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Two years follow-up study of CKD patients in PHO Clinical Hospital Bitola Macedonia

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Abstract
Background: Chronic kidney disease (CKD) is a growing health problem worldwide with prevalence estimates ranging from 23.4–35.8% in persons aged 64 years or older [1]. CKD is characterized by progressive and irreversible loss of renal function. It is a major health issue worldwide, which leads to end-stage renal failure (ESRD).
Findings: We analyzed patients with non-progressive CKD at the baseline and at the follow up visit after two years, and we concluded that they have higher potassium and lower HDL cholesterol at the fist visit compared to the last vis. Patients with progressive CKD at the baseline and at the follow up after two years, have lower levels of urea, creatinine and GFR at the first visit of the examination compared to the last visit – two years later. We compared the progression group to non-proggresive at the first visit and we discovered that they had significantly lower cholesterol and Albumin Creatinine Ratio (mg/mmol) level and significant higher HDL cholesterol (mmol/l) levels in the baseline visit.
Conclusion: We concluded that ACR is very important marker for CKD and its progression. We can use ACR as a predictive marker for CKD. Haemoglobin as biomarkers of anaemia, were reduced in progressive CKD patients. We have to use erythropoietin for stimulation the erythropoiesis in all CKD patienst to prevent serious anaemia in CKD patients.

Keywords: chronic kidney disease (CKD), albumin-creatinine ratio (ACR), estimated glomerular filtration rate (EGFR)

Introduction
Chronic kidney disease (CKD) is a growing health problem worldwide with prevalence estimates ranging from 23.4–35.8% in persons aged 64 years or older [1]. CKD is characterized by progressive and irreversible loss of renal function. It is a major health issue worldwide, which leads to end-stage renal failure (ESRD) [2].
Chronic kidney disease (CKD) is defined as the presence of kidney damage or an estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 mt2, persisting for 3 months or more, irrespective of the cause [3]. The 2012 KDIGO CKD classification recommends details about the cause of the CKD and classifies into 6 categories based on glomerular filtration rate (G1 to G5 with G3 split into 3a and 3b). It also includes the staging based on three levels of albuminuria (A1, A2, and A3), with each stage of CKD being sub-categorized according to the urinary albumin-creatinine ratio in (mg/gm) or (mg/mmol) in an early morning "spot" urine sample [4].

The 6 categories include
G1: GFR 90 ml/min per 1.73 m2 and above
G2: GFR 60 to 89 ml/min per 1.73 m2
G3a: GFR 45 to 59 ml/min per 1.73 m2
G3b: GFR 30 to 44 ml/min per 1.73 m2
G4: GFR 15 to 29 ml/min per 1.73 m2
G5: GFR less than 15 ml/min per 1.73 m2 or treatment by dialysis
The three levels of albuminuria include an albumin-creatinine ratio (ACR)
A1: ACR less than 30 mg/gm (less than 3.4 mg/mmol)
A2: ACR 30 to 299 mg/gm (3.4 to 34 mg/mmol)
A3: ACR greater than 300 mg/gm (greater than 34 mg/mmol).

The causes of CKD vary globally, and the most common primary diseases causing CKD and ultimately end-stage renal disease (ESRD) are as follows: diabetes mellitus type 1 & 2, hypertension, primary glomerulonephritis, chronic tubulointerstitial nephritis, hereditary or cystic diseases, secondary glomerulonephritis or vasculitis, plasma cell dyscrasias or neoplasm [5].

Materials and Methods
Study population
We conducted a two years follow up study on patients with CKD G3b stage with GFR 30 to 40 in Clinical Hospital Bitola from January 2019 to September 2021 year. Patients were excluded if they had CKD stage other than G3b. The patient range in age from 43 to 78 years. We separated the patients in two groups. Patients with progression of CKD and patients with non-progressive CKD. Non-progressive group had 76±6.28, progressive group had 61, 6 ± 12 years.
Ethics Committee of Health Organization Clinical hospital "D-r Trifun Panovski" approved the study, and all of the procedures were performed in accordance with ethical approval institutional guidelines. The study protocol followed the ethical guidelines of the most recent Declaration of Helsinki. All participants provided informed consent prior to enrolment in the trial.
AFollow-up - Participants were to be seen at every 3 months until final follow-up. We do 12 visits for each patient.
Information on all serious adverse events was sought at each visit and further documentation collected on events of interest (including initiation of renal replacement therapy and possible VEs) by study staff.

Laboratory methods
Samples of non-fasting blood and urine (whenever in the

day the visit occurred) were collected from all participants.

Complete blood count (CBC) - CBC was determined in ethylenediaminetetraacetic acid (K-EDTA) blood samples - using Sysmex XP 300/ Sysmex XS 1000 (Sysmex Co, Kobe, Japan) according to the manufacturer's instructions

Biochemical analyses-Biochemiacal analyses were Performed on Abbot Architect CI 4100 according to the manufacturer's instructions.

Estimated glomerular filtration rate (eGFR) was calculated for each patient using the Modification of Diet in Renal Disease Study equation: The CKD-EPI equation, expressed as a single equation, is:

GFR = 141 * min (Scr/κ, 1) α* max Scr/κ, 1)-1.209 * 0.993Age * 1.018 [if female] * 1.159 [if black]

Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1[6].

The data are presented as mean± standard deviation (SD). The results were done with the SPSS version 13. We use *T*-Test for 2 Independent Means.

Results

In this study we analyze 16 patients with CKD for a two years follow upperiod. We divided CKD patients in two groups: progression and non-progression group after two years follow up study. All participants were examinateted every three mounts. The mean age of the progression and non-progression group were 76± 6.28 and 61.6 ± 12years, respectively, and 69% of the patients were male (n = 11). After a median follow-up of 2 years among survivors, 5 participants had reached ESRD. ACR displayed strong associations with the risk of ESRD after adjustment for age, sex and eGFR

Table 1: Biochemical variables of the patients in non-progression group at the first visit compared to the last visit.

	Non- Progression Baseline (n=11)	**Non- Progression Follow –up (n=11)**	***t*-value**	***p*-value**
Sodium (mmol/l)	139±2.5	139±1.4	0.20412.	0.42016.
Potassium (mmol/l)	5±0.66	4.8±0.42	1.83728	0.036712
BUN (mmol/l)	12.45±5.38	12.54±3.48	0.30438	0.381436
Creatinine(µmol/l)	179.1±23.9	179.36±32.2	-0.02253	0.491126
GFR-CKD-EPI Equation (ml/mon/1.73)	32.18±6.38	32.18±7.15	0	0.5
Albumin (g/l)	40.18±3.4	40±3.19	0.12926	0.449221
Total Cholesterol (mmol/l)	4±0.97	4.2±1.12	0.12918	0.448917
HDL (mmol/l)	1±0.32	1±0.36	-1.73698	0.045043
LDL(mmol/l)	2.3±0.86	2.31±1	-0.60694	0.273618
Triglyceride (mmol/l)	1.54±0.75	1.83±1	-0.33997	0.367828
Haemoglobin (g/l)	126.18±16.3	128.72±11	-0.42905	0.336238
Urine albumin (mg/l)	535.5±1280	627.86±1253	-0.23972	0.406177
Urine creatinine (µmol/l)	7077.27±5013.39	9001.81±6742.2	-0.70519	0.244045
Albumin Creatinine Ratio (mg/mmol)	66.16±140	129.12±12	-0.61502	0.271317
iPTH (pmol/l)	11.6±4.5	12.62±6.63	-0.10577	0.458147

The result is *not* significant at p <.05.

The biochemical variables of the patients with non-Progressive CKD are presented in the Table1.

We analyzed patients with non-progressive CKD at the baseline and at the follow up after two years, and we concluded that they have higher potassium and lower HDL cholesterol at the Fist visit compared to the last visit.

Table 2: Biochemical variables of the patients in progression group at the first visit compared to the last visit.

	Progression Baseline (n=5)	**Progression Follow–up (n=5)**	***t*-value**	***p*-value**
Sodium (mmol/l)	139±2.5	137.4±3.2	0.87287	0.204084
Potassium (mmol/l)	5.1±0.55	4.96±1	0.1351	0.447108
BUN (mmol/l)	13.86±2.21	25.7±6.74	-2.86717	0.007082
Creatinine(µmol/l)	193.6±54.88	359.8±170.53	-2.07441	0.035868
GFR-CKD-EPI Equation (ml/mon/1.73)	28.6±9.28	14.2±5	3.04937	0.007918
Albumin (g/l)	39.2±3.34	39.4±0.89	0.1291	0.450233
Total Cholesterol (mmol/l)	5.6±1.1	5.4±0.8	1.73389	0.050016
HDL (mmol/l)	0.95±0.35	1.28±0.41	0.4905	0.314852
LDL(mmol/l)	3.6±0.98	3.02±1.41	1.18092	0.126946
Triglyceride (mmol/l)	3.68±2.4	3.1±1.8	1.06437	0.150616
Haemoglobin (g/l)	118.2±10.32	113.6±11.73	0.65781	0.264564
Urine albumin (mg/l)	945.1±1075	1555.6±1974	0.83023	0.21394
Urine creatinine(µmol/l)	6169.8±3291.53	8190.8±2001.87	1.17303	0.137262
Albumin Creatinine Ratio (mg/mmol)	202.4±202.9	182.16±214.8	0.39977	0.349324
iPTH (pmol/l)	13.92±4.38	21.6±12.12	1.10604	0.142059

The result is *not* significant at p <.05.

The biochemical variables of the patients with progressive CKD are presented in the Table 2. We analyzed patients with progressive CKD at the baseline and at the follow up after two years, and we concluded that they have lower levels of urea, creatinine and GFR at the first visit of the examination compared to the last visit – two years later.

Table 3: Biochemical variables of the patients in Progression and non-progression group at the baseline of the examination

	Non- Progression (n=11)	Progression (n=5)	*t*-value	*p*-value
Sodium (mmol/l)	139±2.5	139±2.5	0.39295	0.350136
Potassium (mmol/l)	5±0.66	5.1±0.55	0.46183	0.323952
BUN (mmol/l)	12.45±5.38	13.86±2.21	0.05344	0.47893
Creatinine(µmol/l)	179.1±23.9	193.6±54.88	-0.7551	0.231352
GFR-CKD-EPI Equation (ml/mon/1.73)	32.18±6.38	28.6±9.28	0.90561	0.190233
Albumin (g/l)	40.18±3.4	39.2±3.34	0.53773	0.299604
Total Cholesterol (mmol/l)	4±0.97	5.6±1.1	-2.56349	0.007808
HDL (mmol/l)	1±0.32	0.95±0.35	-2.15778	0.019538
LDL(mmol/l)	2.3±0.86	3.6±0.98	-0.85828	0.199014
Triglyceride (mmol/l)	1.54±0.75	3.68±2.4	0.02177	0.49139
Haemoglobin (g/l)	126.18±16.31	118.2±10.32	0.99636	0.167992
Urine albumin (mg/l)	535.5±1280	945.1±1075	-0.7486	0.231634
Urine creatinine(µmol/l)	7077.27±5013.39	6169.8±3291.53	0.12526	0.450992
Albumin Creatinine Ratio (mg/mmol)	66.16±140	202.4±202.9	-2.26218	0.017208
iPTH (pmol/l)	11.6±4.5	13.92±4.38	-0.61337	0.272207

The result is *not* significant at $p < .05$.

The biochemical variables of the patients with non-progressive CKD and progressive CKD at the first visit of examination are presented in the Table3.

The biochemical variables of the patients are presented in the Table 3. The progression group had significantly lower cholesterol and Albumin Creatinine Ratio (mg/mmol) level and significant higher HDL cholesterol (mmol/l) levels in the baseline visit.

Table 4: Biochemical variables of the patients in Progression and non-progression group at the Follow- up- after two years

	Non- Progression Follow–up (n=11)	Progression Follow–up (n=5)	*t*-value	*p*-value
Sodium (mmol/l)	139±1.4	137.4±3.2	1.73358	0.052474
Potassium (mmol/l)	4.8±0.42	4.96±1	-1.12021	0.135757
BUN (mmol/l)	12.54±3.48	25.7±6.74	-4.00758	0.000319
Creatinine(µmol/l)	179.36±32.2	359.8±170.5	-3.51607	0.001712
GFR-CKD-EPI Equation (ml/mon/1.73)	32.18±7.15	14.2±5	5.04067	0.00009
Albumin (g/l)	40±3.19	39.4±0.89	0.40582	0.345506
Total Cholesterol (mmol/l)	4.2±1.12	5.4±0.8	0	0.5
HDL (mmol/l)	1±0.36	1.28±0.41	0.09652	0.461896
LDL(mmol/l)	2.31±1	3.02±1.41	0.94915	0.175064
Triglyceride (mmol/l)	1.83±1	3.1±1.8	1.16285	0.127184
Haemoglobin (g/l)	128.72±11	113.6±11.73	2.50046	0.012722
Urine albumin (mg/l)	627.86±1253	1555.6±1974	-1.47955	0.078643
Urine creatinine(µmol/l)	9001.81±6742.2	8190.8±2001.87	0.01897	0.492557
Albumin Creatinine Ratio (mg/mmol)	129.12±12	182.16±214.8	-0.63558	0.265804
iPTH (pmol/l)	12.62±6.63	21.6±12.12	-1.67286	0.052747.

The result is *not* significant at $p < .05$.

At the present table 4 we can see that after two years patients with CKD progression have higher serum urea, creatinine and GFR, and lower haemoglobin levels.

Discussion

We analyzed patients with non-progressive CKD at the baseline and at the follow up visit after two years, and we concluded that they have higher potassium and lower HDL cholesterol at the Fist visit compared to the last vis. Patients with progressive CKD at the baseline and at the follow up after two years, have lower levels of urea, creatinine and GFR at the first visit of the examination compared to the last visit – two years later.

This findings are in a correlation with previous studies. In patients classified as progressive demonstrated increased serum creatinine and urea, while eGFR was decreased [7].

We compared the progression group to non-proggresive at the first visit and we discovered that they had significantly lower cholesterol and Albumin Creatinine Ratio (mg/mmol) level and significant higher HDL cholesterol (mmol/l) levels in the baseline visit.

In the present study, we observed an association between Albumin Creatinine Ratio (ACR) and progression of CKD, and the predictive power of ACR for progressive kidney disease. Persistent albuminuria is one criterion for the diagnosis of CKD, and an independent risk factor for adverse kidney and cardiovascular outcomes. Albuminuria, measured on more than one occasion, as a spot urine albumin to creatinine ratio (ACR), is now included as one of the diagnostic criteria for CKD [8]. Screening for albuminuria is recommended in certain high-risk groups such as those with diabetes mellitus, however results should be confirmed by a central laboratory [9]. Kidney measurements, such as serum creatinine, urea, albumine, eGFR and ACR have been studied extensively in the context of CKD and its progression [10]. Proteinuria is a major prognostic indicator of renal progression in both children and adults with CKD [11, 12, 13, 14].

Neither ACR provided any additional prognostic information for ESRD risk over and above each other. The predictive power of ACR for ESRD was also similar in various subgroups; in men and women; among White and Asian participants; among those with an eGFR 30 mL/min/1.73 m2 and eGFR<30 mL/min/1.73 m2 at

baseline; and when the population was separated into groups by age, weight or blood pressure [15].

After two years patients with CKD progression have higher serum urea, creatinine and GFR, and lower haemoglobin levels. This findings are in a correlation with previous studies. Haematocrit and haemoglobin, as biomarkers of anaemia, were reduced in progressive CKD patients of the Biomarker Discovery cohort. This observation in the Biomarker discovery cohort was not unexpected as anaemia is a known complication of CKD [7].

Conclusion

We concluded that ACR is very important marker for CKD and its progression. We can use ACR as a predictive marker for CKD.

Haematocrit and haemoglobin, as biomarkers of anaemia, were reduced in progressive CKD patients. We have to use erythropoietin for stimulation the erythropoiesis in all CKD patienst to prevent serious anaemia in CKD patients.

Conflict of interest

None

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