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Determination of Serum Zinc, Ferritin, and Ceruloplasmin Levels in Diabetic Nephropathy

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ABSTRACT

Background: Diabetic nephropathy (DN) is one of the most serious microvascular complications of type 2 diabetes mellitus (T2DM) and a leading cause of end-stage renal disease worldwide. Oxidative stress, inflammation, and trace element imbalance have been implicated in its pathogenesis, and biomarkers such as zinc, ferritin, and ceruloplasmin may aid in early detection of renal involvement. The present study aimed to evaluate serum zinc, ferritin, and ceruloplasmin levels as potential early biomarkers of diabetic nephropathy.

Methods: This cross-sectional study included 142 participants, comprising 86 patients with T2DM and 56 healthy controls. Diabetic patients were categorized based on urinary albumin-to-creatinine ratio into diabetes mellitus (DM) and DN groups. Serum zinc was measured by the colorimetric method, while ferritin and ceruloplasmin were estimated using immunoturbidimetric methods. Glycemic and renal function parameters were also assessed. Statistical analysis was performed using ANOVA, with $p<0.05$ considered significant.

Results: Serum zinc levels were significantly reduced in diabetic and DN groups compared with controls ($p<0.001$), whereas ceruloplasmin levels showed a significant progressive increase across groups ($p<0.001$). Serum ferritin levels were higher in patients with diabetic nephropathy, but the difference did not reach statistical significance. Glycemic parameters (fasting blood glucose and HbA1c) and renal function parameters (blood urea and serum creatinine) were significantly elevated in the DN group ($p<0.001$).

Conclusion: Reduced serum zinc and elevated ceruloplasmin levels are significantly associated with diabetic nephropathy and may serve as useful early biomarkers for detecting and monitoring renal involvement in patients with T2DM. Larger prospective studies are required to confirm their clinical utility.

Key-words: T2DM, Diabetic nephropathy (DN), Diabetes mellitus (DM), Zinc, Ferritin, Biomarkers

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a rapidly increasing metabolic disorder worldwide and represents a major public health challenge, particularly in developing countries such as India [1,2]. Chronic hyperglycemia leads to progressive microvascular complications, among which diabetic nephropathy (DN) is one of the most serious causes of morbidity and mortality and remains the leading cause of end-stage renal disease globally [3–5]. Approximately one-third of patients with T2DM develop DN, characterized by persistent albuminuria, declining glomerular filtration rate, and progressive structural renal damage [6]. Although microalbuminuria is commonly used for early detection, renal injury may begin before detectable albuminuria, necessitating the identification of additional early biochemical markers [7]. Oxidative stress, inflammation, and trace element imbalance play a critical role in the pathogenesis of diabetic nephropathy [8]. Zinc is an essential trace element involved in insulin synthesis, antioxidant defence, and immune function, and reduced zinc levels have been associated with poor glycemic control and

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increased risk of diabetic complications [9,10]. Ferritin, a marker of body iron stores and inflammation, has been linked with insulin resistance and oxidative stress, contributing to renal tissue damage in diabetes [11,12]. Ceruloplasmin, a copper-containing acute-phase protein involved in iron metabolism, is also elevated in inflammatory and oxidative stress states and has been associated with diabetic microvascular complications [13,14].

Although individual associations of zinc, ferritin, and ceruloplasmin with diabetes-related complications have been reported, their combined role as early biomarkers of diabetic nephropathy has not been extensively explored, particularly in the Indian population [15]. Therefore, the present study was undertaken to evaluate serum zinc, ferritin, and ceruloplasmin levels in patients with diabetic nephropathy.

MATERIALS AND METHODS

Study Design and Setting- After obtaining permission and approval from the Institutional Ethics Committee, a cross-sectional study was carried out in the Department of Biochemistry, in collaboration with the Department of Medicine, Dr. Rajendra Prasad Government Medical College, Kangra (Tanda), District Kangra, Himachal Pradesh, India, over a period of three years between 2018 and 2021. Written informed consent was obtained from all participants before enrolment.

Study Participants- A total of 142 participants were included in the study, comprising 86 patients diagnosed with type 2 diabetes mellitus (T2DM) and 56 age- and sex-matched healthy controls. Patients attending the outpatient and inpatient departments during the study period who fulfilled the diagnostic criteria for T2DM according to the American Diabetes Association (ADA) guidelines were recruited consecutively.

Inclusion Criteria

- Age 18 years or older
- Confirmed T2DM
- Agreed to provide consent to participate in the study.

Exclusion Criteria

- acute infections
- chronic inflammatory diseases
- liver disorders
- malignancy
- pregnancy
- chronic kidney disease due to causes other than diabetes
- those receiving mineral supplementation or iron therapy
- Refusal to provide consent to participate

Methodology- Diabetic patients were categorized into groups based on urinary albumin-to-creatinine ratio (ACR) according to KDIGO 2012 guidelines. Patients with ACR less than 30 mg/g were classified as normoalbuminuria (A1), those with ACR between 30–300 mg/g as microalbuminuria (A2), and those with ACR greater than 300 mg/g as macroalbuminuria (A3).

After overnight fasting, approximately 5 mL of venous blood was collected from each participant under aseptic precautions. Blood samples were centrifuged, and serum was separated for biochemical analysis. Spot urine samples were collected for estimation of urinary albumin-to-creatinine ratio. Serum zinc levels were measured by colorimetric analysis on an automated biochemistry analyzer (Erba XL-640) using commercially available Randox diagnostic kits. Serum ferritin and ceruloplasmin were measured using immunoturbidimetric methods with Agappe Diagnostics kits. Fasting blood glucose, HbA1c, serum urea, and creatinine were measured using standard enzymatic methods on the same analyzer with appropriate internal and external quality control procedures.

Statistical Analysis- Data were entered into Microsoft® Excel 2019 and exported into SPSS v21.0 for statistical analysis. Data were presented as frequency, percentage, mean, and standard deviation (SD) as applicable. Comparison of quantitative variables among more than 2 groups was performed using one-way ANOVA followed by Bonferroni post hoc correction. p-value <0.05 was considered statistically significant.

Ethical approval

The study was initiated following approval from the Institutional Ethics Committee at Dr RPGMC, Kangra, at Tanda (vide letter number HFW-H(DRPGMC)/Protocol/2018/55, dated 01/12/2018). Participants were included if they provided consent to participate.

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RESULTS

The baseline characteristics of the study participants are shown in Table 1. The mean age increased progressively from the control group (47.21±15.07 years) to the diabetes mellitus group (58.08±11.36 years) and the diabetic nephropathy group (60.78±7.14 years). The mean body mass index (BMI) was comparable across groups, measuring 25.76±6.56 kg/m² in controls, 25.68±4.08 kg/m² in diabetic patients, and 23.90±3.17 kg/m² in patients with diabetic nephropathy. Males constituted 60.7% of the control group, 46.8% of the diabetes mellitus group, and 44.4% of the diabetic nephropathy group, while females accounted for 39.3%, 53.2%, and 55.5% of the respective groups. Smoking prevalence was low, reported in 5.4% of controls and 9.1% of diabetic patients, with no smokers in the diabetic nephropathy group. Alcohol consumption was reported by 30.4% of controls, 23.4% of diabetic patients, and 11.1% of patients with diabetic nephropathy, indicating broadly comparable baseline demographic and lifestyle characteristics among the study groups.

Table 1: Baseline Characteristics of Study Participants

Variable	Control (n=56)	Diabetes Mellitus (n=77)	Diabetic Nephropathy (n=9)
Age (years)	47.21±15.07	58.08±11.36	60.78±7.14
BMI (kg/m²)	25.76±6.56	25.68±4.08	23.90±3.17
Gender; n (%)	34 (60.7%)	36 (46.8%)	4 (44.4%)
Male	34 (60.7%)	36 (46.8%)	4 (44.5%)
Female	22 (39.3%)	41 (53.24%)	5 (55.5)
Smoking, n (%)	3 (5.4%)	7 (9.1%)	0 (0%)
Alcohol intake, n (%)	17 (30.4%)	18 (23.4%)	1 (11.1%)

Data presented as mean±SD, unless otherwise mentioned.

Table 2 shows a progressive and statistically significant increase in glycemic parameters from the control group to diabetes mellitus (DM) and further to diabetic nephropathy (DN) patients. The mean fasting blood sugar (FBS) levels were lowest in controls (88.32±7.43 mg/dl), increased markedly in the DM group (172.60±65.07 mg/dl), and were highest in the DN group (258.56±100.37 mg/dl), with the overall ANOVA demonstrating a highly significant difference ($p<0.001$). Post-hoc analysis revealed that all pairwise comparisons for FBS (Control vs DM, Control vs DN, and DM vs DN) were highly significant ($p<0.0001$), indicating progressive worsening of glycemic status across the groups. Similarly, HbA1c levels increased significantly from controls (4.93±0.58%) to DM (7.99±1.81%) and DN (9.08±1.98%), with a significant overall ANOVA result ($p<0.001$). Pairwise comparisons showed highly significant differences between the control group and both patient groups (Control vs DM and Control vs DN, $p<0.0001$). In contrast, the difference between the DM and DN groups was not statistically significant ($p = 0.11$), suggesting that although HbA1c levels were higher in DN patients, the increase compared with DM patients was not statistically significant.

Table 2: Glycemic Profile Comparison

Group	FBS (mg/dl)	HbA1c (%)
Control	88.32±7.43	4.93±0.58
Diabetes Mellitus	172.60±65.07	7.99±1.81
Diabetic Nephropathy	258.56±100.37	9.08±1.98
p-value	<0.001	<0.001

FBS: Control vs DM: p<0.0001; Control vs DN: p<0.0001; DM vs DN: p<0.0001

HbA1c: Control vs DM: p<0.0001; Control vs DN: p<0.0001; DM vs DN: p=0.11

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Table 3 demonstrates a progressive rise in renal function parameters from the control group to diabetes mellitus (DM) and further to diabetic nephropathy (DN) patients. Mean blood urea levels increased from 24.06±7.35 mg/dl in controls to 30.72±9.18 mg/dl in DM patients and were highest in DN patients (41.44±17.55 mg/dl), with the overall difference being highly significant ($p<0.001$). Pairwise analysis showed significant differences among all groups, including Control vs DM ($p<0.0001$), Control vs DN ($p<0.0001$), and DM vs DN ($p = 0.004$), indicating progressive deterioration of renal function. Similarly, serum creatinine levels increased from 0.97±0.21 mg/dl in controls to 1.04±0.25 mg/dl in DM patients and 1.39±0.49 mg/dl in DN patients, with a highly significant overall difference ($p<0.001$). However, pairwise comparisons showed that the difference between the control and DM groups was not statistically significant ($p = 0.41$). In contrast, both Control vs DN ($p<0.0001$) and DM vs DN ($p = 0.001$) comparisons were significant, suggesting that serum creatinine rises substantially only after progression to diabetic nephropathy.

Table 3: Renal Function Parameters

Group	Blood Urea (mg/dl)	Serum Creatinine (mg/dl)
Control	24.06±7.35	0.97±0.21
Diabetes Mellitus	30.72±9.18	1.04±0.25
Diabetic Nephropathy	41.44±17.55	1.39±0.49
p-value	<0.001	<0.001

Blood Urea: Control vs DM: p<0.0001; Control vs DN: p<0.0001; DM vs DN: p=0.004
Serum Creatinine: Control vs DM: p=0.41; Control vs DN: p<0.0001; DM vs DN: p=0.001

Table 4 shows significant alterations in trace elements and inflammatory biomarkers across the study groups. Serum zinc levels were highest in the control group (111.40±44.20 µg/dl) and were markedly reduced in both DM (57.57±37.25 µg/dl) and DN (64.01±29.66 µg/dl) patients. Pairwise comparisons demonstrated significant reductions in zinc levels between Control vs DM ($p < 0.0001$) and Control vs DN ($p = 0.003$). In contrast, the difference between DM and DN groups was not statistically significant, indicating that zinc depletion occurs early in diabetes and does not differ substantially with progression to nephropathy. Serum ferritin levels showed no statistically significant differences among the three groups, suggesting comparable iron storage status across the study population. In contrast, ceruloplasmin levels increased progressively from controls (26.46±6.05 mg/dl) to DM (45.42±25.13 mg/dl) and were highest in DN patients (58.16±10.39 mg/dl). Pairwise analysis revealed highly significant increases in Control vs DM and Control vs DN (both $p<0.0001$). In contrast, the difference between DM and DN was not significant ($p = 0.18$), indicating elevated oxidative stress and inflammatory activity in diabetic states compared to healthy individuals.

Table 4: Biomarker Comparison

Group	Serum Zinc (µg/dl)	Serum Ferritin (ng/ml)	Ceruloplasmin (mg/dl)
Control	111.40±44.20	116.47±86.32	26.46±6.05
Diabetes Mellitus	57.57±37.25	119.95±108.80	45.42±25.13
Diabetic Nephropathy	64.01±29.66	133.21±73.71	58.16±10.39

***Serum Zinc**: Control vs DM: p<0.0001; Control vs DN: p=0.003; DM vs DN: No significant*
***Serum Ferritin**: No significant*
***Ceruloplasmin:** Control vs DM: p<0.0001; Control vs DN: p<0.0001; DM vs DN: p=0.18*

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DISCUSSION

The present study evaluated the role of serum zinc, ferritin, and ceruloplasmin as potential early biomarkers of diabetic nephropathy (DN) in patients with type 2 diabetes mellitus (T2DM). The findings demonstrated significantly reduced serum zinc levels and significantly elevated ceruloplasmin levels in diabetic and diabetic nephropathy groups compared with controls. In contrast, serum ferritin levels showed an increasing trend but did not reach statistical significance. These results highlight the importance of trace element imbalance and oxidative stress in the pathogenesis of diabetic renal complications.

In the present study, serum zinc levels were markedly reduced in patients with diabetes and in those with diabetic nephropathy. Zinc plays a crucial role in insulin synthesis, storage, and secretion and functions as an important antioxidant by stabilizing cell membranes and protecting against oxidative damage [9,10]. Chronic hyperglycemia has been shown to increase urinary zinc excretion, resulting in systemic zinc deficiency, which may further impair insulin action and enhance oxidative stress, thereby accelerating the development of diabetic microvascular complications [16]. Similar reductions in serum zinc levels among patients with diabetic nephropathy have been reported in previous studies, supporting the hypothesis that zinc deficiency may contribute to renal tissue injury [17].

Ceruloplasmin levels were significantly elevated across the disease groups, with the highest values observed in patients with diabetic nephropathy. Ceruloplasmin is a copper-containing acute-phase protein involved in iron metabolism and functions as an antioxidant enzyme during inflammatory states [18]. Elevated ceruloplasmin levels reflect increased oxidative stress and systemic inflammation, both of which play a central role in the progression of diabetic nephropathy [19]. Previous studies have also demonstrated higher ceruloplasmin concentrations in patients with diabetic microvascular complications, suggesting that it may serve as an early marker of vascular injury [13].

Although serum ferritin levels were higher in diabetic and diabetic nephropathy groups compared with controls, the difference was not statistically significant in the present study. Ferritin reflects body iron stores and acts as an acute-phase reactant associated with inflammation and insulin resistance [11]. Increased iron stores can promote the generation of reactive oxygen species through iron-catalyzed oxidative reactions, leading to endothelial dysfunction and renal damage [12]. Several earlier studies have reported significant associations between elevated ferritin levels and diabetic nephropathy. In contrast, others have shown inconsistent findings, possibly due to differences in sample size, population characteristics, and nutritional status [20].

The glycemic and renal function parameters in the present study showed significant deterioration from the control group to diabetic nephropathy patients, as reflected by progressively higher fasting blood glucose, HbA1c, blood urea, and serum creatinine levels. Poor glycemic control is a well-established risk factor for the development and progression of diabetic nephropathy, as persistent hyperglycemia promotes the formation of advanced glycation end products, oxidative stress, and inflammatory pathways that lead to glomerular injury [4,5].

Overall, the combined evaluation of serum zinc, ferritin, and ceruloplasmin provides important insights into the metabolic and inflammatory mechanisms underlying diabetic nephropathy. Among the studied biomarkers, zinc and ceruloplasmin demonstrated strong associations with disease severity, suggesting their potential utility as early, non-invasive indicators of renal involvement in patients with T2DM. Early identification of biochemical alterations may facilitate timely intervention and improved prevention of renal complications [1,21].

LIMITATIONS

The present study has certain limitations, including a cross-sectional design and a relatively small sample size in the diabetic nephropathy group, which may limit the generalizability of the findings. Longitudinal studies with larger populations are required to establish causal relationships and determine the predictive value of these biomarkers in the progression of diabetic kidney disease.

CONCLUSIONS

The present study demonstrates that significant alterations in trace element and inflammatory biomarker levels are associated with diabetic nephropathy in patients with type 2 diabetes mellitus. Serum zinc levels were markedly reduced, while ceruloplasmin levels were significantly elevated in diabetic and diabetic

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nephropathy groups, indicating increased oxidative stress and inflammatory activity with disease progression. Although serum ferritin levels showed an increasing trend, the difference was not statistically significant in the present analysis. These findings suggest that assessment of serum zinc and ceruloplasmin may provide useful adjunctive biomarkers for early detection and monitoring of diabetic nephropathy. Early identification of such biochemical alterations may facilitate timely therapeutic interventions to improve glycemic control and prevent progression of renal complications. Further large-scale longitudinal studies are required to validate the predictive value of these biomarkers and establish their role in routine clinical screening of patients with type 2 diabetes mellitus.

CONTRIBUTION OF AUTHORS

Research concept- Suman Bisht
Research design- Suman Bisht
Supervision- Suman Bisht
Materials- Vikas Shama
Data collection- Vikas Shama
Data analysis and interpretation- Suman Bisht
Literature search- Vikas Shama
Writing article- Vikas Shama
Critical review- Suman Bisht
Article editing- Vikas Shama
Final approval- Suman Bisht

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