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Prevalence of micronutrient deficiency and its impact on the outcome of chronic myeloid leukemia

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ABSTRACT

Introduction: Chronic Myeloid Leukemia (CML) is a clonal myeloproliferative disorder driven by the BCR-ABL fusion gene, leading to uncontrolled myeloid proliferation. Although tyrosine kinase inhibitors have improved survival, disease progression and resistance remain challenges. Emerging evidence suggests that oxidative stress and imbalance of trace elements such as copper, selenium, zinc, iron, and chromium may influence leukemogenesis and treatment response, highlighting their potential prognostic significance in CML.
Aim: The present study aimed to assess the prevalence of micronutrient deficiency and its impact on the outcome of chronic myeloid leukemia.
Methods: The case control study was conducted on 100 subjects, in which 60 Patients of CML and 40 Controls adjusted for Age and Sex from January 2023 to January 2024.
Results: Chromium and Selenium levels were significantly lower in CML patients compared to controls. Iron levels were slightly lower in CML patients compared to controls, in contrast to other studies that noted elevated levels. Copper levels were higher in newly diagnosed CML cases and drug-resistant cases, but not significantly different in other groups compared to controls. This implicates the role of copper toxicity in treatment resistance. Zinc levels were generally lower in CML patients compared to controls.
Conclusion: The study shows that serum trace elements are valuable indicators of disease progression in leukemia patients. Their levels are not affected by non-specific acute-phase reactions, and monitoring changes in these trace elements can help evaluate treatment response. Therefore, keeping track of trace element levels in CML patients could be a crucial aspect of their management.

Keywords*: Chronic Myeloid Leukemia; BCR-ABL; Trace elements; Copper; Selenium; Zinc; Iron; Chromium; Oxidative stress; Drug resistance; Prognostic biomarkers.*

INTRODUCTION

Chronic myeloid leukemia (CML), also known as chronic myelogenous leukemia, is a type of blood cancer caused by a genetic abnormality involving a translocation between chromosomes 9 and 22. This results in the fusion of the BCR and ABL1 genes, creating the BCR-ABL1 oncogene, which continuously activates the tyrosine kinase pathway. This leads to the uncontrolled proliferation of mutant hematopoietic stem cells (HSCs) at the expense of normal HSCs.[1]

CML symptoms can range from none to severe, with hyperleukocytosis (high white blood cell count) being common across all disease phases: chronic, accelerated, and blast phases. The blast phase, which closely mimics acute leukemia, is particularly serious. Diagnosis typically involves blood tests and genetic analysis to identify chromosomal abnormalities.[2]

The introduction of tyrosine kinase inhibitors (TKIs) has revolutionized CML treatment, transforming it from a once-fatal condition to a manageable disease, with patient life expectancy now comparable to that of individuals without CML.[3]
Micronutrients are essential for supporting numerous physiological processes in the human body, including immune function, DNA repair, and cellular metabolism. In the context of chronic myeloid leukemia (CML), a type of cancer characterized by abnormal white blood cell production in the bone marrow, the importance of micronutrients is heightened. Recognizing the influence of micronutrients on the course of CML and detecting potential deficiencies are critical for enhancing patient care and treatment effectiveness.

Impact of Micronutrients on CML Outcome:
Immune Function: Micronutrients such as vitamins A, C, D, E, and minerals like zinc and selenium are vital for maintaining a robust immune system. In chronic myeloid leukemia (CML), where the immune system is pivotal in battling cancerous cells, ensuring sufficient intake of these micronutrients can bolster immune function and augment the body's capacity to combat the disease.

Antioxidant Defense: Micronutrients like vitamin C, vitamin E, selenium, and zinc serve as antioxidants, countering detrimental free radicals that can harm cells and DNA. In chronic myeloid leukemia (CML), where oxidative stress is heightened due to elevated production of reactive oxygen species by cancer cells, ensuring adequate levels of antioxidants via dietary intake or supplementation might mitigate oxidative damage and potentially impede disease advancement.
DNA Repair and Cell Cycle Regulation: Various micronutrients, such as folate, vitamin B12, vitamin D, and zinc, fulfill crucial functions in DNA repair mechanisms and the regulation of the cell cycle. Disruption of these processes is a characteristic feature of cancer, including chronic myeloid leukemia (CML). Maintaining an ample supply of these micronutrients may aid in sustaining normal cellular activity and lowering the likelihood of genetic mutations that could promote cancer onset and advancement.

Supportive Therapy: Micronutrients can serve as adjuncts to conventional cancer therapies like chemotherapy and targeted therapy by alleviating treatment-associated side effects, promoting overall well-being, and enhancing quality of life throughout the treatment process.

Deficiency of Micronutrients in CML:
Malnutrition: Individuals with chronic myeloid leukemia (CML) may encounter malnutrition stemming from factors like diminished appetite, nausea, and gastrointestinal issues triggered by the disease or its therapeutic interventions. Malnutrition can precipitate deficiencies in vital micronutrients, compromising immune function, heightening vulnerability to infections, and undermining overall well-being.[4]

Increased Nutrient Requirements: The hypermetabolic state characteristic of cancer, including chronic myeloid leukemia (CML), elevates the body's nutrient requirements. Consequently, patients may necessitate higher-than-usual levels of micronutrients to sustain metabolic activities, bolster immune function, and facilitate tissue repair.
Drug Interactions: Certain medications utilized in the management of CML could disrupt the absorption, metabolism, or elimination of specific micronutrients, resulting in deficiencies. For instance, tyrosine kinase inhibitors (TKIs), a prevalent class of drugs employed in CML treatment, have been linked to changes in vitamin D metabolism, potentially heightening the likelihood of vitamin D deficiency in certain patients. Gastrointestinal Dysfunction: Gastrointestinal complications like mucositis, diarrhoea, and malabsorption may arise as adverse effects of CML treatment, thereby worsening nutrient deficiencies. These gastrointestinal issues can hinder the absorption of vital micronutrients, potentially resulting in deficiencies even when dietary intake is sufficient.

Individual Variability: Nutrient requirements and metabolism vary among individuals, and factors such as age, gender, comorbidities, and genetic predisposition can influence micronutrient status in patients with CML. Therefore, personalized nutritional assessment and intervention strategies are essential to address individual needs and optimize nutritional status in this population.[4]

In conclusion, micronutrients play a multifaceted role in the outcome of chronic myeloid leukemia, influencing immune function, antioxidant defense, DNA repair, and overall health. Identifying and addressing micronutrient deficiencies in patients with CML are crucial steps in optimizing treatment outcomes, minimizing treatment-related complications, and improving quality of life. A comprehensive approach that integrates nutritional assessment, supplementation when necessary, and dietary counselling can help support patients with CML throughout their treatment journey.

MATERIALS AND METHODS
The case control study was conducted on 100 subjects, in which 60 Patients of CML and 40 Controls Adjusted for Age and Sex from January 2023 to January 2024.

INCLUSION CRITERIA

Patients diagnosed with Chronic Myeloid Leukemia, previously diagnosed or recently diagnosed, after 18 years of age, Subjects who had given written consent, and normal healthy adults matched for age and sex

EXCLUSION CRITERIA
Subjects suffering from various Malabsorption syndromes
Subjects taking micronutrient supplements previously
Subjects not willing to give consent
Patient not compliant to medication or unable to take medication
Other severe diseases that would preclude study participation

METHODOLOGY
Detailed history and clinical assessment of all cases were carried out and recorded in the Proforma. 3 ml of venous blood was taken after consent and placed in a plain red vial for separation of serum, which was placed in an Atomic Absorption spectrometer. Controls matched to age and sex with no CML, which means relatives of patients of CML were also enrolled after written consent.

The study population was divided into 4 groups-
1. Patients in chronic phase responding to 1line TKI
2. Patients recently diagnosed with CML
3. Patients resistant to 1line TKI
4. Patients in blast crisis phase

After the collection of all data, the prevalence of micronutrient deficiency was calculated in each group, and its impact on treatment outcome was studied-Responsiveness to 1st line TKI. However, during the study period, there was no patient with CML in blast crisis phase who participated in the study.
Based on the objective of the study, descriptive and inferential statistics were drawn. Statistical correlation was analysed using various parametric and nonparametric tests. If a strong correlation was observed, mathematical prediction models were developed.

Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency, and proportion for categorical variables. Statistical significance of the pairwise differences was assessed by a paired t-test. $P < 0.05$ was considered a statistically significant difference. IBM SPSS statistical software version 21 was used for data analysis. $P < 0.05$ was considered statistically significant. IBM SPSS version 22 was used for statistical analysis.

Ethical Approval
The study was approved by the Institutional Ethics Committee of the Institute of Medical Sciences, Banaras Hindu University, Varanasi, India (Letter No. Dean/2022/EC/3845, dated 15 April 2023; ECR/526/Inst/UP/2014/RR-20). The study was conducted in accordance with the ethical standards laid down in the Declaration of Helsinki.

RESULTS

Table 1: Baseline characteristics

Age in years	**Case**		**Control**	
	N	%	N	%
16-30	9	15	8	20
31-45	13	21.67	10	25
46-60	25	41.67	20	50
61-75	13	21.67	2	5
Gender				
Male	27	45	15	37.5
Female	33	55	25	62.5
Region				
Rural	11	18.33	4	10
Urban	49	81.67	36	90

The age distribution among cases and controls reveals a varied age study population from the age group 16-30 years, where there were 9 cases, and the 31-45 years age group, where there were 13 cases and 10 controls. The 46- group had the highest number of participants, with 25 cases and 20 controls **[Table No. 1].** The 61-75 years age group had 13 cases and only 2 controls. The gender distribution among cases and controls shows a higher number of males compared to females in both groups. Among the cases, there are 27 females and 33 males. In the control group, there are 15 females and 25 males. The regional distribution of cases and controls shows that there are significantly more patients from urban areas compared to

rural areas in both groups. Among the cases, 49 are from urban areas, and 11 are from rural areas. Similarly, in the control group, 36 are from urban areas, and 4 are from rural areas.
Karyotyping results show that among the Chronic Myeloid Leukemia (CML) patients, 26 had 100% karyotyping and 4 had less than 100% In the new CML group. 12 patients had 100% karyotyping, and 3 had less than 100%. Among the resistant cases, all 15 patients had 100% karyotyping, indicating a trend towards complete karyotypic evaluation in resistant cases compared to new diagnoses **[Table No.2].**

Table 2: Distribution of participants according to karyotyping

Karyotyping	CML		New CML		Resistant		P Value
	N	%	N	%	N	%	
>100%	26	86.67	12	80	15	100	0.56
<100%	4	13	3	20	0	0	

The case group had a variety of comorbidities, including 12 patients with hypertension (HTN), 10 with diabetes mellitus (DM), 3 with hypothyroidism, 3 with tuberculosis, 2 with hyperthyroidism, and I each with benign prostatic hyperplasia (BPH) and asthma. In contrast, the control group had fewer comorbidities, with 3 patients with HTN, 2 with DM, and 1 each with hypothyroidism and tuberculosis **[Tables 3 and 4].**

Table 3: Distribution of patients according to co-morbidities

Co-morbidities	CML		New CML		P Value
	N	%	N	%	
HTN	12	20	3	7.5	0.08
DM	10	16.67	2	5	0.08
Hypothyroid	3	5	1	2.5	0.53
TB	3	5	1	2.5	0.53
Hyperthyroid	2	3.33	0	0	-
BPH	1	1.67	0	0	-
Asthma	1	1.67	0	0	-

Table 4: Distribution of patients according to CBC

Karyotyping	CML		New CML		Resistant		P Value
	Mean	SD	Mean	SD	Mean	SD	
Hb	10.27	1.54	10.74	2.73	8.88	1.53	0.05
TLC	55497	25084.78	80909.93	69500.65	82787.33	97487.60	0.26
Platelets	2.81	2.42	3.4	2.95	2.51	1.80	0.59

The mean hemoglobin (Hb) levels for patients with Chronic Myeloid Leukemia in the chronic phase (CML-CP), new CML cases, and resistant cases were 10.27 g/dL, 10.34 g/dL, and 8.88 g/dl, respectively. The total leukocyte count (TLC) averaged 55,497 cells/nm in CML-CP, 80,909.93 cells/nm in new CML cases, and 82,787.33 cells/nm in resistant cases. Platelet counts were 2.81 lakhinm for CML-CP. 3.4 lakh/nm for new CML cases, and 2.51 lakh/nm for resistant cases.

Table 5: Distribution of patients according to micronutrients

Chromium	Case		Control		P value
	Mean	SD	Mean	SD	
CML	0.003	0.001	0.23	0.26	<0.001
CML (New)	0.004	0.001	0.23	0.26	<0.001
Drug resistance	0.002	0.001	0.23	0.26	<0.001
Iron					
CML	73.78	20.05	84.9	14.64	0.003
CML (New)	66.61	13.51	84.9	14.64	<0.001
Drug resistance	68.4	12.83	84.9	14.64	0.0002
Copper					
CML	107.48	18.69	110.37	11.55	0.36
CML (New)	140.13	11.88	110.37	11.55	<0.0001
Drug resistance	123.02	14.54	110.37	11.55	<0.0001
Selenium					
CML	1.32	1.17	4.17	2.21	0.36
CML (New)	1.58	0.75	4.17	2.21	<0.0001
Drug resistance	1.42	1.63	4.17	2.21	<0.0001

Zinc					
CML	0.41	0.08	0.44	0.07	0.07
CML (New)	0.45	0.03	0.44	0.07	0.45
Drug resistance	0.43	0.05	0.44	0.07	0.6

The mean chromium levels in the case group (CML), new CML, and drug-resistant CML were 0.003, 0.004, and 0.002, respectively. The control group had a consistent mean chromium level of 0.23 across all categories. Among the CML cases, the mean iron level was recorded at 73.78 units, while in newly diagnosed CML patients, it slightly decreased to 66.61 units. Interestingly, those classified as drug- resistant CML exhibited a mean iron level of 68.4 units. In contrast, the control group serving as the baseline maintained a steady mean iron level of 84.9 units across all categories. Among CML cases, the mean copper level was measured at 107.48 units, while in newly diagnosed CML. patients (CML- NEW), it notably increased to 140.13 units. Patients classified as drug-resistant in the CML group exhibited a mean copper level of 123.002 units. In contrast, the control group maintained a consistent mean copper level of 110.37 units. In CML cases, the mean selenium level was measured at 1.32 units, while in newly diagnosed CML patients (CML-NEW), it showed a slight increase to 1.58 units. Among those classified as drug-resistant in the CML group, the mean selenium level was 1.42 units. In comparison, the control group exhibited a higher mean selenium level of 4.17 units. In patients diagnosed with CML, the mean zinc level was 0.41, while in newly diagnosed CML patients (CML-NEW), it slightly increased to 0.45. Among those classified as drug-resistant in the CML group, the mean zinc level was 0.43. In comparison, the control group showed a consistent mean zinc level of 0.44.

DISCUSSION

In the present study, the majority of Chronic Myeloid Leukemia (CML) patients were within the 46–60 year age group, with male predominance and a higher representation from urban areas. These findings are consistent with epidemiological data reported in regional and international studies conducted between 2010 and 2023, which demonstrate a higher incidence of CML in middle-aged males and improved detection in urban populations.[12–15] The predominance of Chronic Phase CML (CML-CP) in our cohort aligns with global registry data indicating that approximately 80–90% of cases are diagnosed in the chronic phase in the tyrosine kinase inhibitor (TKI) era.[16,17] The major BCR-ABL (p210) transcript was the most common molecular subtype observed, similar to findings reported in large molecular profiling studies.[18,19]

Trace element imbalance has increasingly been implicated in leukemogenesis and oxidative stress. In our study, serum copper levels were elevated in newly diagnosed and drug-resistant CML patients compared to controls. Elevated copper levels have been associated with tumor progression, angiogenesis, and inflammatory activation in hematological malignancies.[20–23] Several studies conducted between 2012 and 2023 reported significantly higher serum copper and ceruloplasmin levels in leukemia patients, correlating with disease burden and adverse prognosis.[24–26] Furthermore, the copper/zinc ratio has been proposed as a potential prognostic biomarker in leukemia.[27,28] Increased copper levels may enhance reactive oxygen species generation, contributing to genomic instability and treatment resistance.[29]

In contrast, selenium levels were lower in CML patients compared to controls. Selenium plays a vital role in antioxidant defense through selenoproteins such as glutathione peroxidase. Reduced selenium levels have been linked to increased oxidative stress and poorer outcomes in hematologic malignancies.[30–33] Prospective studies from 2014 to 2022 demonstrated that low plasma selenium levels were independently associated with relapse risk and inferior survival.[34,35] Experimental evidence suggests selenium may modulate apoptosis pathways and redox balance, though clinical evidence remains limited.[36]

Zinc levels in our study showed minor variation across disease phases. Zinc is essential for immune regulation, DNA synthesis, and antioxidant activity. Previous studies have shown inconsistent results, with some reporting zinc deficiency in leukemia patients, while others observed no significant difference.[37–39] Recent literature emphasizes that the copper/zinc ratio may better reflect inflammatory status and disease severity than zinc alone.[40]

Serum iron levels were lower in newly diagnosed and drug-resistant CML patients compared to controls. While earlier literature reported iron overload in leukemia due to transfusion dependence,[41] more recent studies distinguish treatment-naïve patients and highlight functional iron deficiency and anemia of chronic disease mechanisms.[42–44] Altered iron metabolism has been associated with inflammatory cytokine activity and disease progression.[45]

Chromium levels were markedly reduced in CML cases compared to controls. Literature regarding chromium in leukemia is limited and heterogeneous. Some studies report altered chromium metabolism associated with oxidative imbalance, whereas others show minimal variation.[46–48]

The biological role of chromium in leukemogenesis remains unclear and requires further investigation. Comorbidities such as hypertension and diabetes mellitus were common in our cohort. With improved survival in the TKI era, metabolic and

cardiovascular comorbidities are increasingly recognized as important determinants of long-term outcomes in CML.[49,50] Comprehensive management strategies should therefore address both hematological control and systemic metabolic health. Overall, our findings reinforce emerging evidence that trace element imbalance—particularly elevated copper and reduced selenium—may reflect oxidative stress and disease burden in CML. However, variations across studies suggest that geographic, nutritional, and therapeutic factors may influence trace element profiles. Larger longitudinal studies are required to establish their prognostic utility in clinical practice

CONCLUSION

The study provides a detailed insight into the epidemiology, clinical profile, treatment patterns, and biochemical aspects of Chronic Myeloid Leukemia. It highlights the importance of complete karyotyping in resistant cases and identifies potential differences in micronutrient levels associated with CML. The findings underscore the complex interplay of demographic factors, clinical characteristics, and biochemical parameters in the manifestation and management of CML. This comprehensive understanding is crucial for refining diagnostic strategies, optimizing treatment protocols, and enhancing patient outcomes in CML management. Future research could further explore the mechanistic roles of trace elements and genetic markers identified in this study, aiming for more targeted and effective therapeutic interventions.

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