ASSOCIATION OF TROPONINS WITH SEX HORMONES IN STABLE HEMODIALYSIS PATIENTS

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ABSTRACT

Background

Cardiovascular events are one of the major causes of death in dialysis. Usually, troponins are regarded gold standard for detecting cardiovascular complications. In addition, studies have confirmed a difference between men and women regarding cardiovascular and renal diseases.

Objectives

To investigate the relation between troponins (Hs-TnT) and biomarkers, including sex hormone binding globulin (SHBG), estradiol, total and free testosterone, ferritin, Albumin, CRP and estimated glomerular filtration rate (eGFR) in hemodialysis.

Patients and Methods

Sixty-one hemodialysis patients were enrolled in this study. Hs-cTnT, cTnI, total testosterone, free testosterone, SHBG, estradiol, Albumin, CRP, ferritin, urea and creatinine were estimated.

Results

Hs-cTnT was associated with Albumin (R=-0.3; P=0.01). Troponin showed no association with the rest of the markers. The mean values in the dialysis group were: Hs-cTnT 93.8 pg/ml; ferritin 222.1 µg/l; albumin 4.18 g/dl; CRP 18.4 mg/l; urea 143.3 mg/dl; creatinine 9.4 mg/dl; total testosterone 1.46 ng/ml; free testosterone 28.75 pg/ml when compared to the control group, the differences between serum values in dialysis group were significant $P < 0.05$. The rest of the biomarkers showed no significant differences.

Conclusion

The most interesting finding was a negative association of Albumin with Hs-cTnT, indicating the possible use of albumin-adjusted Hs-cTnT rather than troponin alone to better predict critical cardiac events in hemodialysis. Troponin did not associate with SHBG, estradiol and testosterone hormones, possibly indicating no obvious role of these hormones in troponin regulation. Estimated GFR levels showed no correlation, suggesting troponin might be further degraded before renal elimination.

Keywords: *Estradiol, SHBG, troponins, cardiovascular diseases, renal function, testosterone.*

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INTRODUCTION

About half of renal failure patients die from cardiovascular diseases and in some studies, coronary artery disease was prevalent in 44.3 % of chronic renal failure patients [1]. Dialysis is the last option for end-stage renal failure, and although it prolongs life, dialysis has many complications, such as myocardial infarction (MI) and acute coronary syndrome [1]. In recent years, troponin markers have emerged as the gold standard for assessing myocardial dysfunction. However, numerous studies showed elevated troponin levels in stable dialysis patients showing no signs of cardiac damage [2]. Moreover, new studies reported a noticeable difference in troponin levels between males and females [2]. Interestingly, kidney function also differs between women and men and chronic kidney disease is more prevalent in men than women [3].

Although the exact cause is still under investigation, it is logical to assume a possible role of steroid sex hormones to account for these differences among men and women [3]. For example, androgens regulate many cellular and molecular pathways; genetically chronic kidney disease is associated with elevated testosterone levels [4]. Of note, steroid hormones are usually transported in blood by protein carriers such as sex hormone binding globulin (SHBG), which affect the concentration, activity and bioavailability of sex hormones including testosterone; also, free testosterone might contribute to CKD progression[5].

In men, better renal function was correlated with higher SHBG serum levels [6] and lower testosterone levels were correlated with lower eGFR among men [6]. Moreover, in women, elevated testosterone levels were associated higher prevalence of kidney cyst growth, with or without ovariectomy [7].

In vitro, animal studies reported that sex hormones might contribute to cardiovascular disease [8]. However, the exact role of endogenous sex hormones has not been studied extensively in men.

Human studies reported that low testosterone and follicle-stimulating hormones were associated with kidney dysfunction [9,10] and troponin T levels are usually higher in men than in women; this general assumption is caused by differences in cardiac mass between women and men [11] and a 2-fold higher cut-off value for men was suggested to use for myocardial infarction diagnosis [11].

Additionally, in the past few decades, SHBG is used as a possible marker for metabolic syndrome [12] and a predictor of cardiovascular disease and type 2 diabetes mellitus [12]. To our knowledge no studies have investigated the association between SHBG and troponin levels in hemodialysis patients. Few conflicting studies focused on the relation of troponin with testosterone and estradiol in dialysis patients. Most previous studies focused on stable renal disease and omitted the role of these hormones at later (4,5) stages of kidney disease.

To better understand the role of troponin in dialysis patients, we studied the relation between steroid sex hormones and troponin levels in dialysis patients (stage 4,5). The main aims of this study were to investigate the association between cardiac biomarker troponin T with renal function, Albumin, ferritin, CRP and sex steroid hormones (SHBG, estradiol, total testosterone and free testosterone).

PATIENTS AND METHODS

Ethical approval of this study was provided by the Faculty of Science, University of Sulaimani research board in October/ 2021. Furthermore, all participants consented to use their information before sample collection.

We enrolled 61 patients with end-stage renal disease (eGFR < 20) who were on regular dialysis (twice or thrice per week) for more than three months at Sulaimani Shar's Hospital dialysis department Figure 1. The number of cases at Sulaimani City during the study period determined the sample size.

We recorded patient profile which included age, gender, residential area, education status, duration of dialysis, frequency of dialysis per week along with short and long intradialytic intervals, smoking status, vascular access, medications, underlying diseases and covid-19 contraction. This study excluded patients diagnosed with acute myocardial infarction, heart failure, pulmonary embolism, major surgery, trauma, and valvular intervention before six months. In addition, patients with non-alcoholic fatty liver diseases were also excluded. Forty-two (68.8 %) patients were treated with hemodialysis two times a week and 19 (31.2 %) thrice a week. Regarding short and long interdialytic intervals, (72.0 %) samples were taken in short interval, while (28.0 %) were taken in long interval. For patients receiving weekly hemodialysis three times, the long interdialytic interval was two-day interval between hemodialysis sessions. The short interdialytic interval was one-day interval between hemodialysis sessions. For patients who have received dialysis two times, the long interdialytic interval was three-day interval between hemodialysis sessions. The short interdialytic interval was two-day interval between hemodialysis sessions.

Among the asymptomatic patients (80.4 %) patients were receiving low flux hemodialysis, while (19.6 %) were high flux using AK 200 ultra–S and Baxter AK 98 hemodialysis machine. Blood flow was between 250 – 350 mL/ min with a mean (of 307.8 ± 41.1 mL/min), and dialysate temperature was between 35 – 37 °C. The standard dialysate fluid compositions were sodium 140 mmol/L, potassium 2 mmol/L, calcium 1.5 mmol/L, magnesium 0.5 mmol/L, chloride 111 mmol/L, [CH3COO] − 3 mmol/L, HCO3 32 mmol/L, with the initiation of dialysis, each patient was given heparin dose of 5000 IU. After dialysis, an erythropoietin dose of 4000 IU was recommended for the patients.

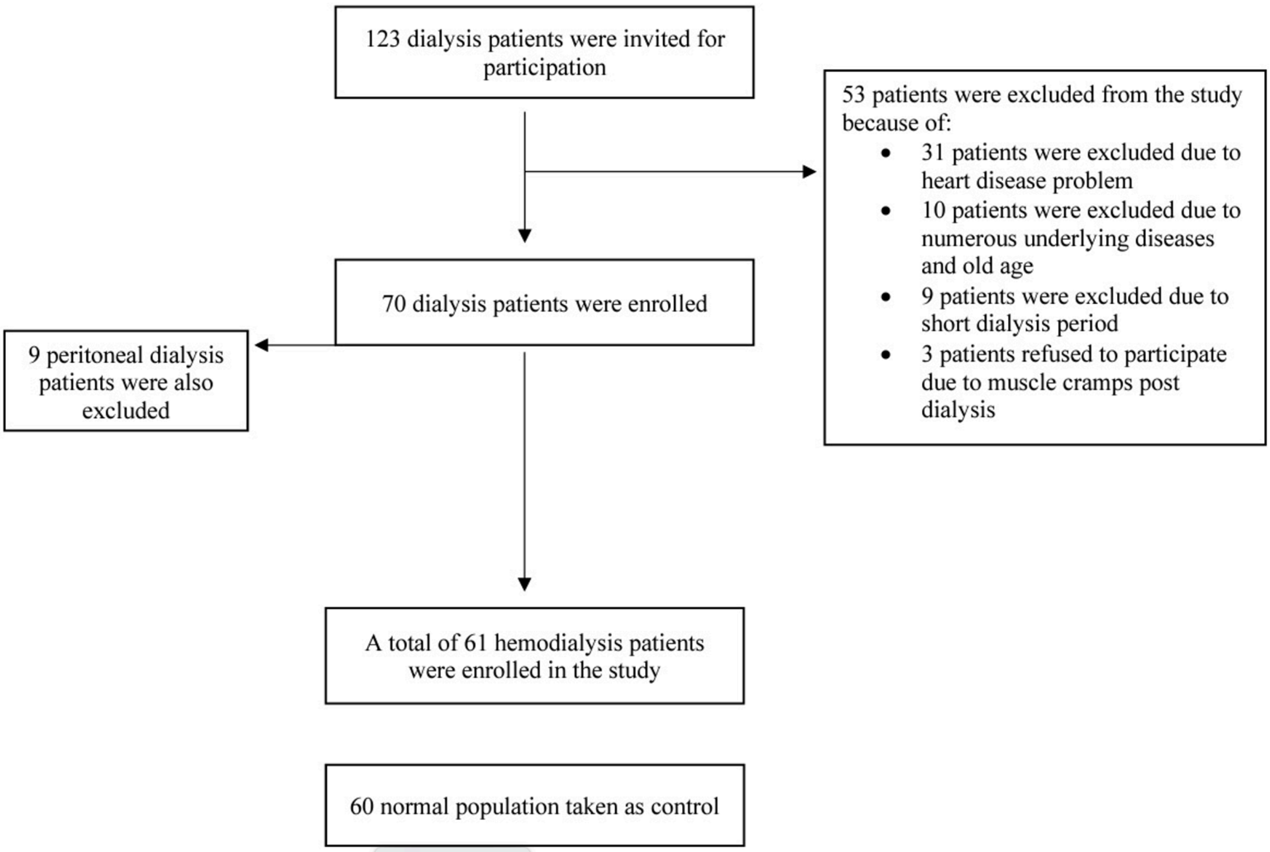

Figure 1. Flow chat of study participants.

Laboratory analysis

Blood samples were collected from the subjects at baseline before the initiation of hemodialysis and after the completion of dialysis. High-sensitive cardiac troponin T, cTnI, total testosterone, free testosterone, SHBG, estradiol (E2), c-reactive protein (CRP), Albumin, urea, creatinine, eGFR, ferritin, were measured for all selected patients. All assays were analyzed using electrochemiluminescence immunoassay Cobas e411 and absorbance photometry Cobas C111 systems by Roche Diagnostics. The detection limit of hs-Tn T was five pg./ml, a cut-off points at 99th percentile was 14 pg./ml, and coefficient of variation less than or equal to 10 % was 13 pg./ml. As for hs-cTn I, the detection limit and a cut-off at 99th percentile was 0.16 ng/ml, with coefficient of variation less than or equal to 10 % was 0.3 ng/ml. The estimated glomerular filtration rate (eGFR) was calculated using CKD-EPI-2021 (Chronic Kidney Disease Epidemiology Collaboration) creatinine equation [13]. Free testosterone was calculated according to Vermeulen et al 1999 formula [14].

Statistical analysis

Results are expressed as mean ± SD and results with non-normal distribution are expressed as median (interquartile range). Kolmogorov-Smirnov was used to check for the normality of distribution for continuous variables. The paired t-test and Wilcoxon test were used to compare parametric and non-parametric continuous variables, respectively. An unpaired t-test was used to compare variables between hemodialysis and control population. Spearman's Rho correlation was used to association cTnT levels with other studied biomarkers. The SPSS version 11.0 (SPSS, Inc., Chicago, IL, USA) was used to achieve all statistical calculations, p-values < 0.05 were statistically significant.

RESULTS

Demographic data of hemodialysis patients

This case-control study included hemodialysis patients registered at dialysis centre of Shar Hospital.

The participants were asked to fill a questionnaire with the aid of a professional nurse and a postgraduate student. Patient baseline characteristics are summarized in (Table 1). Sixty-one hemodialysis patients were enrolled of whom (12.2%) suffered from adverse clinical outcome within 120 days and were deceased.

The mean age of our study participants was 53.85 ± 7.19 which was matched to our control group 57.4 ± 7.31. The percentage of patients who were smokers was 21.3 % of the patients were smokers and none of our study participants had any types of allergies. Most of the study participants were on supplements which mainly included vitamin B 12. The study participants were on various antihypertensive medications, and 56 % of the study participants were on blood transfusion. The general dialysis parameters of our hemodialysis patients are illustrated in Table 2. The majority (84%) of patients were on dialysis for more than one year and the remaining group were at least three months on dialysis. All patients were stable patients and has not suffered previously or at the time of the dialysis from cardiac complications. The majority (68.8 %) of patients were on dialysis twice per week. After two hours rest at the dialysis center, we withdrew blood from the patients at the dialysis center. Pre and post dialysis blood pressure was recorded for all the patients, blood pressure levels dropped for all patients after dialysis. Pre and post dialysis weight was also recorded and as expected, due to ultrafiltration, the patients' weights dropped in all of the patients. Measured laboratory parameters in studied population and in control population

The difference in serum biomarker levels between hemodialysis patients and the control group is shown in (Table 3). The difference in mean ± standard deviation was statistically tested by using unpaired, parametric student's t-test and difference in median (interquartile range) was statistically tested by using an unpaired, non-parametric t-test with p-value (<0.05) considered statistically significant. Hs-cTnT levels was significantly higher in hemodialysis patients 93.78 (109.23) compared to levels in control subjects 6.22 (5.36), P ≤ 0.001. The results of this study also showed that ferritin, CRP, urea, creatinine, and total and free testosterone levels were significantly different from the control group. In contrast, we found that there was no significant difference in cTnI, E2 and SHBG between the two groups. *P < 0.05 considered significant. The student's T-test was to analyze the difference between the two groups. Hs-cTnT: high-sensitive troponin T; cTnI: cardiac troponin I; SHBG: sex hormone binding globulin; T. testosterone: total testosterone; F. testosterone: Free testosterone, association of Troponin T with hormones and other study biomarkers

Using statistical test of Spearman's Rho correlation, there was a negative correlation between Albumin and hs-TnT (R=-0.3; P=0.01); the rest of the parameters had very weak association with hs-cTnT and none of the associations showed statistical significance, (Table 4).

Table 1. Basic characteristics of study participants.

	Hemodialysis patients (n=61) %)	Control group (n=50) (%)
Mean age (Year)	53.85 ± 7.19	57.4 ± 7.31
Sex		
Male	51	67
Female	49	33
Smoking	21.30	3
Allergy	None	None
Residential area City	60	85
Urban	40	15
Supplement intake	85	3
Medications		
Statins	14	5
Diuretics	28	-
Beta-Blockers	4	2
Calcium channel - blocker	8	-
Co-morbidities		
Diabetes Miletus	64	None
Hypertension	100	2
Covid-19 contraction	28	39
Blood transfusion	56	-

Table 2. Dialysis parameters.

Dialysis parameter	Prevalence No (%)
Dialysis duration	
≤ 1 Year	16
>1 Year	84
Frequency of dialysis per week	
Thrice	19 (31.2)
Twice	42 (68.8)
Ultrafiltration rate (ml/hr./kg)	12.2 ± 5.5
Blood flow (ml/min)	307.8 ± 41.1
High flux membrane	12 (19.6)
Low flux membrane	49 (80.4)
Duration of the dialysis session	
Three hours	(67.2)
Four hours	(32.8)
Vascular access	
Arteriovenous fistula	(96)
Central Venous Catheter	(4)
Blood pressure (mmHg)	
SBP pre-dialysis	162.6 ± 23.1
DBP pre-dialysis	82.8 ± 14.6
SBP post-dialysis	159.3 ± 36.5
DBP post-dialysis	83.8 ± 16.2
Body weight (Kg)	72.3 ± 14.3
Pre-dialysis	69.2 ± 14.0
Post-dialysis	

Table 3. Differences in study parameters between hemodialysis patients and controls.

Biomarkers	Mean ± SD Median (IQR)		p-value
	Cases	Control	
Hs-cTnT (pg./ml)	93.78 (109.23)	6.22 (5.36)	< 0.001*
cTnI (ng/ml)	0.1 ± 0.0	0.1 ± 0.0	0.114
SHBG (nmol/l)	40.32 ± 21.22	38.03 ± 18.87	0.600
Estradiol (pg./ml)	26.63 (24.07)	26.13 (21.44)	0.91
T. Testosterone (ng/ml)	1.46 ± 1.51	3.12 ± 2.05	< 0.001*
F. Testosterone (pg./ml)	28.75 ± 28.35	7.49 ± 8.46	< 0.001*
Ferritin (μg/l)	222.1 ± 310.7	88.64 ± 90.80	0.049
Albumin (g/dl)	4.18 ± 0.45	3.89 ± 0.53	0.001
CRP (mg/l)	18.47 ± 50.33	2.51 ± 1.65	0.014
Urea (mg/dl)	143.3 ± 38.8	28.8 ± 8.38	< 0.001 *
Creatinine (mg/dl)	9.4 ± 2.7	0.84 ± 0.18	< 0.001 *

Table 4. Spearman's Rho association of troponin T with hormones and other study biomarkers

Biomarkers	Troponin T Spearman's Rho correlation		p-Value
	R	R2	
SHBG (nmol/l)	-0.2133	0.045	0.241
Total testosterone (ng/ml)	0.11	0.012	0.42
Estradiol (pg./ml)	0.47	0.222	0.2
Free testosterone (pg./ml)	0.082	0.006	0.65
Ferritin (µg/l)	0.194	0.038	0.149
Albumin (g/dl)	- 0.369	0.136	0.01*
CRP (mg/l)	0.215	0.046	0.11
Urea (mg/dl)	0.238	0.0566	0.08
Creatinine (mg/dl)	0.05	0.003	0.71
eGFR (ml/min/1.73 m2)	0.006	0.000	0.96

***P <0 .05 considered significant. Spearman's Rho test was used to analyze the association. Hs-TnT: high-sensitive troponin T; SHBG: sex hormone binding globulin.**

DISCUSSION

Troponin association with renal function

Although troponin is considered the standard gold biomarker for myocardial infarction detection, however, it is well established now that elevated troponin levels are prevalent in stable dialysis patients [15]. This poses a clinical challenge to physicians who try to diagnose patients with acute MI in dialysis patients; numerous data reported conflicting results about the role of renal function in troponin clearance [15]. In this study, we investigated the association of renal function with troponin levels in dialysis patients (stage 4,5).

Our data revealed no association between eGFR and troponin T levels in dialysis patients, indicating no possible role of kidney in clearing troponin from body; this is in agreement with the large molecular weights of both troponin T (35 kDa respectively) which cannot be filtered by glomerular filtration. However, the role of the renal glomerular in troponin clearance is also still controversial [16]. Most previous studies investigating the relation between troponin and eGFR are performed on different study designs. For example, a study on stable (non-dialysis) end stage renal disease [17], there was a gradual increase in troponin T levels and a strong association between troponin T levels and eGFR [17], this discrepancy with our results might be attributed to the fact that they have used non dialysis patients. Studies in normal populations also showed a slight decrease in eGFR levels was associated with increased troponin levels [18]. In addition, we think our data might not be statistically significant because we used a narrow range of patients eGFR less < 20; hence, it is not possible to show the association of small changes in serum creatinine with troponin levels; larger sample size and patients with different stages of end renal disease (stages 2,3) might be necessary to draw firm conclusion about the relation between renal function and troponin levels.

Troponin relation with Albumin

The most interesting and unpublished finding in this study is the negative association of Hs-cTnT levels with Albumin (R2=-0.369, P=0.01). Of note, many previous studies showed an obvious relationship between low albumin levels with coronary heart disease [19,20]. A study reported low albumin level was an independent risk factor for acute coronary syndrome (ACS) and albumin level lower than 4.71 g/dL had 84.3% sensitivity and 84.5% specificity in identifying individuals at higher risk of ACS [20]. This finding is also supported by another investigation showing albumin levels lower than 4.5 g/dL were correlated with higher risk of coronary heart disease incidence [20].

These results have important clinical relevance for future studies; we here suggest using troponin-albumin ratio as a more accurate predictor for survival in end stage renal disease; in a similar manner, many previous studies proposed using CRP albumin ratio as an important prognostic ratio. Our results verify the association between albumin levels and troponin might aid in clinical decision of cardiovascular diseases especially in dialysis patients. Notably, a study reported raising serum albumin levels in end stage renal disease might be preventing ACS [21]. These results indicate that we might be able to use Albumin adjusted troponin levels to differentiate between acute and chronic rise of troponin secretion [21], although further research might be needed to confirm this hypothesis.

Troponin association with SHBG in hemodialysis

To our knowledge this is the first study which investigated the relationship between SHBG and troponin in hemodialysis patients. This study showed no apparent differences between SHBG levels between hemodialysis patients and control groups. Also, there was no association between SHBG levels with troponin T levels. These results might indicate no apparent role of SHBG in end stage renal disease patients. Previous studies investigating the role of SHBG on CKD has been controversial. A study on diabetic patients with chronic kidney disease also found no association between SHBG and renal disease progression [22,23]. In a cross-sectional study of 1470 men in the United States who attended the morning session of Phase I of the Third National Health and Nutrition Examination Survey (NHANES III) there was also no association between SHBG and eGFR after adjusting eGFR with age [24]. Conversely, few studies concluded a lower SHBG was associated with lower eGFR levels. In a cohort of 889 men, SHBG levels in the highest quartile range were negatively associated with a risk of low eGFR. However, this study was performed on men with normal renal function and who were overweight and glucose intolerance [6].

Troponin Association with Testosterone in Hemodialysis patients

Research on the role of circulating testosterone levels in cardiovascular disease has been inconclusive, and in particular less is known about the testosterone levels in dialysis patients and whether there is association between testosterone change in cardiovascular events. In this current study, we looked into the association between testosterone with troponin T and eGFR levels in stable hemodialysis patients. The results showed no association between troponin with total testosterone and free testosterone, indicating that in late-stage renal disease testosterone might not contribute to development of cardiac events, although it is hard to speculate the role of these hormones in cardiovascular diseases and further cellular and molecular studies might be needed to further confirm these results, these observational results have clinical implications in daily practice. For example, it is still not clear whether administration of testosterone might improve glycemic control and insulin sensitivity in diabetic patients [25]. however, in practice, exogenous testosterone administration has many unwanted side effects, and our results further support no need for testosterone administration in diabetic patients, although further larger clinical and molecular studies are needed to draw firm conclusions about testosterone therapy.

Large observational and prospective studies concluded low serum testosterone was associated with higher cardiovascular risk in older men [26,27]. Conversely, several studies also showed that testosterone was not contributing to development of cardiovascular diseases[28].

These contradicting results are expected as several factors such as study design, bias and confounding factors might cause these variations. Analytical limitation of testosterone measurements also is a strong contributor to inconsistent results, in particular, testosterone radioimmune assays and chemiluminescence have many limitations, and mass spectrometry is recommended to assess testosterone accurately, and it is also still under debate whether to measure free testosterone or not [29].

Troponin association with estradiol

Our data showed no association between troponin and estradiol serum levels. Suggesting that estradiol might not be associated with troponin levels in hemodialysis patients. Studies investigating a direct relationship between estradiol and troponin T levels are limited. Therefore, we couldn't compare our results directly to previous results. Estrogens have been repeatedly found to be cardio-protective in women through many pathways, menopausal women generally have higher risk of cardiovascular incidents compared to non-menopausal women. Notably, in women patients who underwent heart surgery and took 17β-estradiol, the troponin I levels was similar to the placebo group; these findings might indicate no direct relation between estradiol and troponin levels [30].

Although this study showed no apparent relation between serum estradiol levels and troponin and eGFR levels (Not shown), these finding cannot exclude a possible role of estrogen in cardiac and troponin regulations in renal disease. Cellular and genetic studies indicate a strong role estrogen in renal disease, for instance, estrogen receptor and estradiol regulate more than 10.000 renal genes [31], and in both animal models and clinical studies, abnormalities in estradiol and estrogen receptor pathways were associated with glomerular necrosis and cardiac abnormalities [32,33]. In addition, a study found lower estradiol were significantly associated with higher hs-TnT in both men and post-menopausal women [34]. However, this study was performed on healthy participants with no cardiac or renal complications.

This study has several limitations, the obvious one is small sample size. Also, it would be better to study patients at earlier stages of end stage renal disease. In addition, pituitary hormones such as luteinizing and follicle stimulating hormones together with DHEA might help us to better understand the differences between males and females with regard of the roles of these hormone and sex differences in kidney disease. In addition, in the future, it is possible to include non-stable hemodialysis patients i.e., dialysis patients suffering from various cardiac complications.

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