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CYSTATIN-C AS AN EARLY INDICATOR FOR INCIPIENT RENAL DISEASE IN RHEUMATOID ARTHRITIS- A CROSS SECTIONAL STUDY FROM A TEACHING HOSPITAL IN JODHPUR.

Medicine

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ABSTRACT

Introduction: Serum Cystatin–C is a considered as better marker of renal function than creatinine in early stages of renal dysfunction which helps in early therapeutic intervention and possibly favorable outcome.

Materials & Methods: A hospital based cross sectional study conducted at Dr. S.N. Medical College & Associated hospitals where various laboratory tests were performed to compare the serum cystatin-C with other biomarkers to indicate the early renal disease among the 50 patients suffering from chronic RA disease.

Results: Out of 50 patients 28 patients were aged between 31-50 years. 42 were females while only 8 males were part of study. Low prevalence of Cystatin-C and serum creatinine was recorded in RA patients having normal glomerulus filtration rate. An increase Cystatin-C level was observed in 62% patients while only 2% patients found to have increase serum creatinine among the patients with altered/abnormal glomerulus filtration rate.

Conclusion: Cystatin-C is a better biomarker than serum creatinine in detecting the renal involvement among the patients suffering from chronic rheumatoid arthritis.

KEYWORDS

INTRODUCTION:

Rheumatoid arthritis (RA) is the chronic, inflammatory, systemic autoimmune disease and hence an important cause of potentially presenting disability. The characteristic feature of RA is a persistent inflammatory synovitis, usually involving peripheral joints in a symmetric distribution. The potential of synovial inflammation to cause cartilage damage and bone erosions and subsequent changes in the joint integrity is the hallmark of the disease. Despite its destructive potential, the evolution of RA can be varied. Long- term survival of patients with rheumatoid arthritis is shorter relative to the general or control population without RA.[1]

In RA, renal involvement is relatively common and clinically significant because it worsens course the primary disease. There is still a lack of consensus on the prevalence of renal disorders in RA: data analysis originates from different sources, as autopsies, clinical and laboratory findings and kidney biopsies, each with its limitations.[2]

In patients with acute kidney injury (AKI), serum creatinine level does not increase until moderate to severe reduction in glomerular filtration rate (GFR) occurs. Thus, it is use for estimating GFR in early AKI delays detection of kidney damage and making important therapeutic decisions. Multiple analysis revealed Cystatin–C based GFR reflecting decline in GFR with worsening AKI in better index than creatinine based GFR. Serum Cystatin–C is a better marker of renal function in early stages of renal dysfunction, helps in early therapeutic intervention and possibly favorable outcome.[3] Plasma Cystatin–C reflects glomerular filtration rate (GFR) better than serum creatinine, blood urea nitrogen [4-8] since the later is affected by many nonrenal factors, such as muscle mass, hydration, physical activity, body surface area, sex, and age [9,10]. Cystatin-C is produced by all nucleated cells with a stable production rate unaffected by change in muscle mass, sex and chronic inflammatory conditions.[8,11,12-14] These biochemical and biological features suggest Cystatin–C as a sensitive and specific clinical marker of GFR.[4,6-8,11-13]

The present study was conducted to examine the diagnostic capacity of this new parameter towards early signs of renal disease in patients suffering from prolonged RA requiring potential nephrotoxic therapy.

MATERIAL & METHODS:

A hospital based cross sectional study was conducted in Department of Medicine, Mathura Das Mathur Hospital, Dr. S.N. Medical College, Jodhpur for a period of 6 months. Ethical clearance taken from institutional ethical committee to conduct the study.

After obtaining a written informed consent from 50 patients with an established diagnosis of Rheumatoid Arthritis, as defined by the ACR/EULAR criteria for Rheumatoid arthritis of 1-year duration were included in the study. All the patients were subjected to following investigations.

1.	Complete Blood Count (Sysmex 5–part differential hematology analyzer)
2.	Blood Urea, Serum Creatinine, Serum Uric Acid (By RemiR 80 machine)
3.	SGOT, SGPT, Serum Total Bilirubin, Serum Albumin, Serum Globulin, Prothrombin Time (By RemiR 80 machine)
4.	Urine Complete
5.	USG abdomen for kidney size (By AKOLA prosound alpha6)
6.	Microscopic albuminuria
7.	24 hours urine creatinine
8.	Cystatin–C

STATISTICAL ANALYSIS:

Quantitative data with normal distribution were compared by one-way analysis of variance (ANOVA), whereas those with non-normal distribution were subjected to the Kruskal-Wallis non-parametric test. Statistical analysis was performed with SPSS 24.0 (SPSS, Inc., Somers, NY, USA). A value of $P < 0.05$ was considered statistically significant.

RESULT:

Among the 50 patients included in the study the male to female ratio was 1:5.25. Most of the subjects included in the study were aged between 31-50 years.

Table: 1 Age And Gender Wise Distribution Of Cases

Age (in years)	Male	Female	Total
20 – 30	03 (37.50%)	09 (19.05%)	24.00
31 – 40	02 (25.00%)	12 (28.57%)	28.00
41 – 50	02 (25.00%)	12 (28.57%)	28.00
>50	01 (12.50%)	09 (19.05%)	20.00
Total	**08 (100%)**	**42 (100%)**	**50 (100%)**
Mean age (in years)	37.37±10.63	42.02±12.92	**P=0.344**

Table: 2 Laboratory Parameters

Parameters	Mean ±SD	Median	95%C.I.	IQR
Cystatin-C	1.03 ± 0.23	1.02	0.96-1.10	0.312
Blood urea (mg/dl)	25.48 ± 5.63	25.00	23.87-27.08	9.25

Serum creatinine (mg/dl)	0.94 ± 0.16	0.92	0.89-0.98	0.142
eGFR	79.18 ± 19.38	76.00	73.66-84.69	28.00
24 hours urine creatinine	0.92 ± 0.91	0.79	0.66-1.18	0.307
24hrs urine creatinine clearance	92.36 ± 21.69	85.00	86.18-98.53	32.50
NIL	30 (60.0%)	-	-	-
Trace	15 (30.0%)	-	-	-
Positive	05 (10.0%)	-	-	-

Table: 3 Co-relation Between Biomarker Of Severity Of Kidney Disease With Egfr

eGFR	Number (%)	Cystatin C	Creatinine	24 hours urine creatinine	24hrs urine creatinine clearance
GFR >80 ml/min [Normal]	19 (38.0%)	0.81 ± 0.10	0.86 ± 0.10	0.88 ± 0.27	116.05 ± 13.94
GFR 60–80 ml/min: [mild]	24 (48.0%)	1.12 ± 0.15	0.93 ± 0.12	1.01 ± 1.29	81.62 ± 4.61
GFR 30–59 [ml/min] [moderate]	07 (14.0%)	1.34 ± 0.21	1.17 ± 0.25	0.67 ± 0.18	64.85 ± 7.58
GFR 15–29 ml/min: [severe]	00 (0.0%)	--	---	--	--
Total	50 (100%)	1.03 ± 0.23	0.94 ± 0.16	0.92 ± 0.91	92.36 ± 21.69
ANOVA		**<0.0001**	**<0.0001**	**0.678**	**<0.0001**

DISCUSSION

Renal involvement is a significant problem in RA patients. There are numerous potential causes of nephropathy in RA; nephrotoxicity of DMARDs and NSAID analgesic drugs, secondary disease induced by chronic inflammation (especially amyloidosis) and renal manifestations linked to primary disease process (predominantly mesangial glomerulonephritis). During the last decades, the picture of renal disease has change due to earlier and more aggressive therapy of arthritis. Now days many of nephrotoxic drugs such as d-penicillamine and gold are no longer or very rarely used. NSAIDs are less frequently prescribed in high doses and used for short period.

Acute renal failure is now very infrequent, but chronic kidney disease still makes an important contribution to morbidity and mortality.[15,16]

In current study decreased GFR in 60% patients were recorded which is in concordance with the study of Daoussis et al. who had studied 400 RA patients in the term of the relation between renal function and signs of metabolic syndrome; HTN, hyperlipidemia, obesity and insulin resistance and found 55% patients with GFR between 60 and 90 ml/min, 11.5% patients with GFR less than 60 and only 1% patients with GFR <30. They found that GFR deterioration was strongly associated with age, disease duration and extra articular disease manifestations.[17]

Sivhonen et al. studied the relationship between RA nephropathy and mortality where 604 patients were screened, isolated proteinuria was present in 4.5%, isolated hematuria was present in 9%., combined hematuria and proteinuria in 1.2%, microalbuminuria in 5.6% and CRF in 5.8%. All except isolated hematuria were associated with increased mortality.[18] In the present study no hematuria was found in any patient however albuminuria in 10% patients was detected which is much higher than above study. High rate of albuminuria may be due to analgesic abuse.

In current study all marker including serum creatinine and eGFR showed significant difference between patients with Cystatin-C level <0.95 mg/dl and those with >0.95mg/dl. Jeon et al. found Cystatin-C level is increased with increasing CKD stage 1 to 3 and from normo-to microalbuminuria and showed a positive co-relation with ACR (Albumin to creatinine ratio). In a comparison of renal function markers in diabetic patients according to serum Cystatin-C level, all markers including ACR, serum creatinine and eGFR showed significant differences between patients with Cystatin-C level<1. 06mg/l and those with >1.06mg/l.[19]

An increase Cystatin-C level in 62% patients and only 2% patients with increase serum creatinine was recorded in the present study. M S N Murty studied 200 healthy subjects and 130 AKI patients over a period of 2 years where 56.2% of patients had normal level of serum creatinine, while all the patients have elevated serum Cystatin-C.[2] A study done by Herald Mangge, the lower co-relation between Cystatin-C and plasma creatinine was explained by the fact that 60% of the RA patients showed elevated plasma Cystatin-C level, whereas creatinine was increased in 5% patients only. A decreased creatinine clearance in 57% of RA patients strengthens the notion of renal dysfunction despite largely normal plasma creatinine.[20]

In the present study majority of patients were 20–50 years of age (80%) and mean age 41.28±12.60 and Male/Female ratio =1:5.25 while in the study of Herald Mangge et al mean age was 62.1±13.8 and Male /Female ratio = 1:4.09.[20]

In current study 1 patient (2%) has elevated serum creatinine level (Normal<1.2 mg/dl) and 49 patients (98%) have normal creatinine level and 30/50 RA (60%) patients have decrease creatinine clearance. while Herald Mangge et al. found 3 patients (5%) with elevated serum creatine level and 53 patients (95%) having normal serum creatinine level and 32/56 RA (57%) patients have decrease creatinine clearance.[20]

In the current study 19 patient (38%) patient had normal Cystatin–C level (Normal<0.95 mg/dl) and 31 (62%) patients had high cystatin–C level. The result of the Cystatin-C level was found similar with the study of Herald Mangge et al where 60% patient have elevated Cystatin–C level & 40% patient have normal Cystatin-C level.[20]

It turned out that 60% of the investigated patients who showed a pathologically decreased creatinine clearance in spite of normal creatinine serum levels indicating an early renal impairment, which cannot be detected by serum creatinine measurement. Creatinine clearance values were by far better correlated with serum Cystatin-C than with serum creatinine. This diagnostic inaccuracy of serum creatinine especially in RA patients may be due to the fact that it is influenced by physical activity and muscle mass, which both are usually low in RA patients because of chronic joint pain.

CONCLUSION

The study generated important conclusion that would enhance our understanding that compared to serum creatinine, the determination of serum cystatin C is relatively simple, but immeasurably more sensitive for the diagnosis of incipient renal damage in RA, and therefore valuable for clinical screening particularly in cases with prolonged antirheumatic treatment.

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