Urinary neopterin and indices of renal involvement in rheumatoid arthritis

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ABSTRACT

There is increasing evidence that renal disease is presumed to be one of the main causes of mortality among rheumatoid arthritis (RA) patients. Thus, it is important to periodically carryout sensitive and reliable measures for renal function to pickup the earliest signs of renal dysfunction. In this regard, the aim of the present work is to look for the most predictable urinary index for early renal involvement in RA. Moreover, the study tried to find whether urinary neopterin levels give an indication about the renal affection in RA.

Urine samples were obtained from 49 RA patients. Most of the studied RA patients (91.84%) were on combined therapy [non-steroidal anti-inflammatory drugs (NSAIDs), disease modifying anti-rheumatic drugs (DMARDs), and/or steroids]. The activity of the disease was evaluated on the basis of clinical and routine investigations. In addition, 15 urine samples were obtained from healthy controls. For all the studied groups traditional kidney function tests were performed. Specific urinary measures for renal function were determined namely, microalbuminuria, beta-2-microglobulin (β_2M), N-acetyl glucosaminidase (NAG), and gamma glutamyl transferase (GGT). Furthermore, urinary neopterin levels were estimated in all the studied groups. Receiver Operating Characteristics (ROC) curve was used to select the best cutoff values for identifying the sensitivity and the specificity of the diagnostic test.

The present study recorded 23 out of 49 (46.93%) RA patients had low creatinine clearance (CrCl), 13 (26.53%) had macroalbuminuria, 17 (34.69%) had microalbuminuria, and 9 (18.36%) had haematuria. A significant elevation of the levels of microalbumin, β_2M, and neopterin, and activities of NAG and GGT was revealed in urine of RA patients as compared to control group. However, there were only an increase in the levels of microalbuminuria and urinary neopterin in RA patients with extra-articular manifestations as compared to RA patients without. On the other hand, RA patients at risk of renal affection (with macroalbuminuria and/or low CrCl) had high microalbuminuria and β_2M levels. Also, the significant increase of the activities of NAG and GGT was observed in those patients when compared to those with normoalbuminuria and/or normal CrCl. Regarding the ROC plot, the area under the curve (AUC)>0.7 indicates a discriminating strength of statistical significance. ROC plot analysis showed that microalbuminuria, β_2M, NAG, GGT and

neopterin had discriminating power for renal affection among RA patients (AUC 0.90, 0.956, 0.77, 0.92, and 0.71 respectively). Urinary neopterin was positively correlated with ESR, urea, microalbumin, and urinary β_2M ($r=0.6$, $p<0.001$; $r=0.31$, $p<0.05$; $r=0.51$, $p<0.001$ and $r=0.43$, $p<0.01$ respectively).

In conclusion, the regular urine examination by simple and sensitive indices for early identification of renal affection in RA could guide the clinicians for a suitable line of therapy. The elevation of urinary neopterin levels was related to extra-articular manifestations as well as some kidney function tests. Such findings might clarify to some extent the role of urinary neopterin as an indicator of renal involvement in RA patients particularly those with active disease.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic disease, which mainly affects the joints. It can also lead to extra-articular organ manifestations. There is increasing evidence that renal disease is presumed to be one of the main causes of mortality among RA patients [1&2].

Clinically, manifest renal involvement in RA has been commonly attributed to secondary amyloidosis and renal vasculities [3&4]. Nephrotoxic medication as non-steroidal anti-inflammatory drugs (NSAIDs) some disease modifying anti-rheumatic drugs (DMARDs), and even anti-TNF-alpha therapy is the other major etiology of kidney involvement [5,6&7]. The incidence of nephropathy in RA patients is not known, since RA patients frequently show subclinical renal dysfunction[3].

Traditionally, the approach to detect any renal disease has always been first the urinary examination followed by histopathological examination. Although renal biopsy is the gold standard, it is being invasive and cannot be done at regular interval to diagnose renal disease early [8].

Many reports have looked at glomerular and tubular proteinuria as markers of nephropathy in RA. These were preferred over serum creatinine (Cr) and Cr clearance (CrCl), the usually available simple tests. The latter tests lack the sensitivity especially in RA patients due to their reduced muscle mass, whereas, proteinuria is more sensitive to detect renal diseases [9&10]. Microalbuminuria is defined as a persistent values of albumin in urine between >30-<300 mg/day [11]. It is considered as a simple and sensitive test to detect early subclinical renal dysfunction as drug induced renal damage in RA [3&12].

A protein of low molecular weight, beta-2-microglobulin (β_2M) is composed of 100 amino acids [13]. Because of its small size, β_2M is filtered at the glomerulus and almost totally reabsorbed and catabolised by proximal tubular cells. Therefore, serum and urine β_2M levels were determined to assess glomerular and tubular damage respectively [14]. In addition, some enzyme activities as N-acetyl glucosaminidase (NAG, EC 3.2.1.30) and gamma glutamyl transferase (GGT, EC 2.3.2.2) were

determined and used as early sensitive indicators for kidney damage in RA patients [15&16]. They are proximal tubular enzymes whose urinary levels have been reported to increase during episodes of renal damage[17&18].

A pyrazino-pyrimidine compound, neopterin serves as a marker of cellular immune system activation. It is of clinical value compared to other laboratory findings to define prognosis, extra-articular manifestations and efficacy of ongoing therapy in RA [19&20]. Nevertheless, few reports documented the increased serum and urinary neopterin levels in different renal diseases [21,22&23].

Irrespective of the causes of renal affection in RA, it is important to periodically carryout sensitive and reliable measures for renal function to pickup the earliest signs of renal dysfunction. In this regard, the present work aimed to investigate specific urinary indices besides the routine kidney function tests in RA. In addition, the statistical study looked for the most predictable urinary index for early renal involvement in RA. Moreover, the study tried to find whether urinary neopterin levels give an indication about the renal affection in RA.

PATIENTS & METHODS

The current study included 64 subjects. Forty-nine patients with RA (32 female and 17 male) aged 25-65 years (mean $\pm$ SE= 44.64 $\pm$ 1.43) admitted to Rheumatology and Rehabilitation Department, Assiut University Hospital. Also, 15 healthy volunteers matched by sex and ages were considered as a control group. All RA patients fulfilled the American Rheumatism Association, 1987 revised criteria [24]. They were selected by the criteria of no casts and serum creatinine and blood urea in the normal range. Most of the studied RA patients (91.84%) were on combined therapy (NSAIDs, DMARDs and/or steroids).

Exclusion criteria: Subjects with other autoimmune disease, gouty arthritis, past or present history of renal affection, essential hypertension, liver diseases, diabetes mellitus, malignancy and pregnancy were excluded.

Clinical investigations: Thorough medical history was taken. The signs of activity of the disease were detected by: 1- Morning stiffness (min.) according to **Mallaya and Mace** [25]. 2- Joint tenderness was assessed by Ritchie articular index[26]. The following joints were considered as a single joint, namely tempromandibular joints, acromioclavicular joints, metacarpophalangeal joints, proximal interphalangeal joints of each hand, and metatarsophalangeal joints of each foot. 3- Pain severity was evaluated according to American Collage of Rheumatology recommendation [27]. 4- Functional capacity was performed [28].

Routine Investigations: Radiological assessment was performed by plain X-ray[29]. Abdominal ultrasonography was assessed to exclude congenital abnormalities of kidneys, polycystic

kidney disease, stones, hydronephrotic kidney, and tumors. Erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), peripheral haemogram, and complete urinalysis were evaluated. Routine kidney function tests were performed namely, serum and urinary Cr (by Jaffe reaction), CrCl and macroalbuminuria. Determination of blood glucose levels, liver function tests, and ECG were done to exclude the presence of some diseases.

Specific Biochemical Investigations: Early morning urine samples were collected for measurement of specific urinary indices for renal function. Microalbuminuria levels were estimated by an indirect solid phase enzyme linked immunosorbent assay (ELISA) kit [30] (ORGENTEC Diagnosticka Gmbh, Mainz, Germany). Determination of β_2M levels according to Crisp et al. [31] by ELISA kit (DRG Intrnational Inc, USA). NAG activities were measured enzymatically by using 4-nitrophenyl-*N*-acetyl-β-D-glucosaminide as substrate [32]. Glycyl-glycine and L-glutamyl-3-carboxy-p-nitroanilide were used as substrates for estimation of GGT activities [33] by kit (QUIMICA CLINICA APLICADA SA, Spain). Neopterin levels were determined using ELISA kit [34] (IBL, Gmbh, Hamburg, Germany; RE59321).

Statistical analysis: Data were analyzed using Prism software program, graphPad version 3.0 [35]. Data of clinical and routine laboratory parameters were expressed as mean ± SE or number. Statistical differences were calculated with Man-Whittney test and Kruskal-Wallis test (Dunn's multiple comparison post-test) were used for non-parameteric values. Spearman's rank correlation coefficient was used for evaluating the correlation between the biochemical variables. $p< 0.05$ was considered a significant. The threshold value for optimal sensitivity and specificity of the specific urinary indices and neopterin was determined by Receiver Operating Characteristics (ROC) curve, which was plotted by calculating sensitivity and 1-specificity at several cutoff points. The ROC curve can be used to select the best cutoff for identifying the sensitivity and the specificity of the diagnostic test. This is useful for comparing the ability of test to discriminate between the RA patients at risk of renal affection and the remaining RA patients. The area under the curve (AUC) of the ROC plots range from 1.0 (perfect separation of test values into two groups) to 0.5 (no distributional difference). An AUC>0.7 indicates a discriminating strength of statistical significance; an AUC>0.8 indicates excellent discriminating power of the test [36].

RESULTS

Clinical characteristics of RA patients are shown in table (1). Table (2) demonstrates the routine investigations of the disease activity, and liver as well as kidney function tests. Considering that most RA patients (91.84%) received combined therapy (NSAIDs, DMARDs and/or

steroids), the present study recorded 23 (46.93%) out of 49 RA patients had low CrCl, 13 (26.53%) had macroalbuminuria, 17 (34.69%) had microalbuminuria, and 9 (18.36%) had haematuria.

A significant elevation of the levels of microalbumin, β_2M, and neopterin, and activities of NAG and GGT was revealed in urine of RA patients as compared to control group (table 3). However, there were only increase in the levels of microalbuminuria and neopterin in RA patients with extra-articular manifestations as compared to RA patients without (table 4). On the other hand, table (5) clarified that RA patients with macroalbuminuria and/or low CrCl had higher microalbuminuria and β_2M levels. Also, a significant increase of the activities of NAG and GGT was observed in those pateints when compared to those with normoalbuminuria and/or normal CrCl. The enzymes NAG and GGT could differentiate between RA patients with macroalbuminuria and those with microalbuminuria (table 6). From the ROC curves (figure 1), the best cut-off values were identified; and sensitivity, specificity, positive predictive value (+PV), negative predictive value (-PV), to discriminate RA patients at risk of renal affection from the remaining RA patients were showed in table (7).

Table (1): Clinical characteristics of RA patients.

Item	**RA (n= 49)**
Duration of disease (year)	6.17 ± 0.89
Treatment:	
Combined therapy (NSAIDs,DMARDs and/or Steroids)	45(91.84%)
NSAIDs	47 (95.91%)
DMARDs	36 (73.46%)
Steroids	36 (73.46%)
Morning stiffness (min.)	88.8 ± 6.3
Articular index (AI)	19.34 ± 9.39
Functional capacity:	
Grade I	15 (30.6%)
Grade II	24 (49.0%)
Grade III	9 (18.4%)
Grade IV	1 (2.0%)
Extra-articular manifestations	23 (46.9%)

Data are expressed as mean±SE or number (percentage). NSAIDs, non-steroidal anti-inflammatory drugs; DMARDs, disease modifying anti-rheumatic drugs.

Table (8) demonstrates the correlation between the studied biochemical parameters and other clinical and laboratory investigations. Urinary neopterin was positively correlated with ESR, urea, microalbuminuria, and urinary β_2M (r=0.6, p<0.001; r=0.31, p<0.05; r=0.51, p<0.001 and r=0.43, p<0.01 respectively). Also, urinary GGT was positively correlated with urea, microalbuminuria, and urinary β_2M (r=0.31, p<0.05; r=0.7, p< 0.001 and r=0.6, p<0.001 respectively). Urinary NAG was positively correlated with both microalbuminuria (r=0.48, p<0.01) and urinary β_2M (r=0.41, p<0.01). Furthermore, there was positive correlation between urinary β_2M and microalbuminuria (r=0.58, p<0.001).

Table (2): Routine investigations for RA patients.

Item	RA (n= 49)
X ray	
Grade I	5 (10.2%)
Grade II	20 (40.8%)
Grade III	17 (34.7%)
Grade IV	7 (14.3%)
RF (IU)	
-ve	18 (36.7%)
+ve	31 (63.3%)
ESR1	63.29 ± 4.18
Hb (g/dl)	10.95 ± 0.22
WBCs (x10^3/mm^3)	7.48 ± 0.26
Platelets (x10^3/mm^3)	276.38 ± 12.51
Serum bilirubin (µmol/L)	7.1 ± 0.46
AST (U/L)	23.82 ± 1.31
ALT (U/L)	19.02 ± 0.94
Serum albumin (g/L)	36.73 ± 0.56
Macroalbuminuria (g/L)	0.27 ± 0.06
Urinary RBCs	9 (18.36%)
Urinary pus	4 (8.16%)
Serum urea (mmol/L)	4.74 ± 0.19
Serum creatinine (µmol/L)	60.08 ± 2.07
Creatinine clearance (ml/min.)	97.62 ± 5.31

Data are expressed as mean ± SE or number (percentage). RF, rheumatoid factor; ESR1, erythrocyte sedimentation rate at first hour; Hb, hemoglobin; WBCs, white blood cells; AST, aspartate transaminase; ALT, alanine transaminase; RBCs, red blood cells.

Table (3): Specific urine parameters of control and RA groups.

Parameters	Control (n=15)	RA (n=49)	*U*	*P*
Microalb. (μg/ml) *Mean ± SE* *Median (25th, 75th percentile)*	 4.57 ± 1.7 1.5 (0.85, 6)	 104.2 ± 19.91 35 (2.75,300)	144.5	0.0004
β_2M (μg/g Cr) *Mean ± SE* *Median (25th, 75th percentile)*	 467.6 ± 15.1 449 (423,518.5)	 791 ± 56.09 767 (457,1033)	179	0.003
NAG (IU/g Cr) *Mean ± SE* *Median (25th, 75th percentile)*	 6.03 ± 0.166 6.1 (5.7, 6.6)	 8.46 ± 0.26 7.8 (7.13, 9.25)	15	<0.001
GGT (U/g Cr) *Mean ± SE* *Median (25th, 75th percentile)*	 12.1 ± 0.91 13 (8.5, 15.3)	 28.11 ± 1.66 27 (17.7, 39)	42	<0.001
Neopterin (μmol/mol Cr) *Mean ± SE* *Median (25th, 75th percentile)*	 162 ± 16.01 125 (117.5, 250)	 316.7 ± 16.89 300 (250,372.5)	67.5	<0.01

Microalb., microalbuminuria; β2M, β-2-microglobulin; NAG, N-acetyl glucosaminidase; GGT, gamma-glutamyl transpeptidase; U, indicates Mann-Whitney value.

Table(4): Specific urine parameters in relation to extra-articular manifestations.

Parameters	Control (n=15)	RA (n=49)		K-W
		No extra-art. (n= 27)	Extra-art. (n= 22)	
Microalb. (μg/ml)		*	*** #	
Mean ± SE	4.57 ± 1.7	55.2 ± 19.39	164.3 ± 33.69	19.53
Quartiles	1.5 (0.85, 6)	20 (1.0, 52.5)	40 (30, 337.5)	
β_2M (μg/g Cr)		*	***	
Mean ± SE	467.6 ± 15.1	677.8 ± 55.37	929.9 ± 98.5	13.52
Quartiles	449 (423,518.5)	802(442.5,963)	829(496,1241)	
NAG (IU/g Cr)		***	***	
Mean ± SE	6.03 ± 0.166	7.96 ± 0.28	9.08 ± 0.45	34.95
Quartiles	6.1 (5.7, 6.6)	7.4 (7.02, 9.2)	8.6 (7.5, 10.1)	
GGT (U/g Cr)		***	***	
Mean ± SE	12.1 ± 0.91	26.3 ± 1.95	30.33 ± 2.8	27.61
Quartiles	13 (8.5, 15.3)	25 (17.7, 35)	29 (17.4, 42)	
Neopterin (μmol/mol Cr)		**	*** #	
Mean ± SE	162 ± 16.01	277.1 ± 20.44	353 ± 15	27.9
Quartiles	125(117.5, 250)	265.(225,337)	311.5(294.3,531)	

Microalb., microalbuminuria; β2M, β-2-microglobulin; NAG, N-acetyl glucosaminidase; GGT, gamma-glutamyl transpeptidase; Extra-art., extra-articular manifestations; Quartiles, Median (25^{th}, 75^{th} percentile); K-W, indicates Kruskal-Wallis value; $^{*}p< 0.05$, $^{**}p< 0.01$, $^{***}p< 0.001$ vs. control group; $^{\#}p< 0.05$ vs. no extra-art. group.

Table (5): Specific urine parameters in relation to macroalbuminuria and/or creatinine clearance.

Parameters	Control (n=15)	RA (n=49)		K-W
		Macroalb. and/or low CrCl (n= 29)	Normoalb. and normal CrCl (n= 20)	
Microalb. (µg/ml)		***	###	
Mean ± SE	4.57 ± 1.7	166.6 ± 28.31	84 ± 26.04	26.78
Quartiles	1.5 (0.85, 6)	70 (32.5, 322.5)	20 (1.3, 172.5)	
β_2M (µg/g Cr)		***	###	
Mean ± SE	467.6 ± 15.1	1008 ± 67.18	476.8 ± 32.37	42.02
Quartiles	449 (423,518.5)	956(793.6, 1185)	447.5 (418, 471)	
NAG (IU/g Cr)		***	** ##	
Mean ± SE	6.03 ± 0.166	9.20 ± 0.37	7.4 ± 0.22	41.63
Quartiles	6.1 (5.7, 6.6)	8.6 (7.6, 10.15)	7.13 (6.8, 7.65)	
GGT (U/g Cr)		***	###	
Mean ± SE	12.1 ± 0.91	34.87 ± 1.79	18.30 ± 1.27	44.41
Quartiles	13 (8.5, 15.3)	35 (28.35, 42)	17.40 (15.6, 21.8)	
Neopterin (µmol/mol Cr)		***	**	
Mean ± SE	162 ± 16.01	354.1 ± 23.83	262 ± 17.06	27.5
Quartiles	125(117.5, 250)	300 (262, 500)	262.5 (225, 312.5)	

Microalb., microalbuminuria; β2M, β-2-microglobulin; NAG, N-acetyl glucosaminidase; GGT, gamma-glutamyl transpeptidase; Macroalbu., macroalbuminuria; Normoalb., normoalbuminuria. Low CrCl; creatinine clearance < 90 ml/min.; Normal CrCl ; creatinine clearance ≥ 90 ml/min.; Quartiles, Median (25^{th} , 75^{th} percentile); K-W, indicates Kruskal-Wallis value; $^{**}p< 0.01$, $^{***}p< 0.001$ vs. control group; $^{\#\#}p< 0.01$, $^{\#\#\#}p< 0.001$ vs. macroalbuminuria and/or low CrCl group.

Table (6): Specific urine parameters in relation to microalbuminuria.

Parameters	RA (n=49)			K-W
	Normoalbuminuria (n=19)	**Microalbuminuria (n=17)**	**Macrolbuminuria (n=13)**	
β_2M (µg/g Cr) *Mean ± SE* *Quartiles*	 547.1 ± 45.0 459 (428, 733)	 ** 884.1 ± 77.48 956 (482, 1139)	 *** 1026 ± 140.5 856(629, 1260)	43.7
NAG(IU/g Cr) *Mean ± SE* *Quartiles*	 7.67 ± 0.28 7.3 (6.97, 8.4)	 8.22 ± 0.30 8.2 (7.35, 8.9)	 $^{** \#}$ 9.95 ± 0.68 9.7 (8.2, 11.2)	25.8
GGT (U/g Cr) *Mean ± SE* *Quartiles*	 19.94 ± 1.1 17.7 (16.85, 25.2)	 27.03 ± 2.77 27.7 (18.25, 35)	 $^{*** \#}$ 41.46 ± 1.5 41 (39.5, 45)	17.1
Neopterin (µmol/mol Cr) *Mean ± SE* *Quartiles*	 240.8 ± 14.59 250(200, 287.5)	 ** 357.1 ± 23.25 325(275, 425)	 ** 375 ± 41.60 375 (250, 537.5)	14.3

β2M, β-2-microglobulin; NAG, N-acetyl glucosaminidase; GGT, gamma-glutamyl transpeptidase Quartiles, Median (25^{th}, 75^{th} percentile); K-W, indicates Kruskal-Wallis value; $^{**}p< 0.01$, $^{***}p< 0.001$ vs. normoalbuminuria; $^{\#}p< 0.05$ vs. microalbuminuria.

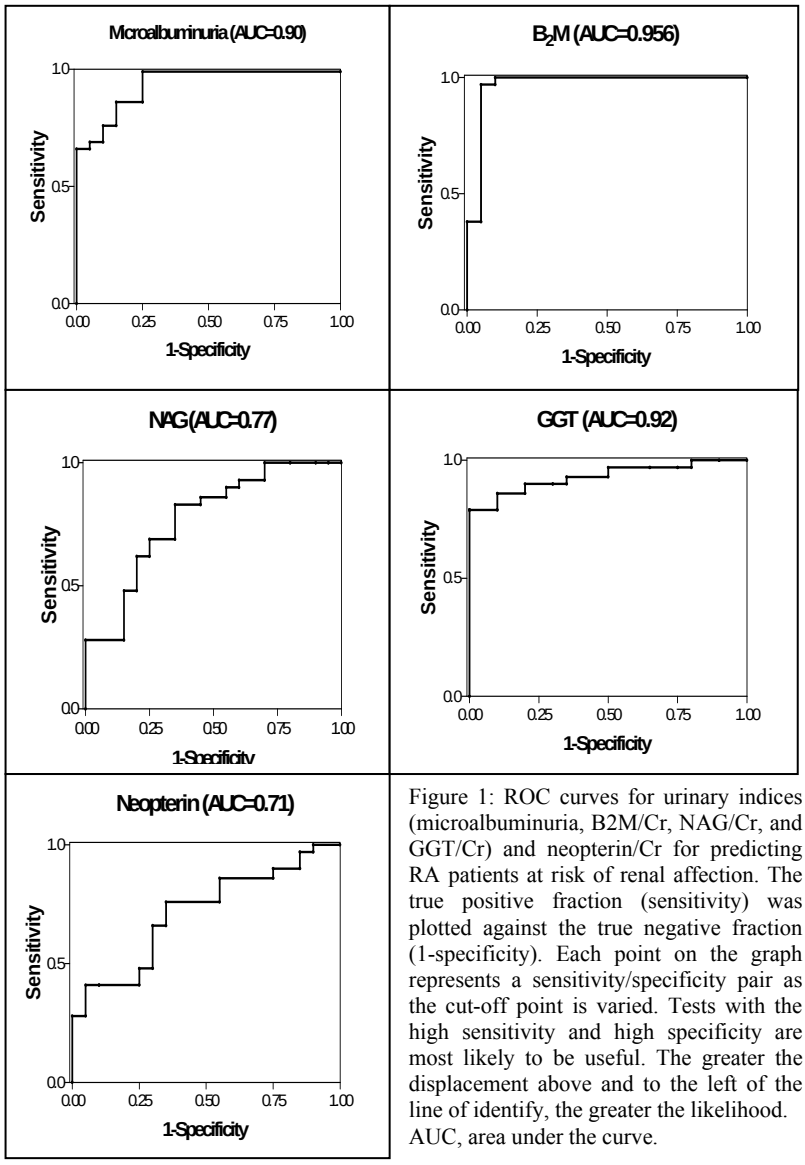

Figure 1: ROC curves for urinary indices (microalbuminuria, B2M/Cr, NAG/Cr, and GGT/Cr) and neopterin/Cr for predicting RA patients at risk of renal affection. The true positive fraction (sensitivity) was plotted against the true negative fraction (1-specificity). Each point on the graph represents a sensitivity/specificity pair as the cut-off point is varied. Tests with the high sensitivity and high specificity are most likely to be useful. The greater the displacement above and to the left of the line of identify, the greater the likelihood. AUC, area under the curve.

Table (7): Sensitivity, specificity, positive predictive value (+PV), negative predictive value (-PV), according to the best cut-off value of urinary indices to discriminate RA patients at risk of renal affection from the remaining RA patients.

Parameter	Cut-off value	Sensitivity%	Specificity %	+PV %	-PV %
Microalb.	30 µg/ml	75.86	85	88	70.8
β_2M	518 µg/g Cr	96.55	95	96.6	95
NAG	7.4 IU/g Cr	75.87	60	73.3	63.2
GGT	23 U/g Cr	86.21	80	86.2	80
Neopterin	275µmol/mol Cr	65.52	65	74.1	59.1

Microalb., microalbuminuria; β2M, β-2-microglobulin; NAG, N-acetyl glucosaminidase; GGT, gamma-glutamyl transpeptidase.

Table (8): Correlations between the studied parameters among RA patients.

Item	Microalb.	β_2M	NAG	GGT	Neopt.
Age	-0.15	0.03	-0.003	-0.21	0.11
Disease duration	0.033	0.22	0.33*	0.113	0.02
Morning stiffness	0.025	0.014	0.145	-0.14	0.10
AI	0.014	0.07	0.135	0.031	0.19
ESR	0.17	0.092	0.07	0.067	0.60**
RF	-0.27	-0.065	-0.19	0.096	-0.079
Hb	-0.014	0.07	0.23	0.21	-0.02
Serum urea	0.22	0.16	0.07	0.31*	0.38**
Serum creatinine	0.21	0.28	0.26	0.08	0.03
Microalb.		0.58***	0.48**	0.70***	0.51***
β_2M			0.41**	0.61***	0.43**
NAG				0.37	0.26
GGT					0.25

Microalb., microalbuminuria; β2M, β-2-microglobulin; NAG, N-acetyl glucosaminidase; GGT, gamma-glutamyl transpeptidase; AI, articular index; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; Hb, hemoglobin.

DISCUSSION

The present investigation determined urinary excretion of β_2M, NAG, and GGT as markers of tubular damage. Macroalbuminuria and microalbuminuria were assayed as indicators of glomerular dysfunction. Serum Cr, CrCl, and blood urea were determined to assess glomerular filtration. In the present study 23 out of 49 (46.93%) RA patients had low CrCl, 13 (26.53%) had macroalbuminuria, 17 (34.69%) had microalbuminuria, and 9 (18.36%) had haematuria; considering that most of the studied RA patients (91.84%) were on combined therapy (NSAIDs, DMARDs and/or steroids).

Niederstädt et al. [12] reported that 32% of RA patients had pathological albuminuria. **Pederson et al.** [37] **and Nordin et al.** [38] recorded 27.7% of RA patients with microalbuminuria. Glomerular and tubular proteinuria as markers of nephropathy were preferred over serum Cr and CrCl [9&39], which have been shown to lack sensitivity to detect renal dysfunction in RA. This is attributed to loss of muscle mass and hence Cr production as also to altered renal handling of Cr due to either intrinsic renal disease or drug therapy [12].

The present findings revealed an elevation of microalbuminuria levels in all RA patients as compared to control group. The increase in the levels of microalbuminuria was detected in RA patients with extra-articular manifestations as compared to RA patients without. On the other hand, RA patients with macroalbuminuria and/or low CrCl had higher microalbuminuria levels than those with normoalbuminuria and/or normal CrCl. The statistical analysis showed that microalbuminuria determination might be useful in predicting renal affection among RA patients (AUC=0.90, +PV=88% and –PV=70.8%). These data are compatible with other previous studies [12,37&38], which demonstrated that microalbuminuria is a simple and sensitive test to detect early subclinical renal dysfunction as during induced renal damage in RA [3]. Microalbuminuria is defined as a persistent value of albumin in urine between 30-300 mg/day [11]. It is considered a subclinical increase of the albumin excretion in urine, since values above 300 mg/day are considered to represent overt proteinuria [40]. The present data did not observe any correlation between microalbuminuria levels and disease duration or disease activity among RA patients. However, other investigations suggested that the urinary excretion of albumin might reflect a systemic reaction in the acute phase response [38&41]. The association of albuminuria and disease duration has been reported and explained by two ways; either severe and longstanding RA tends to affect the kidneys and the systemic vascular permeability or patients with more severe and longstanding disease receive more nephrotoxic treatment [38].

Increased urinary excretion of β_2M reflects primarily tubular cell damage,

although it has the disadvantage of instability in urine of pH<6.0[42&43]. In the present investigation, RA patients showed significant increase in urinary β_2M levels than normal levels. Further increment of these levels was revealed among the RA patients at risk of renal affection, who had macroalbuminuria and/or low creatinine clearance. The ROC plot confirmed the role of β_2M as a sensitive predictor index for renal affection (AUC=0.956, sensitivity=96.55%, specificity= 95%, +PV= 96.6%, and –PV=95%). In addition, the positive correlation observed between microalbuminuria and excretion of β_2M might clarify the association of elevated urinary β_2M levels with renal involvement. **Lewandowshki et al.** [44] reported that the concentration of urinary β_2M in RA patients was higher than in controls. Serum and urine β_2M levels were determined to assess glomerular and tubular damage respectively [14], because β_2M is filtered at the glomerulus and almost totally reabsorbed and catabolised by proximal tubular cells [45].

Recently, **Pathan and Joshi** [3] suggested that tubulointerstitial damage in RA was reflected by an increased excretion of β_2M and NAG and defective urinary concentrating capacity. The present study confirmed this suggestion, as it was found that urinary NAG activities were positively correlated with both microalbuminuria and urinary β_2M levels among RA patients. Moreover, the RA patients with macroalbuminuria and/or low CrCl showed higher urinary NAG activities than those patients without. The urinary NAG activities were significantly elevated in patients with macroalbuminuria as compared to those with microalbuminuria. The study revealed a positive correlation between urinary NAG activities and duration of disease. **Iqbal et al.** [46] observed a correlation between the total activity of urinary NAG and severity of the disease. The author evaluated isoenzymes of NAG (NAG-B and NAG-A) in urine and showed that the ratio of NAG-B to NAG-A significantly increases in severe cases of seropositive RA. The present results from ROC plot showed that urinary NAG activities had the lowest discriminating power of renal affection in RA patients (AUC=0.77, sensitivity=75.87%, specificity=60%, +PV=73.3%, and –PV=63.2%) than β_2M, GGT, and microalbuminuria. Electrophoresis divides urinary NAG into three isozymes, preA, A, and B forms. The measurement of urinary NAG isozymes is useful to determine the type and severity of renal disease [47]. Concerning RA, **Iqbal et al.** [46] suggested that subclinical renal injury without compromising renal function is a possibility in RA especially in severe cases of this disease. Also, they reported that it is unclear which factors lead to increased excretion of NAG (especially the isoenzyme form B) in RA patients.

GGT is a membrane-bound enzyme that is primarily synthesized in the brush border membrane of proximal tubules, and it is present in cell membranes of kidney, liver, and other organs [48&49]. Urinary GGT activity was used as an indicator of tubular damage for early renal

injury[50]. In the current investigation the activities of urinary GGT were significantly increased more than two folds in RA patients than control group. The RA patients with macroalbuminuria and/or low CrCl had higher urinary activities than those without. During tubular injury, brush-border surface glycoproteins, which contain various enzymes, are shed and released into the urine [51]. Herein, for distinguishing the RA patients at high resk of renal affection from the remaining RA patients, the ROC curve detected an excellent discriminating power of urinary GGT (AUC=0.92, sensitivity=86.21%, specificity=80%, +PV=86.2 and –PV=80%). A positive correlation between urinary GGT and both microalbuminuria and urinary β_2M levels was found. **Rambabu et al.** [15] observed a significant correlation between urinary GGT and serum albumin. They suggested that enhanced excretion of urinary GGT may be stimulated by decreased albumin concentration or oncotic pressure but does not appear to be due to leakage from plasma. Increased excretion of that protein implies injury to the brush border membrane with loss of microvillus structure. Losses of significant fraction of the microvillus surface area are also leads to reduced reabsorption and increased excretion of filtered proteins such as β_2M and retinal-binding protein [52]. Urinary GGT activities were positively correlated with serum urea in the present study. **Hofmeister et al.** [53] reported that the increase in enzymuria (as GGT) was associated with a drastic increase in serum urea nitrogen and Cr. The authors concluded that the determination of only some urinary enzymes is sufficient for diagnosis of proximal tubule damage. On the other hand, highly reactive oxygen species play an important role in the etiology of tissue injury in RA [54]. Recently, GGT had been reported to be a marker of inflammation and oxidative stress[55&56]. During oxidative stress, GGT gene expression is increased,

The urinary levels of neopterin in RA were above the normal levels in the present study. The higher urinary levels were shown in RA patients with extra-articular manifestations than the patients without. Moreover, the data revealed that urinary levels of neopterin are positively correlated with ESR. All the aforementioned findings confirmed the strong relation between the excreted neopterin and the activity of RA as reported before[57,58&59]. Neopterin is of clinical value to define prognosis, extra-articular manifestations and efficacy of ongoing therapy [19&20]. The increased amounts of neopterin are produced by human monocytes/macrophages upon stimulation with the cytokine interferon γ. It is furthermore produced constitutively. The amount of neopterin secreted correlates with the capacity of the same cells to produce reactive oxygen species [60&61]. Therefore, measurement of neopterin concentration in the body fluids provides information about activation of T-helper cell 1 derived cellular immune activation [61].

Neopterin is excreted in an unchanged form via kidneys [23]. In a

study on chronic renal disease **Godai et al.** [21] suggested that the neopterin levels in serum are closely linked with glomerular filteration rate and yet the urinary neopterin/Cr ratios may reflect the predominance of increased tubular secretion of neopterin over the renal injury per se. Increasing serum neopterin concentrations and urinary neopterin/Cr ratios may reflect disordered cell-mediated immunity in the nephritic syndrome, irrespective of glomerular histology or interstitial cell infiltration [22]. In the present work, no significant difference was detected regarding urinary levels of neopterin between RA patients with macroalbuminuria and/or low CrCl and those without. The statistical analysis from ROC curve to discriminate RA patients at risk of renal affection from the remaining RA patients showed that AUC=0.71, sensitivity=65.52, specificity=65, and +PV=74.1. A positive correlation between urinary levels of neopterin and both microalbuminuria levels and urinary β_2M levels among RA patients was obsereved. The present investigation did not identify the pathological etiology of renal affection in RA patients involved in the study. Thus, the present work suggested that the elevation of urinary neopterin in RA may be related to renal affection due to severity of the autoimmune disease itself or due to vasculities which is usually accompanied by perturbation of cell-mediated immunity. All the previous reports lend further support to the notion that subclinical damage to kidney may occur in RA.

In conclusion, the regular urine examination by simple and sensitive indices for early identification of renal affection in RA could guide the clinicians for a suitable line of therapy. The elevation of urinary neopterin levels was related to extra-articular manifestations as well as some kidney function tests. This may clarify to some extent the role of urinary neopterin as an indicator of renal involvement in RA patients particularly those with active disease.

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النيوترين البولى و مؤشرات تأثر الكلى فى مرضى الروماتويد المفصلى

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تعد أمراض الكلى واحدة من أسباب الوفاة لمرضى الروماتويد المفصلى. لذا فمن المهم أن نقوم دوريًا باجراء بعض القياسات الحساسة و الموثوق بها لوظائف الكلى للتعرف مبكراً على اختلال وظائف الكلى. طبقاً لذلك فان الدراسة الحالية بحثت عن أكثر المؤشرات توقعاً لتأثر الكلى المبكر فى الروماتويد المفصلى. بالاضافة الى ذلك فان الدراسة حاولت ايجاد ان كانت مستويات النيوترين البولى قد تشير الى الاختلال الكلوى فى الروماتويد المفصلى.

فى هذه الدراسة تم الحصول على عينات بول من ٤٩ مريضاً بالروماتويد المفصلى وقد كان معظم المرضى (٩١,٤٨%) يتعاطون خليطاً من الأدوية (أدوية غير استرويدية مضادة للالتهاب و/أو ادوية مضادة للروماتيزم ومحولة للمرض و/أو أسترويدات). وتم تقييم نشاط المرض على أساس اكلينيكى ومعملى. بالاضافة الى ذلك فانه تم الحصول على ١٥ عينة بول من أصحاء كمجموعة ضابطة. أجريت الاختبارات الروتينية لوظائف الكلى لكل المجموعات المدروسة. أيضاً قد تم تقدير قياسات خاصة فى البول وهى الميكروألبيومين البولى ، والبيتا-٢ميكروجلوبيولين ، وال ان-أسيتيل-جلوكوز أمينيديز ، و الجاما جلوتاميل ترانسفيريز . كذلك قد تم قياس مستويات النيوترين البولى لكل المجموعات المدروسة. وقدُ أستخدم منحنى الروك لاختيار أحسن قيم قاطعة للتعرف على الحساسية والتخصصية للأختبار المُشخص للمرض.

سجلت الدراسة الحالية أن ٢٣(٤٦,٩٣%) مريضاً من ٤٩ مريضاً بالروماتويد المفصلى كان لديهم قلة فى تصفية الكرياتينين، و ١٣ (٢٦,٥٣%) كان لديهم ماكروألبيومين بولى، و ١٧(٣٤,٦٩%) كان لديهم ميكروألبيومين بولى، و ٩(١٨,٣٦%) كان لديهم دم فى البول. وأتضح وجود زيادة ذات قيمة إحصائية فى مستويات الميكروألبيومين والبيتا-٢ميكروجلوبيولين و النيوترين، و نشاط كل من انزيمى ال ان-أسيتيل-جلوكوز أمينيديز ، و الجاما جلوتاميل ترانسفيريز فى بول مرضى الروماتويد المفصلى عند مقارنتهم بالمجموعة الضابطة. مع ذلك فكانت هناك زيادة فقط فى مستويات الميكروألبيومين البولى ، والنيوترين البولى لدى مرضى الروماتويد المفصلى ذوى الأعراض الاضافية على المفاصل عن باقى المرضى. و كان هناك زيادة فى مستويات الميكروألبيومين البولى ، والبيتا-٢ميكروجلوبيولين البولى لدى مرضى الرماتويد المفصلى المعرضين لخطر أمراض الكلى (ذوى الماكروألبيومين البولى و/أو قلة تصفية الكرياتينين). أيضاً لوحظت زيادة ذات دلالة احصائية فى نشاط كل من انزيم ال ان-أسيتيل-جلوكوز أمينيديز ، و الجاما جلوتاميل ترانسفيريز فى هؤلاء المرضى عند مقارنتهم بباقى المرضى ذوى مستويات الماكروألبيومين البولى و تصفية الكرياتينين الطبيعية. أما عن منحنى الروك فان المساحة تحت المنحنى التى أكبر من ٠,٧ تشير الى قوة تفرقة ذات دلالة احصائية. وتبعاً لمنحنى الروك فان الميكروألبيومين البولى والبيتا-٢ميكروجلوبيولين وال ان-أسيتيل-جلوكوز أمينيديز و

الجاما جلوتاميل ترانسفيريز و النيوترين لهم قوة تفرقة متفاوتة لمعرفة التأثر الكلوى بين مرضى الروماتويد المفصلى. وقد تبين أن النيوترين ارتبط بعلاقة ارتباط إيجابية مع معدل ترسيب كريات الدم الحمراء و الميكروألبيومين البولى والبيتا-٢ميكروجلوبيولين.

تشير نتائج هذه الدراسة الى أن فحص البول المنتظم بطرق سهلة و حساسة للمعرفة المبكرة للتأثر الكلوى قد يوجه الاطباء الى العلاج المناسب لمرضى الروماتويد المفصلى. كما أن علاقة الزيادة فى مستويات النيوترين البولى بالأعراض الاضافية على المفاصل و بعض اختبارات وظائف الكلى من الممكن أن توضح الى حد ما دور النيوترين البولى كمؤشر لتأثر الكلى لدى مرضى الروماتويد المفصلى خاصة ذوى المرض النشيط.