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Changes in Biomarker Profile and Left Ventricular Hypertrophy Regression: Results from the Frequent Hemodialysis Network Trials

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Abstract

Background—Regression of left ventricular hypertrophy (LVH) is feasible with more frequent hemodialysis. We aimed to ascertain pathways associated with regression of left ventricular mass (LVM) in patients enrolled in the Frequent Hemodialysis Network (FHN) trials.

Methods—This was a post hoc observational cohort study. We hypothesized LVH regression with frequent hemodialysis was associated with a different cardiovascular biomarker profile. Regressors were defined as patients who achieved a reduction of more than 10% in LVM at 12 months. Progressors were defined as patients who had a minimum of 10% increase in LVM at 12 months.

Results—Among 332 randomized patients, 243 had biomarker data available. Of these, 121 patients did not progress or regress, 77 were regressors and 45 were progressors. Mean LVM change differed between regressors and progressors by −65.6 (−74.0, −57.2) g, $p < 0.001$. Regressors had a median (interquartile range) increase in dialysis frequency (from 3.0 (3.0, 3.0) to 4.9 (3, 5.7) per week, $p = 0.001$) and reductions in pre-dialysis systolic (from 149.0 (136.0, 162.0) to 136.0 (123.0, 152.0) mmHg, $p <0.001$) and diastolic (from 83.0 (71.0, 91.0) to 76.0 (68.0, 84.0) mmHg, $p<0.001$) blood pressures. Klotho levels increased in regressors versus progressors (76.9 (10.5; 143.3) pg/ml, $p = 0.024$). Tissue inhibitors of metalloproteinase (TIMP) – 2 levels fell in regressors compared to progressors (−7853 (−14653; −1052) pg/ml, $p = 0.024$). TIMP – 1 and LogBNP levels also tended to fall in regressors. Changes in LVM correlated inversely with changes in Klotho ($r = −0.24$, $p = 0.014$).

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Conclusions—Markers of collagen turnover and changes in klotho levels are potential novel pathways associated with regression of LVH in the dialysis population, which will require further prospective validation.

Keywords

Frequent Hemodialysis; Cardiac Biomarkers; Klotho; Markers of collagen turnover; Left ventricular hypertrophy; Copeptin; Brain natriuretic peptide

Introduction

Left ventricular hypertrophy (LVH) is prevalent in end-stage renal disease (ESRD) and contributes to the high annual mortality rate seen in these patients (15-20%). While conventional hemodialysis (CHD) [3 times per week, 3-4 hours per session] is the standard renal replacement therapy in North America, it does not correct abnormal left ventricular geometry[1].

Recent studies have highlighted the salutary effects of increased frequency or duration of hemodialysis on left ventricular (LV) mass. Given that reduction of LVH is associated with decreased risk of cardiovascular events[2], LV mass is a logical surrogate outcome of interest. Three randomized controlled trials in the field of intensive hemodialysis (HD) have included LV mass as a primary outcome[3-5]. Culleton et al. assigned 52 prevalent patients to 5-6 times per week nocturnal hemodialysis (NHD) or conventional hemodialysis (CHD). After 6 months, mean LV mass was −15.3 g (95% CI −29.6 to −1.0 g; P = .01) lower in the NHD group compared to controls. Similarly, the Frequent Hemodialysis Network Daily and Nocturnal Trials demonstrated a fall in LV mass with adjusted mean LV mass differences of −13.1 g (95% CI −21.3 g to −5.0 P=0.002) and −10.9 g (95% CI –23.7 to 1.8, p=0.09), respectively. Predictors of LV mass response to intensive HD included LVH at baseline and reduction in pre-dialysis systolic blood pressure[6]. It is important to note that changes in blood pressure accounted for less than 50% of the variability attributable to the changes in LV mass suggesting that other important pathways may play a role in the pathogenesis of LVH and its regression in ESRD.

This is a post hoc study using data from the Frequent Hemodialysis Network Trials. We aimed to explore potential pathways associated with LVH regression and hypothesized that patients who experienced LVH regression with frequent hemodialysis (short daily and/or nocturnal hemodialysis) would manifest different responses in a series of a priori selected cardiovascular biomarkers. Given that biomarkers are also influenced by baseline level of LVH, we have also examined the impact of LVH regression on biomarker changes amongst individuals with evidence of LVH at baseline.

Concise Methods

FHN Trials

The FHN Daily and Nocturnal Trials were multicenter, randomized, prospective trials of in-center daily hemodialysis and home nocturnal hemodialysis, respectively, sponsored by the National Institute of Health, National Institutes Diabetes, Digestive and Kidney Diseases

(NIDDK) and the Center for Medicare and Medical Services (CMS). The designs, inclusion and exclusion criteria of both Daily and Nocturnal Trials have been described previously [7, 8]. Patients were enrolled between March 2006 and May 2009 and the trials concluded in May 2010. Both trials were approved by the local Institutional Review Board at each participating site. An independent Data Safety Monitoring Board provided oversight of both trials.

Dialysis Intervention

Patients in the conventional arm of both trials remained on their usual three times per week hemodialysis prescription subject to a prescribed equilibrated Kt/V_{urea} >1.1, a standardized Kt/V_{urea} of >2.0 and a treatment time ≥2.5 hours/session. Patients randomized to the frequent arm (six times per week hemodialysis) of the Daily Trial were targeted to an equilibrated Kt/Vn, where $Vn = 3.271 \times V^{2/3}$, of 0.9 provided that the length of the session was between 1.5 and 2.75 hours. Patients randomized to the frequent arm of the Nocturnal Trial followed hemodialysis prescriptions subject to a standardized Kt/V_{urea} of ≥4.0 and a treatment time of ≥6 hours. (72 of 87 patients in the Nocturnal Trial received therapy at home, rather than in-center).

Cardiac Magnetic Resonance Imaging (CMRI)

We measured LV mass (LVM) and biventricular volumes by CMRI in all randomized patients at baseline and at 12 months where feasible. All CMRI images were analyzed centrally in a blinded manner. CMRI was performed on 1.5-T MRI systems (minimum gradient performance: peak strength ≥12 mT/m, slew rate ≥ 40 mTm/s) with dedicated surface coils. Sites were required to use standardized protocols utilizing breath-held, retrospective ECG-gated steady-state free precession imaging in contiguous short-axis views (8-mm slice thickness, 2 mm gap) that were carefully prescribed from localizer long-axis images. Imaging parameters were adjusted on each specific CMRI scanner to provide 20-25 cardiac phases with an in-plane spatial resolution superior of ≤2 mm and a temporal resolution <50 ms. Using validated software (Argus, Siemens medical Solutions, Erlangen, Germany), we measured myocardial volume on end- diastolic frames by manual tracing of endocardial and epicardial contours. We excluded papillary muscles from the calculation of myocardial mass. Subsequently, this volume was multiplied by the specific density of the myocardium (1.05 g/cm^3) to obtain LVM [9]. Similarly, we traced biventricular endocardial contours in end-diastole and end-systole to derive end-diastolic and end-systolic volumes. We used the formula of DuBois and DuBois to index LVM to body surface area [10]. We calculated anthropometric volume using the Watson equation [11].

Regression of LVM (“regressors”) was defined as patients who achieved a reduction of more than 10% in LVM at 12 months. “Progressors” was defined as patients who had a minimum of 10% increase in LVM at 12 months. A 10% cut-off was used to define regression as London et al[12] had previously demonstrated favourable outcomes with a 10% LVM decrease in hemodialysis patients. LVH was defined as LVM index (LVM/body surface area) > 84.1 g/m^2 (male) or >76.4 g/m^2 (female)[13] according to Patel et al.

Cardiac Biomarkers Measurements

A priori, our consortium defined a select group of serum cardiac biomarkers which have been shown to be associated with various pathogenetic pathways leading to LVH development including: (1) brain natriuretic peptide (extracellular volume overload and ventricular stretch) (Millipore, St. Charles MO, USA), with minimum detectability 11.5 pg/mL, intra-assay coefficient of variation (CV) 8.3%, and inter-assay CV 8.4%; (2) copeptin (EISA Phoenix Pharmaceuticals Inc. Burlingame CA, USA), with intra-assay CV < 10% and inter-assay CV < 15% (neurohormonal activation); (3) matrix metaloproteinases (MMP) using a metallic bead kit enzyme-linked immunoassay (Millipore, St. Charles MO, USA), with MMP 2 inter-assay CV 18% and intra-assay CV 5.4%, MMP 7 inter-assay CV 7.1% and intra-assay CV 3.7%, MMP 9 inter-assay CV 9.0% and intra-assay CV 1.9%; (4) tissue inhibitors of metalloproteinases (TIMP, Matrix remodeling and collagen deposition); (5) highly sensitive C reactive protein (CRP, inflammation) using a Polychem nephelometric assay (Polymedco, Cortland Manor NY, USA), with assay range 0.08 −160 mg/L, intra-assay CV 2.73-5.17 and inter-assay CV 4.67-5.67; (5) fibroblast growth factor 23 (FGF23) using a sandwich ELISA assay (Millipore, St. Charles MO, USA) with inter-assay CV 2.45-11.31% and intra-assay CV 7.8-11.2%; and (6) Klotho (Immuno-Biological Laboratories Co., Ltd., Japan, with intra-assay CV 2.7-3.5% and inter-assay CV 2.9-11.4%) which has been shown to be a marker of myocardial fibrosis and LVH development in uremic animal models). In order to minimize variability between assays, all assays for time paired samples were carried out in duplicate on the same plate.

Data Analysis and Outcome Measures

Descriptive statistics for continuous variables were summarized using mean ± SD or median (interquartile range, IQR). Categorical variables were summarized using proportions. We compared groups by LVM response status using standard statistical methods, including Students t-test for continuous variables and chi-squared or Fisher's exact test for categorical variables. The effects of LVM response on changes of biomarkers were estimated by applying a mixed effects model to baseline and 12-month values using an unstructured covariance matrix. We examined the association between changes in LVM and changes in cardiac biomarkers using Pearson correlations. In order to ascertain the effect of baseline LVH on biomarker evolution, the participants were further sub-classified according to LVH status. All analyses were conducted using SAS statistical software (version 9.2, Cary NC) and a p-value criterion of <0.05 was chosen as the threshold for statistical significance.

Results

Among the 332 patients randomized across both trials (245 Daily, 87 Nocturnal), of whom 243 patients had LVM measurements as well as adequate serum samples for cardiac biomarker analyses. Of these, there were 77 patients classified as regressors (Daily: N=25, 3×/week and N=36, 6×/week; Nocturnal: N=6, 3×/week and N=10, 6×/week) and 45 patients classified as progressors (Daily: N=18, 3×/week and N=11, 6×/week; Nocturnal: N=10, 3×/week, N=6, 6×/week), with the remaining 121 patients not fulfilling either inclusion criteria. Selected baseline and clinical variables are shown in Table 1A and 1B. Mean LVM change differed between regressors and progressors by −65.60 (95% confidence

interval, CI −74.04, −57.15) g, p<0.001. Specifically, LVM increased in the progressor group from 120 ± 41.5 to 151 ± 55.7 g and decreased in the regressor group from 158 ± 56.6 to 123 ± 43.9 g. At the end of follow-up, LV ejection fraction increased by 2.98±10.6% in regressors and fell by −1.9±9.30% in progressors, p=0.01. Of note, patients who had LVM regression had higher ESRD vintage (p=0.009) and tended to have a higher proportion with congestive heart failure (p=0.045). There were no differences in the biomarker levels at baseline when comparing regressors and progressors (Table 1A). Regressors had a median (interquartile range) increase in dialysis frequency (from 3.0 (3.0, 3.0) to 4.9 (3.0, 5.7) per week, p = 0.001) and median (interquartile range) reductions in pre-dialysis systolic (from 149.0 (136.0, 162.0) to 136.0 (123.0, 152.0) mmHg, p <0.001) and diastolic (from 83.0 (71.0, 91.0) to 76.0 (68.0, 84.0) mmHg, p<0.001). (Table 2)

Table 3 summarizes the differences in 12 month changes in all a priori defined biomarkers between progressors and regressors. Amongst the various cardiac biomarkers of interest, Klotho levels increased significantly in patients with LVM regression versus those who had LVM progression. FGF23 fell in both groups and did not differ between regressors and progressors. This was accompanied by a significant decrease in phosphorus in both groups. Similarly, TIMP-1 and TIMP-2 levels fell and logBNP levels tended to fall in patients who had LVM regression in comparison to LVM progression. Aldosterone levels increased among regressors and decreased in progressors. After adjustment for changes of potassium and blood pressure, the difference in (log) aldosterone change between regressors and progressors (10.8, 95% CI −20.6, 54.7) was not significant (p =0.54). Of note (Figures 1 and 2), changes in LVM correlated inversely with changes in Klotho (r = −0.24, p = 0.014) and changes in logBNP were associated with changes in LVM (r = 0.32, p = 0.013). Similarly, changes in pre- systolic and diastolic blood pressures correlated with changes in LVM (r = 0.52; p < 0.001, r = 0.47, p < 0.001, respectively).

Amongst those patients with either LVH progression or regression, 34 patients had LVH at baseline and 88 patients did not meet LVH criteria. Their demographics and biomarker results are described in Table 4. The proportion of patients with baseline LVH which regressed had higher ESRD vintage (81%) than those who progressed (43%). Among those with LVH at baseline, copeptin increased from baseline to 12 months in progressors and declined in regressors with a difference of −87.2 ng/ml (95% CI −178.8; 4.7, p =0.06).

Discussion

LVH is an important risk factor for cardiovascular morbidity and mortality in patients with ESRD. Our group has previously documented the effect size of LVM reduction with the use of frequent hemodialysis. We have also reported the association between changes in blood pressure and reduction in LVM. While hemodynamics alteration may represent an important component of the clinical benefits of frequent hemodialysis on LV remodelling, the impact of frequent hemodialysis on cardiovascular biomarkers and pathogenetic pathways have not been explored. In the present study, we aimed to generate new hypotheses and were able to demonstrate that markers of collagen turnover and changes in klotho levels are novel potential pathways, which may provide mechanistic insights into the development of LVH in patients with ESRD.

There is an emerging body of work that suggests pathological turnover of collagen is associated with LVH in the general population. Simplistically, excessive deposition of collagen may be controlled by overproduction of matrix, reduced removal or degradation of collagen or both. Indeed, biomarkers reflecting changes in extracellular matrix fibrillary collagen homeostasis was predictive of LVH and diastolic dysfunction in a cross sectional analysis in 144 patients without ESRD[14]. Further, the matrix metalloproteinases/tissue Inhibitors of metalloproteinases ratio was investigated in 103 general patients with hypertension and LVH. MMP/TIMP balance was suggested to play a role in predicting LV structure in the setting of hypertensive cardiac disease[15]. Additionally, a high level of TIMP was predictive of LVH and congestive heart failure in animal models and humans with hypertension[15]. The present observation suggests that MMP/TIMP balance is modifiable with the use of frequent hemodialysis. Specifically, regression in LVM was associated with a reduction in TIMP-2 levels resulting in a favourable MMP/TIMP ratio favoring extracellular matrix degradation. Whether the hypotensive effect of frequent hemodialysis or enhancement of solute or volume removal may affect MMP/TIMP in patients with ESRD is unknown. It is important to note that BNP tended to fall with LVH regression and correlated with changes in LVM. It is tempting to speculate that minimization of extracellular volume excess will lead to reduction in ventricular stretch, which is known to induce pathological extracellular matrix deposition[16, 17]. Our present data is consistent with the hypothesis that LVH regression in ESRD is dependent not only on changes in blood pressure alone; normalization of the MMP/TIMP may be a novel therapeutic target in patients with CKD and LVH.

Klotho is an anti-aging protein[18] which beneficially regulates various cellular processes, such as senescence, inflammation, apoptosis, fibrosis, and calcium and phosphate metabolism[19]. Uremic solutes retention is associated with reduction in Klotho levels[20]. In 86 patients with chronic kidney disease, LVH was inversely associated with Klotho levels. In normal mice, intraperitoneal injection of indoxyl sulfate induced LVH was also accompanied by downregulation of Klotho. In vitro, Klotho inhibited cardiomyocyte hypertrophy by inhibiting p38 and extracellular signal regulated protein kinase 1 / 2 signaling pathways[21]. Restoration of Klotho is feasible through an enhancement of peroxisome proliferation-activated receptor gamma acetylation[22] and is decreased through promoter hypermethylation[23]. Indeed, superTAG methylation has been demonstrated to be associated with uremia-induced epigenetic dysregulation of atherosclerosis-related genes[24]. The present observation extends the existing literature by describing the potential therapeutic impact of frequent hemodialysis on the augmentation of Klotho levels in patients with ESRD and LVH. It is tempting to speculate that frequent hemodialysis may modify epigenetic regulation of various genes[25], which may result in an augmentation of klotho levels.

It is intriguing to note that LVH regression with frequent hemodialysis may occur in the setting of elevated levels of fibroblast growth factor 23 (FGF23)[26]. Given that FGF 23 has been suggested to induce LVH in in vitro and in vivo models[27], the independent therapeutic effect of klotho on the heart requires additional prospective investigations. In our study, FGF23 levels declined in both progressors and regressors. FGF23 levels also declined significantly in all treatment groups, suggesting improvement in phosphate balance

throughout the enrolled population. It is therefore unclear whether reduction in FGF23 may have played a permissive role among the population that responded to increased dialysis intensity.

It is interesting to note that there was a significant interaction between copeptin and LVH. Previously, our group has described a more pronounced reduction of LVM by frequent hemodialysis in patients with minimal residual renal function[28]. Using an observational study design, the MONDO investigators have also substantiated an independent association between pre-dialysis serum sodium and blood pressure variations[29]. Copeptin is part of the 164 amino acid precursor protein preprovasopressin together with vasopressin and neurophysin II. Recently, there is an emerging body of literature implicating the association between copeptin and cardiovascular mortality in patients with chronic kidney disease or end- stage renal disease [30]. Taken together, it is unclear whether copeptin may provide additional insights into the volume regulation of patients with ESRD and its cardiac sequelae.

Although our study represents the largest cohort of ESRD patients undergoing frequent hemodialysis with cardiac MRI imaging and biomarker analyses, it is important to acknowledge the exploratory nature of the present work. Our sample size is limited to discern all potential pathways associated with LVH regression. In the future, additional biomarkers may be tested to enhance our present understanding of the biomarker profile of our patients with ESRD and LVH. We have also made multiple comparisons to explore potential mechanistic pathways. We also acknowledge that the present associative results cannot address causality but rather provide a novel trajectory of investigation. LVH is an important surrogate marker in ESRD. Using the Toronto nocturnal hemodialysis cohort, survival was demonstrated to be superior in patients with LVH regression[31]. We have illustrated two potentially important pathways contributing to LVM reduction in ESRD. Given the clinical impact of LVH regression in ESRD and the novel therapeutic potential of klotho and extracelullar matrix homeostasis, our results may provide new therapeutic and dialysis targets for patients with ESRD.

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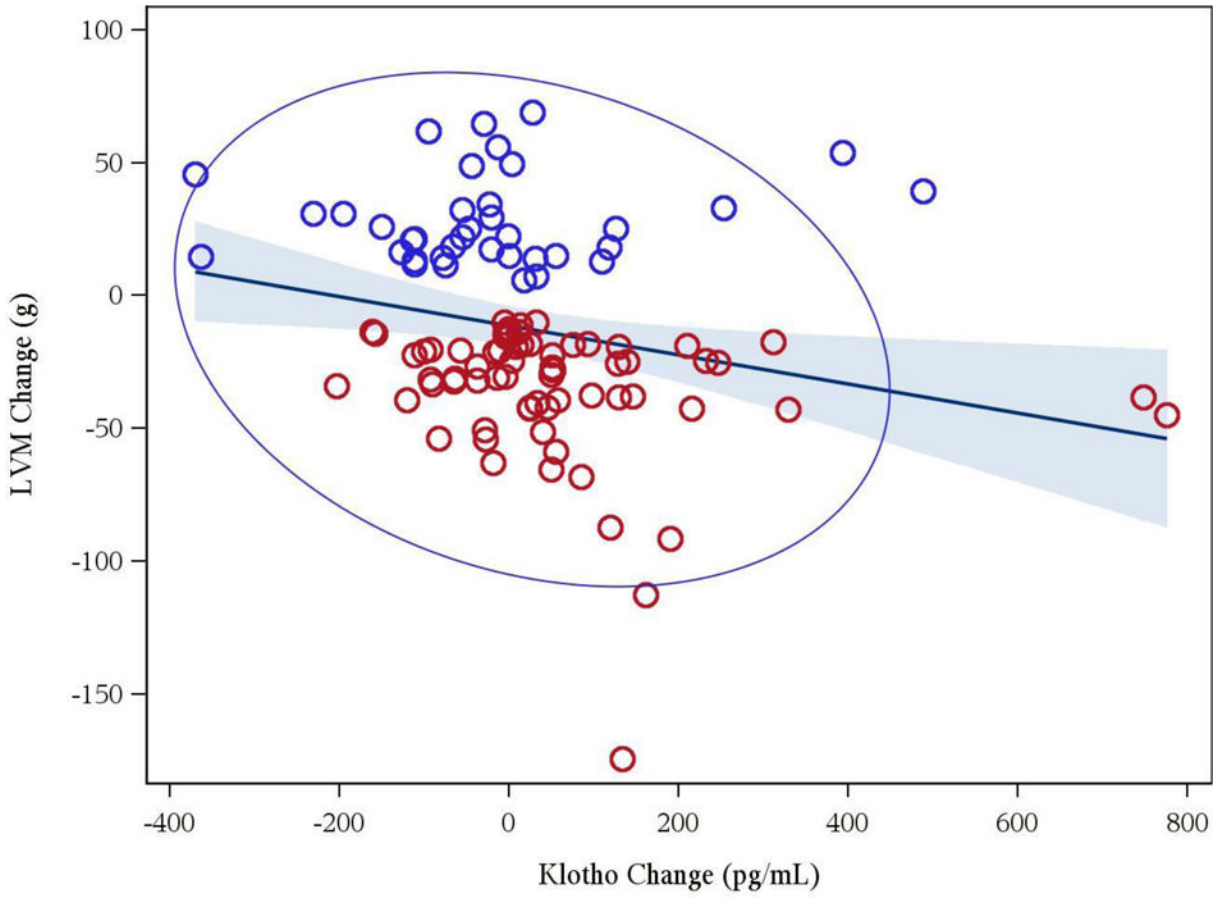

Figure 1.

Association between changes in Klotho and changes in left ventricular mass (r = −0.24, p = 0.014) [red circles denote regressors, blue circles denote progressors]

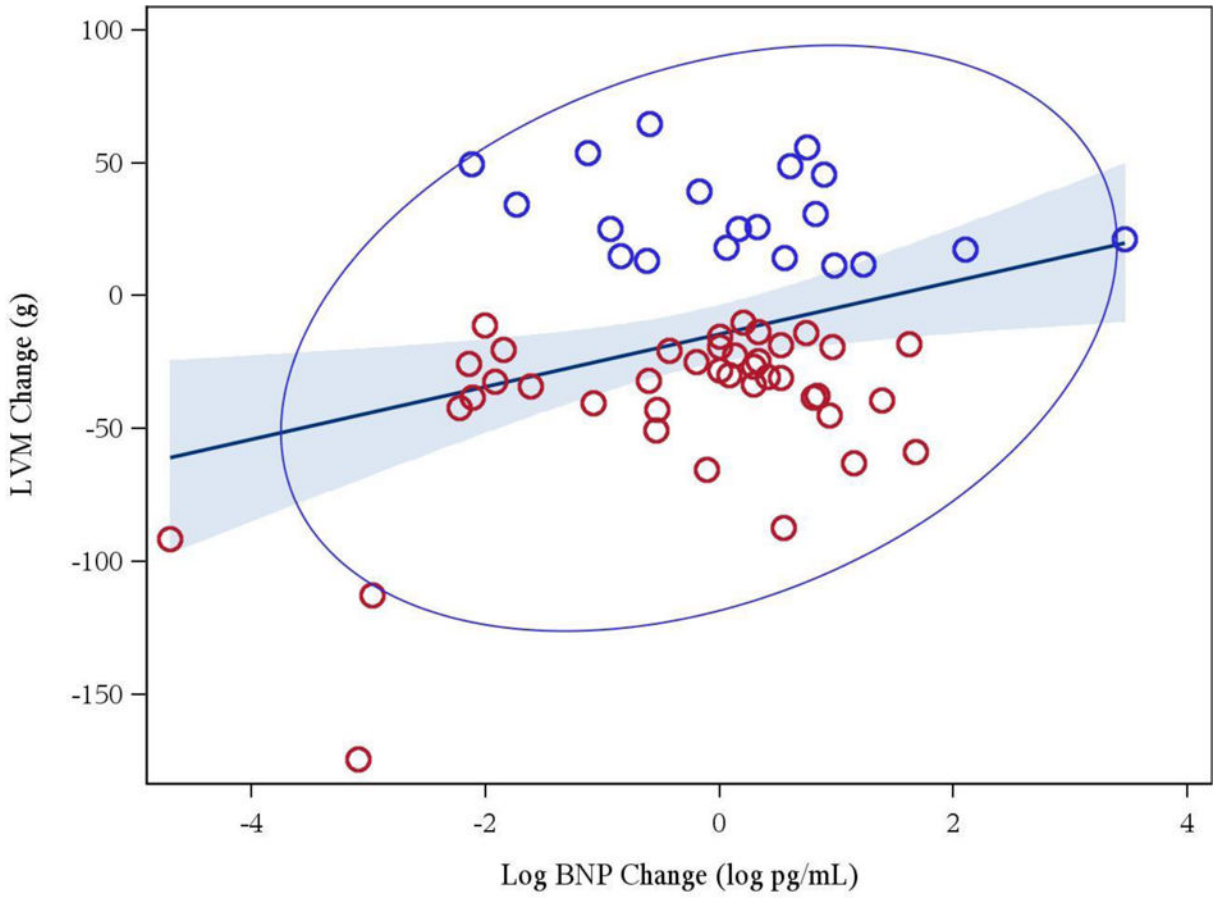

Figure 2.

Association between changes in log of brain natriuretic peptide and changes in left ventricular mass (r = 0.32, p = 0.013) [red circles denote regressors, blue circles denote progressors]

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Table 1

FHN Combined Daily and Nocturnal Trials

A								
Variables	**LVM Progress or Regress**					**Not Progress or Regress**		**P-value**
	Progress (N=45)		**Regress (N=77)**		**P-value**	**(N=121)**		
	N	**N(%) or Mean ± SD**	**N**	**N(%) or Mean ± SD**		**N**	**N(%) or Mean ± SD**	
Age	45	51.5 ± 12.3	77	50.5 ± 13.4	0.68	121	52.4 ± 14.4	0.33
Female	45	23 (51.1%)	77	27 (35.1%)	0.082	121	44 (36.4%)	0.51
Race/Ethnicity	45		77		0.69	121		0.58
Non-Hispanic White		14 (31.1%)		19 (24.7%)			37 (30.6%)	
Black (Hispanic or Non-Hispanic)		18 (40.0%)		36 (46.8%)			46 (38.0%)	
All Other		13 (28.9%)		22 (28.6%)			38 (31.4%)	
Years since ESRD	45	3.30 ± 3.75	77	5.81 ± 6.76	0.009	121		0.79
(Vintage)								
< 2 years		20 (44.4%)		26 (33.8%)	0.24		47 (38.8%)	
>= 2 years		25 (55.6%)		51 (66.2%)			74 (61.2%)	
LVM (g)	45	120 ± 41.5	77	158 ± 56.6	< .0001	121	139 ± 51.8	0.45
LVM Index (g/m^2)	45	62.0 ± 18.0	77	80.2 ± 30.4	< .0001	120	72.0 ± 25.1	0.68
LV Ejection Fraction (%)	45	59.7 ± 9.77	77	55.3 ± 10.6	0.027	121	56.2 ± 12.4	0.64
ALDOSTERONE (pg/mL)	41	387 ± 484	74	276 ± 468		113	277 ± 345	
ALDOSTERONE Log (pg/mL)	41	5.38 ± 1.05	74	5.07 ± 0.90	0.10	113	5.21 ± 0.81	0.80
BNP (pg/mL)	35	189 ± 197	61	334 ± 352		94	352 ± 372	
BNP Log (pg/mL)	35	4.70 ± 1.12	61	5.14 ± 1.36	0.10	94	5.16 ± 1.39	0.36
Copeptin (ng/mL)	44	220 ± 129	74	234 ± 155	0.61	118	236 ± 127	0.69
CRP (mg/dL)	44	0.95 ± 1.68	76	1.07 ± 1.89		121	1.35 ± 2.30	
CRP Log (mg/dL)	44	−.95 ± 1.48	76	−.86 ± 1.41	0.73	121	−.65 ± 1.40	0.19
FGF23 (pg/mL)	43	3290 ± 3419	75	4121 ± 4323		116	3206 ± 3846	
FGF23 Log (pg/mL)	43	7.29 ± 1.50	75	7.47 ± 1.60	0.53	116	7.22 ± 1.47	0.36
Klotho (pg/mL)	44	688 ± 297	75	648 ± 206	0.44	118	705 ± 290	0.23
MMP-2 (pg/mL)	43	129E3 ± 32566	73	137E3 ± 37099		113	136E3 ± 32814	

A								
Variables	**LVM Progress or Regress**					**Not Progress or Regress**		**P-value**
	Progress (N=45)		**Regress (N=77)**		**P-value**	**(N=121)**		
	N	**N(%) or Mean ± SD**	**N**	**N(%) or Mean ± SD**		**N**	**N(%) or Mean ± SD**	
MMP-2 Log (pg/mL)	43	11.7 ± 0.26	73	11.8 ± 0.28	0.28	113	11.8 ± 0.24	0.48
MMP-7 (pg/mL)	42	41046 ± 26560	73	39983 ± 29386		112	40167 ± 26353	
MMP-7 Log (pg/mL)	42	10.4 ± 0.63	73	10.4 ± 0.66	0.61	112	10.4 ± 0.67	0.98
MMP-9 (pg/mL)	43	113E3 ± 67065	73	128E3 ± 78205		113	124E3 ± 76201	
MMP-9 Log (pg/mL)	43	11.5 ± 0.57	73	11.6 ± 0.64	0.39	113	11.5 ± 0.68	0.86
TIMP-1 (pg/mL)	42	234E3 ± 65653	73	226E3 ± 59899	0.53	108	239E3 ± 53853	0.21
TIMP-2 (pg/mL)	41	125E3 ± 65761	70	113E3 ± 27096	0.27	104	12E4 ± 40344	0.70

B					
Variables	**LVM Progress (N=45)**		**LVM Regress (N=77)**		**P-value**
	N	**N(%) or Mean±SD**	**N**	**N(%) or Mean±SD**	
Dialysis Std Kt/Vurea	45	2.44 ± 0.39	76	2.45 ± 0.32	0.91
Baseline Urine (L / 24 hrs.)	45	0.27 ± 0.37	77	0.20 ± 0.33	0.22
Residual Renal Urea Clearance (mL/min)	45		77		0.39
= 0	45	23 (51.1%)	77	45 (58.4%)	
> 0 – 1	45	5 (11.1%)	77	13 (16.9%)	
> 1 – 3	45	14 (31.1%)	77	14 (18.2%)	
> 3	45	3 (6.7%)	77	5 (6.5%)	
Hypertension	45	42 (93.3%)	77	70 (90.9%)	0.64
Predialysis Diastolic BP (mmHg)	45	79.3 ± 13.5	77	82.7 ± 12.4	0.17
Predialysis Systolic BP (mmHg)	45	146 ± 19.9	77	150 ± 20.1	0.27
Myocardial Infarction	45	2 (4.4%)	77	9 (11.7%)	0.18
Congestive Heart Failure	45	4 (8.9%)	77	18 (23.4%)	0.045
Atrial Fibrillation	45	0	77	4 (5.2%)	0.12
Peripheral vascular disease	45	5 (11.1%)	77	9 (11.7%)	0.923
Cerebrovascular disease	45	4 (8.9%)	77	5 (6.5%)	0.625
Diabetes Mellitus	45	21 (46.7%)	77	29 (37.7%)	0.329

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B

Variables	LVM Progress (N=45)		LVM Regress (N=77)		P-value
	N	N(%) or Mean±SD	N	N(%) or Mean±SD	
Chronic pulmonary disease	45	1 (2.2%)	77	4 (5.2%)	0.424
Liver Disease	45	0	77	1 (1.3%)	0.443
Dialysis Access					0.277
Fistula	45	19 (65.5%)	77	41 (67.2%)	
Graft	45	8 (27.6%)	77	10 (16.4%)	
Catheter	45	2 (6.9%)	77	10 (16.4%)	
Antihypertensives	45	5 (11.1%)	77	18 (23.4%)	0.374
ACEI	45	16 (35.6%)	77	29 (37.7%)	0.816
ARB	45	10 (22.2%)	77	17 (22.1%)	0.985
Dihydropyridine CCB	45	18 (40.0%)	77	39 (50.6%)	0.248
Non-Dihydropyridine CCB	45	3 (6.7%)	77	4 (5.2%)	0.736
Beta Blockers	45	26 (57.8%)	77	42 (54.5%)	0.718
Peripheral Alpha Blockers	45	1 (2.2%)	77	3 (3.9%)	0.616
Centrally Acting Agent	45	9 (20.0%)	77	16 (20.8%)	0.918
Non-Specific Vasodilators	45	7 (15.6%)	77	9 (11.7%)	0.542
Diuretic	45	5 (11.1%)	77	10 (13.0%)	0.890
Statin	45	21 (46.6%)	77	30 (39.0%)	0.098
Phosphorus (mg/dL)	45	5.79 ± 1.47	77	6.26 ± 1.55	0.101
Potassium (mmol/L)	45	4.94 ± 0.83	77	4.95 ± 0.75	0.943

Table 2

The Effect of Frequency of Dialysis and Blood Pressure between Progressors and Regressors

Variable	Treatment Arm	Baseline Median (n) (interquartile range)	Month 12 Median (n) (interquartile range)	Mean Change from Baseline (95% CI)	LVM Response Effect (95% CI)	P-Value
Frequency of Dialysis (per week)	Progressors	3.0 (45) (3.0, 3.0)	3 (44) (3.0, 4.2)	0.61 (0.23 to 0.99)	0.80 (0.32 to 1.28)	0.001
	Regressors	3.0 (77) (3.0, 3.0)	4.9 (76) (3.0, 5.7)	1.41 (1.12 to 1.70)		
Pre-dialysis Diastolic BP (mmHg)	Progressors	77.0 (45) (69.8, 88.0)	83.1 (44) (71.9, 91.0)	2.46 (−0.49 to 5.40)	−7.94 (−11.52 to −4.36)	< 0.001
	Regressors	83.0 (77) (71.3, 90.7)	75.6 (76) (67.6, 84.4)	−5.48 (−7.77 to −3.20)		
Pre-dialysis Systolic BP (mmHg)	Progressors	148.8 (45) (132.3, 155.3)	151.6 (44) (141.5, 164.2)	4.97 (0.09 to 9.84)	−16.73 (−22.64 to −10.83)	< 0.001
	Regressors	149.0 (77) (136.0, 162.3)	136.1 (76) (123.8, 152.4)	−11.77 (−15.57 to −7.96)		

p-values indicate whether the LVM response effect from the mixed model for each variable is significant

Table 3

FHN Combined Daily and Nocturnal Trials Mixed Model Results (Percent Scale for Log Scale)

Variable	Total #	Progress or Regress	LVM Response Effect	95% Confidence Limits		P-Value
				Lower	Upper	
ALDOSTERONE Log (pg/ml)	116	Progress	−10.22	−28.05	12.04	0.34
		Regress	21.70	2.90	43.94	0.022
		Difference	35.55	2.96	78.46	0.030
BNP Log (pg/ml)	114	Progress	11.62	−32.73	85.21	0.67
		Regress	−32.11	−53.24	−1.43	0.042
		Difference	−39.18	−66.40	10.08	0.10
COPEPTIN (ng/ml)	118	Progress	13.99	−12.76	40.74	0.30
		Regress	15.07	−5.19	35.33	0.14
		Difference	1.08	−31.45	33.60	0.95
COPEPTIN Log (ng/ml)	118	Progress	9.89	−1.33	22.40	0.086
		Regress	6.53	−1.76	15.53	0.13
		Difference	−3.06	−15.07	10.65	0.64
CRP Log (mg/dL)	122	Progress	−21.98	−45.32	11.31	0.17
		Regress	−11.10	−31.93	16.09	0.38
		Difference	13.95	−26.13	75.77	0.55
FGF23 Log (pg/ml)	120	Progress	−25.33	−51.37	14.65	0.18
		Regress	−41.49	−57.67	−19.13	0.001
		Difference	−21.64	−53.17	31.11	0.35
KLOTHO (pg/ml)	119	Progress	−21.79	−75.16	31.57	0.42
		Regress	55.08	15.37	94.78	0.007
		Difference	76.87	10.48	143.26	0.024
MMP-2 (pg/ml)	117	Progress	1493.96	−8694.73	11682.65	0.77
		Regress	−8113.96	−15856.3	−371.64	0.04
		Difference	−9607.92	−21801.7	2585.81	0.12
MMP-2 Log (pg/ml)	117	Progress	0.68	−6.82	8.79	0.86
		Regress	−5.93	−11.29	−0.24	0.041

Variable	Total #	Progress or Regress	LVM Response Effect	95% Confidence Limits		P-Value
				Lower	Upper	
		Difference	−6.57	−14.87	2.54	0.15
MMP-7 Log (pg/ml)	117	Progress	−12.63	−23.05	−0.80	0.037
		Regress	−17.92	−25.44	−9.65	0.000
		Difference	−6.06	−19.05	9.01	0.41
MMP-9 Log (pg/ml)	117	Progress	6.51	−13.80	31.60	0.56
		Regress	0.42	−14.85	18.42	0.96
		Difference	−5.72	−26.56	21.03	0.64
TIMP-1 (pg/ml)	117	Progress	−1785	−15274	11703	0.79
		Regress	−16671	−26776	−6567	0.001
		Difference	−14886	−30397	624	0.060
TIMP-2 (pg/ml)	114	Progress	−5967	−14983	3048	0.19
		Regress	−13820	−22004	−5636	0.001
		Difference	−7853	−14653	−1052	0.024

p-values indicate whether the LVM response effect from the mixed model for each variable is significant.

Table 4

Baseline Demographics of Patients with and without Left Ventricular Hypertrophy at Baseline in FHN Combined Daily and Nocturnal Trials

	LVH (N=34)					Not LVH (N=88)				
Variables	**Progress (N=7)**		**Regress (N=27)**		**P-value**	**Progress (N=38)**		**Regress (N=50)**		**P-value**
	N	**N(%) or Mean±SD**	**N**	**N(%) or Mean±SD**		**N**	**N(%) or Mean±SD**	**N**	**N(%) or Mean±SD**	
Age	7	41.9 ± 13.2	27	47.6 ± 13.3	0.32	38	53.3 ± 11.5	50	52.1 ± 13.3	0.66
Female	7	3 (42.9%)	27	4 (14.8%)	0.10	38	20 (52.6%)	50	23 (46.0%)	0.54
Race/Ethnicity	7		27		0.094	38		50		0.95
Non-Hispanic White	7	4 (57.1%)	27	5 (18.5%)		38	10 (26.3%)	50	14 (28.0%)	
Black (Hispanic or Non-Hispanic)	7	1 (14.3%)	27	13 (48.1%)		38	17 (44.7%)	50	23 (46.0%)	
All Other	7	2 (28.6%)	27	9 (33.3%)		38	11 (28.9%)	50	13 (26.0%)	
Years since ESRD (Vintage)	7		27		0.039	38		50		0.99
< 2 years	7	4 (57.1%)	27	5 (18.5%)		38	16 (42.1%)	50	21 (42.0%)	
>= 2 years	7	3 (42.9%)	27	22 (81.5%)		38	22 (57.9%)	50	29 (58.0%)	
ALDOSTERONE (ug/mL)	7	331 ± 499	27	176 ± 173		34	399 ± 488	47	333 ± 568	
ALDOSTERONE Log (ug/mL)	7	5.20 ± 1.04	27	4.87 ± 0.71	0.33	34	5.42 ± 1.06	47	5.19 ± 0.98	0.31
BNP (pg/mL)	6	361 ± 189	24	437 ± 436		29	154 ± 182	37	267 ± 271	
BNP Log (pg/mL)	6	5.72 ± 0.68	24	5.61 ± 1.10	0.82	29	4.48 ± 1.08	37	4.83 ± 1.43	0.28
Copeptin (ng/mL)	7	185 ± 94.3	27	269 ± 205	0.30	37	227 ± 134	47	215 ± 116	0.65
CRP (mg/L)	7	0.54 ± 0.56	27	0.67 ± 1.10		37	1.03 ± 1.82	49	1.29 ± 2.18	
CRP Log (mg/L)	7	−1.2 ± 1.35	27	−1.3 ± 1.48	0.85	37	−.90 ± 1.52	49	−.60 ± 1.31	0.32
FGF23 (pg/mL)	7	4134 ± 4037	27	5622 ± 4687		36	3126 ± 3327	48	3276 ± 3905	
FGF23 Log (pg/mL)	7	7.67 ± 1.37	27	8.14 ± 1.16	0.36	36	7.21 ± 1.53	48	7.10 ± 1.70	0.75
Klotho (pg/mL)	7	909 ± 514	27	603 ± 192	0.17	37	646 ± 224	48	674 ± 211	0.55
MMP-2 (pg/mL)	7	128E3 ± 32069	27	136E3 ± 40610		36	129E3 ± 33111	46	137E3 ± 35340	
MMP-2 Log (pg/mL)	7	11.7 ± 0.30	27	11.8 ± 0.30	0.68	36	11.7 ± 0.25	46	11.8 ± 0.27	0.29
MMP-7 (pg/mL)	7	27795 ± 13379	27	33724 ± 20310		35	43696 ± 27852	46	43657 ± 33258	
MMP-7 Log (pg/mL)	7	10.1 ± 0.55	27	10.2 ± 0.65	0.65	35	10.5 ± 0.63	46	10.5 ± 0.66	0.73
MMP-9 (pg/mL)	7	85090 ± 42252	27	88928 ± 56033		36	118E3 ± 70077	46	151E3 ± 80644	

Variables	LVH (N=34)					Not LVH (N=88)				
	Progress (N=7)		Regress (N=27)		P-value	Progress (N=38)		Regress (N=50)		P-value
	N	N(%) or Mean±SD	N	N(%) or Mean±SD		N	N(%) or Mean±SD	N	N(%) or Mean±SD	
MMP-9 Log (pg/mL)	7	11.3 ± 0.45	27	11.2 ± 0.60	0.91	36	11.5 ± 0.59	46	11.8 ± 0.57	0.04
TIMP-1 (pg/mL)	6	2E5 ± 32958	27	242E3 ± 78423	0.21	36	239E3 ± 68314	46	216E3 ± 43916	0.09
TIMP-2 (pg/mL)	6	103E3 ± 14950	25	12E4 ± 29988	0.20	35	129E3 ± 70385	45	109E3 ± 24891	0.12