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Serum Copeptin and Renalase in Correlation to Left Ventricular Hypertrophy in Hemodialysis Patients

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ABSTRACT

Background: Left ventricular hypertrophy (LVH) is a reaction to increasing cardiac activity that is usually due to combined pressure and volume overload, resulting in cardiac muscle hypertrophy and increasing intercellular matrix. In newly diagnosed hemodialysis (HD) patients, the prevalence of LVH is 75%.

Objective: The aim of the current study is to detect early markers for LVH in HD patients.

Patients and methods: A cross-sectional study included 70 HD patients divided into two groups; *Group I* (40 HD patients with LVH), and *Group II* (30 HD patients without LVH). All cases were subjected to history, clinical examination, complete blood count (CBC), kidney function tests, blood glucose, serum cholesterol (TC), serum triglycerides (TG), serum ferritin, CRP, serum calcium, serum phosphorus, parathyroid hormone (PTH), serum copeptin, renalase, and 2D echocardiography with estimation of left ventricular mass index (LVMI).

Results: LVH is significantly associated with ischemic heart disease (IHD), older age, higher systolic blood pressure (SBP), duration of HD, lower hemoglobin, higher TG, TC, CRP, PTH, serum renalase and copeptin. A positive correlation found between serum copeptin and all of age, duration of dialysis, Left ventricular mass index (LVMI) and serum renalase. A positive correlation found between serum renalase and all of systolic, diastolic blood pressure (DBP), duration of HD, LVMI and serum copeptin.

Conclusion: Serum copeptin and renalase levels are strongly associated with cardiovascular risks specially LVH and heart failure (HF) in HD patients.

Keywords: LVH, Hemodialysis, Copeptin, Renalase.

INTRODUCTION

Left ventricular hypertrophy (LVH) occurs in early stages of chronic kidney disease (CKD), impacting 20% or more of patients with CKD Stages 1 to 3 [(1)] and 80% of individuals with end stage kidney disease (ESRD) [(2)]. Eccentric LVH is due to volume overload and anaemia, while concentric hypertrophy is due to arterial hypertension. Both types of hypertrophy are common in ESRD patients [(3)].

Copeptin is a 39-amino acid glycopeptide with molecular mass of 5 kDa that is generated from Arginine vasopressin (AVP) in similar amounts [(4)]. High levels of copeptin are associated with CKD [(5)]. Additionally, greater copeptin levels in dialysis patients were thought to be high risk indicators for cardiovascular disease (CVD) and mortality [(6)]. In addition, it could also be useful in the diagnosis of left ventricular dysfunction (LVD) and myocardial infarction [(7)].

Renalase is a flavoprotein produced mainly by the kidney [(8)]. Renalase is produced by the kidneys into the blood and urine, where it could metabolize catecholamines [(9)].

One retrospective study including CKD patients revealed a relationship between renalase and poor renal outcomes and all-cause mortality [(10)].

The aim of the current study is to detect early markers for LVH in hemodialysis (HD) patients.

PATIENTS AND METHODS

A cross-sectional study was conducted at Nephrology Unit, Internal Medicine Department, Zagazig University Hospitals, Egypt. The study included 70 HD patients who were split into two groups; *Group I* (40 patients on maintenance HD with LVH), and *Group II* (30 patients on maintenance HD without LVH).

Inclusion criteria: Patients more than 18 years and not more than 60 years, on regular HD for more than six months.

Exclusion criteria: Patients who refused to enter the study or infections, pregnancy, malignancies, extremes of age, or cardiomyopathy.

The following procedures will be done to all participants:

1. Thorough history taking.
2. Clinical examination with stress on: general examination, cardiovascular, edema of lower limb.
3. **All cases were subjected to laboratory investigations including:** kidney function tests, CBC, blood glucose, serum TC, serum TG, serum ferritin, CRP, serum calcium, serum phosphorus, and PTH.
4. Serum copeptin was assessed in fasting plasma samples preserved at -80 ºC with the use of commercially available chemiluminescence sandwich immunoassay with coated tubes (B.R.A.H.M.S AG, Hennigsdorf, Germany) [(11)].
5. Serum renalase was measured using the human renalase specific ELISA kit (WuHan EIAab,Wuhan, China).
6. Echocardiography: using a Philips IE-33 system and S5-1 transducer (1e5 MHz, Philips, Bothell,

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WA), 2D transthoracic color Doppler echocardiography was done to all patients. Physical examination and echocardiography was done to all cases by the same cardiologist.

LVMI is calculated by the following equations:

- LVMI=LVM (left ventricular mass)/body surface area
- Left ventricular mass=0.8{1.04[([LVEDD + IVSd +PWd]3 - LVEDD3)]} + 0.6
- *Where*
- LVEDD = LV end-diastolic dimension (mm)
- IVSd = interventricular septal thickness at end-diastole (mm)
- PWd = posterior wall thickness at end-diastole (mm).

Ethical approval:

The research was approved by Zagazig University's Ethics Board (ZU-IRB #9789), and each subject provided signed informed permission. This research has been done in conformity with the Declaration of Helsinki, the World Medical Association's ethical guidelines for research trial.

Statistical Analysis

The statistical testing was done utilizing the SPSS program (Statistical Package for Social Science version 26 and NCSS 12, LLC, USA). Qualitative variables were provided as frequencies and percentages, and quantitative variables had been given as means and standard deviations (SD) or median and range. For evaluating descriptive data, Chi-square test and Fisher's exacts analysis were utilized, while the independent student's t test and the Mann-Whitney analysis was used for comparing quantitative data. ROC Curve, Spearman's correlation, logistic and multiple regression analysis were also utilized as tests of significances. P value ≤0.05 is considered significant.

RESULTS

Table 1 summarizes sociodemographic and clinical data of studies patients.

Table (1): Baseline data of studied patients.

Qualitative Variable	**N=70**	**%**
Male gender	36	51.4%
Diabetes	12	17.1%
Hypertension	30	42.9%
IHD	17	24.3%
LVH	40	57.1%
Quantitative Variable	**Mean ± SD**	**Range**
Age (Mean ± SD)	49.9 ± 7.39	37 – 67
BMI (Kg/m^2)	24.03 ± 1.99	20 – 29
SBP (mmHg)	130.29 ± 12.16	110 – 160
DBP (mmHg)	82.46 ± 6.85	70 – 100
KT/V (%)	1.43 ± 0.33	1.14 – 1.48
Duration of HD (years)	6.51 ± 2.78	2 – 15
Hemoglobin (gm/dl)	10.8 ± 0.54	9.6 – 11.8
Blood glucose (mg/dl)	107.64 ± 20.5	71 – 173
Serum albumin (gm/dl)	3.86 ± 0.34	3.4 – 4.9
Triglycerides (mg/dl)	223.4 ± 48.45	140 – 298
Cholesterol (mg/dl)	205.67 ± 24.54	160 – 280
Serum ferritin (ng/ml)	366.9 ± 92.35	190 – 540
CRP (mg/l)	5.83 ± 1.78	2.7 – 8.9
Serum calcium (mg/dl)	8.66 ± 0.27	8.0 – 9.2
Serum phosphorus (mg/dl)	4.65 ± 0.32	3.1 – 5.3
Non parametric data	**Median (IQR)**	**Range**
LVMI (gm/m^2)	**130.25 (85.68 – 141.35)**	80.3 – 184.5
PTH (ng/ml)	610 (347.5 – 757.5)	110 – 1110
Serum renalase (ng/ml)	179.5 (95 – 289.25)	80 – 370
Serum copeptin (pg/ml)	188.5 (67 – 266.25)	38 – 299

IQR= interquartile range. Quantitative parametric data were represented as mean and standard deviation and quantitative nonparametric data were represented as median and interquartile range.

LVMI ranged from 80.3 to 184.5 gm/m^2 with median 130.25. Serum renalase ranged from 80 to 370 ng/ml with median 179.5 ng/ml. Serum copeptin level ranged from 38 – 299 pg/ml with median 188.5 pg/ml (**Table 1**). 57.1% of patients had LVH (**Figure 1**).

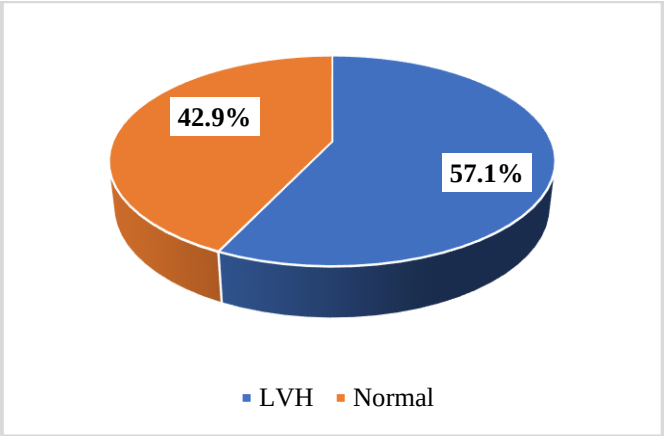

Figure (1): Pie chart showing distribution of studied patients according to occurrence of LVH.

LVH was significantly associated with IHD, older age, higher SBP, duration of HD, lower hemoglobin, higher TG, TC, CRP, PTH, LVMI, serum renalase and copeptin. In contrary, there was no significant relation between LVH and either gender, diabetes, DBP, BMI, blood glucose, serum albumin, calcium, or phosphorus (**Table 2**).

Table (2): Association between occurrence of LVH and patients characteristics.

Variable	Non-LVH group N=30 (%)	LVH group N=40 (%)	χ^2	P-value
Male gender	13 (43.3%)	23 (57.5%)	1.377	0.241
Diabetes	12 (40%)	18 (45%)	0.175	0.676
Hypertension	7 (23.3%)	5 (12.5%)	1.416	0.234
IHD	3 (10%)	14 (35%)	5.827	0.016*
Quantitative Variable	**Mean ± SD**	**Mean ± SD**	T	P
Age (year)	45.57 ± 6.21	53.15 ± 6.53	-4.907	<0.001**
BMI (Kg/m^2)	23.3 ± 2.09	24.83 ± 1.91	0.991	0.325
SBP (mmHg)	126.67 ± 7.58	133.0 ± 14.18	-2.404	0.019*
DBP (mmHg)	81.33 ± 4.14	83.63 ± 8.24	-1.521	0.133
KT/V (%)	1.43 ± 0.03	1.14 ± 0.14	-1.019	0.041*
Duration of HD (years)	4.33 ± 1.18	8.15 ± 2.5	-8.48	<0.001**
Hemoglobin (gm/dl)	11.3 ± 0.32	10.42 ± 0.31	11.647	<0.001**
Blood glucose (mg/dl)	101.4 ± 23.25	114.83 ± 17.95	1.336	0.186
Albumin (gm/dl)	3.89 ± 0.19	3.64 ± 0.17	0.718	0.476
Triglycerides (mg/dl)	176.93 ± 17.77	258.25 ± 31.8	-13.59	<0.001**
Cholesterol (mg/dl)	189.7 ± 12.13	217.65 ± 24.76	-6.215	<0.001**
Serum ferritin (ng/ml)	369.3 ± 80.56	365.1 ± 11.26	0.187	0.852
CRP (mg/l)	5.05 ± 1.8	5.99 ± 1.67	-2.251	0.028*
Serum calcium (mg/dl)	8.6 ± 0.27	8.7 ± 0.26	-1.422	0.16
Serum phosphorus(mg/dl)	4.68 ± 0.22	4.63 ± 0.38	0.637	0.257
	Median (IQR)	**Median (IQR)**	Z	P
LVMI (gm/m^2)	83.7 (81.4 – 90.33)	140.3 (130.4 –174.3)	-1.395	<0.001**
PTH (ng/ml)	564 (311.25 – 726.5)	615 (457.5 – 810)	+7.124	<0.001**
Serum renalase (ng/ml)	95 (90 – 100)	280 (190 – 359.25)	-5.926	<0.001**
Serum copeptin (pg/ml)	67 (57.75 – 89)	248 (192 – 280)	-6.062	<0.001**

*P ≤0.05 is statistically significant. **P ≤0.001 is statistically highly significant. χ^2 Chi square test. t independent sample t test. Z Mann Whitney test. IQR interquartile range Quantitative parametric data were represented as mean and standard deviation and quantitative nonparametric data were represented as median and interquartile range.

The best cutoff of serum copeptin was ≥99 pg/ml with area under curve 0.925, sensitivity 92.5%, specificity 90%, positive predictive value (PPV) was 92.5%, negative predictive value (NPV) was 90%, overall accuracy 91.4% (p<0.001). The best cutoff of serum renalase was ≥115 ng/ml with area under curve 0.916, sensitivity 92.5%, specificity 86.7%, the PPV 90.2%, the NPV 89.7%, overall accuracy 90% (p<0.001) (**Table 3 and Figure 2**).

Table (3): Performance of serum renalase and copeptin in prediction of LVH among patients on HD:

Marker	AUC	Cutoff	Sensitivity	Specificity	PPV	NPV	Accuracy	P-value
Renalase(ng/ml)	0.916	≥115	92.5%	86.7%	90.2%	89.7%	90%	<0.001**
Copeptin(pg/ml)	0.925	≥99	92.5%	90%	92.5%	90%	91.4%	<0.001**

**P ≤0.001 is statistically highly significant. PPV Positive predictive value. NPV Negative predictive value. AUC area under curve.

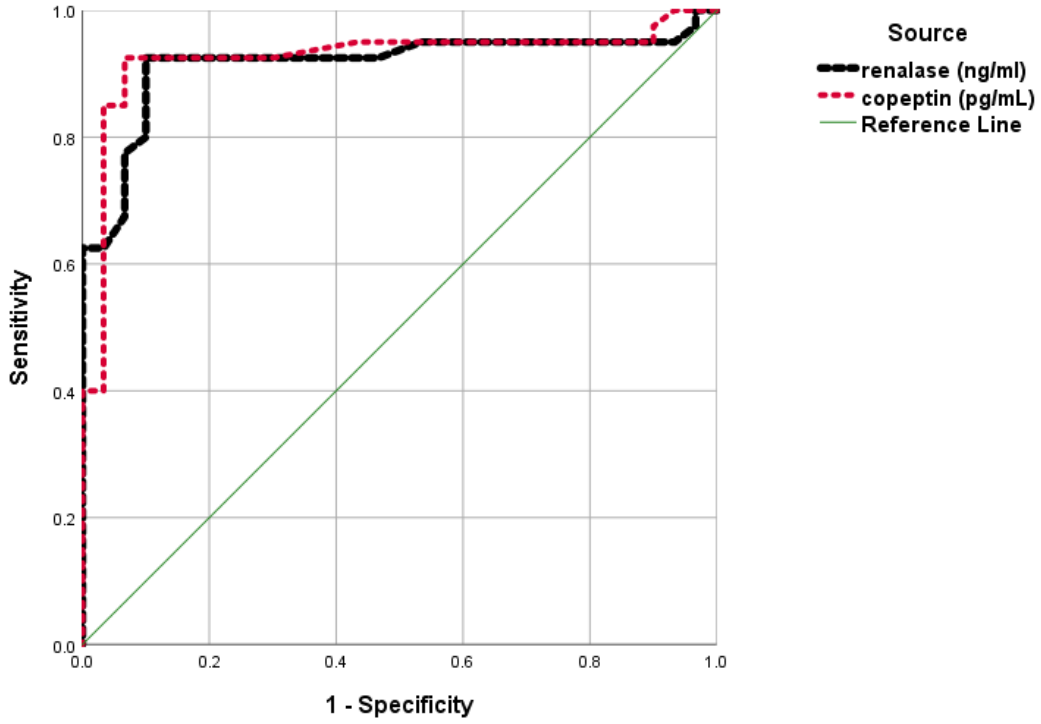

Figure (2): ROC curve showing Performance of serum renalase and copeptin in prediction of LVH among patients on HD.

Older age, increasing duration of HD, higher TG, TC, PTH, IHD, serum renalase, serum copeptin, CRP, SBP, and DBP were non-significantly increased odds with LVH (**Table 4**).

Table (4): Multivariate regression analysis of factors associated with LVH among HD patients.

Variable	B	P-value	AOR
Age per years	0.295	>0.999	1.343
Duration of HD (year)	0.669	>0.999	1.952
Triglycerides (mg/dL)	0.357	>0.999	1.428
Total Cholesterol (mg/dL)	0.013	>0.999	1.013
PTH (pg/mL)	-0.004	>0.999	.996
IHD (present)	2.216	>0.999	9.168
Serum renalase (ng/ml)	0.055	>0.999	1.057
Serum copeptin (pg/mL)	0.085	>0.999	1.089
CRP (mg/l)	2.761	>0.999	15.812
SBP (mmHg)	0.437	>0.999	1.548
DBP (mmHg)	0.421	>0.999	1.432

AOR adjusted odds ratio

Serum renalase had significant positive correlation and all of SBP, DBP, duration of HD, TG, TC, LVMI and serum copeptin. On the other hand, serum renalase was negatively correlated and all of hemoglobin, albumin, Kt/V and blood glucose (Table 5).

Table (5): Correlation between serum renalase and the studied parameters.

Variable	R	P-value
Age (year)	0.328	0.006*
BMI (Kg/m^2)	-0.092	0.449
SBP (mmHg)	0.297	0.013*
DBP (mmHg)	0.323	0.006*
KT/V (%)	-0.335	0.004*
Duration of HD (years)	0.492	<0.001**
Hemoglobin (gm/dl)	-0.604	<0.001**
Blood glucose (mg/dl)	-0.27	0.024*
Serum albumin (gm/dl)	-0.337	0.004*
Triglycerides (mg/dl)	0.524	<0.001**
Total cholesterol (mg/dl)	0.44	<0.001**
Serum ferritin (ng/ml)	0.117	0.335
CRP (mg/l)	0.034	0.78
Serum calcium (mg/dl)	0.099	0.417
Serum phosphorus (mg/dl)	-0.214	0.075
LVMI (gm/m^2)	0.751	<0.001**
PTH (ng/ml)	-0.065	0.595
Serum copeptin (pg/ml)	0.503	<0.001**

**P≤0.001 is statistically highly significant. *P≤0.05 is statistically significant. r Spearman rank correlation coefficient.

Serum copeptin had significant positive correlation and all of age, duration of HD, TG, TC, LVMI and serum renalase. There was statistically significant negative correlation between serum copeptin and Kt/V, hemoglobin, and albumin (**Table 6**).

Table (6): Correlation between serum copeptin and the studied parameters

Variable	R	P-value
Age (year)	0.435	<0.001**
BMI (Kg/m^2)	-0.124	0.307
SBP (mmHg)	0.038	0.755
DBP (mmHg)	0.01	0.931
KT/V (%)	-0.334	0.004*
Duration of HD (years)	0.593	<0.001**
Hemoglobin (gm/dl)	-0.594	<0.001**
Blood glucose (mg/dl)	-0.049	0.685
Serum albumin (gm/dl)	-0.351	0.003*
Triglycerides (mg/dl)	0.589	<0.001**
Total cholesterol (mg/dl)	0.491	<0.001**
Serum ferritin (ng/ml)	-0.066	0.587
CRP (mg/l)	0.034	0.78
Serum calcium (mg/dl)	0.052	0.673
Serum phosphorus (mg/dl)	0.055	0.65
LVMI (gm/m^2)	0.542	<0.001**
PTH (ng/ml)	-0.018	0.88
Serum renalase (pg/ml)	0.503	<0.001**

**P≤0.001 is statistically highly significant. *P≤0.05 is statistically significant. r Spearman rank correlation coefficient.

Among factors significantly correlated to serum renalase, only LVMI (unstandardized β=2.377, P<0.001) and DBP (unstandardized β =2.426, P =0.022) significantly independently associated with it (Table 7).

Table (7): Linear stepwise regression analysis of factors significantly associated with serum renalase.

Variable	Unstandardized Coefficients		Standardized Coefficients	T test	P-value	95% Confidence Interval	
	B	Std. Error	Beta			Lower	Upper
Constant	-296.703	81.380		-3.646	0.001**	-459.139	-134.268
LVMI	2.377	0.199	0.795	11.965	<0.001**	1.980	2.773
DBP (mmHg)	2.426	1.037	0.155	2.339	0.022*	0.356	4.497

**P≤0.001 is statistically highly significant. *P≤0.05 is statistically significant.

Among factors significantly correlated to serum copeptin, only serum renalase (unstandardized β=0.248 p=0.005) and TG (unstandardized β =0.726, P =0.001) significantly independently associated with it (**Table 8**).

Table (8): Linear stepwise regression analysis of factors significantly associated with serum copeptin.

Variable	Unstandardized Coefficients		Standardized Coefficients	T test	P-value	95% Confidence Interval	
	B	**Std. Error**	**Beta**			**Lower**	**Upper**
(Constant)	-100.842	37.021		-2.724	0.008*	-174.756	-26.928
Triglycerides (mg/dL)	0.726	0.214	0.370	3.398	0.001**	0.299	1.152
Serum renalase (ng/ml)	0.248	0.085	0.280	2.912	0.005*	0.078	0.419

**P≤0.001 is statistically highly significant. *P≤0.05 is statistically significant.

DISCUSSION

In our study, LVH was prevalent in 57.1% of hemodialysis population in our cohort. This is in concordance to a study done by **Foley *et al.*** [12] with more than 70% of dialysis patients had LVH. Another study on Japanese HD patients showed about 68% had LVH. Other studies showed that 79% and 85% of HD patients had LVH at start of HD [13,14]. The occurrence of LVH has varied across studies ranging between 36%-77% [15-18].

In our study, LVH is significantly associated with IHD, older age, higher SBP, duration of HD, lower hemoglobin, higher TG, TC, CRP, and PTH. And this going with **Kim *et al.*** [19], **Selim *et al.*** [20], **Jaroszyński *et al.*** [21], **Yamaguchi *et al.*** [22], **Braunisch *et al.*** [23] and **Lu *et al.*** [24].

Our study experienced that serum copeptin was significantly higher in LVH patients on HD as we have here two factors that affect copeptin levels which are CKD and cardiovascular disorders, these results are going with **Kim *et al.*** [19].

Renalase was linked to CKD and CVD in numerous studies. In a previous study by **Xu *et al.*** [25] concluded a direct relationship between renalase and CVD.

CKD is a significant risk factor for the development of CVD like LVH, HF, and CHD, and can lead to an increase morbidity and mortality in HD patients [26]. Patients with CKD are more likely to develop CVD due to secondary risk factors such as inflammation, arterial calcification, disturbed calcium and phosphate metabolism, RAAS activation, elevated sympathetic tone, and oxidative stress in addition to traditional risk factors like hyperlipidemia and hypertension [27]. Regarding this, renalase may serve as a clear mediator for the therapeutic targeting of the cardiorenal syndrome and may represent a link between the kidney and the heart [28]. Renalase therapy restored heart health and partially reversed LVH brought on by CKD [29]. Additionally, in patients with CAD, a synergistic impact of elevated serum renalase and CKD causes a rise in endothelin-1 levels that could enhance the risk of CVD [30]. Our study showed that serum renalase was elevated in LVH group than the other group and this could be explained by the previous role of renalase in LVH and in CKD and this is going with **Gamal *et al.*** [31].

Our results showed a higher sensitivity and specificity of both serum copeptin and renalase where copeptin sensitivity was 92.5% and specificity was 90% while for renalase sensitivity was 92.5% and specificity was 86.7%. And these results indicate the importance of these markers in predicting LVH in HD patients.

Kim *et al.* [19] found that copeptin sensitivity 70%, specificity 80% in predicting LVH in HD patients.

While **Gamal *et al.*** [31] found that renalase Sensitivity was 92.3%, Specificity was 84.0%.

Our study experienced significantly positive correlation between serum renalase and all of SBP, and DBP, duration of HD, TG, TC, LVMI and serum copeptin. These results were going with **Knop *et al.*** [32] **and Gamal *et al.*** [31]**.** While a negative correlation between serum renalase and all of hemoglobin, albumin, Kt/V, and blood glucose.

Also we found that, serum copeptin had a positive correlation with age, duration of HD, TG, TC, LVMI and serum renalase, and a negative correlation with hemoglobin, Kt/V, and serum albumin. This agrees with

Ettema *et al* [33] where they found a correlation between serum copeptin with HD duration, eGFR and SBP**.**

While **Kim *et al.* [19]** found a positive correlation between copeptin and LVD. Also **Türkmen and Babat [34]** found a correlation between copeptin levels with NYHA class (P =0.004), high sensitive-CRP (P =0.01) and pro-BNP (P =0.011).

CONCLUSION

From our previous data we can conclude that high serum copeptin and renalase levels are strongly associated with cardiovascular risks specially LVH and HF in CKD patients on HD and can be used as early diagnostic markers for such risks and can be used as future therapeutic targets for CVD in HD patients.

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Conflict of interest: None.

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