Prognostic value of hepatocyte growth factor in dialysis patients with heart failure

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Objective
The aim of this study was to evaluate hepatocyte growth factor (HGF) as a predictor of short-term mortality in patients with chronic renal failure (CRF) and congestive heart failure (CHF) and study its relation to heart failure severity.
Design
The work was designed as a prospective case–control study.
Patients and methods
The study included 52 CRF patients with heart failure: 41 patients were on regular dialysis (group 1) and 11 patients were on conservative treatment (group 2). They were compared with 11 CHF patients with normal renal function (group 3), 10 CRF patients on regular dialysis and normal cardiac function (group 4), and 15 healthy controls (group 5). Initial baseline characteristics, New York Heart Association Classification of Heart Failure, serum HGF, and cardiac functions by echocardiography were determined. All groups were prospectively followed up for 6 months in order to determine mortality.
Results
The mean HGF level in group 1 (1.3±0.96 ng/ml), group 2 (0.65±0.25 ng/ml), group 3 (1.34±0.61 ng/ml), and group 4 (1.67±0.89 ng/ml) was significantly higher than the level in the control group (0.25±0.24 ng/ml) ($P<0.0001$). Post-hoc test showed a nonsignificant difference in HGF concentration between group 1 and other groups. Patients with a moderate degree of CHF in group 1 had significantly higher HGF than those with a mild degree (1.7±1 vs. 0.78±0.6 ng/ml) ($P=0.002$). In group 1, bivariate correlation analysis showed a positive correlation of HGF and left atrium diameter ($r=0.34$, $P=0.03$) and a negative correlation with ejection fraction ($r=-0.45$, $P=0.0003$). No statistically significant difference was found in HGF levels between patients who survived (1.27±0.94 ng/ml) and those who did not survive (1.26±0.75 ng/ml) in group 1 ($P=0.9$).
Conclusion
In this study, serum HGF was found to be a good marker of severity of heart failure in CRF patients undergoing dialysis. However, it was not associated with mortality.

Keywords:
chronic renal failure, heart failure, hepatocyte growth factor

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Introduction

Mortality among end-stage renal disease and dialysis patients is still high and is strongly related to cardiovascular events [1]. Independently from traditional risk factors, chronic renal failure (CRF) doubles the risk for heart failure [2]. Biomarkers for early prediction of increased risk for mortality and quantification of heart failure severity in CRF patients will allow the creation of an appropriate management plan and will improve the clinical outcome. However, their value in CRF patients is less evident as renal impairment per se could lead to elevation of their levels.

Hepatocyte growth factor (HGF) is a pleiotropic protein that has essential functions in tissue repair, angiogenesis, and antiapoptosis. In the kidney, HGF has a pivotal role in tubular regeneration as it stimulates epithelial proliferation and decreases tubular damage [3]. Also, HGF is associated with myocardial function both in physiological and pathological states [4]. Although HGF has important cardioprotective effects, different studies link increased HGF levels with increased morbidity and mortality [5,6].

The aim of the present study was to investigate HGF as a predictor of 6 months mortality in hemodialysis patients

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with congestive heart failure (CHF) and its relation to heart failure severity as assessed by echocardiography.

Patients and methods

This prospective case–control study was conducted from August 2014 to August 2015. The participants were recruited from the dialysis unit of a tertiary care hospital. The study was approved by the Institutional Ethics Committee of the School of Medicine, Cairo University, Egypt, and all patients provided informed consent to participate in this study.

The study included 73 patients comprising 41 patients with CHF and CRF on dialysis (group 1), 11 patients with renal impairment on conservative treatment (group 2), 11 patients with CHF and normal renal function (group 3), and 10 dialysis patients with a normal echocardiogram (group 4). Fifteen age-matched and sex-matched healthy individuals were selected as controls (group 5).

Exclusion criteria included patients with hepatitis, hepatic malignancy, interstitial lung disease, pancreatitis, pure diastolic heart failure, or heparin intake.

All participants were subjected to a thorough clinical evaluation, including determination of heart failure severity based on New York Heart Association classification, echocardiography, laboratory investigations included blood urea, serum creatinine, estimated glomerular filtration rate (eGFR), alanine aminotransferase, aspartate aminotransferase, anti-hepatitis C virus antibodies, hepatitis B virus surface antigen, and serum HGF. They were followed up for 6 months to determine the mortality rate.

Hepatocyte growth factor sample collection and assay principle

Blood samples were collected in EDTA tubes before the dialysis session and centrifuged at 2800 rpm for 10 min. Serum was collected, frozen, and stored at −20°C. HGF was determined by ELISA (Roche Diagnostics, Mannheim, Germany). The test was performed according to the manufacturer's instructions.

Echocardiography

Echocardiographic studies were performed by a cardiologist who was fully trained in echocardiography. Left ventricular ejection fraction (LVEF) was assessed using the biplane Simpson method or by M-mode method using left ventricular end-systole and end-diastole dimension or was visually estimated by a method that was documented to have accuracy comparable to that of other methods in assessing LVEF. Left ventricular function was considered normal if LVEF was more than 55%, mildly abnormal if LVEF was 45–54%, and moderately and severely abnormal if LVEF was 30–44% and less than 30%, respectively [7].

Statistical analyses

Precoded data were entered into the computer to be statistically analyzed using the statistical package of social science software program, version 18 (SPSS Inc., Chicago, Illinois, USA). The data were summarized using mean and SD for quantitative variables and using frequency and percentage for qualitative variables. Analysis of variance with post-hoc Bonferroni's test was used to compare quantitative normally distributed variables, whereas the non-parametric Mann–Whitney *U*-test was used for quantitative variables that were not normally distributed. *P* values of 0.05 or less were considered significant. Bivariate correlation coefficient analysis was used to correlate different parameters and HGF.

Results

Baseline demographic, laboratory, and echocardiographic data of the study population.

There was no significant difference between the studied groups as regards age (P=0.1), sex (P=0.09), or presence of diabetes (P=0.5). The mean dialysis duration was 41.2±26 months in group 1 and 38.4±13.3 in group 4 (P=0.7) (Table 1).

Hepatocyte growth factor levels among the different groups

One-way analysis of variance showed that HGF level was significantly lower in normal persons in comparison with all other studied groups (P<0.0001) (Fig. 1). Post-hoc analysis revealed no significant difference between HGF level in group 1 and its level in group 2 (P=0.184) group 3(P=1), and group 4 (P=0.784).

Comparison of hepatocyte growth factor levels of patients who survived and those who died

There was no significant difference in HGF levels between patients who survived and those who died in any of the studied groups (Table 2).

Relation of hepatocyte growth factor and degree of heart failure severity

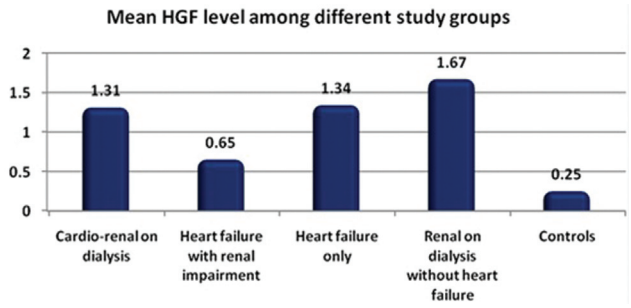
Patients with moderate heart failure in group 1 had significantly higher HGF level than those with mild CHF in the same group (1.7±1 vs. 0.78±0.6, P=0.002). Patients with moderate CHF in group 1 had significantly higher HGF level compared with those

Table 1 Baseline characteristics of the studied groups

Variables	Group 1 (*n*=41)	Group 2 (*n*=11)	Group 3 (*n*=11)	Group 4 (*n*=10)	Group 5 (*n*=15)
Age (years)	52.5±9.2	58.4±5.9	58.8±5.9	52.5±13.7	55.3±6
Male/female (*n*)	17/24	8/3	4/7	8/2	8/7
Diabetes (%)	39	63.6	36.4	60	0
Urea (mg/dl)	96.5±23.3	73.6±15.5	45.5±9.3	75.7±6.5	35.5±5.7
Creatinine (mg/dl)	7.6±1.3	2.6±0.36	1.3±0.21	7.1±1.9	0.98±0.17
eGFR (ml/min/1.73 m^2)	10.5±2.6	31.1±8.6	72±9.2	12.2±5.1	93.7±2.6
ALT (IU/l)	26.4±5.3	26.7±7.2	31.6±4	30.8±3.5	23.1±4.5
LVEF (%)	43±0.04	39±0.06	38±0.06	59±0.03	62±0.04
LVED (cm)	5.9±0.41	6±0.35	6.2±0.67	5.5±0.75	4.8±0.46
LVESD (cm)	4.4±0.48	4.8±0.58	5.1±0.76	3.7±0.58	3.1±0.36
LA diameter (cm)	4.2±0.3	4.2±0.2	4.4±0.47	4.3±0.72	4±0.41
HGF (ng/ml)	1.3±0.96	0.65±0.25	1.3±0.61	1.7±0.9	0.25±0.24

ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; HGF, hepatocyte growth factor; LA, left atrium; LVED, left ventricular end-diastolic dimension LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension.

Figure 1



Mean hepatocyte growth factor (HGF) among different groups. HGF level was significantly lower in normal persons in comparison with all other studied groups. In cardiorenal patients on dialysis (group 1) HGF level was significantly higher than the level in heart failure patients with renal impairment on conservative treatment (group 2) and heart failure patients with normal renal function (group 3) ($P<0.0001$)

Table 2 Hepatocyte growth factor level in patients who survived and those who did not in different groups

Groups	HGF		*P*-value
	N	Mean±SD	
All groups			
Died	26	1.26±0.75	0.9
Survived	47	1.27±0.94	
Group 1			
Died	14	1.5±0.77	0.4
Survived	27	1.2±1.1	
Group 2			
Died	8	0.67±0.29	0.6
Survived	3	0.58±0.04	
Group 3			
Died	4	1.6±0.74	0.3
Survived	7	1.2±0.53	

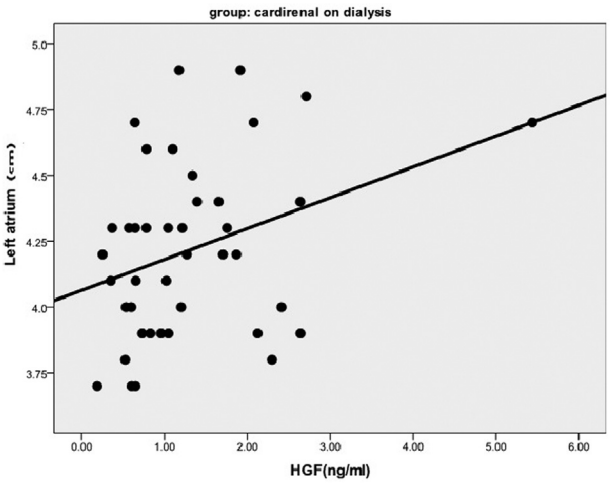
HGF, hepatocyte growth factor.

with moderate CHF in groups 2 and 3 (1.7±1 vs. 1.03±0.6, P=0.03). There was no statistically significant difference in HGF level between patients with mild CHF in group 1 and those in groups 2 and 3 (0.78±0.6 vs. 0.63±0.07, P=0.6).

Correlations between hepatocyte growth factor and different parameters

Bivariate correlation coefficient analysis in group 1 showed significant positive correlation between HGF and LA diameter (r=0.34, P=0.03) (Fig. 2), but negative correlation with LVEF% (r=–0.45, P=0.003) (Fig. 3). None of the echocardiographic parameters correlated with HGF in groups 2, 3, and 4. There was significant positive correlation of HGF and creatinine in group 2 (r=0.6, P=0.05) and group 3 (r=0.7, P=0.004) (Table 3).

Figure 2



Correlation between hepatocyte growth factor (HGF) and left atrium diameter in cardiorenal patients on dialysis. Bivariate correlation analysis showed positive correlation between HGF level and left atrium diameter in cardiorenal patients on dialysis (group 1) (r=0.34; P=0.03)

Discussion

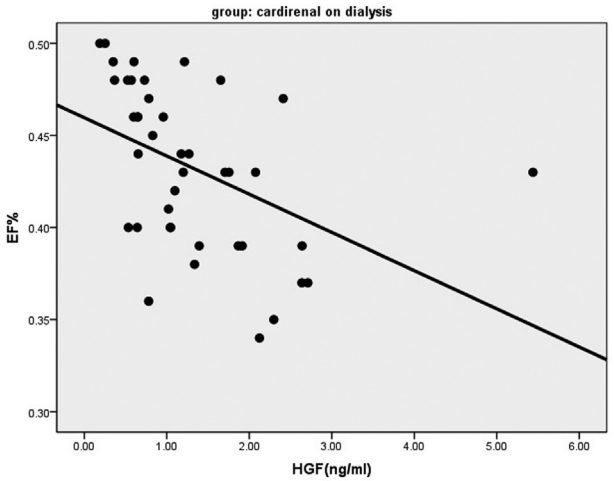
In the present study, HGF was associated with more severe degree of CHF and it was negatively correlated

with ejection fraction in hemodialysis patients with CHF. Previous studies reported the strong association between increased HGF level and severity of heart failure [8,9]. This rise in HGF was partially explained by increased production by vascular endothelium in proportion to the severity of heart failure [10].

Consistent with previous studies we found the serum concentration of HGF to be considerably increased in patients receiving hemodialysis [11,12]. Hemodialysis induces rapid and extensive increase in HGF, mainly by inducing proinflammatory cytokine release [13].

HGF was elevated in many earlier studies in nondialysis patients with renal insufficiency; furthermore, it was correlated with eGFR [14,15].

Figure 3



Correlation between hepatocyte growth factor (HGF) and ejection fraction (EF) in cardiorenal patients on dialysis. Bivariate correlation analysis showed negative correlation between HGF level and left ventricular EF% in cardiorenal patients on dialysis (group 1) (r=–0.45, P=0.0003)

Unexpectedly, we found HGF level in patients with CHF and renal impairment to be nonsignificantly elevated compared with those with CHF and normal renal function. The potential explanation is that patients with normal renal function had more severe heart failure with lower EF%. In addition, HGF was found to correlate with serum creatinine, and patients in group 2 had only a moderate reduction in eGFR and their mean creatinine was 2.6 mg/dl. Finally, in the acute stage of renal injury, there is increased expression of HGF, perhaps in an effort to repair the damage; however, chronic exposure to injurious stimuli eventually leads to the downregulation of HGF [16,17].

CRF patients have a high cardiovascular risk, and both left ventricular and left atrium enlargements are predictors of adverse cardiac events in these patients [18,19]. HGF was associated with LV dimensions and function in patients on hemodialysis [11]. We found HGF to be correlated with LA diameter but not with LV dimensions in dialysis patients with CHF. LA injury in CKD is linked to volume overload and the condition of chronic inflammation. Moreover, LA modulation is strongly linked to its endocrine and regulatory functions [7,20] . Both LA and LV were reported to be predictors of clinical outcome [21]. Furthermore, Kadappu *et al.* [22] found LA strain to be more sensitive and an earlier predictor of cardiac affection than ventricular strain in CKD patients.

Despite the strong evidence of the beneficial effects of HGF on the heart, including antiapoptotic, antifibrotic, anti-inflammatory, and regenerative effects [4], HGF has been reported to be a strong predictor of mortality in advanced heart failure and it might be superior to regular markers [5,6].

Table 3 Correlations between hepatocyte growth factor and different parameters in the different groups

Variables	Hepatocyte growth factor (ng/ml)							
	Group 1		Group 2		Group 3		Group 4	
	r	*P*-value	*r*	*P*-value	*r*	*P*-value	*r*	*P*-value
Age (years)	0.06	0.7	0.44	0.2	0.37	0.3	–0.13	0.7
Dialysis duration (months)	0.15	0.4	–	–	–	–	0.51	0.1
Echo finding								
LVEF (%)	–0.45	0.003	0.18	0.6	–0.58	0.06	0.18	0.6
LVED (cm)	0.18	0.3	0.04	0.9	0.14	0.7	0.44	0.2
LVESD (cm)	–0.01	0.9	0.08	0.8	0.25	0.5	0.26	0.5
LA diameter (cm)	0.34	0.03	–0.03	0.9	0.35	0.3	0.1	0.8
Laboratory investigations								
Urea (mg/ml)	0.02	0.8	–0.42	0.2	0.08	0.8	0.09	0.8
Creatinine (mg/ml)	–0.13	0.4	0.6	0.05	0.79	0.004	0.03	0.9
eGFR (ml/min/1.73 m^2)	0.21	0.2	–0.76	0.007	–0.42	0.2	0.03	0.9

eGFR, estimated glomerular filtration rate; LA, left atrium; LVED, left ventricular end-diastolic dimension LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension.

Previous studies researched the relation of HGF to mortality in CRF patients but few investigated its value in dialysis patients. Serum HGF was associated with increased mortality in CRF in both hemodialysis and peritoneal dialysis patients [11,23,24]. In our study HGF was not related to mortality. The apparent discrepancy between the previous studies and ours may be due to different reasons. First, our patients have been followed up for short-term mortality (6 months) in contrast to 31 months and 6 years in aforementioned studies [11,24]. Second, it has been postulated that HGF increases first to attenuate the cardiovascular damage. However, with long-term exposure, it could become detrimental, possibly due to downregulation of its receptor, and it leads to disease progression [11,25]. Finally, when interpreting the results we should take into consideration the fact that the possible ethnic variability among Egyptians may lead to confounding results.

Conclusion

HGF level was related to the severity of heart failure in dialysis patients. However, HGF was not associated with short-term mortality in this group of participants.

The present study has several limitations. First, this study was performed in a limited number of patients. Second, the mean age of the studied patients was 52 years. Further studies are needed to answer important questions in this area. First, does HGF level have more predictive value for morbidity and mortality if it is estimated in patients having the same criteria but of younger age? Second, does HGF level have a role in diagnosing and following up hemodialysis patients with diastolic rather than systolic heart failure, which is more common in asymptomatic CRF patients on hemodialysis.

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Conflicts of interest

There are no conflicts of interest.

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