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A HOSPITAL BASED STUDY OF CORRELATION OF SERUM COPEPTIN LEVELS WITH PROGRESSION OF CHRONIC KIDNEY DISEASE IN DIABETES MELLITUS

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Abstract

Introduction: Copeptin, a glycopeptide is a C terminal part of preprovasopressin. Copeptin is a surrogate marker of arginine vasopressin and measurement of copeptin is a simple method. The size and half-life of copeptin permits easier immunological testing when compared to vasopressin, so it is also considered as a reliable surrogate marker of arginine vasopressin. Copeptin is considered to be associated with increased risk of developing chronic kidney disease and their clinical consequences in diabetic patients. The aim of our study wasto assess the correlation of serum copeptin levels with progression of chronic kidney disease in diabetics and to assess the correlation of serum copeptin level with, serum creatinine, serum urea,estimated glomerular filtration rate and plasma glucose in chronic kidney disease in diabetes mellitus patients.

Materials and methods: This hospital-based study was conducted in a Medical College, involving the Departments of Biochemistry and Nephrology. Study subjects included patients with diabetic nephropathy as per their medical history, estimated GFR and existence of kidney injury described by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines. Total 90 type 2 diabetic patients with various stages of chronic kidney disease Group-1 included patients in grade 1 to grade 3 of chronic kidney disease (34 subjects) and group 2 included patients in grade 4 to grade 5 Chronic kidney disease. (56 Subjects).

Results: In this study 90type 2 diabetic patients with various stages of chronic kidney disease were included. Group-1 included patients in grade 1 to grade 3 of CKD (34 subjects) and group 2 included patients in grade 4 to grade 5 CKD (56 Subjects). In group 1 and II, majority age groups was 66-70 years, 12 (35.29%), 15 (26.78%) respectively. In both the groups, male predominance was seen in the study, in group I males and females were22 (64.70%), 12 (35.29%) respectively. In group II males 39 (69.64%), females were 17(30.35%). Copeptin levels werecorrelated withplasma glucose r = 0.069 (p = 0.521), urea r = -0.111 (p = 0.300), eGFR r = -0.60 (p = 0.574), Grading r = 0.007 (p = 0.948), creatinine r= 0.60(0.517)

Conclusion: As copeptin is emerging biomarker in diagnosis of many diseases, our results suggest that copeptin could be a useful prognostic marker for kidney function decline in type 2 diabetic patients and by this eventually help prevent kidney complications. Thus, the study supports the strong and independent associations of copeptin with progression to CKD in type 2 diabetic patients that may offer new tools to identify patients with highest risk of progression.

Key Words: Diabetic nephropathy, Glomerular filtration rate, Copeptin, Chronic kidney disease.

INTRODUCTION

Diabetes mellitus (DM) is a heterogeneous metabolic disorder characterized by the presence of hyperglycemia due to impairment of insulin secretion, defective insulin action or both. The chronic hyperglycemia of diabetes is associated with relatively specific long-term microvascular complications affecting the eyes, kidneys and nerves, as well as an increased risk for cardiovascular disease.[1]Diabetic kidney disease (DKD) is a thoughtful complication that take place in 20% to 40% of alldiabetics.[2]The prevalence of diabetes around the world has reached epidemic proportions. While diabetes is already estimated to affect more than 8% of the global population (nearly more than 350 million people), this is predictable to grow to over 550 million people by the year 2035. [3] It has been estimated that more than 40% of people with diabetes will develop chronic kidney disease (CKD)[4]including a significant number who will develop ESKD requiring renal replacement therapies (dialysis and or transplantation). Presently available biomarkers such as serum creatinine have the limitations of being influenced by non-renal factors and low sensitivity to indicate the early stages of kidney disease.[5] Serum creatinine has been observed to be ineffective in the early detection or risk prediction of diabetic nephropathy or CKD and has been found be unreliable in elderly or malnourished patients. Despite the fact that microalbuminuria is still the gold standard for early detection of diabetic nephropathy; it is not a reliable indicator due to various limitations.[6]Inspite of the fact that serum creatinine, urea, BUN, Albumin/Creatinine ratio (ACR), eGFR, and 24-hour urinary albumin excretion rate (UAE) are widely used in the diagnosis of diabetic Nephropathy and Chronic Kidney Disease, these markers are not considered early predictive or prognostic markers. One such biomarker which has been investigated for early detection and prognostic assessment of CKD has been the C-terminal component of Pre-pro vasopressin, Copeptin.

Copeptin is released in equimolar concentrations with arginine vasopressin (AVP) during processing of the AVP precursor peptide in response to osmotic, hemodynamic and stress-related stimuli. [7]AVP is very unstable which makes it unsuited to use routinely as a biomarker. On the other hand, copeptin, the C-terminal fragment of arginine vasopressin prohormone represents the release of AVP. It is stable for days after blood withdrawal, can be readily measured and is considered to be a reliable surrogate marker for AVP [8]

Once released into the circulation, AVP exerts its peripheral effects by binding to tissue-specific G-protein–coupled receptors. The 2 predominant receptors are the V_1 receptor, which mediates

arteriolar vasoconstriction, and the V_2 receptor, which is responsible for the antidiuretic effect in the kidneys. A third AVP receptor, termed the V_3 receptor seems to be restricted to certain cells of the adenohypophysis and is involved in the secretion of ACTH.[9]

Since there was paucity in studies on correlation of copeptin levels with conventional renal function biomarkers especially in Indian population, we investigated the possible role of copeptin as a prognostic marker for nephropathic patients and an indicator of progression of end-stage renal disease.

AIMS AND OBJECTIVES

1) To assess the correlation of serum copeptin levels with progression of Chronic Kidney disease in diabetics.

2) To assess the correlation of serum copeptin level with serum creatinine, urea estimated glomerular filtration rate and plasma glucose in diabetic chronic kidney disease patients.

MATERIALS AND METHODS

Source of Data: This hospital-based study was conducted in a Medical College, involving the Departments of Biochemistry and Nephrology. Study subjects included patients with diabetic nephropathy as per their medical history, estimated GFR and existence of kidney injury described by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines.

Sample size: Total 90 type 2 diabetic patients with various stages of chronic kidney disease Group-1included patients in grade 1 to grade 3 of CKD (34subjects) and group 2 included patients in grade 4 to grade 5 CKD (56 Subjects).

Study Design: Cross sectional study.

Inclusion criteria: Type 2 diabetic patients with various stages of chronic kidney disease between the age 40-70 years including both male and female.

Exclusion Criteria: Chronic liver disease, Malignancy, Thyroid dysfunction, Sepsis, non-diabetic renal disease, Patients with a history of taking angiotensin -converting enzyme inhibitors and angiotensin receptor blockers, history of coronary artery disease (CAD), stroke, or peripheral vascular disease,

Methods: The patients will be categorized into different stages of CKD as per the KDIGO (Kidney Disease Improving Global outcomes) criteria 2012. Group-1 will include patients in grade 1 to grade 3 of CKD (34subjects) and group 2 (56subjects) will include those who have been diagnosed to be in grade 4 to grade 5CKD.

Data of plasma glucose, serum creatinine, serum urea, eGFR was collected. In the serum samples, copeptin levels will be measured by enzyme linked immunosorbent assay (ELISA) using the reagent kits from, and Biorad microplate reader.

Statistical analysis: The collected data was meticulously organized, tabulated, and subjected to comprehensive statistical analysis utilizing SPSS statistical software. For the qualitative data in this study, numerical and percentage, representations were employed.

RESULTS

In this study 90 type 2 diabetic patients with various stages of chronic kidney disease were included. Group-1 included patients in grade 1 to grade 3 of CKD (34 subjects) and group 2 included patients in grade 4 to grade 5 CKD (56 Subjects).

S.No	Age group	Group I	Group II
1	40-45	6(17.64)	7 (12.5)
2	46-50	3(8.82)	14(25)
3	51-55	4 (11.76)	5 (8.92)
4	56-60	5 (14.76)	11 (19.64)
5	61-65	4 (11.76)	4 (7.14)
6	66-70	12 (35.29)	15 (26.78)
7	Total	34 (100%)	56 (100%)

Table 1: Age distribution

In group 1 and II, majority age groups was 66-70 years, 12 (35.29%), 15 (26.78%) respectively.

S.No	Gender	Group I	Group II
1	Male	22(64.70)	39 (69.64)
2	Female	12 (35.29)	17(30.35)
3	Total	34 (100%)	56 (100%)

Table 2: Gender distribution

In Both the groups, male predominance was seen in the study, In group I males and females were22 (64.70%), 12 (35.29%) respectively. In group II males 39 (69.64%), females were 17(30.35%).

S.No	Copeptin	Group I	Group II	P value
1	1.018-2.777	31	40	0.04
2	3.112-5.905	2	8	
3	6.269-14.560	1	8	

Table 3: Copeptin levels

S.No	Glucose	Group I	Group II	P value
1	70-100	4	4	
2	101-120	8	3	

3	121-150	8	10	0.05
4	151-200	4	18	
5	>201	9	14	

Table 4: Glucose

S.No	Creatinine	Group I	Group II	P value
1	0.66-1.4	17	0	0.042
2	1.5-3	16	7	
3	3.03-5	16	0	
4	5.07-10	0	23	
5	10-25	0	10	

Table 5: Creatinine

S.No	Urea	Group I	Group II	P value
1	25-50	21	6	0.031
2	51-100	7	25	
3	101-200	5	21	
4	>201	0	3	

Table 6: Urea

S.No	GFR	Group I	Group II	P value
1	1-25	0	51	0.049
2	26-59	23	5	
3	>60	10	0	

Table 7: Glomerular filtration rate

Variables	Correlation Coefficient(r)	Significance
Plasma glucose	.069	.521
Serum urea	-.111	.300
eGFR	-.060	.574
Grading	.007	.948
Serum creatinine	.060	.517

Table 8: Correlation of serum copeptin with other parameters

In group 2, 51 patients has GFR 1-25, in group 1, no patients was present. This study showed a significant association between elevated copeptin concentrations in type 2 diabetic patients and decreasing eGFR resulting in CKD. Therefore, it is appropriate to draw the conclusion that copeptin is associated with a decrease in eGFR. The results go along with and that reported that positive associations of copeptin with markers of kidney function or with kidney function decline were observed in populations with CKD or at high risk of CKD, such as people with diabetes. Plasma copeptin level was positively correlated with plasma glucose, serum creatininebut negatively correlated with eGFR.

DISCUSSION

Copeptin is co-secreted with the arginine vasopressin (AVP), upon hemodynamic or osmotic stimuli. Unlike the AVP, copeptin is stable in serum and plasma at room temperature and can be measured as a marker for AVP secretion.[10]

This cross sectional study was conducted to find out the relation between serum copeptin level andkidney injury in diabetic patients.

In this study, there was a significantdifference among the studied groups as regards copeptin, blood glucose, serum creatinine, serum urea among Group I and Group II. Group II patients are having much elevated levels of copeptin, blood glucose, serum creatinine, serum urea when compared with group I.[11]

Other researchers reported a significant increase in serum levels of copeptin among type-2 diabetes mellitus patients without and with nephropathy than control. Also, serum copeptin can be an independent risk factor of early decline in renal functionof type-2 diabetes mellitus, especially when combinedwith 24-hours urinary protein estimation.[12]

Elevated serum copeptin levels play a role inthe development of kidney injury or diabetes mellitus, and increasing the daily intake of water can helpreduce serum copeptin and its harmful effects.Increased serum copeptin and AVP may increase eGFRand proteinuria, and their blockage may help to preventthe development of CKD.[13]

To differentiate whether this elevation in the serum copeptin is related to stages of CKD, we tested its correlations with other laboratory investigations. In group II, there was a much positive correlation between copeptin, blood glucose, serum creatinine, serum urea, while there was a less significant correlation in group I. This may explain the higher levels of serum copeptin in stage 4, 5 than those with stage 1, 2, 3.[14]

We demonstrated that high plasma copeptin concentration was strongly associated with the risk of severe renal outcomes (doubling of plasma creatinine concentration and/or ESRD) in patients with type 2 diabetes. This association was independent of relevant covariates such as age, duration of diabetes, blood pressure, and baseline levels of HbA_{1c}, UAE. Plasma copeptin could predict the incidence of renal outcomes, and may add as a prognostic marker.

LIMITATIONS

1. Large sample size is required to generate more accurate correlation.
2. Equal sample size is not taken in the present study.
3. Information relating to urinary protein/albumin excretion as it could have helped us stage the study population using the KDIGO classification.
4. Details of cofounding variables such as dietary, salt and water intake are not available

CONCLUSION

As copeptin is emerging biomarker in diagnosis of many diseases, our results suggest that copeptin could be a useful prognostic marker for kidney function decline in type 2 diabetic patients and by this eventually help prevent kidney complications.Thus, the study supports the strong and independent associations of copeptin with progression to CKD in type 2 diabetic patients that may offer new tools to identify patients with highest risk of progression.

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