations, and radiological findings were recorded in a predesigned proforma.

The following biochemical investigations were performed:

- Serum calcium
- Serum phosphate
- Serum creatinine
- Parathyroid hormone (PTH)
- Serum 25-hydroxyvitamin D
- Serum 1,25-dihydroxyvitamin D
- Routine hematological and biochemical investigations

Radiological evaluation included chest imaging and other investigations as clinically indicated.

Hypercalcemia was defined as a **serum calcium concentration greater than 10.5 mg/dL**.

Patients diagnosed with hypercalcemia were managed according to standard institutional protocols and were followed during anti-tubercular therapy to assess changes in serum calcium levels.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation or median (interquartile range), depending on data distribution. Categorical variables were expressed as frequencies and percentages. The incidence of hypercalcemia and biochemical characteristics were summarized descriptively.

3. Results: Incidence, Severity & Trends

Baseline Characteristics

Forty patients diagnosed with miliary tuberculosis were included in the study. All patients underwent biochemical evaluation for calcium metabolism.

Incidence of Hypercalcemia

Among the 40 patients studied, **9 patients (22.5%)** were found to have hypercalcemia, while **31 patients (77.5%)** maintained normal serum calcium levels. This indicates that approximately one in every five patients with miliary tuberculosis developed hypercalcemia during the study period.

Severity of Hypercalcemia

Among the hypercalcemic patients, the majority had **mild-to-moderate hypercalcemia**, whereas **33.3%** developed severe hypercalcemia requiring closer monitoring and supportive treatment. Despite the severity in a subset of patients, serum calcium normalized following appropriate management and anti-tubercular therapy.

Biochemical Profile

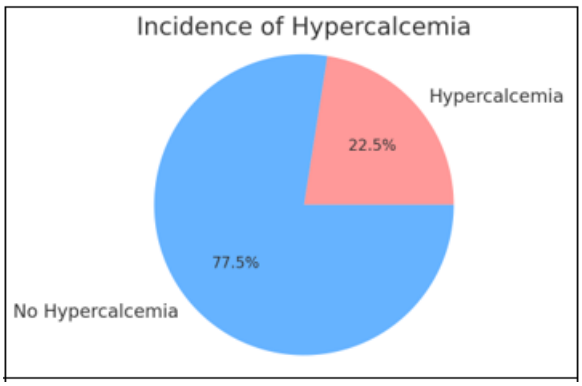
Patients with hypercalcemia demonstrated a characteristic biochemical pattern suggestive of granulomatous vitamin D-mediated hypercalcemia:

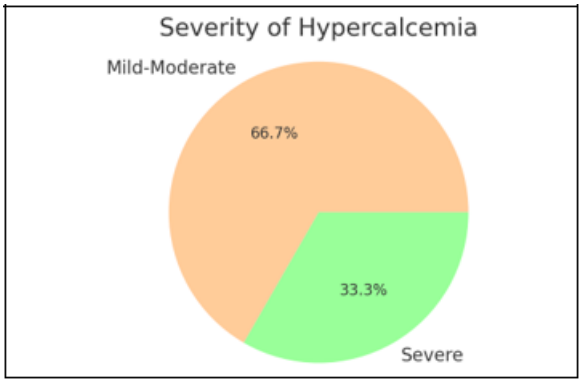
- Elevated serum calcium (>10.5 mg/dL)
- Elevated serum 1,25-dihydroxyvitamin D
- Normal or mildly elevated serum 25-hydroxyvitamin D
- Suppressed parathyroid hormone (PTH)
- Normal serum creatinine in the majority of patients
- Serum phosphate values within or near the normal range

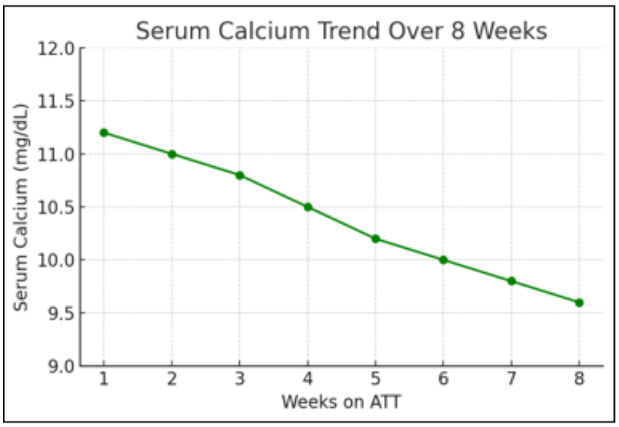
These findings are consistent with increased extrarenal production of active vitamin D by activated macrophages within tuberculous granulomas.

Treatment Response

Serial monitoring demonstrated a progressive decline in serum calcium concentrations after initiation of anti-tubercular therapy. All patients showed normalization of serum calcium during follow-up, supporting the reversible nature of tuberculosis-associated hypercalcemia.







Biochemical Profile of Hypercalcemic Patients (n = 9 out of 40)

LAB Values Table

Parameter	References Range	Observed in Hypercalcemic Patient
Serum Calcium	8, 5- 10,5 mg/dL	>10,5 (Range: 10, 6- 12,2g/dL)
1,25(OH)$_2$D (Active Vit D)	20- 60 pg/mL	Elevated (65- 110 pg/mL)
25(OH)D (Storage Vit D)	30- 100 ng/mL	Normal to mildly elevated (30- 60 ng/mL)
Parathyroid Harmone (PTH)	15- 65 pg/mL	Suppressed (<10 pg/mL)
Serum Phosphate	2, 5- 4, 5 mg/dL	2,2-3,5 mg/dL
Creatinine	6,6-1,3 mg/dL	Normal

4. Discussion

Hypercalcemia is a recognized but uncommon metabolic complication of granulomatous diseases, particularly disseminated tuberculosis. The present prospective study observed hypercalcemia in **22.5%** of patients with miliary tuberculosis, highlighting that disturbances of calcium metabolism are not rare in this patient population.

The principal mechanism involves activation of macrophages within tuberculous granulomas. These activated macrophages express extrarenal **1-α-hydroxylase**, converting 25-hydroxyvitamin D into 1,25-dihydroxyvitamin D independently of parathyroid hormone. Increased circulating calcitriol enhances intestinal calcium absorption, suppresses PTH secretion, and results in hypercalcemia. The suppressed PTH levels observed in all hypercalcemic patients in this study support this well-established mechanism.

The incidence reported in this study is comparable to the higher end of the range described in previous observational studies, although published rates vary considerably depending on patient characteristics, nutritional status, vitamin D exposure, disease severity, and the definition of hypercalcemia used. Geographic variation in sunlight exposure and dietary calcium intake may also influence the occurrence of tuberculosis-associated hypercalcemia.

Clinically, hypercalcemia may remain asymptomatic or present with nonspecific manifestations such as anorexia, nausea, constipation, polyuria, fatigue, dehydration, altered mental status, and muscle weakness. Severe cases may lead to acute kidney injury, nephrocalcinosis, cardiac arrhythmias, and hypercalcemic crisis. Because many of these manifestations overlap with those of disseminated tuberculosis itself, clinicians should maintain a high index of suspicion, particularly in patients with unexplained neurological or renal dysfunction.

One of the important findings of the present study is the normalization of serum calcium following initiation of anti-tubercular therapy. This observation reinforces that tuberculosis-associated hypercalcemia is generally reversible when the underlying granulomatous inflammation is effectively treated. Supportive management, including hydration and correction of electrolyte abnormalities, remains an essential component of care.

The biochemical profile observed in the present study, characterized by elevated calcitriol and suppressed PTH concentrations, is consistent with the pathophysiological mechanism described in previous literature. Recognition of this pattern is useful in distinguishing tuberculosis-associated hypercalcemia from primary hyperparathyroidism and other endocrine causes.

Overall, the findings emphasize the importance of routine serum calcium assessment in patients with miliary tuberculosis. Early identification and timely treatment may prevent avoidable complications and improve overall clinical outcomes.

5. Strengths of the Study

The present study has several strengths. It employed a prospective observational design, reducing recall bias and allowing systematic evaluation of calcium metabolism in patients with miliary tuberculosis. All enrolled patients underwent a standardized biochemical assessment, including serum calcium, phosphate, parathyroid hormone, 25-hydroxyvitamin D, and 1,25-dihydroxyvitamin D, providing a comprehensive evaluation of the underlying mechanism of hypercalcemia. Furthermore, serial monitoring of serum calcium after initiation of anti-tubercular therapy demonstrated the reversibility of the metabolic abnormality, highlighting its clinical relevance.

6. Limitations

The study has certain limitations. It was conducted at a single tertiary care center with a relatively small sample size of 40 patients, which may limit the generalizability of the findings. Long-term follow-up beyond the initial treatment period was not available. In addition, the observational design does not permit conclusions regarding causality. Larger multicenter prospective studies are required to validate these findings and identify predictors of hypercalcemia in patients with disseminated tuberculosis.

7. Clinical Implications

Hypercalcemia should be recognized as an important metabolic complication of miliary tuberculosis. Since its clinical manifestations frequently overlap with those of disseminated tuberculosis, routine serum calcium estimation should be considered in all hospitalized patients with miliary TB, particularly those presenting with altered sensorium, dehydration, renal dysfunction, persistent gastrointestinal symptoms, or unexplained neuropsychiatric manifestations.

Early diagnosis allows prompt initiation of hydration, correction of electrolyte abnormalities, and appropriate anti-tubercular therapy, thereby preventing potentially life-threatening complications such as acute kidney injury, nephrocalcinosis, cardiac arrhythmias, and hypercalcemic crisis.

The characteristic biochemical pattern of elevated 1,25-dihydroxyvitamin D with suppressed parathyroid hormone may help differentiate tuberculosis-associated hypercalcemia from primary hyperparathyroidism and other endocrine causes.

8. Conclusion

Hypercalcemia represents an uncommon yet clinically significant metabolic complication of miliary tuberculosis. In the present study, approximately one-quarter of patients developed hypercalcemia, with most cases being mild to moderate in severity. The biochemical profile, characterized by elevated 1,25-dihydroxyvitamin D and suppressed parathyroid hormone levels, supports macrophage-mediated extrarenal activation of vitamin D as the principal pathogenic mechanism. Importantly, serum calcium normalized following initiation of anti-tubercular therapy and supportive management, indicating that the condition is largely reversible when recognized early.

Routine monitoring of serum calcium in patients with disseminated tuberculosis should therefore be incorporated into clinical practice to facilitate early diagnosis, guide appropriate management, and reduce morbidity associated with this potentially reversible complication.

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