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RESEARCH ARTICLE

IN RHEUMATOID ARTHRITIS: TRADITIONAL AND NON-TRADITIONAL CARDIOVASCULAR RISK FACTORS WORK COLLECTIVELY TO DETERMINE RENAL FUNCTION

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ABSTRACT

Introduction: Patients with rheumatoid arthritis (RA) are more likely to developed reduced kidney function over time. Presence of cardiovascular diseases (CVD) appears to play a role. Also renal dysfunction in RA found to be associated with a higher risk of cardiovascular (CV) disease independently of traditional CV risk factors. On the other hand, presence of RA in individuals with reduced kidney function may lead to an increase in morbidity from CVD development. Objective of this article is to identify the determinants of kidney function; through measuring glomerular filtration rate (GFR) in RA population.

Method: eighty RA participants, without CVD, cerebrovascular, diabetes or renal diseases were recruited. Univariate and multivariate linear regression were used to identify the determinants of GFR.

Results: The mean age of the participants was 46 ±13 years, (71 female and 9 male). The mean GFR was 136 ± 50 ml/min/1.73m^2. The factors that found to determine the GFR level in a negative linear trend were age of the participants (p< 0.001, CI: -0.021, -0.011), age at RA symptoms onset (p<0.001, CI: -0.016, -0.006), age at RA diagnosis (P<0.001, CI: -0.018, -0.008), systolic blood pressure; SBP (p=0.001, CI: -0.012, -0.0030), diastolic blood pressure; DBP (p=0.041, CI: -0.015, -0.000), body weight (p=0.008, CI: -0.010, -0.002), body mass index; BMI (p=0.033, CI: -0.033, -0.001), uric acid level (p<0.001, CI:-0.003, -0.001), erythrocytes sedimentation rate; ESR (p=0.033, CI -0.006, -0.000), c-reactive protein; CRP (p=0.034, CI: -0.006, -0.000), ferritin (p=0.007, CI: -0.003, -0.001), triglyceride; TG (p=0.008, CI -0.271, -0.042), urine microalbumin level (p=0.041, CI: -0.002, -0.000), and microalbumin creatinin ratio (p=0.008, -0.015, -0.002). Multiple model that included all the variables with a significant association with GFR in the univariate analysis showed that the GFR is determined by age, uric acid level, urine microalbumin, BMI, SBP, CRP and triglyceride level (R2=94).

Conclusion: Renal function in RA is shaped by both traditional and non-traditional CVD risk factors. Therefore, traditional and non-traditional risk factor measurements may provide a means for optimizing care of RA patients and reducing mortality related to CV and renal diseases.

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, inflammatory, disabling disease with significant excess mortality and morbidity due to cardiovascular disease (CVD) (Gabriel, 2008; Puttevils *et al*., 2014), and they are more likely to develop reduced kidney function over time. The excess CVD mortality is partly caused by renal disease and renal insufficiency (Nordin and Pedersen, 1996). On the other hand, renal dysfunction is associated with increased CV disease in RA, even after correction for traditional risk factors. Therefore, a decreased renal function helps to identify RA patients at increased risk for future CVD (van Sijl *et al*., 2010). The presence of RA per se in individual with reduced kidney function may lead to an increase in morbidity from CVD (Hickson *et al*., 2014). Subclinical renal dysfunction in RA is quite common and associates with classic cardiovascular risk factors (Boers *et al*., 1990; Daoussis *et al*., 2010). Yet renal disease in RA is usually asymptomatic and is detected only on laboratory investigations (Pathan and Joshi, 2004). Interestingly, although it has been reported that it is often difficult to differentiate between damage due to disease activity and that due to drugs used to treat RA, others found that renal dysfunction in RA is not found to be associated with past or present use of nephrotoxic medications (Daoussis *et al*., 2010). Similarly, no statistical significant association was noted between chronic kidney disease (CKD) and the use of corticosteroids, disease-modifying anti-rheumatic drugs and anti-tumor necrosis factor agents (Haroon *et al*., 2011). The presence of such a "subclinical" nephropathy would explain the

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greater sensitivity of RA patients to other renal insults, and the high prevalence of renal failure at later stages of the disease (Boers, 1990). Therefore, this paper aimed to determine which of the renal parameters, traditional and non- traditional cardiovascular risk factors play a role in the renal dysfunction, as manifested by the GFR.

MATERIALS AND METHODS

Eighty RA patients, fulfilling the American College of Rheumatology criteria for RA attending the rheumatology clinic, were recruited. Participants underwent physical examination and laboratory evaluation. Age, history of smoking ever, smoking duration and number of cigarettes consumed per day (pack year calculated), disease duration from the time of physician's diagnosis and age of onset of RA, drugs history, body mass index (BMI), urine analysis of protein, traditional and non-traditional cardiovascular risk factors, family history of RA and early cerebro-vascular events, co-morbidities and CV/cerbrovascular events were assessed.

Renal function measurements

Renal function was assessed by estimated glomerular filtration rate using the modification of diet in renal disease equation. Risk factors for renal dysfunction were recorded/measured in all participants. Exclusion criteria were: pregnancy, breastfeeding, current or long term use of prednisolone and/NSAIDs, history of myocardial infarction, angina pectoris, stroke, diabetes, hypertension and impaired renal function. The study was approved by the local Ethic Committee and participants provided written informed consent. Joints were examined for tenderness and swelling. Standing height, weight, and blood pressure were measured. Disease activity score (DAS 28) was calculated using erythrocyte sedimentation rate and C-reactive protein. BMI was calculated as Kg/m^2. A fasting blood sample was obtained for measurement of plasma glucose, insulin, total cholesterol, high density lipoprotein (HDL), triglycerides (TG), low density lipoprotein (LDL), and uric acid (UA).

Cardiovascular risk factors were defined as follows: dyslipidemia as a self reported physician diagnosis or a total cholesterol ≥ 200 mg/dl or triglycerides ≥ 150 mg/dl or LDL cholesterol ≥ 130 mg/dl or HDL cholesterol < 50 mg/dl or or use of lipid lowering agents, diabetes as a fasting glucose level ≥ 126 mg/dl (>7mmol/l) and/or oral hypoglycaemic medication or insulin used, a self reported physician diagnosis hypertension as a self reported physician diagnosis or recorded blood pressure ≥ 140/90 or use of antihypertensive medication; or use of antihypertensive medications. Current smoker if the participant smoked ≥ 1 cigarettes per day; family history of premature CV events as myocardial infarction or ischemic stroke in a first degree relative before the age of 55 years in males or before the age of 65 years in females.

Statistical analysis

A summary statistical results of basline characteristics were expressed as percentages for categorical data, and mean ± SD for continuous vaiables. GFR was logarithmically transformed to obtain normal distribution. The correlation between GFR and other variables (renal parameters, traditional and non-traditional cardiovascular risk factors) were studied using simple linear regression analysis for the continouse independent variables, and the 2-sample t-test for the 2-level categorical independent variables. To test for the independence association between GFR and the variables of interest, multiple model was built for the same dependent and independents variables. Statistical significance was accepted as p-value <0.05.

Table 1. Demographic details, RA characteristics, and laboratory values of 80 RA patients

Demographic Details	
Male:Female	9:71
Mean age (SD, yr)	46 (13)
Rheumatoid arthritis characteristics	
Disease duration, mean (SD, months)	65 (105)
Tender joint count (of 28)	6 (4)
Swollen joint count (of 28)	2 (3)
Rheumatoid factor level	64 (93)
Rheumatoid factor positive, n (%)	63 (79%)
Renal parameters and laboratory values	
GFR (ml/min/1.73m²)	136 (50)
Uric acid level	250 (84)
ESR (mm/hr)	43 (28)
CRP (mg/L, normal < 6)	20 (27)
Cholesterol (mmol/L)	4.6 (1.0)
Triglyceride (mmol/L)	1.3 (0.7)
HDL level (mmol/L)	1.3 (0.4)
LDL cholesterol (mmol/L)	2.7 (0.9)
Cardiovascular risk factors	
Body mass index (SD, kg/m²)*	29 (7.0)
Smoking, ever, n (%)	8.0 (10)
Pack year of smoking (SD)	0.6 (2)
Family history of CVD, n (%)	3.0 (3.8)
Systolic blood pressure	128 (17)
Diastolic blood pressure	76 (11)

Results are presented as mean (SD) unless indicated

RESULTS

Eighty consecutive patients with RA meeting the 1987 revised ACR criteria (Arnett *et al*., 1988), attending routine outpatient clinics at the Department of Rheumatology, were enrolled in this cross-sectional study. Basic demographics and clinical characteristics of the study population are shown in Table 1. Of the total 80 patients, 9 (11.25) were men and 71 (88.75) were women. The mean age of the participants was 46 ±13 years, with mean RA duration of 65 (105) months. 63 out of 80 participants (79%) had rheumatoid factor positive RA. Using modified MDRD formula to calculate the GFR showed that the mean GFR of the study sample is 136 ± 50 ml/min/1.73m^2. Using univariate analysis revealed a in a negative linear relationship between GFR and each of the age of the participants (p< 0.001, CI:-0.021,-0.011), age at RA symptoms onset (p<0.001, CI:-0.016, -0.006), age at RA diagnosis (P<0.001, CI:-0.018, 0.008), systolic blood pressure (p=0.001, CI: -0.012, -0.0030), diastolic blood pressure (DBP) (p=0.041, CI: -0.015, -0.000), body weight (p=0.008, CI: -0.010, -0.002), BMI (p=0.033, CI: -0.033-0.001), uric acid level (p<0.001, CI:-0.003, -0.001), ESR (p=0.033, CI -0.006, -0.000), CRP (p=0.034, CI: -0.006, -0.000), ferritin (p=0.007, CI: -0.003, -0.001), triglyceride; TG (p=0.008,CI -0.271, -0.042), urine microalbumin level (p=0.041, CI:-0.002,-0.000), and microalbumin creatinin ratio (p=0.008,-0.015,-0.002). Building a multiple model, including the entire variable with significant association with the GFR in the univariate analysis showed that the GFR is determined by age, uric acid level, urine microalbumin, BMI, SBP, CRP and triglyceride level. The adjusted R2 is 94 (Table 2).

Table 2. Univariate and multivariate linear regression analysis and 2-sample t-test of the relationship between cIMT, selected RA features, traditional and non-traditional CV risk factors and renal parameters in 80 patients with established RA

Variables	R^2	Standardized β coefficient	SE	t	p	CI
Univariate model						
Gender*			0.039		0.552	4.775, 4.933
Age	0.39	-0.016	0.002	-7.08	0.000	-0.021, -0.012
Age at RA onset	0.21	-0.010	0.002	-4.51	0.000	-0.015, -0.006
Age at RA diagnosis	0.28	-0.013	0.002	-5.47	0.000	-0.017, -0.008
History of smoking*			0.132		0.958	-0.271, 0.257
Pack year history	0.00	0.003	0.020	0.20	0.845	-0.036, 0.044
Systolic blood pressure	0.13	-0.007	0.002	-3.38	0.001	-0.012, -0.003
Diastolic blood pressure	0.05	-0.008	0.003	-2.08	0.041	-0.014, -0.000
Body weight (Kg)	0.10	-0.005	0.002	-2.72	0.008	-0.010, -0.001
Body mass index	0.13	-0.017	0.007	-2.23	0.033	-0.033, -0.001
Morning stiffness duration (minutes)	0.01	0.000	0.000	0.85	0.396	-0.000, 0.000
Number of swollen joints (28)	0.00	0.001	0.007	0.21	0.835	-0.013, 0.016
Number of tender joints (28)	0.01	-0.002	0.003	-0.78	0.436	-0.010, 0.004
RF positivity*			0.040		0.897	4.767, 4.929
RF level	0.01	-0.000	0.000	-0.63	0.529	-0.001, 0.001
ESR	0.06	-0.003	0.001	-2.17	0.033	-0.005, -0.000
CRP	0.06	-0.003	0.001	-2.15	0.034	-0.006, -0.000
Ferritin level (mcg/l)	0.14	-0.002	0.001	-2.82	0.007	-0.003, -0.001
Uric acid level (umol/l)	0.25	-0.002	0.000	-5.06	0.000	-0.002, -0.001
LDL	0.01	0.033	0.052	0.64	0.524	-0.071, 0.138
HDL	0.02	0.112	0.104	1.08	0.284	-0.096, 0.321
Cholesterol	0.00	0.016	0.040	0.40	0.688	-0.065, 0.098
Triglyceride(mmol/l)	0.10	-0.156	0.057	-2.72	0.008	-0.271, -0.041
Urine micro-albumin level (mg/l)	0.07	-0.001	0.000	-2.09	0.041	-0.002, -0.000
Microalbumin creatinine ratio	0.11	-0.009	0.003	-2.72	0.008	-0.015, -0.002
Multivariate model (R^2=0.94)						
Age		-0.020	0.002	-11.4	0.000	-0.026, -0.018
Systolic blood pressure		-0.008	0.002	5.04	0.000	0.004, 0.011
Body mass index (BMI)		-0.028	0.004	-6.90	0.000	-0.037, -0.019
TG		-0.074	0.032	2.32	0.033	0.007, 0.143
Uric acid level		-0.001	0.000	-3.48	0.003	-0.002, -0.000
Urine micro albumin level		-0.002	0.000	-5.16	0.000	-0.003, -0.001
CRP		-0.006	0.002	2.64	0.017	0.001, 0.010

Each parameter included in the univariate linear regression analysis and 2-sample t-test* is presented. Variables entered into the multivariate model are shown in italics. Adjusted R^2 of the multivariate linear regression model = 0.94

DISCUSSION

The study found a very strong negative linear relationship between GFR and variouse manifestations in RA population. It is the first cross sectional study to look at the combination of traditional, non traditional CVD risk factors and renal parameters and their role in determining the GFR level in RA populatoin; with normal kidney function and no cardio-cerebro vascular diseases, no diabetis or hypertension and with no current use of NSAIDs. We found a several factors in RA patients that are associated with GFR level in a negative linear trend, many of these factors are related to CVD disease and it's associated factors. At the same time many of the non-traditional CVD risk factors and renal parameters contributed significantly to the GFR level. The GFR of the included participants was slightly above the average. This could be attributed to the fact that in rheumatoid arthritis serum creatinine can overestimate renal function by as much as 30% and it is suggested that more sensitive methods such as measuring urinary albumin excretion and glomerular filtration rate should be used for monitoring renal function (Nordin and Pedersen, 1996). More, it has been reported that MDRD equation overestimate the true GFR with and increasing BMI (Bosma *et al*., 2004). Hence, the above average GFR in our participants could be attributed to their overweight. Daoussis and colleagues demonstrated that renal dysfunction in RA is quite common and associates with classic cardiovascular risk factors such as advanced age and dyslipidaemia, levels of SUA and the presence of extra-articular disease. Renal dysfunction was not related to other RA-related factors including disease activity and duration, disability and past or present use of nephrotoxic medications (Daoussis *et al*., 2010). Our results showed that GFR level in patient with normal kidney function is affected by the same factors, apart from the RA duration which turned to be significantly related to the GFR level in our study patients. This could be due to their recruitment of patients with reduced GFR of 90 ml/minute per $1.73m^2$, while all our patients have normal GFR. The significance association of subclinical renal damage with RA duration (in addition to age) has been reported by Geltner *et al*, and they stated that the subclinical damage is not revealed by routine laboratory tests in patients with rheumatoid arthritis (Geltner *et al*., 1992). In regards to the traditional cardiovascular risk factors the relation of hypertension to CVD onset and progression is known for ages. Hypertension is highly prevalent in patients with RA (McEntegart *et al*., 2001; Erb *et al*., 2004), and target organ damage is highly common in RA and associates independently with hypertension and arterial stiffness (Panoulas *et al*., 2010). In our sample both systolic and diastolic blood pressure showed a significant correlation to GFR in the univariate analysis while the systolic blood pressure maintained this relation in the multivariate analysis. Dyslipidemia is the other well known traditional CVD risk factor. Our study revealed an association between GFR level and TG, and this relation maintained in the multivariate analysis. Other dyslipidemic pattern did not show a significant correlation. TG rich lipoprotein such as very low density lipoprotein (vLDL) and intermediate density lipoprotein (IDL) can cause glomerulosclerosis (Joles *et al*., 1995), and promote the proliferation of mesangial cells (Nishida *et al*., 1999). More, increased concentration of TG-rich, but not cholesterol rich, apolipoprotein B (apo B) containing lipoprotein was

shown to be associated with a rapid loss of renal function (Samuelsson *et al*., 1998). High TG in women (which constitute the majority of our sample) found to be correlated with a decrease in GFR, but not total cholesterol nor LDL cholesterol (Tozawa *et al*., 2002). In another study, it has been found that TG levels are closely associated with a mildly reduced GFR; in a dose-dependent manner, in subjects with normal serum lipid levels (Wang *et al*., 2010; Ji *et al*., 2013). Also, the secretion of interlukin-6, platelet derived growth factor, transforming growth factor-B, and tumor necrosis factor-alfa by mesangial cells were enhanced when mesangial cells were exposed to lipids (Keane *et al*., 1993).

Overweight and obesity are well established risk factors for the development of renal function loss (Kwakernaak *et al*., 2013). The association of BMI with GR showed a graded decrease in GFR with increasing BMI, starting at a BMI of 22.0 kg/m^2 , and those with a BMI>30 kg/m^2 are more likely to develop GFR <60 ml/min/1.73m^2 (Hickson *et al*., 2014). Upper normal weight and overweight or obese individuals showed a mildly reduced GFR (Kwakernaak *et al*., 2013). Several factors contribute to the adverse renal effect of weight excess. Overweight subjects have an increased risk of developing hypertension, dyslipidemia, insulin resistance/diebetis mellitus and cardiovascular complications, all of which promote chronic kidney disease (CKD) (Mokdad *et al*., 2003). However, even in the absence of these risks, obesity itself is associated with the development of CKD and accelerates its progression (Ejerblad *et al*., 2006; Gelber *et al*., 2005). Other mechanisms by which obesity predispose to kidney disease is its association with renal hyperfiltration (Guijarro *et al*., 1996). Thus, BMI is significantly correlated with microalbuminuria in a population based study (Kasiske, 1986). Non-traditional risk factors such as inflammatory markers are reported to play a central role in the atherosclerosis process (Bennett *et al*., 2005; Fosslien, 2005). On the other hand, an elevation in the inflammatory marker ESR was associated with GFR <60 ml/min/1.73 m^2. On the other hand, the presence of CVD is associated with a nearly 2-fold increased risk of GFR <60 (Hickson *et al*., 2014). CRP is another is another inflammatory marker and had been consider as independent CVD risk factor (Lagrand *et al*., 1999). The third inflammatory marker that we looked at its relation to the GFR in our study sample is the ferritin. Ferritin is a high molecular weight protein which reflects body iron stores, but may also rise in the case of an acute phase response (Branten *et al*., 2004). However, serum ferritin level may increase disproportionately to iron stores in inflammatory disease such as RA (Palermo *et al*., 1986). There is no study looked at the level of ferritin level and GFR in RA patients. Our finding of ferritin correlation to the GFR level is in line with the association of other acute phase reactants (CRP and ESR) with the GFR.

Among renal parameters we found that microalbuminuria is associated with the GFR level. Microalbuminuria is significantly increased in patients with rheumatoid arthritis compared to control. And, there is increasing evidence that reumatoid arthritis per se can cause subclinical renal dysfunction with microalbuminuria (Nordin and Pedersen, 1996). Presence of microalbuminuria significantly correlated to the median duration of RA and to C-reactive protein as a marker for disease activity. The measurement of microalbuminuria represents a simple and sensitive test to detect subclinical renal damage and may be a sensitive indicator of disease activity in patients with rheumatoid arthritis. Therefore, it has been suggested to use microalbumin level in the monitoring of patients with rheumatoid arthritis to detect early subclinical renal dysfunction (Nordin and Pedersen, 1996). Uric acid is another renal parameter that we found to be correlated with the GFR level. Uric acid is a strong correlate of renal dysfunction in RA (Daoussis *et al*., 2009), even in the absence of crystal deposition (Nakagawa *et al*., 2006). Recent evidence suggest that UA may not be just an innocent bystander but may be an active player in the pathogenesis of renal disease (Kanellis *et al*., 2004; Feig *et al*., 2006), by causing endothelial dysfunction (Khosla *et al*., 2005), intrarenal vascular disease (Sanchez-Lozada *et al*., 2005) and renal impairment (Johnson *et al*., 2005). Additionally, in RA patients UA had been found to be an independent predictor of hypertension (Panoulas *et al*., 2007) and cardiovascular disease (CVD) (Panoulas *et al*., 2007). Daoussis *et al* found that irrespective of the presence of hyper or normo-uricaemia, uric acid was the strongest independent predictor of GFR in patients with RA, even after adjustments for most of the potential confounding factors. But contrary to our study, the association was not present in patients with normal renal function (Daoussis *et al*., 2009). This might be related to our completely different sample in terms of lifestyle and genetic predisposition. The primary strength of this study is that we were able to perform a comprehensive review of all the RA characteristics, CVD risk factors, and renal parameters, which allowed for more accurate assessment. We had the opportunity to collect existing data related to most for the above potential links and made all of required adjustments in the multivariable analysis. Despite that some studies have suggested that use of estimating equations such as the MDRD; which we used to estimate kidney function of our participants, may underestimate kidney function in patients with RA (Anders *et al*., 2002). Others found that measuring GFR from predictive equations are generally accurate and have been validated in very large cohorts (Richardson, 2006). Specifically with respect to RA patients, predictive equations have shown very good correlation with direct GFR measurements, despite the initial concerns that muscle wasting, a common feature of RA, could lead to overestimation of GFR (Anders *et al*., 2002; Boers *et al*., 1994).

Our study has some potential limitation; such as missing some of the residual confounding that were not included in the study. For example, socioeconomic status, which has been linked to renal dysfunction (Peralta *et al*., 2006), RA (Liao *et al*., 2009), and CVD (Clark *et al*., 2009), was not assessed. More prospective studies are needed to gain more conclusive insight to observe the outcomes of managing these factors that contribute to the GFR level in RA population and its impact on CVD.

Conclusion

This study shows that A combination of RA disease characteristics, CVD-associated factor, and kidney function associated factors appear to play a role in reduced kidney function among RA population" . Due to increase of kidney dysfunction among RA it might be important to follow therapeutic strategies that modify traditional and nontraditional risk factors for CVD, with consistent kidney function monitoring. This strategy may minimize the risk of reduced kidney function and subsequent complications, including CVD and death, in RA population. Therefore, a multidisciplinary team approach managament strategies by rheumatologist,

nephrologist, cardiologist and other paramedical staff to provide the optimal care for RA patients.

Abbreviations

CRP	C-reactive protein
CV	Cardiovascular
CVD	Cardiovascular disease
ESR	Erythrocyte sedimentation rate
GFR	Glomerular filtration rate
NSAIDS	Non-steroidal Anti-Inflammatory drugs
RA	Rheumatoid Arthritis
RF	Rheumatoid factor
SUA	Serum uric acid

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

HS wrote the manuscript and compiled the figures. AI edited the manuscript. All authors analyzed and interpreted the patients' data. All authors read and approved the final manuscript.

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