

**CHRONIC KIDNEY DISEASE IN RHEUMATOID
ARTHRITIS AT KENYATTA NATIONAL HOSPITAL**

**A DISSERTATION SUBMITTED IN PART FULFILLMENT OF THE
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DR. SANAA S. SAID

DEPARTMENT OF CLINICAL MEDICINE AND THERAPEUTICS

REGISTRATION NO - H58/80796/2012

MBBS (IUA), DTMH (LSHTM)

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DECLARATION

This Research dissertation is my original work and has not been presented for a degree at any other university.

SignedDate

**PRINCIPAL INVESTIGATOR,
DR. SANAA S. SAID,
DEPARTMENT OF CLINICAL MEDICINE AND THERAPEUTICS,
UNIVERSITY OF NAIROBI.**

APPROVAL BY SUPERVISORS

This research has been submitted with the approval of my supervisors, namely:

PROF G.OMONDI OYOO,
MBChB, MMed, FRCP (E), FACR, FIPH (Tulane)
ASSOCIATE PROFESSOR IN MEDICINE/RHEUMATOLOGIST,
DEPARTMENT OF CLINICAL MEDICINE AND THERAPEUTICS,
UNIVERSITY OF NAIROBI.

SIGNED.....

DATE.....

PROF. JOSHUA K. KAYIMA,
MBChB, MMed
ASSOCIATE PROFESSOR IN MEDICINE/NEPHROLOGIST,
DEPARTMENT OF CLINICAL MEDICINE AND THERAPEUTICS,
UNIVERSITY OF NAIROBI.

SIGNED

DATE.....

PROF. GODFREY NSEREKO LULE,
MBChB, MMed, MSc in Infectious Diseases, FRCP (E)
PROFESSOR OF MEDICINE/GASTROENTEROLOGIST,
THEMATIC HEAD, UNIT OF INFECTIOUS DISEASES,
UNIVERSITY OF NAIROBI.

SIGNED.....

DATE.....

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DEDICATION

I dedicate this work to my sister, Salwa, who has shown me how to be a strong woman.

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I am indebted to the following for their contributions to this project:

God Almighty for giving me the strength and will to carry out this project. It is only through Him that all things are possible.

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CONTENTS

DECLARATION	ii
APPROVAL BY SUPERVISORS.....	iii
DECLARATION FORM FOR STUDENTS.....	iv
DEDICATION.....	v
ACKNOWLEDGEMENTS.....	vi
CONTENTS.....	vii
LIST OF TABLES	x
LIST OF FIGURES.....	x
ABBREVIATIONS.....	xi
ABSTRACT.....	xiii
INTRODUCTION.....	1
LITERATURE REVIEW	2
RHEUMATOID ARTHRITIS	2
CHRONIC KIDNEY DISEASE	2
EPIDEMIOLOGY Prevalence of rheumatoid arthritis.....	3
Prevalence of chronic kidney disease	4
Prevalence of chronic kidney disease in rheumatoid arthritis.....	4
SCREENING FOR CKD.....	5
CKD SCREENING IN RHEUMATIC DISEASES.....	6
KIDNEY DYSFUNCTION IN RHEUMATOID ARTHRITIS	7
Secondary amyloidosis	7
Glomerulonephritis.....	9
Rheumatoid vasculitis.....	9
RHEUMATOID ARTHRITIS DRUGS AND THE KIDNEY.....	10
DIAGNOSIS OF KIDNEY DYSFUNCTION IN RA	11
Histopathological findings.....	11

EFFECT OF RENAL DYSFUNCTION IN RHEUMATOID ARTHRITIS.....	14
STUDY JUSTIFICATION.....	15
RESEARCH QUESTION.....	15
OBJECTIVES.....	15
BROAD OBJECTIVE.....	15
SPECIFIC OBJECTIVES.....	15
PRIMARY OBJECTIVE.....	15
SECONDARY OBJECTIVES.....	16
METHODOLOGY.....	16
STUDY SITE.....	16
STUDY POPULATION.....	16
STUDY DESIGN.....	16
SAMPLE SIZE.....	17
SAMPLING METHOD.....	17
CASE DEFINITION.....	17
INCLUSION AND EXCLUSION CRITERIA.....	18
INCLUSION CRITERIA.....	18
EXCLUSION CRITERIA.....	18
SERUM CREATININE AND URINALYSIS.....	18
SCREENING AND RECRUITMENT.....	19
DATA COLLECTION.....	20
CLINICAL METHODS.....	20
LABORATORY METHODS.....	21
SPECIMEN ANALYSIS.....	21
QUALITY ASSURANCE.....	22
STUDY VARIABLES INDEPENDENT VARIABLES.....	22
DEPENDENT VARIABLES.....	23

DATA MANAGEMENT AND ANALYSIS	23
STUDY ADMINISTRATION.....	24
ETHICAL CONSIDERATION	24
RESULTS	26
DISCUSSION	34
LIMITATIONS.....	38
CONCLUSIONS.....	38
RECOMMENDATIONS.....	38
REFERENCES.....	39
APPENDIX.....	49
Appendix 1: The 2010 ACR/EULAR criteria for classification of rheumatoid arthritis	49
Appendix 2: Data Extraction Tool	50
Appendix 3: Patient explanation and consent form.....	55
KNH/UON-ERC LETTER OF APPROVAL	59

LIST OF TABLES

Table 1	3
Table 2	3
Table 3: SUMMARY OF PREVALENCE STUDIES OF KIDNEY DISEASE IN RHEUMATOID ARTHRITIS.....	5
Table 4: Demographic characteristics of patients in the study.....	27
Table 5: Rheumatoid arthritis medication in ambulatory RA patients attending KNH Rheumatology clinic	28
Table 6: Stage of CKD among ambulatory patients with RA presenting at KNH outpatient rheumatology clinic	31
Table 7, Association of disease activity of RA with eGFR	32
Table 8: Association of drugs used for RA treatment and eGFR.....	33
Table 9, Comparison of studies on CKD in RA.....	36

LIST OF FIGURES

Figure 1:screening of renal co-morbidity in rheumatic disease	6
Figure 2.....	8
Figure 3: The recruitment process.....	26
Figure 4.Use of NSAIDs and prednisone among the study population	29
Figure 5: RA disease activity among ambulatory patients with RA presenting at KNH outpatient rheumatology clinic	30
Figure 6: Prevalence of CKD among ambulatory patients with RA presenting at KNH outpatient rheumatology clinic	31

ABBREVIATIONS

ACR:	American College of Rheumatology
ANOVA:	Analysis of Variance
CG:	Cockcroft Gault
CKD:	Chronic Kidney Disease
CVD :	Cardio Vascular Disease
DAS28:	Disease Activity Score 28
DMARD:	Disease Modifying Anti-Rheumatic Drug
EDTA:	Ethylenediaminetetraacetic acid
eGFR :	estimated Glomerular Filtration Rate
ESKD:	End Stage Kidney Disease
ESR:	Erythrocyte Sedimentation Rate
ESRD:	End Stage Renal Disease
ESRF:	End Stage Renal Failure
EULAR :	European League Against Rheumatism
GN :	Glomerulonephritis
HLA:	Human Leucocyte Antigen
IL :	Interleukin
KNH:	Kenyatta National Hospital
MDRD:	Modification of Diet in Renal Disease
MI:	Myocardial Infarction

NAG N:	Acetyl Glucosamine
NICE:	National Institute for Health Care and Excellence
NSAID:	Non-Steroidal Anti-Inflammatory Drugs
PI :	Principle Investigator
PG:	Prostaglandins
RA :	Rheumatoid Arthritis
RBC:	Red Blood Cells
SPSS:	Statistical Package for Social Sciences
SSA:	Sub-Saharan Africa
USA:	United States of America
WHO:	World Health Organisation

ABSTRACT

Background

Rheumatoid arthritis is a global health problem with an increase in prevalence especially in Sub-Saharan Africa. The disease has high morbidity and mortality even with recent improvements in disease management. Majority of those with rheumatoid arthritis die from cardiovascular diseases and this risk is augmented in the presence of chronic kidney disease.

Objectives

To determine the prevalence and stage of chronic kidney disease in patients with rheumatoid arthritis on follow up at the rheumatology outpatient clinic at Kenyatta National hospital. To determine the association of renal dysfunction with: duration of rheumatoid arthritis, disease activity of rheumatoid arthritis and treatment used for rheumatoid arthritis.

Methods

A total of 104 participants with a diagnosis of rheumatoid arthritis were recruited from the Kenyatta National Hospital rheumatology outpatient clinic. In this cross-sectional survey, continuous sampling was applied. Participants had to be of age 18 or more years. Data was collected over a ten week period. Patients' records were examined for medication used and duration of illness. Demographic data and medical history were collected by the use of pre-structured questionnaires and a brief physical exam undertaken. This was followed by blood collection for assessment of creatinine levels and ESR as well as a urine sample for urinalysis. Serum creatinine was analysed by an automated biochemistry machine. Urinalysis was performed via urinary dipstick and ESR by the Wintrobe method.

Analysis

Data was presented using tables, pie charts and bar charts. Continuous data was summarized using measures of central tendency (means, medians, mode and standard deviations). Dependent variables were analysed for correlation with a p value of 0.05 or less considered significant. Chronic kidney disease was correlated with: disease duration using the Kruskal Wallis test, disease activity using the ANOVA test and treatment modality using the Chi-square test.

Outcomes

A total of 104 patients were recruited over a ten week period. Out of these, 93 (89.4%) were female with a female to male ratio of 9:1. Mean age of patients was 48.7(\pm 15.6) years. Majority of the patients (86.5%) were on at least one DMARD. Methotrexate was the commonest DMARD used. Others were leflunomide, sulfasalazine and hydroxychloroquine. None of our patients was on a biologic agent. Use of NSAIDs and /or prednisone was very frequent (88.5%). Median duration of disease since time of diagnosis was 4 years. Majority of patients (60%) had active disease. We found the prevalence of chronic kidney disease to be 28.7% (95% CI 19.1-37.2%) based on estimated glomerular filtration rate using the Cockcroft-Gault formula. Majority (50%) of which was stage 3a disease and none with end stage renal disease. We found no patients with proteinuria using a urinary dipstick.

Conclusion

Although we did not find any proteinuria in our study population, prevalence of chronic kidney disease based on estimated glomerular filtration rate was high. The majority of chronic kidney disease was in the early stages. Use of urine strips alone is not an adequate screening tool in this population.

INTRODUCTION

Rheumatoid arthritis (RA) is a worldwide health problem. The global prevalence is estimated at 0.24% (1). The World Health Organisation (WHO) considers it as one of the diseases with the greatest impact on society (2) and it is the 42nd highest contributor to global disability (1).

Patients with RA are at increased risk of death more than their age and sex matched non-rheumatoid controls. Even with improvement of disease management, there has been no decrease in mortality for patients with RA (3). Renal disease is a common cause of mortality in patients with rheumatoid arthritis. This may be as a result of disease itself, drugs used in treatment and other rheumatoid nephropathy (4). As most patients with rheumatoid arthritis are above the age of forty (5), age itself and other co-morbid conditions like diabetes and hypertension also have a negative impact on their kidney function.

Cardiovascular complications are the major cause of mortality in these patients. They are at higher risk of silent myocardial infarction and lower risk of angina pectoris. Mortality after these events is also higher than in their non-RA counterparts (6).

The effects of kidney dysfunction in RA are adverse. A low estimated glomerular filtration rate (eGFR) increases cardio-vascular disease (CVD) risk and vice versa. Since CVD is the major cause of mortality in these patients, frequent screening and modification of risk factors is of importance in this population (7).

Assessment of eGFR is also warranted in RA for drug adjustment. Methotrexate is the commonest disease modifying anti rheumatic drug (DMARDs) used in the control of RA. Its use is contraindicated in any person with an eGFR of less than 30 ml/min/1.73m² (8). The use of other drugs, such as non-steroidal anti-inflammatory drugs (NSAIDs) must also be approached with caution in such patients as they can exacerbate kidney injury.

CKD is progressive with rapid decline in function if it goes unrecognized and is not addressed early especially in the presence of continued injury. Therefore screening for CKD is of vital importance especially in this group of patients who have several factors that may cause or worsen kidney damage.

LITERATURE REVIEW

RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is defined as a chronic inflammatory disease of unknown etiology marked by symmetric, peripheral polyarthritis (9). It is characterized by joint swelling, joint tenderness and destruction of synovial joints leading to severe disability and premature mortality (10). It is considered an auto-immune disease. Women are affected up to four to five times more than men (11,12)

RA may present with extra-articular manifestations. These can occur at any age after the onset of RA and include the skin, eye, heart, renal, pulmonary, nervous and gastro-intestinal system (13). Although RA is commonly a disease of females, extra-articular manifestations are more common in males and affect about 40% of patients with a diagnosis of RA (14). They are also seen more commonly in patients with severe disease and are a predictor of increased mortality(13,15).

Diagnosis of RA depends on the aggregation of signs, symptoms, laboratory and radiological findings. The 2010 American College of Rheumatology – European League against rheumatism (ACR-EULAR) classification criteria for RA is a tool that aids in early classification of patients who present with joint pain and may have a risk of persistence of symptoms requiring the use of DMARDs (9,10).

CHRONIC KIDNEY DISEASE

It is defined as abnormalities of kidney structure or function, present for more than 3 months, with implications for health. Chronic kidney disease (CKD) is classified based on cause, estimated glomerular filtration rate (eGFR) category and albuminuria category.

The criteria used are eGFR less than 60 ml/min/1.73 m² (GFR categories G3a–G5) or markers of kidney damage (albuminuria, urine sediment abnormalities, electrolyte and other abnormalities due to tubular disorders, abnormalities detected by histology, structural abnormalities detected by imaging and history of kidney transplantation) (17). The eGFR and albuminuria categories are depicted in tables 1 and 2 below. Table 1 also contains USA estimates of prevalence rates for the various stages of CKD. Prevalence rates of Europe are said to be similar to those in the United States of America (USA) while data for the developing world is lacking (18).

Table 1

GFR Categories (ml/min/1.73m²)	Description	Range	Prevalence
G1	Normal or high	Greater than 90	1.8%
G2	Mildly decreased	60-89	3.2%
G3a	Mildly to moderately decreased	45-59	7.7%
G3b	Moderately to severely decreased	30-44	
G4	Severely decreased	15-29	0.35%
G5	Kidney failure	Less than 15	

Table 2

Persistent albuminuria categories	Description	Range
A1	Normal to mildly increased	Less than 30mg/g or 3mg/mmol
A2	Moderately increased	30-300 mg/g or 3-30mg/mmol
A3	Severely increased	Greater than 300mg/g or 30mg/mmol

EPIDEMIOLOGY

Prevalence of rheumatoid arthritis

In the past, rheumatoid arthritis was considered rare in Africa. A case of rheumatoid arthritis in Kenya in 1962 was considered novel enough to warrant a publication as a case report (22). However, in 1979 L. R Bagg et al managed to describe 76 patients with rheumatoid arthritis over an 18 month period (22), showing either increasing recognition or an increase in the number of patients with the diagnosis.

More evidence has shown that rheumatoid arthritis is increasing in frequency in East, Central and South Africa (24,25). A recent systematic analysis has shown a significant rise in the

prevalence of RA from 0.36% in 1990 to a projection of 0.42% in 2010 with a corresponding burden increase from 2.3 million to 4.3 million affected individuals.

All prevalence studies done on RA in Africa have shown an increase in prevalence with age (23). With the majority of the African population being youth (26) and the increasing life expectancy on the continent (27), one may expect a future increase in the burden of the disease. Furthermore, urbanization has been linked to development of RA (28). The continuing rural to urban migration in most African countries and rapid development of towns may also be expected to be a contributing factor to the increase in disease prevalence.

Prevalence of chronic kidney disease

Chronic kidney disease is an increasing global health problem. Due to the fact that it is a silent condition, its prevalence is considered an underestimate (29). A systematic review by Qiu-Li Zhang et al that reviewed 26 studies done in various populations, none of which included Africa, showed a prevalence of CKD of 7.2% in persons aged 30 years or older and between 23.4 – 35.8% in persons with 64 or more years (30). Another systematic review estimates prevalence in Africa at 13.9% (31). However, CKD is reported to be 3-4 times more common in Africa than in developed countries (19).

Among hospital based studies of CKD in various patient groups in our setting, prevalence of CKD ranges between 20-75% with the majority being in stage 3 (32–34)

Prevalence of chronic kidney disease in rheumatoid arthritis

The association between RA and kidney disease has been noted for several years. Unfortunately, there is no consensus yet on the true prevalence of renal disease in this population. Several studies have been done and give varying figures. Ranges of stage 3 and below kidney disease were found to be 25.3% in the MATRIX study (35), D. Daoussis et al found it to be 12.75% (36) while Hill A.J. et al found a prevalence of 18% (37). The prevalence findings are summarized in table 3 below.

Among the patients with CKD in the MATRIX study, the prevalence according to stage was as follows stage 3: 95%, stage 4: 5% and stage 5: 0% (35). Participants in the study by Daoussis et al were classified as moderate renal impairment (stage 2, 3a and 3b) and severe renal impairment

(stage 4 and 5). The prevalence rates were 92% and 7.8% for moderate and severe renal impairment respectively (36).

Table 3: SUMMARY OF PREVALENCE STUDIES OF KIDNEY DISEASE IN RHEUMATOID ARTHRITIS

AUTHOR - YEAR OF STUDY	TYPE OF STUDY	N SAMPLE SIZE	FINDINGS (eGFR less than 60ml/min)
S. Karie et al – 2008 (33)	Prospective observational study	129	25.3% [~] 15% ^a
Daoussis et al – 2010 (34)	Cross sectional study	400	12.75% ^a
Hill AJ et al – 2009 (35)	Cross sectional study	351	18% ^a
Hickson J et al (6)	Retrospective review	1626	9% ^a
Karstila et al – 1988 (33)	Population based cross sectional study	604	3% [*]
Yalcin et al – 2012	Retrospective review	441	8.4% [*]

***Assessed deranged creatinine and not eGFR**

[~] Assessed eGFR using the Cockroft Gault formula

^a Assessed eGFR using the MDRD equation

SCREENING FOR CKD

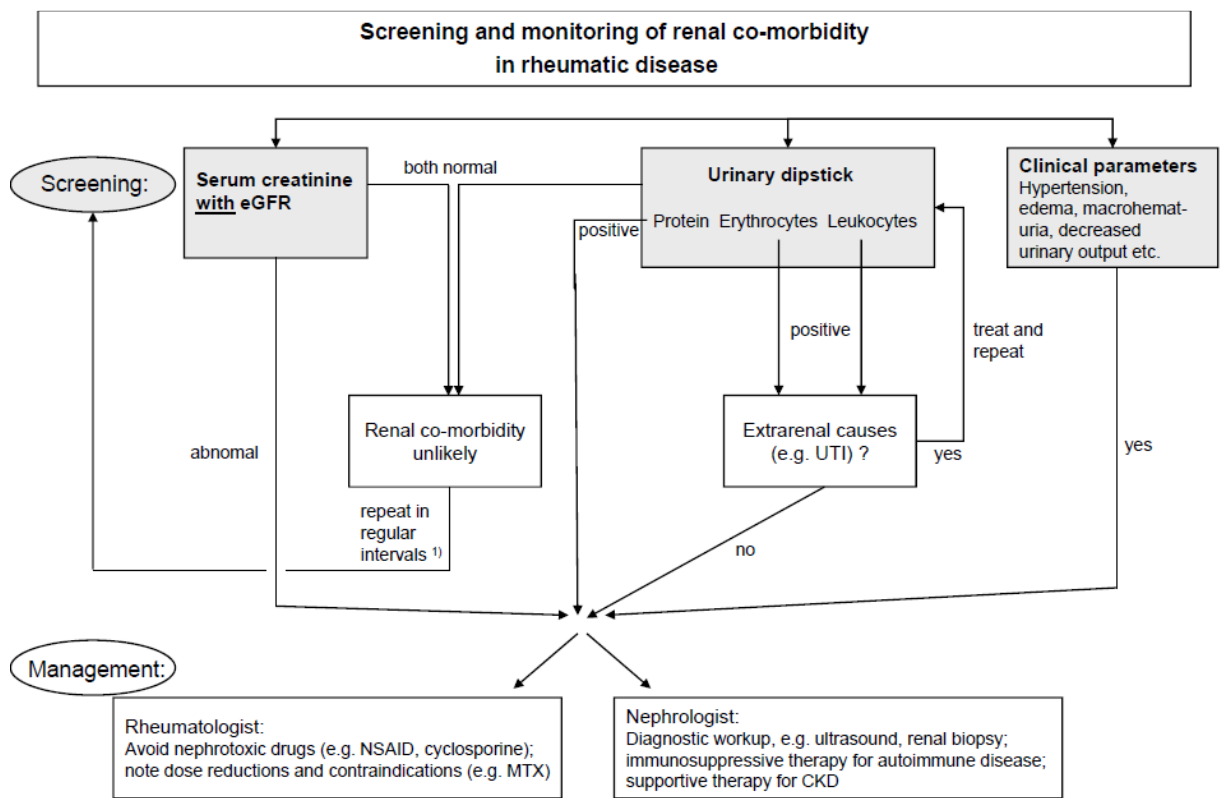
Although CKD is considered a silent disease, routine screening for non-high risk patients is not advocated. Screening is indicated for patients with diabetes, hypertension or age above 55years (29). The NICE guidelines also advocate for screening in patients with multisystem diseases that

have potential kidney involvement. Screening may be carried out with a spot eGFR calculation which if found to be less than 60ml/min/1.73m² would require a urinalysis with albumin/protein excretion quantified (30).

CKD SCREENING IN RHEUMATIC DISEASES

A majority of rheumatic diseases are associated with renal dysfunction. These patients must routinely be screened both by urinalysis and assessment of an estimated glomerular filtration rate. If these are both normal, the patient may undergo repeat screening in six months. Any other abnormality must be addressed by treating the cause, drug adjustment or further workup. Referral to a nephrologist is advised at stage 3 CKD and beyond. This algorithm is depicted in figure 1 below.

Figure 1: screening of renal co-morbidity in rheumatic disease



Hans-Joachim Anders et al. Renal co-morbidity in patients with rheumatic diseases. Arthritis research and therapy. 2011. 13:222

KIDNEY DYSFUNCTION IN RHEUMATOID ARTHRITIS

Kidney disease in RA has been attributed to different causes. Boers M et al categorises it as, due to the disease itself, drugs used in treatment such as NSAIDs or DMARDs (gold, penicillamine, methotrexate and cyclosporine) or “RA nephropathy” which classifies abnormalities not attributable to vasculitis, amyloidosis or drug intake (4). Other factors that may have an impact on kidney function in RA are age and other co-morbid illnesses.

In a retrospective study done on 101 patients with RA and renal disease, the most common histopathologic finding was mesangial glomerulonephritis, followed by amyloidosis and membranous glomerulonephritis. Focal proliferative glomerulonephritis, minimal change nephropathy, and acute interstitial nephritis were less common (38).

In Japan, a study done on 158 RA patients, biopsy findings in order of decreasing frequency were mesangial proliferative glomerulonephritis followed by membranous nephropathy and secondary amyloidosis (39).

More recent studies have stated that renal complications in RA are mainly due to amyloidosis or drugs used (40,41). A review done by Horak et al states that GN in RA is very rare. It was extensively described by studies done in the past on autopsy and biopsy studies but with little clinical significance in terms of patient management (41).

The common kidney abnormalities are outlined below.

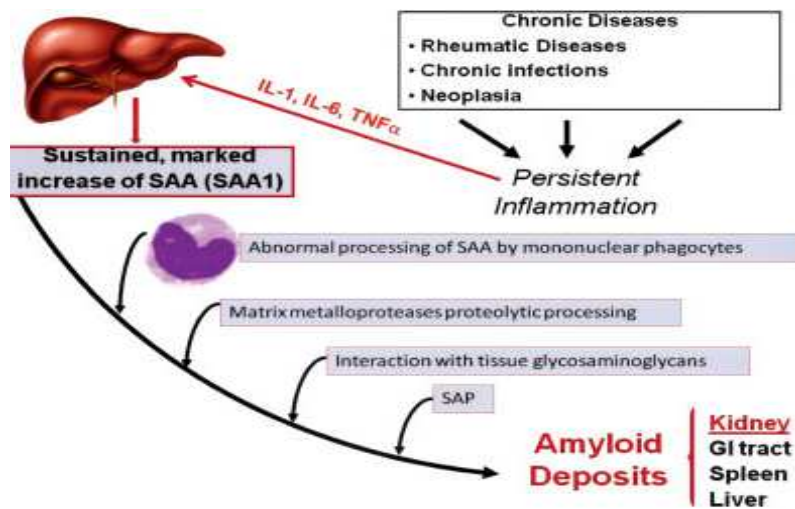
Secondary amyloidosis

Amyloidosis is the term for diseases caused by the extracellular deposition of insoluble polymeric protein fibrils in tissues and organs. Secondary amyloidosis occurs in the setting of chronic inflammatory or infectious diseases (9). Rheumatoid arthritis is one of the commonest causes of secondary amyloidosis (42) which is said to be one of the most severe complications of RA due to its risk of progression to ESRD (43).

Persistent inflammation either from chronic diseases, chronic infection or neoplasm cause a sustained elevation of pro-inflammatory cytokines (IL-1, IL-6 and TNF α). This leads to an increased production of acute-phase protein serum amyloid A (SAA). When this protein is abnormally processed, it leads to the production of amyloidogenic peptides and amyloid fibrils

which may then be deposited in different organs. The main organ targeted is the kidney (43). The pathogenesis of amyloidosis is depicted in figure 2.

Figure 2.



Obici L, Raimondi S, Lavatelli F, Bellotti V, Merlini G. Susceptibility to AA amyloidosis in rheumatic diseases: a critical overview. *Arthritis Rheum.* 2009 Oct 15

Amyloidosis is more common in patients who have severe, poorly controlled, sero-positive and long standing illness (44). It has been reported to be a cause of death in 9.5% of RA patients (45). Other studies have attributed amyloidosis to 5-17% of RA deaths (43). Unfortunately it may go clinically undetected in up to 50% RA patients (43) until they develop kidney dysfunction in the form of proteinuria, deranged creatinine levels or end-stage renal failure (ESRF) (46).

Glomerulonephritis

Glomerulonephritis (GN) with immune deposits occurs secondary to deposition of immune complexes in the glomeruli (47). RA associated GN is either immune mediated or associated with the drugs used in treatment and these patients present with proteinuria and hematuria which then progresses to CKD (48).

Membranous nephropathy occurs when immune deposits are fixed on the glomerular basement membrane leading to complement activation and damage (49). In RA it is most often induced by therapy with penicillamine or gold (50). These drugs are now rarely used in RA and therefore membranous nephropathy is observed less often than in the past. A few case reports have been published of RA patients developing membranous nephropathy even without use of gold or penicillamine throughout the course of their treatment (49–51) and in these cases RA was concluded to be the cause of the nephropathy.

Rheumatoid vasculitis

It is said to be the most serious systemic manifestation of RA and occurs in conjunction with other extra-articular manifestations (52). It occurs in less than 1-5% of RA patients who are usually seropositive and have environmental or genetic triggers like male sex, smoking, rheumatoid nodules and older disease onset. However, prevalence is said to be declining probably due to better disease management (52).

In rheumatoid vasculitis there is mononuclear and neutrophilic infiltration of the vessel wall of small and medium sized vessels. Features of vessel destruction include necrosis, leukocytoclasia, and disruption of the internal and external elastic lamina.

Morbidity and mortality are reported to be higher with a five year mortality of up to 30-50% (52).

RHEUMATOID ARTHRITIS DRUGS AND THE KIDNEY

The effect of drugs used in RA treatment on the kidney has long been noted (41,48). Analgesic nephropathy, which was defined by a National Kidney Foundation position paper as “a disease resulting from the habitual consumption over several years of a mixture containing at least two anti-pyretic analgesics and usually codeine or caffeine.” It is characterized by kidney papillary necrosis and chronic interstitial nephritis that leads to insidious onset of progressive kidney failure (53). In the past, analgesic nephropathy was very common in phenacetin drug users (53). Recently however, classical analgesic nephropathy which is characterized by renal papillary necrosis is considered absent in western countries since the ban of phenacetin drugs (54).

DMARDs are the cornerstone of treatment in RA (55) with methotrexate the most commonly used (56,57). Methotrexate is an antimetabolite and a folate analogue. It works via its anti-inflammatory effects and is mainly excreted through the kidney (58). The pharmacokinetics of low dose methotrexate are said to be unpredictable and variable even in patients with normal renal function (59). In those with underlying renal dysfunction or those who use nephrotoxic drugs there is decreased renal excretion and serum accumulation of methotrexate with consequent adverse effects (8). Concomitant use of other drugs, like aspirin and non-steroidal anti-inflammatory drugs (NSAIDs), also lowers the systemic and renal clearance of methotrexate (8,60,61). Low dose methotrexate is contra-indicated in patients with an eGFR of less than 30ml/min (8).

Leflunomide, sulfasalazine and hydroxychloroquine are also other DMARDs used in RA. They have no known effects on the kidney although few case reports have been published implicating them. A case report in the British Medical Journal implicated sulfasalazine as a cause for nephrotic syndrome (62). Use of these drugs in patients with kidney impairment requires caution.

NSAIDs are commonly used in rheumatoid arthritis. They work by inhibiting prostaglandin (PG) synthesis. The kidney synthesises prostaglandins PGI₂ (prostacyclin), PGE₂, and PGD₂ which cause vascular dilatation, decrease vascular resistance thus increasing renal perfusion with redistribution of blood flow from the renal cortex to nephrons. PGE₂ causes diuresis and natriuresis by inhibiting the transport of sodium and chloride. Prostacyclin together with PGE₂, serves to maintain the glomerular filtration rate (63).

In volume depleted states renin-angiotensin-aldosterone axis is stimulated with increased renin, angiotensin II, and aldosterone production resulting in renal vasoconstriction and increased sodium and chloride reabsorption. In this setting, prostaglandins provide compensatory vasodilatation of renal vascular bed and ensure adequate renal blood supply (63).

Normal healthy individuals with good renal function do not require a major role of PGs. They become vital in individuals with decreased renal perfusion. Decreased perfusion may be due to hypovolemia or decreased circulatory volumes such as in congestive heart failure, renal failure or cirrhosis (64). NSAIDs lead to an inhibition in local prostaglandin production thus leading to constriction and increased vascular resistance.

NSAIDs are the second most common cause of nephrotoxic acute renal failure (63) with the risk reportedly higher in the elderly (65). This effect may be in the form of reversible renal insufficiency, acute tubular necrosis and acute interstitial nephritis. In rare cases, NSAIDs may cause papillary necrosis, nephritic syndrome and renal vasculitis (63).

DIAGNOSIS OF KIDNEY DYSFUNCTION IN RA

Even though the link between RA and renal disease has been established, no consensus has been reached on what is the best tool for screening patients. Renal biopsy is considered the gold standard so far (4,66). To date, several researchers have used different markers to assess kidney function in RA patients.

Histopathological findings

In the past, several studies have been undertaken to determine the renal lesions found in RA patients. A study done between 1958 and 1984 by Boers et al on 132 patients with a mean disease duration of 14.5 years, found the commonest pathological finding to be nephrosclerosis in 90%, glomerular change (43%), tubulointerstitial damage (41%), renal amyloidosis (11%) and renal vasculitis (6%) in the necropsies done. The authors were also able to show a clear relation between the presence of amyloidosis and duration of RA.

Renal biopsy is however an invasive procedure and cannot be routinely recommended.

Serum creatinine and estimated glomerular filtration rate

Serum creatinine alone is inadequate for assessing renal function in patients with RA. Also, without the routine use of urine dipstick is unreliable as a marker of kidney disease as seen in the MATRIX study (35). If serum creatinine is to be used as a marker it must be assessed with caution, considering the patient's age, sex and weight.

Estimated glomerular filtration rate (eGFR) is one of the markers used to assess renal function in many patients. It has been shown that the Cockcroft-Gault (CG) formula had the best correlation in RA patients (69). The modification of diet in renal disease (MDRD) equation is not validated for use in patients with RA (70).

Urinalysis

Microalbuminuria has been found to be higher in patients with RA than in the general population. That is, 27.7% versus 7.8% and treatment with gold and penicillamine seemed to increase this risk. Therefore, urinary albumin may be used as a marker of early renal disease or drug induced nephropathy (71).

In a prospective study of renal disease in early RA patients, it was concluded that a raised serum creatinine level and persistent proteinuria was predominantly drug related while persistent hematuria was associated with disease activity (73).

Urinalysis alone is an unreliable predictor of renal dysfunction (38) and even in patients on nephrotoxic drugs it is important to investigate the cause of the urinary abnormalities (74).

Immunological markers

In contrast to other extra articular manifestations of RA, renal disease has not been associated with circulating immune complexes. It was found that there was no significant difference in immunological markers (rheumatoid factor, anti-nuclear antibody, complement 3 and 4) in RA patients with and without renal involvement, thus rendering these markers poor predictors of renal involvement (75).

N-acetyl glycosaminidase

Urinary N-acetyl glycosaminidase (NAG) is another marker of renal disease and nephrotoxicity. It has been noted that patients with RA have higher levels of NAG than their matched controls and the levels correlate with disease activity (4).

The use of NAG is not widespread owing to the variations in analytical methods which are tedious and thus increase limitations. Kidney Disease – Improving Global Outcomes (KDIGO) guidelines have not yet advocated the routine use of NAG as a marker of kidney disease (17).

Cystatin C

This is one of the markers approved for estimation of GFR by KDIGO (17). It is superior to serum creatinine in GFR prediction. Its use in RA patients is recommended as demonstrated by Manngé et al (4) who noted that cystatin C was elevated in 60% of patients who had decreased creatinine clearance in comparison to serum creatinine which was elevated in only 5% of the same patients. Guidelines have not yet recommended its use as a replacement of eGFR in RA patients.

Bone Mineral Disease

Bone loss occurs early in rheumatoid arthritis and is usually related to disease activity (77). Glucocorticoids which may be used for RA also have a negative impact on bone density. Effective disease activity reduction has been shown to limit this effect. The coexistence of CKD in this group of patients is likely to have an increased negative effect in terms of bone mineral disease. This is usually in the form of hyperparathyroidism with associated bone effects (77). Low serum calcium and increased serum phosphate must be recognized as manifestations of CKD and must be done together with routine assessment for CKD (70).

EFFECT OF RENAL DYSFUNCTION IN RHEUMATOID ARTHRITIS

The impact of renal disease in patients with RA is adverse. Patients with RA have an increased mortality of more than twice that of their age and sex-matched controls (78,79). Even with the advancement in management of RA, patients have not enjoyed an improved survival (3,80). The cause of the widening mortality gap between RA patients and their age and sex-matched controls has not yet been determined.

In a national study done in Scotland, between the years 1981 and 2000, it was shown that patients with RA had an increased risk of mortality from renal failure of 3.5 times (81). Suzuki et al demonstrated that renal failure was a cause of death in 9.9% of RA patients assessed on autopsy (82).

The causes of death in RA are mainly non-articular (83). Reports suggest increased risk from cardiovascular, infectious, hematologic, gastrointestinal, and respiratory diseases among RA patients compared with control individuals (6). Cardiovascular disease (CVD) was the commonest cause of death in these patients which accounts for about 40% (84). Patients with RA were at a 3.17 fold higher risk of developing a myocardial infarction (MI) and nearly a six fold risk increase of having silent myocardial infarctions than non RA counterparts (6). At the same time, those who had an MI had a 47% greater risk of death post MI than their control counterparts (85). In contrast, the incidence of angina pectoris in this group is less than that of the non-RA arthritis population, meaning that the risk of silent MI is much greater (6). All this data goes to show that patients with RA had a significantly increased risk of cardiovascular risk and subsequently increased mortality risk. This increased risk may remain silent and may present as sudden cardiac death.

The CVD risk in this population is contributed to by both traditional risk factors and nontraditional ones. Deranged kidney function is one of the highest contributors to these risks. A reduction of eGFR to below 45ml/min/1.73m² had a 93% increased risk of CVD. Cardiovascular disease itself worsens kidney function and the presence of CVD at baseline was associated with a 77% increased risk of an eGFR below 60 (7). Of note however is that in RA, renal dysfunction is associated with a higher risk of CVD independently of traditional cardiovascular risk factors (37,86). It has therefore been suggested that RA patients be considered high risk for CVD both due to traditional risk factors and additional factors from RA.

STUDY JUSTIFICATION

Chronic kidney disease is a global health problem. In rheumatoid arthritis, CKD is the third most common cause of death while cardiovascular disease is the first. Having CKD multiplies the risk of cardiovascular disease thus increasing both morbidity and mortality in this group of patients. Detecting CKD early will ensure timely intervention and decrease in rate of CKD progression therefore decreasing morbidity from CKD.

Some of the drugs used for treatment of RA have severe toxic effects on the kidney even in patients with only mild renal insufficiency and therefore require dosage adjustment. Assessment of kidney function in patients with rheumatoid arthritis is necessary for appropriate dosing or change to less nephrotoxic drugs.

There is no local data on the burden of renal disease in this patient group. This study will form a baseline survey on the magnitude of renal dysfunction in this patient group as well as associated factors and inform on modes of intervention. The findings of this study will also increase surveillance of renal disease among RA patients and improve the quality of care.

RESEARCH QUESTION

What is the burden of CKD as measured by eGFR and proteinuria among ambulatory patients with RA attending KNH?

OBJECTIVES

BROAD OBJECTIVE

To determine the prevalence of CKD in patients with RA attending KNH rheumatology clinic.

SPECIFIC OBJECTIVES

PRIMARY OBJECTIVE

1. To determine the prevalence and stage of CKD among ambulatory patients with RA presenting at KNH outpatient rheumatology clinic.

SECONDARY OBJECTIVES

1. To describe the demographic characteristics of the study population
2. To determine the association of renal dysfunction with:
 - i) Duration of RA
 - ii) Disease activity of RA
 - iii) Drugs used for RA treatment

METHODOLOGY

STUDY SITE

Kenyatta National Hospital is a tertiary and referral teaching hospital situated in Nairobi, Kenya. It is the largest hospital in East and Central Africa, with a bed capacity of 2000. It is the only public hospital with a specialized rheumatology clinic offering care to RA patients. The clinic is held on a weekly basis every Thursday with the exception of public holidays.

The Rheumatology outpatient clinic receives on average 70 patients per clinic, of which about 10 patients per clinic are RA. The clinic is mainly run by consultant rheumatologists who are assisted by residents in Internal Medicine.

STUDY POPULATION

Patients with a file diagnosis of RA seeking ambulatory care from the rheumatology outpatient clinic at Kenyatta National Hospital.

STUDY DESIGN

Cross-sectional descriptive survey

SAMPLE SIZE

The sample size was calculated using the finite population correction formula as follows:

$$n' = \frac{NZ^2 \times P(1-P)}{d^2(N-1) + Z^2 P(1-P)}$$

n' = sample size with finite population correction

N = population size (146 RA patients in the clinic) (87)

Z = confidence interval at 95% (standard value of 1.96)

P = estimated prevalence of renal disease from Karie et al study, 2008 = 25% (33)

d = precision (0.05)

The sample size for this study = 98 patients

The study recruited 104 patients.

SAMPLING METHOD

Consecutive sampling method

CASE DEFINITION

RA: Any ambulatory patient attending the KNH Rheumatology clinic during the study period with a diagnosis of RA meeting the 2010 ACR-EULAR criteria (Appendix I) for RA was eligible to participate in the study.

CKD: eGFR of less than or equal to 60ml/min/1.73m² using the Cockcroft Gault formula and/or a proteinuria of 30mg/dl detected on urinary dipstick.

UTI: urine dipstick positive for leukocytes with or without blood or nitrites using the URIT 10V urinary dipsticks.

INCLUSION AND EXCLUSION CRITERIA

INCLUSION CRITERIA

1. Patients diagnosed to have rheumatoid arthritis according to ACR-EULAR criteria
2. Patients 18 years and above
3. Patients who gave written informed consent

EXCLUSION CRITERIA

1. Patients who were diagnosed to have a current urinary tract infection on urinalysis were excluded from further urine analysis although their eGFR assessment was included.

SERUM CREATININE AND URINALYSIS

Renal dysfunction in this population was diagnosed based on the patient's weight and laboratory parameters using an estimated GFR by the Cockcroft Gault formula. This is calculated as:

$$\frac{(140 - \text{Age}) \times \text{Mass (Kg)} \times \text{Constant}}{\text{Serum creatinine } (\mu\text{mol/l})}$$

Where constant is 1.23 for men and 1.04 for women

Based on the calculated eGFR patients were categorized in stages of kidney disease as follows:

G1 eGFR more than or equal to 90 ml/min/1.73m²

G2 eGFR 60-89 ml/min/1.73m²

G3a eGFR 45-59 ml/min/1.73m²

G3b eGFR 30-44 ml/min/m²

G4 eGFR 15-29 ml/min/m²

G5 eGFR less than 15ml/min/ m²

A urine analysis using the URIT 10V dipsticks was performed. This was used to assess for proteinuria. Any sample found to have leukocytes or nitrites positive was exempted from analysis. The results were categorized as positive for a protein level of 30mg/dl or more.

SCREENING AND RECRUITMENT

The principle investigator (PI) with the help of study assistants reviewed files of patients attending the clinic. The research assistants were two qualified clinical officers with diplomas from Medical Training College (MTC). The principal investigator ensured the training of the research assistants, prior to commencement of the study. The training covered assessment of disease activity and how to draw blood samples following standard procedures. The PI ensured the competency of the research assistants by carrying out a pilot run.

The files of patients who met the criteria were selected prior to the start of each clinic. The PI sat privately with the patients who met the study criteria in a side room at the rheumatology clinic. The participant could be accompanied with a next of kin if he/she so wished. The PI explained the purpose of the study, what the study entailed and the benefits to those who wished to participate. The patients were then allowed to read and understand the information form (Appendix 4). They were encouraged to ask any questions they may have had of which the PI answered to their satisfaction. If the patient had fully understood the information given and consented to participating in the study they were provided with the consent form to sign. Any patient who declined participation was allowed to do so with no repercussions whatsoever.

Once written informed consent was acquired a questionnaire was administered, physical examination undertaken and appropriate investigations carried out.

DATA COLLECTION

CLINICAL METHODS

The principal investigator took a history from the participant as per the study proforma. The data included age, gender, marital status, level of education and whether the participant was diagnosed to have diabetes mellitus or hypertension.

Patients' files were reviewed to obtain information on disease duration, hypertension, previous creatinine level and medication used as well as duration. This information was recorded in the study proforma for later analysis.

Participants were also weighed in kilograms (Kg) on an Ashton Meyer weighing scale. Shoes and other accessory clothing were removed prior to a measurement being taken. The scale was used in accordance with the manufacturer's instructions and the dial calibrated to zero before each measurement.

A blood pressure (BP) measurement was taken. The PI ensured that patients had been seated and relaxed five minutes prior to the reading. The arm in which the measurement was recorded was supported at the level of the heart. The cuff was placed on the patient's arm and the PI ensured that it covered at least 80% and was in accordance with the index line on the cuff to ensure that it was not too big or too small. The brachial artery was palpated and the cuff inflated until the pulsation disappeared. An estimate of the systolic BP was then made. A stethoscope was placed over the same artery and the cuff was again inflated to a reading 30mm of mercury above the estimate and then deflated at a rate of 2-3mm of mercury per second. A systolic and diastolic measurement was recorded to the nearest 2mm of mercury.

Assessment of 28 joints (shoulders, elbows, wrists, knees, metacarpo-phalangeal joints, proximal interphalangeal joints) for the DAS 28 score (appendix 2) was done. Joints were assessed for swelling and tenderness and patients asked to score on a visual analogue scale their assessment of disease.

LABORATORY METHODS

Specimen collection, transportation, storage

8 mls of venous blood were collected from each patient by the research assistants. The sample was collected under sterile techniques from the cubital vein either of the left or right arm. The blood was divided equally into two vacutainers. Four milliliters were placed in a plain vacutainer (red top) while the remaining 4mls were placed in a vacutainer with EDTA (purple top). Cooler boxes with ice packs at approximately 4⁰C (2-8⁰C) were used for temporary storage and to facilitate transport to the laboratory. Samples were delivered to the laboratories at the end of the day's collection. These were analysed immediately upon delivery to the laboratory.

Patients were also asked to provide a urine sample in a container. A minimum of 10mls of midstream urine was required. This was collected in a sterile, capped urine collection bottle and was analysed by the PI at the clinic by dipstick. Results obtained were recorded immediately in the study proforma.

SPECIMEN ANALYSIS

Serum creatinine was analysed in the renal unit laboratory using the Mindray BS 400 which is an automatic biochemistry analyser.

Urine analysis was performed by the PI at the site of collection using the URIT 10V kit. The method required use of a urine dipstick with assessment of the parameters on a coloured visual scale. After 30 seconds of exposing the dipstick to urine, a reading for proteinuria was made. Nitrites and blood were read at 60 seconds while leukocytes were interpreted at 120 seconds.

ESR interpretation was undertaken at the hematology laboratory, UoN. It was done by the Wintrobe method where non-hemolysed blood collected in an EDTA tube was placed in a tube and rate of fall of RBCs was measured in mm after one hour.

QUALITY ASSURANCE

Standard operating procedures for specimen collection and transport were followed with timely delivery to the laboratory to minimize pre-analytical errors. Quality control for the biochemistry analyser was performed daily at the renal unit laboratory and when discrepant results were received. Both these laboratories undergo internal and external quality control measures. After every 20 samples, one blood and urine sample was then taken to Lancet Laboratory (an external independent laboratory) for comparison of values.

The weighing scale was used according to manufacturer's instructions and calibrated prior to each clinic attended.

STUDY VARIABLES

INDEPENDENT VARIABLES

This included socio-demographic and clinical variables. These were:

- a) Age – It was recorded as the nearest number of years from reported date of birth.
- b) Gender – It was determined by the phenotypical sexual appearance of the subjects. That is, the secondary sexual characteristics.
- c) Disease duration from diagnosis – This was determined to the nearest year by documented date of when the disease was diagnosed for the first time.
- d) Treatment modality – This was defined as drug therapy used and the duration of use. It was obtained from the subjects records.
- e) Level of education – It was reported as the highest level of education the patient has acquired as reported by the patient.
- f) Marital status – This was categorized as single, married, divorced or widowed and was documented as reported by the patient.
- g) Hypertension – This was noted as patient's awareness of having the above diagnosis, being on treatment for hypertension, a documented diagnosis in the patient's records or a spot blood pressure reading of greater than or equal to 140/90 mm of mercury.
- h) Diabetes - This was noted as patient's awareness of having the above diagnosis, being on treatment for diabetes or a documented diagnosis in the patient's records.

DEPENDENT VARIABLES

Estimated glomerular filtration rate (eGFR) which was calculated using serum creatinine by the Cockcroft-Gault formula.

Proteinuria of greater than or equal to 30mg/dl on urinary dipstick.

DAS28 score which is graded from 0-10. This was categorized as mild moderate or severe according to the score:

- i) Remission: less than 2.6
- ii) Mild: DAS28 score of 2.6-3.2
- iii) Moderate: DAS28 score of 3.3- 5.0
- iv) Severe: DAS28 score of greater than 5.1

DATA MANAGEMENT AND ANALYSIS

Data was collected by the PI and research assistant and entered into a password protected Microsoft Access database managed by the statistician. Once data entry was complete, entries in the database were compared to the hard copies to ensure accurateness. Inconsistencies were detected by use of simple frequencies and correlations and those identified were rectified before data analysis began. Data was analysed using SPSS software version 20 for windows.

Independent variables were presented as follows:

- a) age was presented as mean plus or minus the standard deviation
- b) gender was presented as a ratio
- c) disease duration was presented as a median plus or minus the standard deviation
- d) treatment modality was presented as three categories. Use of non-steroidal anti-inflammatory drugs, use of prednisolone or use of both. These were each presented as a percentage of the total.
- e) level of education was in categories of none, primary school, secondary school and tertiary and these were each presented as a percentage of the total
- f) marital status was categorized as single, married, widowed or divorced and each presented as a percentage of the total.
- g) hypertension was presented as a percentage of the total.
- h) diabetes was presented as a percentage of the total.

Dependent variables were analysed for correlation with a p value of 0.05 or less considered significant. These were correlated with eGFR of greater than or equal to 90mls/min, eGFR of between 90-60mls/min and an eGFR of less than 60mls/min. The correlations were analysed as follows:

- a) disease duration and eGFR level by the Kruskal Wallis test
- b) disease activity (mild, moderate, severe) and eGFR level by the ANOVA test
- c) treatment modality (NSAIDs, prednisolone or NSAIDS and prednisolone) and eGFR by the Chi-square test

STUDY ADMINISTRATION

It was the responsibility of the PI to inform RA patients about the study. The PI then recruited those willing to participate in the study and obtained their informed consent. The research assistants worked with the PI to ensure that data was collected efficiently, on time and that it was recorded accurately. All recorded data was verified by the PI, who also ensured that all relevant forms were completed. The supervisors offered guidance to the PI throughout the process. The statistician offered guidance during proposal development, data entry, analysis and presentation of the final statistical analysis

ETHICAL CONSIDERATION

The study was undertaken only after approval by the Department of Clinical Medicine & Therapeutics, University of Nairobi and the KNH/UoN Scientific and Ethical Review Committee. The objectives and purposes of the study were clearly explained to eligible participants in a language suitable to them prior to inclusion into the study. Only patients who gave informed consent were enrolled. Patients were free to withdraw during the study period without discrimination. Information gathered from the study participants was kept confidential.

Only blood samples intended for study were drawn and thereafter discarded after analysis. The study results were disseminated to health care providers to aid in patient care.

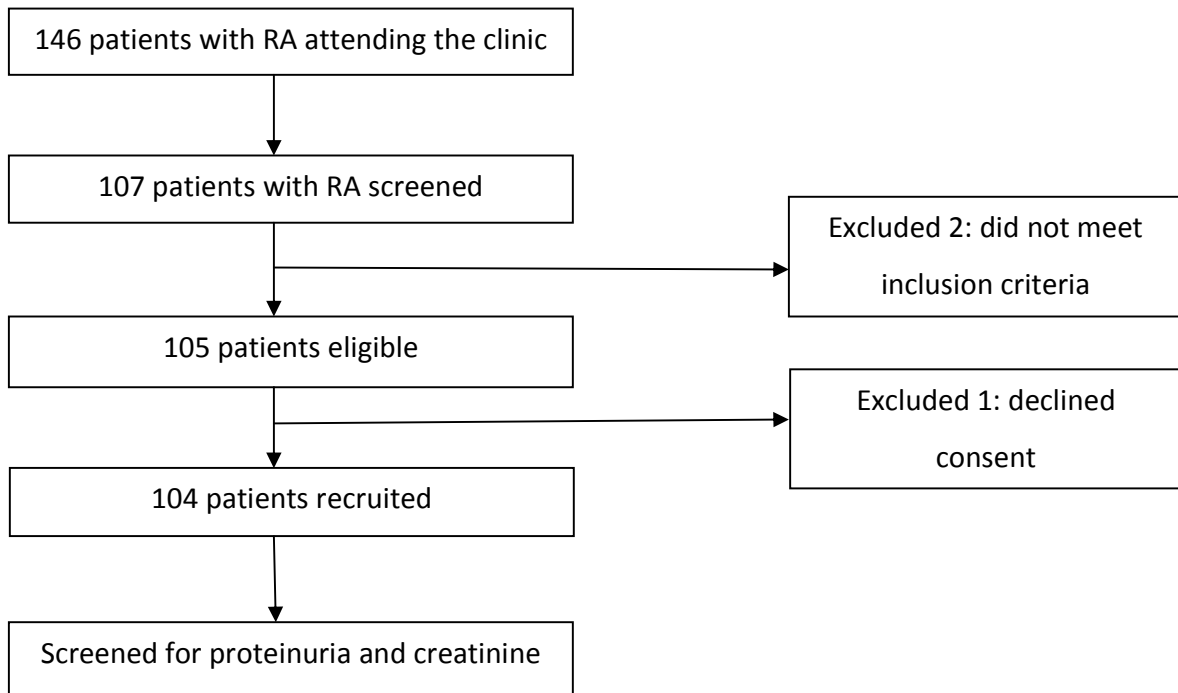
All information collected from patients and their records was entered onto the data collection tools which were stored in a locked cabinet accessible only to the principal investigator. The information collected was only used for the purposes of this study and will not be shared with any other persons. This will be stored for two years upon completion of the study in the event of any need for verification or clarification purposes. Upon the lapse of two years, the stored data will then be destroyed.

All study participants found to have stage 3 CKD and beyond were informed. This diagnosis was also shared with the rheumatologist and any nephrotoxic medication that the patient was taking stopped. Patients were then provided with a referral note to attend the nephrology clinic to initiate follow up by a nephrologist.

RESULTS

Data was collected over a ten week period. Out of the population of 146 RA patients at the clinic we managed to screen a total of 107. Out of these, two did not meet the inclusion criteria and were excluded. One declined consent thereby leaving a total of 104 patients who were enrolled. On screening for proteinuria, 5 patients were found to have a current UTI and thus were not evaluated for proteinuria. This led to proteinuria being evaluated in 99 of the study participants. Of the total 104 patients screened, results for creatinine level were available for only 102. The flow chart in figure 3 below depicts patient recruitment process.

Figure 3: The recruitment process



In our study population, mean age was 48.7 ± 15.6 years and majority of patients were female 93 (89.4%), married 71 (68.3%) and having attained some level of formal education 94 (90.4%).

Table 4 below shows their demographic and clinical characteristics.

Table 4: Demographic characteristics of patients in the study

	Frequency (n)	Percent (%)
Age		
18-24 years	7	6.7
25-34 years	11	10.6
35-44 years	26	25
45-54 years	24	23.1
55-65 years	20	19.2
65 years and above	16	15.4
Sex		
Male	11	10.6
Female	93	89.4
Level of formal education		
None	10	9.6
Primary	41	39.4
Secondary	26	25
Tertiary	27	26
Marital status		
Married	71	68.3
Single	17	16.3
Divorced/ separated/ widowed	16	15.4

Treatment modality and co-morbid illness

Majority of patients were on at least one DMARD 90 (86.5%) therapy with methotrexate being the most frequently used drug. Other drugs used in our setting were leflunomide, sulfasalazine and hydroxychloroquine. None of our patients was on a biologic agent.

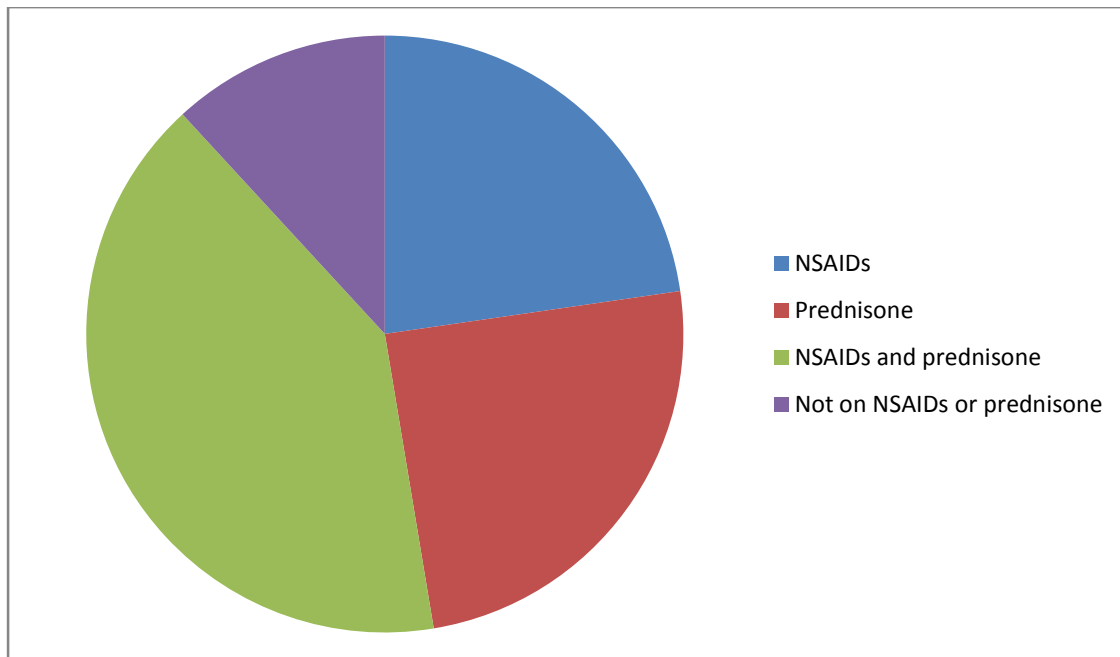
We also assessed use of NSAIDs and prednisone. Most of the study subjects were on both NSAIDs and prednisone 43 (41.3%), followed by those on prednisone alone 26 (25%) and NSAIDs 23 (22.1%). A few patients were on neither of these drugs 12 (11.5%).

When assessing co-morbid illnesses, we looked at presence of diabetes and hypertension and these had a prevalence of 7.7% and 35.6% respectively. Table 5 below summarises the data on drugs used while figure 4 is a chart representation of NSAID and prednisone use in the study population.

Table 5: Rheumatoid arthritis medication in ambulatory RA patients attending KNH Rheumatology clinic

	Frequency (n)	Percent (%)
Use of NSAIDs and prednisone		
NSAID+prednisolone	43	41.3
NSAID	23	22.1
Prednisolone	26	25
Not on NSAIDs or prednisone	12	11.5
DMARD Use		
Yes	90	86.5

Figure 4. Use of NSAIDs and prednisone among the study population



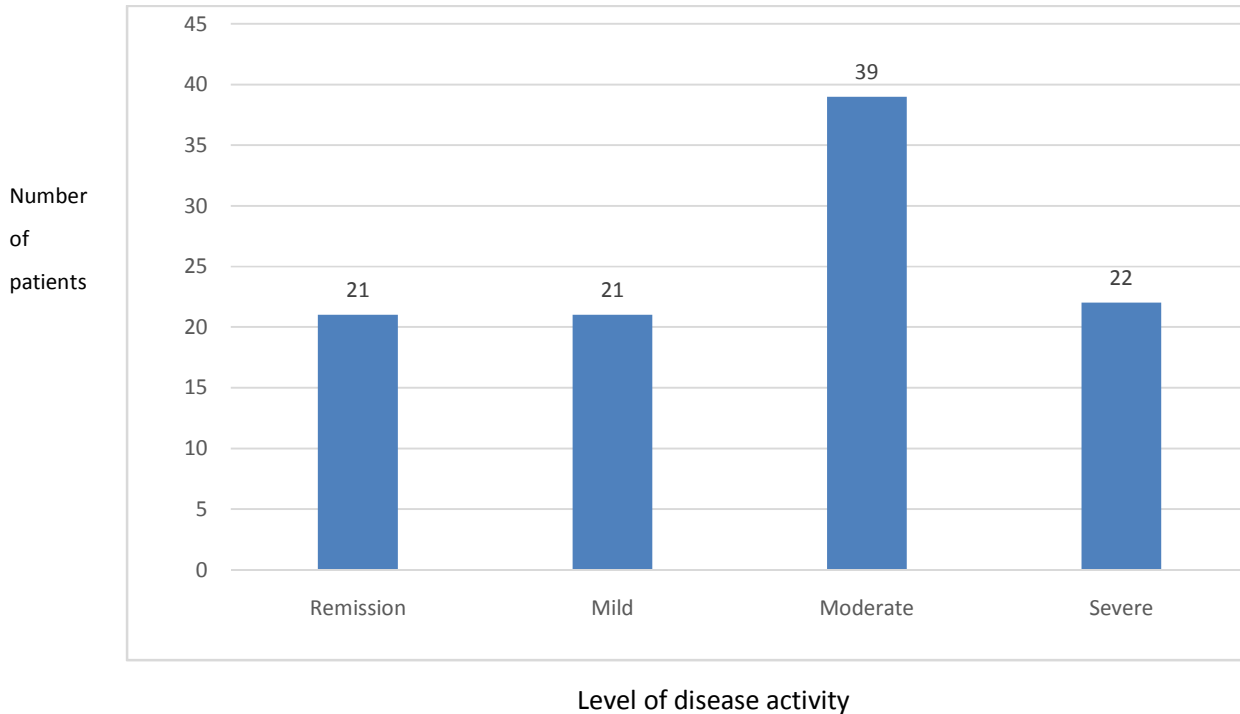
Disease duration

Majority of patients (49%) had been diagnosed with RA between 1-5 years from the time the study was undertaken. Median duration of disease was 4 years. Only 17.3% of patients had been diagnosed in a period of less than a year and the remainder 33.7% had had five or more years of RA disease diagnosis.

Level of disease activity

Disease activity was assessed using the DAS 28 score. Out of 103 patients, 21 were in remission. Of those with active disease, 21 had mild disease, 39 moderate disease and 22 with severe disease. This is depicted in figure 5 that follows.

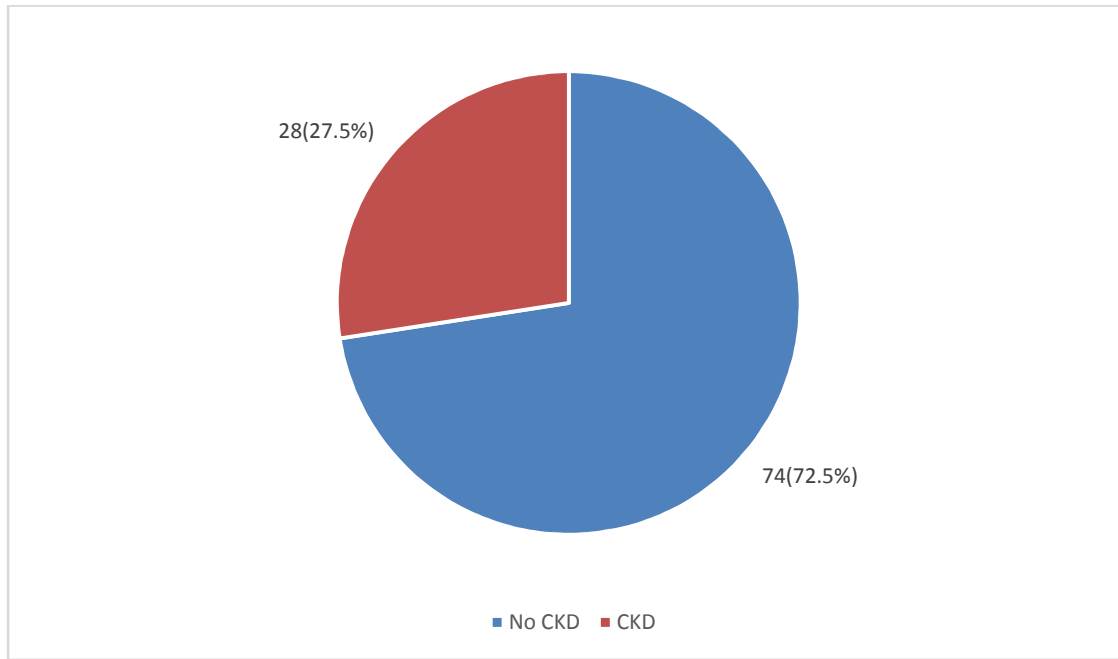
Figure 5: RA disease activity among ambulatory patients with RA presenting at KNH outpatient rheumatology clinic



Prevalence of CKD

Of 104 patients, creatinine results were available for 102. Using the Cockcroft-Gault formula, a total of 28 (27.5%) patients were found to have kidney disease. The staging for kidney disease was as follows; stages 3a (13.7%), 3b (7.8%) and stage 4 at (5.9%). There was no patient with stage 5 kidney disease. Figure 6 is a representation of the number of patients with CKD while table 6 below gives the distribution of patients with CKD according to the KDIGO criteria.

Figure 6: Prevalence of CKD among ambulatory patients with RA presenting at KNH outpatient rheumatology clinic



Prevalence 27.5% (95% CI 19.1%-37.2%)

Table 6: Stage of CKD among ambulatory patients with RA presenting at KNH outpatient rheumatology clinic

	Frequency (n)	Percent (%)
CKD staging		
Stage 3a	14	50
Stage 3b	8	28.6
Stage 4	6	21.4

Prevalence of proteinuria

On assessing for proteinuria, 5 patients had to be excluded due to the presence of a current urinary tract infection on dipstick. Out of the remaining 99 patients, 3 were found to have proteinuria but none was significant enough to reach the level defined by the study (30mg/dl).

Association of eGFR with duration of RA

eGFR was categorized was correlated with duration of disease using the Kruskal Wallis test. There was no association found between the two variables.

Association of eGFR with disease activity

There was no association found between eGFR level with disease activity which was categorized as remission, mild, moderate and severe disease activity. This is summarized in table 8.

Table 7, Association of disease activity of RA with eGFR

	Filtration rate ml/min per 1.73m ²			P value
	>90	60-90	<60	
Disease activity				
Remission	9(42.9)	6(28.6)	5(23.8)	0.871
Mild	13(61.9)	3(14.3)	5(23.8)	0.263
Moderate	14(35.9)	13(33.3)	12(30.8)	0.178
Severe	12(54.5)	4(18.2)	6(27.3)	0.631

Association of eGFR with drugs used

We assessed whether there was any correlation between use of NSAIDs, prednisolone or both with eGFR level and found no association as portrayed in table 9 below.

Table 8: Association of drugs used for RA treatment and eGFR

	Filtration rate ml/min per 1.73m ²			P value
	>90	60-90	<60	
Drugs used for RA treatment				
NSAID+prednisolone	21(48.8)	12(27.9)	10(23.3)	0.706
NSAID	8(34.8)	6(26.1)	9(39.1)	0.297
Prednisolone	14(53.8)	5(19.2)	7(26.9)	0.644
Not on NSAIDs or prednisolone	5(41.7)	3(25.0)	2(16.7)	0.847

DISCUSSION

There is paucity of data on chronic kidney disease in rheumatoid arthritis. Majority of the studies were undertaken in the developed countries and we were unable to access any studies done in Africa.

Rheumatoid arthritis is a disease that predominantly affects females. We also found a similar gender distribution (female preponderance) as was expected at a male to female ratio of 1:8.

Our study population was middle aged, with a mean age of 48.7 years. This is a relatively young population mostly in their prime and at a productive age. Our study subjects were much younger than those in the study by Karie et al in France whose subjects had a mean age of 55.2 years (35), Hickson et al with a mean age of 56 years in the United States of America (7) and Daoussis et al in the United Kingdom with a mean age of 61.6 years (36).

Disease duration was calculated in years and was found to be at a median of 4 years. This shows that majority of our patients had recently been diagnosed with rheumatoid arthritis when compared to other studies, Karie et al found a median disease duration of 9.5 years (35), Daoussis et al a duration of greater than 9 years (36).

Hypertension and diabetes are major causes of CKD. In our study population, prevalence of hypertension was 35.6%. In the Kenyan general population prevalence of hypertension is estimated to be 21.4% in a cross-sectional survey undertaken by Hendricks et al (88). The prevalence of hypertension is higher in patients with RA as compared to age and sex matched controls a finding confirmed by Kirui et al (5). This may be due to the older age among patients with RA as hypertension is a disease that has increasing incidence with age.

Prevalence of diabetes is greater in patients with RA than in the general population (5,89). Some authors relate this to the use of steroids among patients with RA (5). In our study, we found a prevalence of only 7.7% while studies quote the prevalence to be 4.2% in the Kenyan general population (90).

Whilst assessing eGFR, prevalence of CKD was found to be 27.5% as measured by an eGFR of less than 60ml/min/1.73m² (Cockcroft-Gault formula). When compared to other studies assessing CKD in patients with rheumatoid arthritis, the figures are much higher than 25.3% as noted by

Karie et al (35), 12.75% by Daoussis et al (36) and 18% found by Hill et al (37) which are studies undertaken in Europe. The higher prevalence of CKD in our population may be explained by the fact that CKD is increased in blacks more than in their white counterparts (91,92). The prevalence of CKD in USA is estimated at 13.1% (93) and this number is expected to rise at a rate of 5-8% per year (94). The prevalence of CKD in Europe and in the USA are said to be similar (94). In Africa, CKD prevalence is estimated at 13.9% from a systematic review (31) and this is thought to be an underestimation. The higher prevalence among Africans been attributed to genetic predisposition, low socio-economic status and inequities in access to healthcare (95), factors which may apply to our population although were not assessed by our study.

It has been previously thought that kidney dysfunction in RA may be indicator of severe disease (73). Of our study population, 43% had active disease. Our clinic is limited in the choice of DMARD use and biologics are not a feasible option for our patients due to cost. The other studies in which we used to compare our findings also included patients on biologic therapy (35,36). However, no association has been found between disease control and eGFR in other studies (36).

Majority of those found to have CKD were at stage 3a. This is early CKD which leaves room for interventions that may slow progression. We did not find any patients with end stage renal disease (stage 5 CKD) probably due to the shorter median duration of RA disease among our study population. We postulate that the absence of any patients with stage 5 CKD may either be due to the increased cardiovascular risk with a decreased eGFR implying that patients may be dying before they reach ESRD. Another possibility may be the lack of progression of CKD in this group of patients. Proteinuria is a strong predictor of progression. Lack of proteinuria in this population may indicate a non-progressive CKD which may explain the absence of any patients with stage 5 CKD. Of note, the study undertaken by Karie et al also found a similar finding. That is, absence of any patients with stage 5 CKD (35). Unfortunately, no explanation was given for this finding.

We found no patients with proteinuria which was a lower prevalence than that found by Karie et al of 16.2% (35) or Karstila et al of 5% (72). Proteinuria is usually related to drug use such as gold and penicillamine which are not used for rheumatoid arthritis in our setting. This may explain the low prevalence in this study. On the other hand, proteinuria may occur as a result of

glomerulonephritis in RA which is now considered to be rare. Horak et al notes it to be of little clinical significance and was only noted on either autopsy or biopsy in the past (41). Another factor that may explain the lack of proteinuria in our study population is due to the fact that proteinuria is not recommended for screening of CKD in a young population because of the low diagnostic yield (96). Table 10 below shows a comparison of our study with others that assessed CKD in RA.

Table 9, Comparison of studies on CKD in RA

STUDY DETAILS	FINDINGS	CONCLUSION OF STUDY
Said et al, 2015 104 patients Kenya	27.5% CG formula 0% proteinuria CKD stages 3, 4 and 5 at 78.6%, 21.4% and 0%	High prevalence of CKD probably due to black population Absence of stage 5 CKD
Karie et al, 2008 129 patients France	25.3% CG formula 16% with proteinuria CKD Stages 3, 4 and 5 at 95%, 5% and 0% respectively	High prevalence Serum creatinine not a good measure of CKD Proteinuria should be routinely assessed Absence of stage 5 CKD
Daoussis et al , 2010 400 patients UK	12.75% MDRD equation 5.1% proteinuria CKD stages 2, 3a and 3b at 92.2%, stages 4 and 5 at 7.8%	Decreased eGFR common among patients with RA
Hickson et al, 1980-2007 1626 patients USA	9% MDRD equation	Patients with RA more likely to develop CKD CVD and associated factors played a role.

95%, stage 4: 5% and stage 5: 0% (35). Participants in the study by Daoussis et al were classified as moderate renal impairment (stage 2, 3a and 3b) and severe renal impairment (stage 4 and 5). The prevalence rates were 92% and 7.8% for moderate and severe renal impairment respectively (36).

Although our study set out to explore associations between CKD and various parameters, we were not powered to make significant conclusions out of these findings. Majority of patients (49%) had been diagnosed with rheumatoid arthritis between 1-5 years from the time the study was undertaken. The median disease duration was 4 years similar to a previous study done in our setting by Biomdo et al (97) who found a median duration of 5 with a range of 4-10 years. There was no association between disease duration and presence of CKD, a finding similar to that found by Daoussis et al (36). Longitudinal studies may be better designed to assess for an association between disease duration and CKD.

Majority of patients (59.2%) had active disease. This was mostly moderately active disease (37.9%). These numbers show an improvement in disease control amongst patients in our setting as evidenced by active disease of 88% in 2009 (98) in a study carried out by Owino et al. We think that this improvement in disease control is probably due to the increased use of DMARDs among the study population where 90% were on at least one disease modifying agent in our study as compared to only 46.7% in 2009 (98). We did not find a correlation between disease activity and presence of CKD in the population studied, a finding similar to Daoussis et al (36).

Despite the significant use of NSAIDs and prednisolone (88.5%), either singly or in combination, it is worth noting that there was no association between NSAID or steroid use and CKD. The lack of correlation between the drugs used and kidney disease may be attributed to poor drug compliance by our study population although this was not assessed by this study.

Our study was a cross-sectional study and was therefore unable to show a causal relationship between RA and CKD. We also did not undertake exclusion of other causes of CKD. Considering the significant prevalence of CKD found in this study, we therefore advocate screening for early renal disease among these patients as they could have multiple risk factors for kidney dysfunction.

LIMITATIONS

Our study had several limitations. Being a cross sectional study, we could not assess progression of CKD. Also, any urine samples that had been excluded because patient had a urinary tract infection were not re-evaluated for proteinuria.

Our study was unable to quantify duration of use of steroids or NSAIDs, both of which have renal effects. We had a significant number of patients on these drugs but we cannot accurately indicate the duration in which patients were on these drugs and the degree of compliance.

CONCLUSIONS

Although our study did not show any proteinuria in our population, a significant number of study participants still had chronic kidney disease (eGFR of less than 60ml/min/1.73m³) which had an association with increasing age and diabetes. This still implies that patients with rheumatoid arthritis require screening for kidney disease, regular monitoring of progression and initiation of appropriate management especially with long-term follow up.

Proteinuria is a marker of progression in CKD. In this population where we found non-proteinuric CKD and no patients in ESRD (stage 5 CKD) one therefore wonders whether it is a non-progressive kidney disease.

Monitoring for CKD is also warranted since methotrexate, the cornerstone of RA treatment, requires cessation of use with decreased renal function.

RECOMMENDATIONS

Further studies are needed to ascertain the cause of high CKD prevalence in this population with longitudinal studies for determining disease progression.

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APPENDIX

Appendix 1: The 2010 ACR/EULAR criteria for classification of rheumatoid arthritis

Classification criteria for RA (score-based algorithm: add score of categories A–D;
A score of $\geq 6/10$ is needed for classification of a patient as having definite RA)

A. Joint involvement

1 large joint = **0**

2-10 large joints = **1**

1-3 small joints (with or without involvement of large joints) = **2**

4-10 small joints (with or without involvement of large joints) = **3**

>10 joints (at least 1 small joint) = **5**

B. Serology (at least 1 test result is needed for classification)

Negative RF *and* negative ACPA = **0**

Low-positive RF *or* low-positive ACPA = **2**

High-positive RF *or* high-positive ACPA = **3**

C. Acute-phase reactants (at least 1 test result is needed for classification) ††

Normal CRP *and* normal ESR = **0**

Abnormal CRP *or* abnormal ESR = **1**

D. Duration of symptoms

<6 weeks = **0**

≥ 6 weeks = **1**

Appendix 2: Data Extraction Tool

PREVALENCE OF RENAL DYSFUNCTION IN AMBULANT PATIENTS WITH RHEUMATOID ARTHRITIS ATTENDING THE RHEUMATOLOGY CLINIC AT KENYATTA NATIONAL HOSPITAL

Data Extraction Tool

1. Study no
2. Hospital no
3. Participant initials
4. Participant's contacts
5. Age (in years)
6. Gender: Male Female
7. Marital status: Single Married Separated Divorced Widowed
8. Level of education: None Primary Secondary Tertiary
9. History of RA: When was the diagnosis of RA made?
Duration since diagnosis.....
10. Has any medication been started? Yes No
11. Previous serum creatinine results eGFR calculation
12. Which medication have you been using?
 - a) NSAIDs Yes No
If yes, for how long have you been using NSAIDs?.....
 - b) DMARDs
 - i) Methotrexate Yes No
If yes, for how long have you been using methotrexate?
 - ii) Hydroxychloroquine Yes No
If yes, for how long have you been using hydroxychloroquine?
 - iii) Prednisolone Yes No
If yes, for how long have you been using prednisolone?
 - iv) Leflunomide Yes No
If yes, for how long have you been using Leflunomide?
 - v) Sulfasalazine Yes No

If yes, for how long have you been using sulfasalazine?.....
vi) Biologic agents yes No
If yes, for how long have you been using biologic agents?

Diabetic Yes..... No.....

Hypertensive YesNo.....

Weight in kilograms BP measurement

LABORATORY RESULTS

1. Serum creatinine measured in mg/dl.....
2. Urinary dipstick measuring proteinuria.....

PHYSICAL EXAM

DAS28 form

Observer name Date ____ - ____ - ____

	Left		Right	
	Swollen	Tender	Swollen	Tender

Shoulder				
Elbow				
Wrist				
MCP 1				
2				
3				
4				
5				
PIP 1				
2				
3				
4				
5				
Knee				
Subtotal				
Total	Swollen		Tender	

Not active at all

Extremely active

Swollen Joint Count (0-28)

Tender Joint Count (0-28)

ESR

VAS disease activity (0-100mm)

A vertical rectangular box with a solid black border. It is divided into four horizontal sections by three horizontal dotted lines. The sections are of equal height and are currently empty.

The DAS28 is a clinical score of RA disease activity. It is a validated tool and compares well with the comprehensive DAS tool which evaluates 44 joints. The DAS 28 assesses 28 joints for both tenderness and swelling. The joints evaluated are the proximal interphalangeal and metacarpo-phalangeal joints of both hands, the wrists, elbows, shoulders and knees. An ESR measured in mm/hr and the patient must provide a global health assessment measured on visual analog scale (VAS) of 100mm. The score is then calculated as:

$$\mathbf{DAS28 = 0.56 (\sqrt{t28}) + 0.28 (\sqrt{sw28}) + 0.70(ESR) + 0.014(VAS)}$$

The score ranges between 0-10 whereby a score of 5.1 or above indicates high disease activity and a score of 3.2 or less indicates low disease activity

Appendix 3: Patient explanation and consent form

Introduction

I, Sanaa S. Said, am a postgraduate student at the University of Nairobi, currently doing a masters' degree in Internal medicine. I am conducting my research project for which I request your participation.

I am carrying out a study on patients with rheumatoid arthritis to see how many of these patients have kidney dysfunction and how it relates to the length of time and type of medication one is using for treatment of rheumatoid arthritis.

The study is part of my university requirements but the results of the study will be used to offer recommendations which, if implemented, may lead to improved management and quality of life of patients with rheumatoid arthritis.

Once you agree to participate in the study, you will have to answer questions of a personal nature as outlined in the study questionnaire, undergo a physical examination, provide a urine sample and we will draw about 8 mls of blood. All the information you provide will be handled in a confidential manner and will not be divulged to any other person without your consent.

The blood collected will be used to assess your kidney function by use of the creatinine level and to assess ESR which will be used to determine how severe your rheumatoid arthritis is. The urine sample will be used to check whether you could be having any protein in your urine. This may also tell us if you have a kidney problem. In case we discover that you may be having a urinary tract infection during analysis of the urine sample, we shall inform you and write a prescription for treatment of the infection.

During our examination, we will assess 28 of your joints and ask you to rate how well you feel your disease has been managed. This is not routinely carried out in the clinic. It is an assessment of how severe your rheumatoid arthritis may be.

You may feel a slight pain/ discomfort when the blood is being withdrawn but this is no different from when blood was drawn for other tests. There may be a slight swelling at the site of the prick but this will disappear on its own after a few days. The amount of blood that will be drawn will not affect your health.

Participation in this study is absolutely voluntary and in the event that you decide not to participate, this will in no way affect your treatment whatsoever. You may choose to withdraw from the study at any time whatsoever with no consequences to your treatment.

Your participation in the study and the laboratory tests bear no cost to you but the findings will be used for your individual benefit.

PATIENT CONSENT FORM

I ofhereby consent/decline to participate in this study, of which I have fully read and understood the explanation given to me. All my questions have been satisfactorily answered by the investigators.

Signed Date

Witness (PI/Assistant) Date

CONTACTS

For further information, you may contact any of the following:

1. Dr. Sanaa S. Said (Principal investigator)

P.O Box 4199, Zanzibar.

Tel 0718 013131

2. Kenyatta National Hospital/University of Nairobi Ethics and Research Review Committee,

P.O Box 20723 NAIROBI.

Tel 020-726300

FOMU YA MAELEZO

Mimi, Sanaa S Said, ni mwanafunzi katika chuo kikuu cha Nairobi. Ninatarajia kufanya uchunguzi kuhusu magonja ya figo na ningependa wewe uhusike.

Ninafanya utafiti kwa wagonjwa wenye jongo ili kujua wangapi kati yao wana matatizo ya figo na kulinganisha matatizo hayo na muda wa ugonjwa na aina za dawa zinazotumika kutibu jongo.

Utafiti huu unahitajika kama sehemu ya masomo yangu lakini matokeo yatakayopatikana yatumika kutoa nasaha, ambayo ikiwa itatumika inaweza kuleta manufaa katika matibabu na hali ya maisha ya wagonjwa wa jongo.

Utakapokubali kujiunga na utafiti huu, utahitajika kujibu maswali ya kibinafsi kama yalivyodokezwa katika karatasi ya maswali, utapimwa kimwili, utahitaji kutoa mkojo na utatolewa damu kiasi kidogo kama kijiko kikubwa cha chakula. Habari yoyote utakayotoa itawekwa kwa usiri na haitatolewa kwa mtu yeyote bila ya idhini yako.

Damu ambayo itatolewa itatumika kupima figo na kufanya kipimo kinachoitwa ESR ili kuweza kujua hali ya ugonjwa wako wa gongo. Mkojo utatumika kupima kiwango cha protini katika mkojo ambayo ni njia nyingine ya kupima maradhi ya figo. Ikiwa wakati wa kupima mkojo utakatikana na uchafu wa mkojo (urinary tract infection) basi utaelezwa papo hapo na tutakuandikia cheti cha kununua dawa ili upate matibabu.

Wakati wa uchunguzi, tutaangalia viungo 28 na kuulizwa jinsi unavyohisi ugonjwa wako unatibiwa. Uchunguzi ambao haufanyiki unapohudhuria kliniki. Uchunguzi huu unapima jinsi ugonjwa wako umetibika.

Unaweza kusikia maumivu kidogo wakati wa kutolewa damu. Maumivu haya, hayana tofauti na ale uliyosikia wakati wowote mwingine wa kutolewa damu. Unaweza kupata uvimbe kidogo sehemu ya kutolewa damu ambao utaondoka baada ya siku chache. Damu ambayo itatolewa haitaathiri afya yako.

Uamuzi wa kujiunga na utafiti huu ni wa hiari. Iwapo utakataa kujiunga hotathiri matibabu yako kwa njia yeyote. Unaweza kuamua kujitoka katika utafiti huu wakati wowote bila ya madhara kwa matibabu yako.

Kujiunga na utafiti huu na vipimo vya maabara havitakugharimu kiwango chochote cha pesa lakini vipimo vitatumika kwa manufaa yako.

FOMU YA IDHINI

Mimi kutoka

Nimekubali/kataa kujiunga na utafiti huu ambao umeelezwa kwa ukamilifu kwangu. Nimesoma na kuelewa maelezo yote. Maswali yangu yote yamejibiwa kwa ukamilifu na mtafiti.

Sahihi Tarehe

Shahidi.....(mtafiti mkuu/msaidizi) Tarehe

MAWASILIANO

Ukiwa na maswali yoyote ya ziada, unaweza kuwasiliana na wafuatao:

1. Dkt. Sanaa S. Said (Principal investigator)

P.O Box 4199, Zanzibar.

Tel 0718 013131

2. Kamati ya Maadili ya Hospitali ya Kenyatta na Chuo kikuu cha Nairobi

SLP 20723 NAIROBI

Simu: 020-726300

KNH/UON-ERC LETTER OF APPROVAL



UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
(254-020) 2726300 Ext 44355

Ref: KNH-ERC/A/31

Dr. Sanaa S. Said
Dept of Clinical Medicine & Therapeutics
School of Medicine
University of Nairobi

Dear Dr. Said

Research Proposal: Chronic kidney diseases in Rheumatoid Arthritis at Kenyatta National Hospital (P495/08/2014)

This is to inform you that the KNH/UoN-Ethics & Research Committee (KNH/UoN-ERC) has reviewed and **approved** your above proposal. The approval periods are 2nd February 2015 to 2nd February 2016.

This approval is subject to compliance with the following requirements:

- a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
- b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH/UoN ERC before implementation.
- c) Death and life threatening problems and severe adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH/UoN ERC within 72 hours of notification.
- d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH/UoN ERC within 72 hours.
- e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
- f) Clearance for export of biological specimens must be obtained from KNH/UoN-Ethics & Research Committee for each batch of shipment.
- g) Submission of an *executive summary* report within 90 days upon completion of the study
This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/or plagiarism.

For more details consult the KNH/UoN ERC website www.erc.uonbi.ac.ke

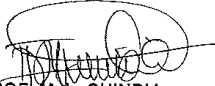


KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

2nd February, 2015

Protect to discover

Yours sincerely



PROF. M. L. CHINDIA
SECRETARY, KNH/UON-ERC

- c.c. The Principal, College of Health Sciences, UoN
 The Deputy Director CS, KNH
 The Assistant Director, Health Information, KNH
 The Chairperson, KNH/UON-ERC
 The Dean, School of Medicine, UoN
 The Chairman, Dept of Clinical Medicine & Therapeutics,
 Supervisors: Dr. G.O. Oyoo, Prof J.K. Kayima, Prof. G.N. Lule

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