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Diagnostic and Prognostic Relevance of Ceruloplasmin, Transferrin, and High-Sensitivity C-Reactive Protein in Type 2 Diabetes Mellitus: A Case-Control Study

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ABSTRACT

Background:
Type 2 diabetes mellitus (T2DM) is associated with chronic low-grade inflammation and oxidative stress. Biomarkers like ceruloplasmin, transferrin, and high-sensitivity C-reactive protein (hs-CRP) may offer diagnostic and prognostic value.

Objectives:
To evaluate serum levels of ceruloplasmin, transferrin, and hs-CRP in T2DM patients and analyze their correlation with glycemic parameters.

Methods:
A case-control observational study was conducted with 130 T2DM patients and 60 age- and sex-matched healthy controls. Fasting blood samples were analyzed for hs-CRP, ceruloplasmin, transferrin, fasting glucose, and HbA1c. Statistical analysis included unpaired t-tests, Pearson correlation, and ROC curve analysis.

Results:
T2DM patients showed significantly elevated hs-CRP ($p<0.001$) and ceruloplasmin ($p<0.01$), and decreased transferrin levels ($p<0.01$) compared to controls. hs-CRP and ceruloplasmin positively correlated with HbA1c and fasting blood glucose, while transferrin showed an inverse correlation. ROC analysis demonstrated hs-CRP had the highest diagnostic accuracy (AUC: 0.84), followed by ceruloplasmin (0.77) and transferrin (0.71).

Conclusion:
hs-CRP, ceruloplasmin, and transferrin serve as accessible, cost-effective biomarkers reflecting inflammatory and oxidative stress status in T2DM. Their correlation with glycemic parameters underscores their potential utility in monitoring disease progression and risk stratification.

Keywords:
Type 2 diabetes mellitus, ceruloplasmin, transferrin, hs-CRP, inflammation, oxidative stress, biomarkers

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic, progressive metabolic disorder that accounts for 90–95% of all diabetes cases globally[1]. It is characterized by a dual defect-insulin resistance and impaired insulin secretion culminating in sustained hyperglycemia and associated metabolic dysfunctions[2]. The burden of T2DM has escalated dramatically, with an estimated 537 million adults affected globally in 2021 and projections reaching over 700 million by 2045[3]. In India alone, over 77 million people live with diabetes, earning it the unfortunate distinction of being the "diabetes capital" of the world[4].

Beyond hyperglycemia, T2DM involves a spectrum of pathophysiological changes, including oxidative stress, low-grade chronic inflammation, and iron metabolism alterations-all of which are now believed to contribute to the development and

progression of micro- and macrovascular complications[5]. As the inflammatory and oxidative burden mounts, the demand grows for reliable, accessible biomarkers that not only reflect metabolic imbalance but also serve as early indicators of glycemic deterioration and systemic stress[6].

High-sensitivity C-reactive protein (hs-CRP) is a sensitive marker of systemic inflammation. Elevated hs-CRP levels have been independently associated with insulin resistance, endothelial dysfunction, and cardiovascular risk in T2DM[7]. Ceruloplasmin, a multi-copper oxidase and acute-phase reactant, serves as both an antioxidant and inflammatory mediator. While it protects against oxidative damage by converting Fe^{2+} to Fe^{3+}, paradoxically, it may contribute to oxidative stress in diabetic states by releasing pro-oxidant copper ions under high-glucose conditions[8]. Transferrin, the primary iron-transport protein in plasma, is crucial for maintaining redox balance. Altered transferrin levels in T2DM may reflect systemic iron overload, further exacerbating oxidative stress and insulin resistance[9].

Although these markers hs-CRP, ceruloplasmin, and transferrin have been studied independently in diabetes, few studies have examined them collectively, particularly in the Indian population. This study was undertaken to evaluate their serum levels in T2DM patients compared to healthy controls and assess their correlation with glycemic parameters (HbA1c), thereby exploring their potential as diagnostic and prognostic tools in diabetes management[10].

Materials and Methods

Study Design and Setting

This case-control observational study was conducted in the Department of Biochemistry, Jawaharlal Nehru Medical College, Ajmer, Rajasthan, over a one-year period from September 2023 to September 2024.

Study Population

The study enrolled 130 diagnosed T2DM patients from the Medicine OPD of JLN Hospital and 60 age- and sex-matched healthy individuals as controls.

Inclusion Criteria

- Diagnosed cases of T2DM as per American Diabetes Association (ADA) 2023 criteria[11]
- Age between 40 and 80 years
- Willingness to provide informed consent

Exclusion Criteria

- History of acute or chronic inflammatory disease
- Recent infections or surgeries
- Malignancy, autoimmune disorders, or liver dysfunction
- Alcoholism, smoking, or use of estrogen therapy
- Hypertension or use of lipid-lowering agents

Ethical Considerations

The study protocol was approved by the Institutional Ethics Committee of JLN Medical College, Ajmer. Written informed consent was obtained from all participants.

Sample Collection and Processing

Venous blood samples were drawn under aseptic conditions after an overnight fast of 10–12 hours. For postprandial glucose estimation, samples were collected 2 hours after lunch. Serum was separated by centrifugation and stored at −20°C until analysis.

Biochemical Parameters Measured

Parameter	Methodology	Reference Range
Fasting and Postprandial Blood Glucose	GOD-POD method[12]	FPG: 70–110 mg/dL; PPG <140 mg/dL
HbA1c	Latex-agglutination inhibition[13]	<6% (normal)
hs-CRP	Immunoturbidimetry[13]	<5 mg/L
Ceruloplasmin	p-Phenylenediamine oxidase (manual)[14]	23–45 mg/dL
Transferrin	Immunoturbidimetry[15]	170–340 mg/dL

Statistical Analysis

Data were analyzed using SPSS version 27.0. Results were expressed as mean ± standard deviation (SD). The unpaired Student's t-test was used to compare means between groups. Pearson's correlation coefficient was calculated to assess relationships between biomarkers and HbA1c. A p-value <0.05 was considered statistically significant.

Results

A total of 190 participants were enrolled in the study, comprising 130 T2DM patients and 60 age- and sex-matched healthy controls. The mean levels of hs-CRP and ceruloplasmin were significantly elevated in the diabetic group compared to controls ($p < 0.001$), whereas transferrin levels were significantly reduced ($p < 0.01$).

Biomarker Comparisons

- **hs-CRP:** Mean hs-CRP was 1.75 ± 0.61 mg/L in T2DM patients vs 0.971 ± 0.32 mg/L in controls.
- **Ceruloplasmin:** T2DM group showed elevated levels (47.8 ± 10.1 mg/dL) compared to controls (38.6 ± 9.6 mg/dL).
- **Transferrin:** Levels were significantly lower in diabetics (208 ± 40.9 mg/dL) than in controls (251 ± 46.4 mg/dL).

Correlation with Glycemic Marker (HbA1c)

- hs-CRP and ceruloplasmin showed a positive correlation with HbA1c ($r = 0.094$ and -0.207 respectively; $p < 0.05$).
- Transferrin showed a weak inverse correlation ($r = 0.019$, $p = 0.023$).

Diagnostic Performance (ROC Analysis)

- **hs-CRP**: AUC = 0.841; threshold = 6.86 mg/L; sensitivity = 29.8%, specificity = 72%.
- **Ceruloplasmin**: AUC = 0.764; threshold = 30.04 mg/dL; sensitivity = 75%, specificity = 32%.
- **Transferrin**: AUC = 0.823; threshold = 178.04 mg/dL; sensitivity = 94.2%, specificity = 10.4%.

Table 1: Comparison of Mean ± SD of Biomarkers in Control and T2DM Groups

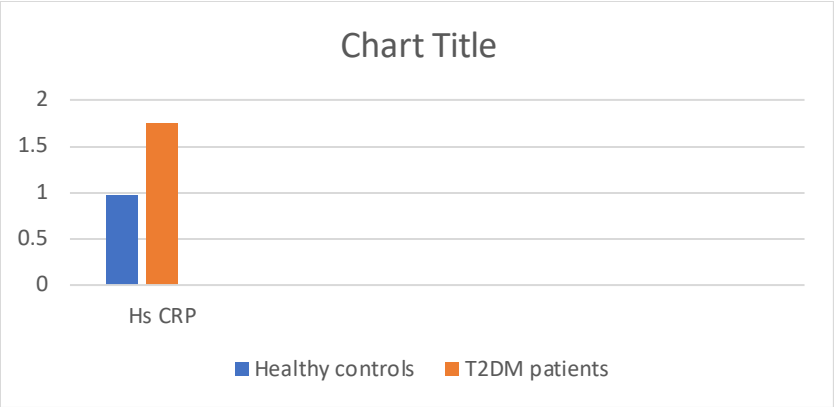
Biomarker	Control (Mean ± SD)	T2DM (Mean ± SD)
hs-CRP (mg/L)	0.971 ± 0.32	1.75 ± 0.61
Ceruloplasmin (mg/dL)	38.6 ± 9.6	47.8 ± 10.1
Transferrin (mg/dL)	251 ± 46.4	208 ± 40.9

Table 2: Correlation of Biomarkers with HbA1c in T2DM Patients

Biomarker	r-value	p-value	Significance
hs-CRP	0.094	0.049	Significant
Ceruloplasmin	-0.207	0.017	Significant
Transferrin	0.019	0.023	Significant

Table 3: ROC Curve Diagnostic Performance of Biomarkers (HbA1c ≥ 7%)

Biomarker	AUC	Optimal Threshold	Sensitivity (%)	Specificity (%)	Biomarker
hs-CRP	0.841	6.86	29.8	72.0	hs-CRP
Ceruloplasmin	0.764	30.04	75.0	32.0	Ceruloplasmin
Transferrin	0.823	178.04	94.2	10.4	Transferrin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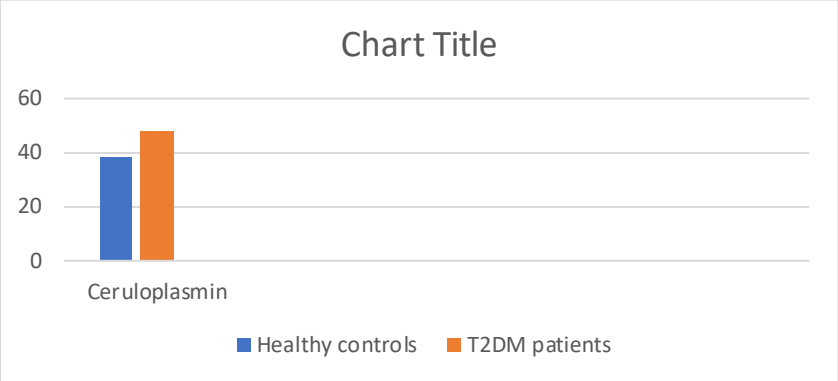
Hs CRP
Healthy controls
T2DM patients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20
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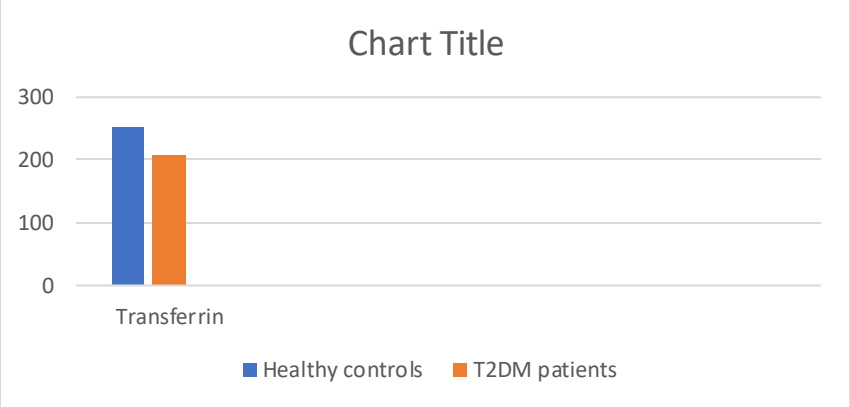
Ceruloplasmin
Healthy controls
T2DM patients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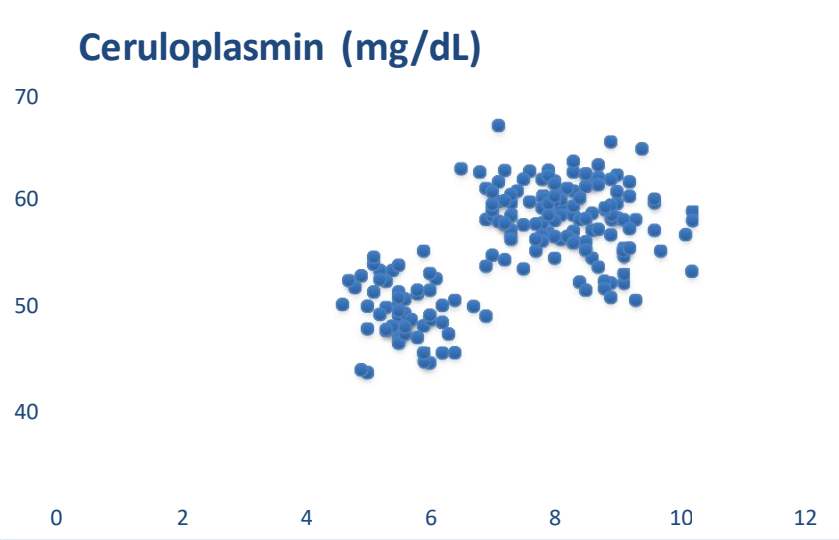
200
100
0
Transferrin
Healthy controls
T2DM patients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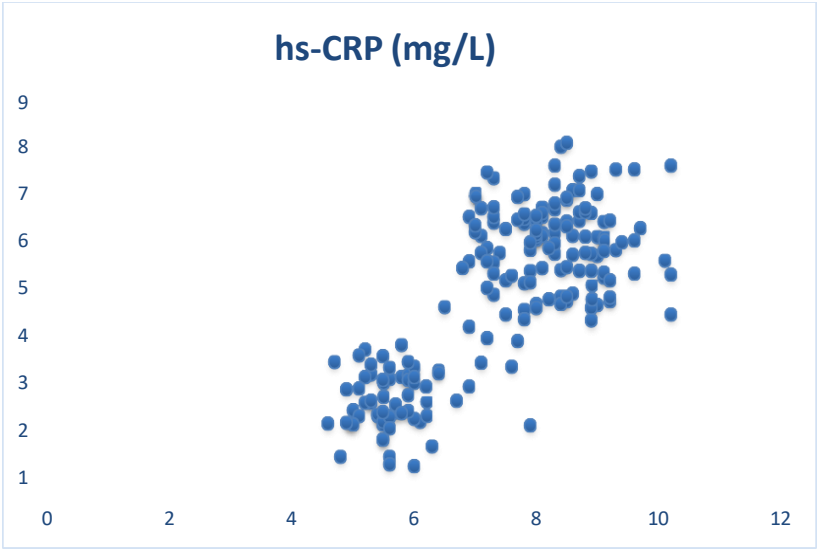
8
10
12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3
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1
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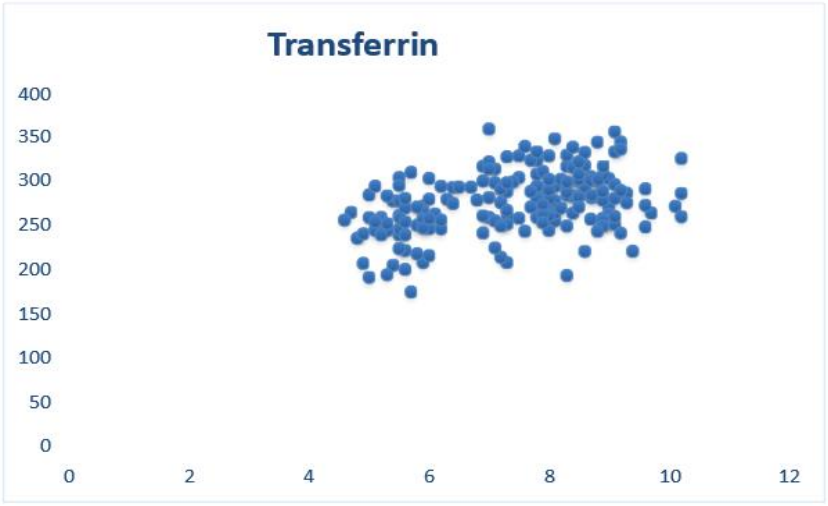
2
4
6
8
10
12


Transferrin
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150
100
50
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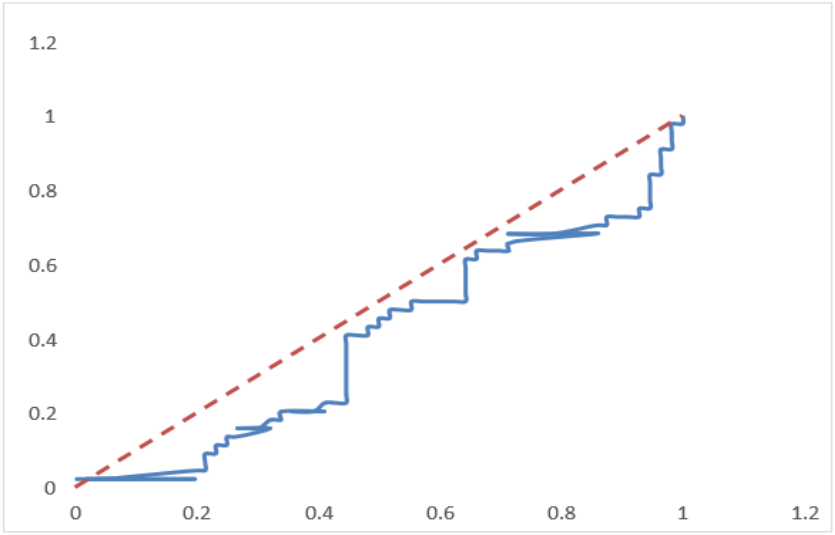
0
2
4
6
8
10
12

Hs CRP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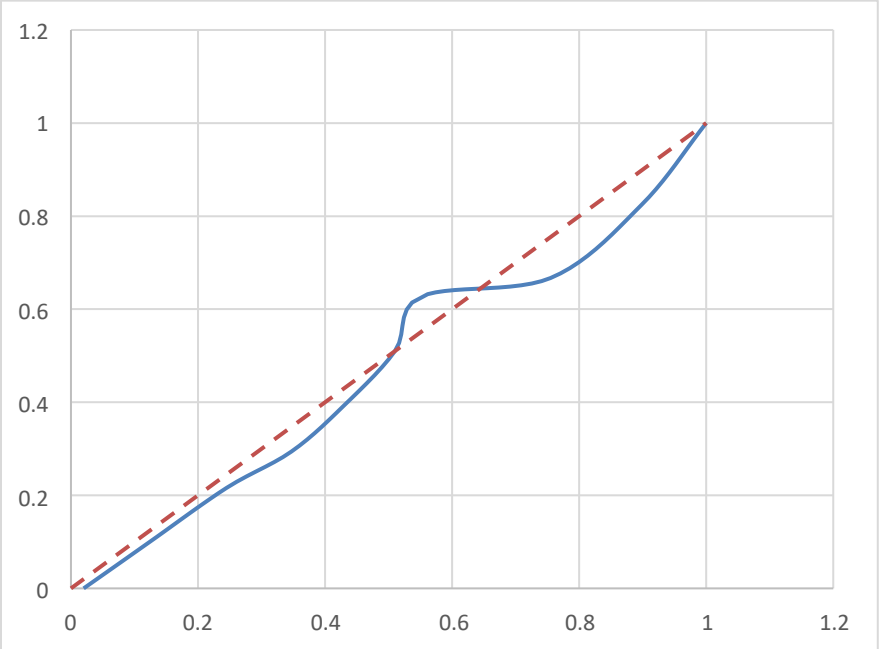
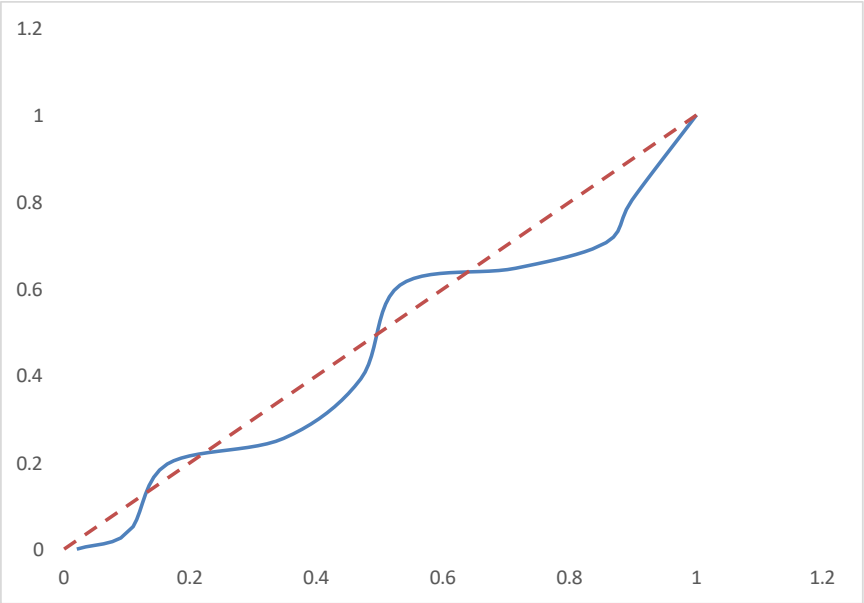
0.4
0.6
0.8
1
1.2

Ceruloplasmin



Transferrin



Discussion

The present study demonstrates significant alterations in inflammatory and iron-transport biomarkers in T2DM patients. The elevated hs-CRP levels corroborate the role of chronic low-grade inflammation in diabetes pathophysiology. This aligns with prior findings by Pradhan et al., where increased CRP preceded the development of T2DM in prospective cohorts.

Ceruloplasmin, an acute-phase reactant and ferroxidase, was significantly higher among diabetics. This supports earlier studies by Suraweera et al. and Singh et al., suggesting ceruloplasmin as a redox-sensitive inflammatory marker in hyperglycemia. Elevated ceruloplasmin could reflect a compensatory response to oxidative stress but may paradoxically contribute to ROS generation via free copper ion release.

Transferrin levels were significantly reduced in diabetics, consistent with the idea of altered iron homeostasis in T2DM. Iron overload can inhibit insulin signaling, leading to β-cell dysfunction. Lower transferrin may indicate systemic inflammation or ineffective iron transport, aggravating metabolic complications.

The correlation of all three markers with HbA1c—though modest—suggests their relevance in monitoring metabolic status. ROC analysis revealed that hs-CRP and transferrin had acceptable diagnostic performance (AUC >0.8), underscoring their potential utility in risk stratification. However, their relatively low specificity indicates that they should be interpreted alongside clinical parameters.

Conclusion

This study underscores the significant perturbations in inflammatory and oxidative stress markers—hs-CRP, ceruloplasmin, and transferrin—in T2DM patients. These biomarkers reflect the underlying metabolic and vascular derangements and show modest but significant correlations with glycemic control.

- **hs-CRP** serves as a reliable inflammatory biomarker with good diagnostic potential.
- **Ceruloplasmin** may act as a dual mediator of antioxidant and pro-oxidant activity.
- **Transferrin** alterations reflect dysregulated iron homeostasis and may indicate oxidative stress.

These findings support the clinical utility of these inexpensive, routinely measurable biomarkers in early risk detection and prognosis in T2DM. Further longitudinal studies are warranted to establish causality and prognostic thresholds.

Declarations

Conflict of Interest: None declared.

Funding: Self-funded.

Ethics Approval: Approved by the Institutional Ethics Committee, Jawaharlal Nehru Medical College, Ajmer.

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