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Original Article

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Predicting Chronic Kidney Disease Progression from Cardiac Fibrosis: An Interplay Between Two Major Organ Systems

Sidar Copur[1], Haydar Can Dokuyan[1], Terman Gumus[2], Ecem Kalemoglu[3], Nuri Baris Hasbal[4], Mehmet Kanbay[4]

[1]Department of Internal Medicine, Koç University School of Medicine, İstanbul, Türkiye
[2]Department of Radiology, Koç University School of Medicine, İstanbul, Türkiye
[3]Department of Internal Medicine, Koç University School of Medicine, İstanbul, Türkiye
[4]Division of Nephrology, Department of Internal Medicine, Koç University School of Medicine, İstanbul, Türkiye

ABSTRACT

Objective: Cardiovascular disease and chronic kidney disease are two major medical conditions leading to significant morbidity, mortality, and medical spending globally; nevertheless, the exact underlying pathophysiological background linking those two conditions is missing without known predictive variables.
Methods: We have performed a retrospective cohort study in a tertiary university hospital on 12 patients in order to investigate the association between fibrosis score on cardiac magnetic resonance imaging study and estimated glomerular filtration rate over a 24-month follow-up period. We have referred to fibrosis scores below 1050 as no fibrosis, fibrosis scores between 1050 and 1100 as mild-to-moderate fibrosis, and scores above 1100 as severe fibrosis on T1-weighted imaging.
Results: Twelve patients, 9 males and 3 females, with a mean age of 49.3 have been included in this cohort study. We have demonstrated that T1-weighted magnetic resonance imaging global fibrosis score, basal segment fibrosis score, and septal fibrosis score have been negatively associated with baseline and follow-up estimated glomerular filtration rate measurements while only T1-weighted mid-segment fibrosis score has been linked to delta estimated glomerular filtration rate. Additionally, we have demonstrated that the T1-weighted cardiac fibrosis score has been linked to serum C-reactive protein level.
Conclusion: We have demonstrated the association between T1-weighted cardiac magnetic resonance imaging fibrosis scores and kidney functions in our cohort study. Our study is significant by being the first clinical study investigating such an association. Nevertheless, there is a clear need for future large-scale randomized clinical trials in order to better understand the link between cardiac fibrosis and kidney functions.
Keywords: Clinical nephrology, cardiac fibrosis, cardiac magnetic resonance, chronic kidney disease

Corresponding author: Nuri Baris Hasbal ✉ nbhasbal@gmail.com

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INTRODUCTION

Chronic kidney disease (CKD) serves as a strong risk factor for the development of cardiovascular disease (CVD) as well as contributing to its progression and development of associated morbidity factors while vice versa is also applicable.[1,2] Such association between acute or chronic CVDs and kidney diseases is referred to as cardiorenal syndrome with 5 defined types.[3] Multiple underlying pathological events including pro-inflammatory response, fibrosis, oxidative stress, apoptosis, and epigenetic and immunological alterations have been implicated in the mechanism of such crosstalk; nevertheless, the exact underlying mechanism is widely unknown, requiring further studies.[4-6] Irrespective of the triggering event and complex mechanisms mediating the damage, the result in both CKD and CVD is fibrosis. Cardiac fibrosis may be assessed via few modalities including cardiac magnetic resonance imaging (MRI), single photon emission computed tomography, positron emission tomography, or peripheral blood matrix metalloproteinase type 1 to tissue inhibitor of metalloproteinase type 1 or carboxyl-terminal pro-peptide of

pro-collagen type I ratio.[7,8] However, no clinical study has yet investigated the potential association between the degrees of cardiac fibrosis assessed on either methodology on kidney functions despite significant interplay between two organ systems.

Cardiac fibrosis refers to the accumulation of type I collagen molecules at the extracellular matrix mediated via activation of cardiac fibroblasts and their differentiation into myofibroblasts, leading to extracellular matrix stiffness and disruption of the cardiac function.[7] Three major types of cardiac fibrosis have been described as reactive interstitial fibrosis referring to extracellular matrix deposition without loss of cardiac myocytes as seen in cardiomyopathies, infiltrative interstitial fibrosis referring to the accumulation of mainly glycolipids as seen in storage disorders, and replacement fibrosis that is seen after considerable damage to cardiac muscle tissue as seen in myocardial infarction or myocarditis.[7,9]

With this background in mind, we aimed to identify and analyze the effect of quantitative analysis of cardiac fibrosis via MRI technique on decline in kidney function and C-reactive protein level.

METHODS

Study Population

Our retrospective cohort study included all patients undergoing cardiac MRI study between January 2018 and December 2020 in a tertiary care university hospital. Participants with baseline estimated glomerular filtration rate (eGFR) at or below 30 mL/min/1.73 m^2 had been excluded from the study. The ethical approval for the conduction of the study has been granted by the Ethical Committee of Human Research, Koç University on December 5, 2022, with the number of 2022.432.IRB1.158.

Data Collection and Definition

The electronic database of the tertiary care university hospital had been utilized to access the demographic data, laboratory results, follow-up clinical visits, and MRI scans. The MRI scans have been blindly assessed by a radiology specialist experienced in the field of cardiac imaging. Gadolinium-based contrast material had been employed in the MRI scans while cardiac fibrosis had been assessed on T1-weighted imaging.[10] The patients were categorized into 3 categories based on their fibrosis score. The fibrosis scores equal to and greater than 1100 are defined as severe fibrosis, the fibrosis score less than 1050 is defined as no fibrosis, and the score between 1100 and 1050 is defined as mild to moderate fibrosis.[11,12] There were 4 patients in the severe fibrosis group, 2 patients in the mild to moderate fibrosis group, and 6 patients in the no fibrosis group. The patients' baseline (date of the MRI scan), 6th month, 12th month, and 24th month of the eGFR and C-reactive protein (CRP) levels were evaluated. Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)-EPI equation was used to calculate eGFR.[13]

Statistics

Statistical analysis was performed using Statistical Package for the Social Sciences 16.0 (SPSS Inc.; Chicago, IL, USA). Data are shown as mean ± SD. Data were checked for normality. Correlation analysis was done by Spearman or Pearson test where appropriate.

RESULTS

Twelve patients, 9 males and 3 females, with a mean age of 49.3 (range: 17-86 years, SD: 19.11 years) have been included in our retrospective cohort study. Among the 12 included participants, 3 participants are smokers, 1 participant has a known diagnosis of diabetes mellitus, 4 have a diagnosis of hypertension, and 2 have the diagnosis of coronary artery disease (Table 1). The mean ejection fraction that has been assessed via transthoracic echocardiography via the same operator is 56.4% (SD: 10.9%) while the mean serum C-reactive protein level is 4 mg/L. The mean baseline eGFR is 107.91 ± 17.93 mL/min/1.73 m^2. Baseline characteristics including the demographic data and medical comorbidities are shown in Table 1. Additionally, detailed data regarding the fibrosis score on T1-weighted MRI are included in Table 1. None of the patients were using SGLT2 inhibitors.

Baseline serum CRP level is significantly correlated with T1-weighted MRI fibrosis score at the global score (r = 0.825, P = .001), basal segment (r = 0.636, P = .026), mid-segment (r = 0.792, P = .002), and septal compartment (r = 0.669, P = .017). The correlations between CRP and MRI-T1 mappings are shown in Table 2. Nevertheless, the baseline ejection fraction assessed via transthoracic echocardiography or body mass index has not been correlated with T1-weighted MRI fibrosis score at any segment in a statistically significant manner.

Baseline eGFR has been negatively correlated with T1-weighted MRI fibrosis score at global score (r = −0.597, P = .020), basal segment (r = −0.694, P = .006), and septal compartment (r = −0.529, P = .038) but not with T1-weighted MRI fibrosis score at mid-segment (P = .306). Estimated glomerular filtration rate

MAIN POINTS

- This is the first clinical study to investigate the potential association between the degrees of cardiac fibrosis assessed on either methodology on kidney functions despite significant interplay between the heart and the kidneys.
- T1-weighted cardiac fibrosis score has been linked to serum C-reactive protein level as an inflammatory marker and estimated glomerular filtration rate (eGFR) at all time periods except T1-weighted mid-segment fibrosis score.
- T1-weighted mid-segment fibrosis score is correlated with eGFR change over a 2-year follow-up period.
- Large-scale randomized and double-blind clinical trials are needed to fully understand and better establish the association between cardiac fibrosis and kidney functions with a potential of cardiac fibrosis being used as a predictor of future kidney functional deterioration.

Table 1. Baseline Characteristics Including the Demographic Data and Medical Comorbidities of Cases

	Sex	Age	BMI (kg/m^2)	Smoking	DM	HT	HL	CAD	RAS Blocker	EF (%)	CRP (mg/L)	eGFR (mL/min/1.73m^2)	MRI T1 Mapping Score of Heart			
													Global	Base	Middle	Septal
No inflammation or fibrosis according to T1 mapping MRI score																
Case 1	M	27	31.2	N	N	N	N	N	Y	54	2.4	135	997	1060	1049	1024
Case 2	M	43	24.6	N	N	N	N	N	N	59	2.3	92	987	1026	1018	937
Case 3	F	65	29.5	N	N	Y	N	N	Y	52	4.2	110	1035	1043	1029	1023
Case 4	F	42	28.2	N	N	N	N	N	Y	64	1.0	122	1021	1009	1028	1017
Case 5	F	55	22.1	Y	N	N	Y	N	N	64	0.4	105	1017	1047	1001	988
Case 6	M	18	27.5	N	N	N	N	N	N	56	1.3	120	1016	1008	1018	1014
Mild or moderate inflammation or fibrosis according to T1 mapping MRI score																
Case 7	M	43	26.8	Y	N	Y	N	N	N	43	4.8	120	1084	1081	1099	1063
Case 8	M	39	30.5	N	N	N	N	N	Y	40	5.2	124	1060	1000	1167	965
Severe inflammation or fibrosis according to T1 mapping MRI score																
Case 9	M	86	27.6	N	N	Y	N	Y	Y	73	5.6	70	1177	1281	1115	1190
Case 10	M	43	26.9	Y	N	N	N	N	N	67	6.7	106	1126	1185	1072	1129
Case 11	M	69	24.5	N	N	N	N	N	Y	40	7.2	100	1126	1150	1118	1103
Case 12	M	63	28.3	N	Y	Y	Y	Y	Y	65	7.0	91	1106	1106	1109	1102

BMI, body mass index; CAD, coronary artery disease; CRP, C-reactive protein; DM, diabetes mellitus; EF, ejection fraction; eGFR, estimated glomerular filtration rate; F, female; HL, hyperlipidemia; HT, hypertension; M, male; MRI T1, magnetic resonance imaging T1 mapping; N, no; RAS, renin-angiotensin-aldosterone system; Y, yes.

Table 2. Correlations Between C-Reactive Protein, Magnetic Resonance Imaging T1 Mapping, and Estimated Glomerular Filtration Rate and Delta Change in Estimated Glomerular Filtration Rate at 6 Months, 12 Months, and 24 Months

		MRI-T1 Global	MRI-T1 Basal	MRI-T1 MID	MRI-T1 Septal
Baseline CRP	*R*	0.825	0.636	0.792	0.669
	P	*.001*	*.026*	*.002*	*.017*
Baseline eGFR	*R*	−0.597	−0.694	−0.163	−0.529
	P	*.020*	*.006*	.306	*.038*
eGFR at 6 months	*R*	−0.666	−0.612	−0.349	−0.533
	P	*.009*	*.017*	.133	*.037*
eGFR at 12 months	*R*	−0.709	−0.654	−0.390	−0.572
	P	*.005*	*.010*	.105	*.026*
eGFR at 24 months	*R*	−0.727	−0.680	−0.424	−0.582
	P	*.004*	*.007*	.085	*.024*
Delta GFR at 12 months	*R*	0.381	0.036	0.572	0.203
	P	.111	.455	*.026*	.264
Delta GFR at 24 months	*R*	0.457	0.170	0.609	0.271
	P	.068	.289	*.018*	.197

CRP, C-reactive protein; Delta GFR, eGFR difference; eGFR, estimated glomerular filtration rate; MRI T1, magnetic resonance imaging T1 mapping.

trajectories are shown in Figure 1. The T1-weighted MRI global fibrosis score has been correlated with eGFR at follow-up of the participants at month 6 (r = −0.666, P = .009), month 12 (r = −0.709, P = .005), and month 24 (r = −0.727, P = .004). Similarly, T1-weighted MRI basal segment fibrosis score and septal fibrosis score have been correlated with eGFR at follow-up period of the participants at month 6 (r = −0.612 and −0.533; P = .017 and .037, respectively), month 12 (r = −0.654 and −0.572; P = .010 and .026, respectively), and month 24 (r = −0.680 and −0.582; P = .007 and .024, respectively). However, delta eGFR at either year 1 or year 2 has not been associated with T1-weighted MRI cardiac global fibrosis score or basal segment fibrosis score or septal fibrosis score at a statistically significant degree. The correlations between eGFRs and MRI-T1 mappings are shown in Table 2.

T1-weighted mid-segment fibrosis score is statistically significantly associated with delta eGFR at year 1 (r = 0.572, P = .026) and at year 2 (r = 0.609, P = .018).

DISCUSSION

In this retrospective cohort study, we analyzed the association between cardiac fibrosis score at a global scale or segmentally and serum CRP or eGFR change over a follow-up period of 2 years. We have demonstrated that the T1-weighted cardiac fibrosis score has been linked to serum CRP level as an inflammatory marker and eGFR at all time periods except the T1-weighted mid-segment fibrosis score. On the other hand, the T1-weighted mid-segment fibrosis score is the only statistically significantly correlated with eGFR change over a 2-year follow-up period.

Fibrotic cardiac tissue expresses higher levels of angiotensin-2 which is involved in vasoconstriction and blood pressure

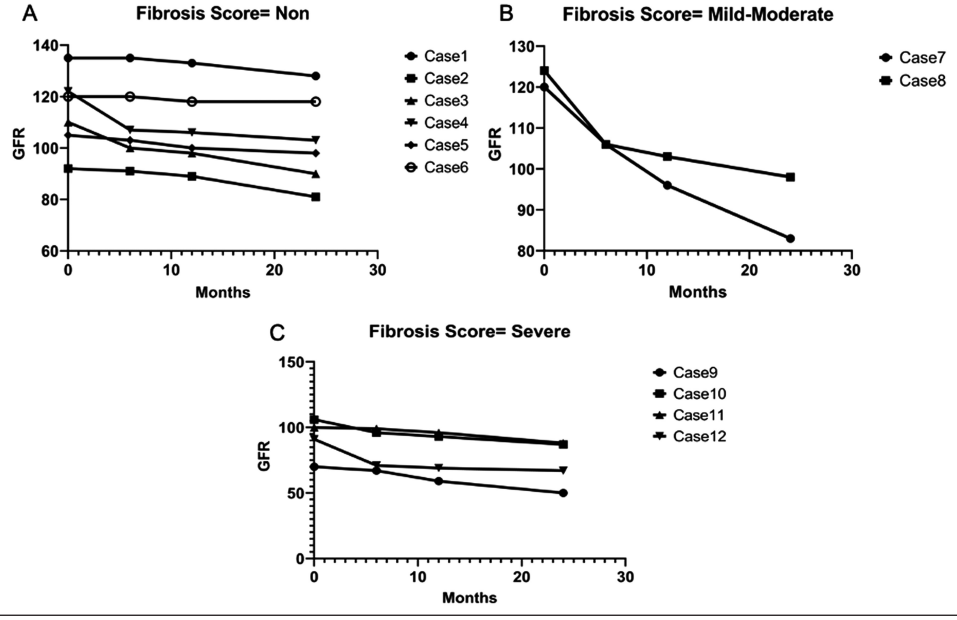

Figure 1. (A) Estimated glomerular filtration rate at baseline, 6th, 12th, and 24th months in patients without inflammation or fibrosis according to magnetic resonance imaging of the heart. (B) Estimated glomerular filtration rate at baseline and 6th, 12th, and 24th months in patients with mild to moderate inflammation or fibrosis according to magnetic resonance imaging of the heart. (C) Estimated glomerular filtration rate at baseline and 6th, 12th, and 24th months in patients with severe inflammation or fibrosis according to magnetic resonance imaging of the heart.

elevation while the levels of primary mediators of angiotensin-2, namely renin and angiotensin-converting enzyme, are elevated as well.[14,15] Angiotensin-2 mediates its pro-fibrotic effects on cardiac tissue via transforming growth factor-beta mediated via type 1 angiotensin receptors and release of pro-inflammatory cytokines such as interleukin-6.[16-18] Moreover, aldosterone secreted from adrenal cortex have pro-fibrotic effects on cardiac tissue mediated via regulation of matrix metalloproteases and transforming growth factor-beta, upregulation of pro-inflammatory cytokines such as tumor necrosis factor-α via nuclear factor kappa B activation.[19] Additionally, activation of β2-adrenergic receptors may lead to cardiac fibrosis which is mediated via the p38 mitogen-activated protein kinase signaling pathway leading to secretion of growth factors and cytokines.[19] Endothelin-1 and platelet-derived growth factor are the 2 other major mediators of cardiac fibrosis.[19-22] Similar pathophysiological mechanisms and similar molecules including pro-inflammatory cytokines such as interleukins and tumor necrosis factor-α or pro-fibrotic cytokines such as transforming growth factor-beta and platelet-derived growth factor are involved in the pathophysiology of CKD. A possible association between heart fibrosis and eGFR decline is shown in Figure 2. As demonstrated in our study population, cardiac fibrosis has been associated with serum inflammatory markers such as CRP. However, we have not measured the serum levels of other pro-inflammatory or pro-fibrotic cytokines which may be considered as a major limitation of our study and may shed light on future studies in this field.

Another crucial aspect of the similar pathophysiological basis between cardiac and kidney pathology in such circumstances is the potential therapeutic perspective. In a study conducted on streptozotocin-treated rats, treatment with spironolactone, an aldosterone receptor antagonist, and pirfenidone, an inhibitor of transforming growth factor-beta 1-mediated signaling pathway, reverses cardiac and kidney fibrosis, leading to a decline in diastolic stiffness without any change in cardiac or kidney functions.[23] In another study conducted on rat models of cardiorenal syndrome with preserved ejection fraction, treatment with telmisartan, an angiotensin receptor blocker, leads to improvement in left ventricular diastolic function and reversal of cardiac fibrosis potentially via renin–angiotensin–al dosterone system modulation.[24] However, there is a clear need for future clinical trials conducted on human subjects assessing the effects of such therapeutic agents on cardiac and/or kidney fibrosis assessed via imaging studies or histopathological examinations.

Our study is significant by being the first clinical study investigating the association between cardiac fibrosis score and changes in kidney function over a follow-up period. Nevertheless, our study is not with considerable limitations, including the low number of participants, heterogeneity of the study population in terms of age and comorbidities, its design as a retrospective and non-blind clinical study, use of serum creatinine as the only indicator of eGFR, and lack of

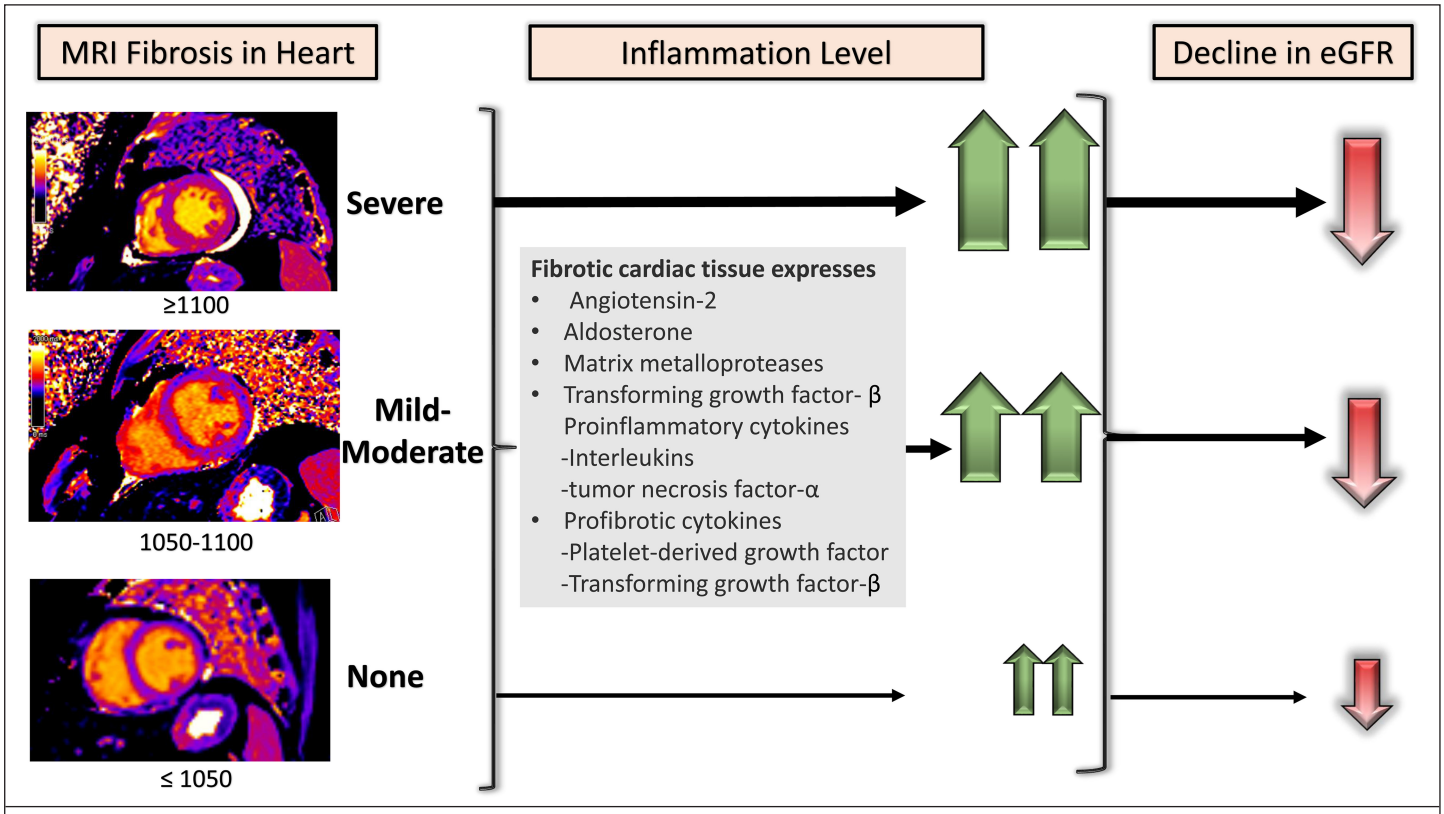

Figure 2. A possible association between heart fibrosis and eGFR decline.

assessment of albuminuria or proteinuria as a marker of kidney function.

CONCLUSION

Cardiac MRI findings may be associated with inflammation and eGFR decline and, therefore, may be used for predicting the outcome of the patients. Large-scale randomized and double-blind clinical trials are needed to fully understand and better establish the association between cardiac fibrosis and kidney functions with a potential of cardiac fibrosis being used as a predictor of future kidney functional deterioration.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Koç University (Approval No: 2022.432.IRB1.158, Date: December 5, 2022).

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