JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1323971
J Contemp Med 2023;13(6):1033-1038

Original Article / Orijinal Araştırma

The Association between Serum Soluble Klotho Level and Cardiovascular Disease and Mortality in Routine Hemodialysis Patients

Rutin Hemodiyaliz Hastalarında Serumda Soluble Klotho Seviyesi ile Kardiyovasküler Hastalıklar ve Mortalite Arasındaki İlişki

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Abstract

Aim: Serum sKlotho plays a role in identifying the risk of cardiovascular disease or death in some human populations and animal experiments. In this study, the relationship between sKlotho levels and echocardiographic parameters after 18 months of follow-up and mortality at 30 months of follow-up in routine hemodialysis patients was investigated.

Matarial and Method: Groups of patients with different sKlotho rates (≥1.24 ng/ml and <1.24 ng/ml) and ages (<54 years and ≥54 years) were compared.

Results: No significant difference was found between the left ventricular mass index and left ventricular mass parameters calculated between the sKlotho <1.24 and ≥1.24 groups. No significant difference was found between the left ventricular mass index and left ventricular mass parameters calculated between the two different age (<54 years and ≥54 years) groups. In order to determine the association between sklotho and all-reason mortality in 136 patients followed for 30 months, two groups of 34 patients who died and 102 patients who survived were compared. A significant difference was observed between these two groups in terms of age, entry creatinine, sodium bicarbonate, C-reactive protein, albumin level and existence of Diabetes Mellitus. Although there was no considerable distinction in the two groups with regards to sklotho values, the sklotho level was found to be lower in the deceased group.

Conclusion: We think that sKlotho is not an appropriate indicator to predict uremic cardiomyopathy in the long term, but sKlotho levels may be useful in predicting mortality in studies with larger patient populations.

Keywords: Cardiomyopathy, hemodialysis, sKlotho

Öz

Amaç: Serum sKlotho, bazı insan populasyonlarında ve hayvan deneylerinde kardiyovasküler hastalık veya ölüm riskini belirlemede rol oynar. Bu çalışmada rutin hemodiyaliz hastalarında 18 aylık takip sonrası sKlotho düzeyleri ile ekokardiyografik parametreler ve 30 aylık takipteki mortalite arasındaki ilişki araştırıldı.

Gereç ve Yöntem: Farklı sKlotho oranları (≥1,24 ng/ml ve <1,24 ng/ml) ve yaşları (<54 ve ≥54) olan hasta grupları karşılaştırıldı.

Bulgular: sKlotho <1,24 ve ≥1,24 grupları arasında hesaplanan sol ventrikül kütle indeksi ve sol ventrikül kütle parametreleri arasında anlamlı fark bulunmadı. İki farklı yaş (<54 yaş ve ≥54 yaş) grubu arasında hesaplanan sol ventrikül kütle indeksi ve sol ventrikül kütle parametreleri arasında anlamlı fark bulunmadı. 30 ay takip edilen 136 hastada sKlotho ile tüm nedenlere bağlı ölüm arasındaki ilişkiyi belirlemek için, ölen 34 hasta ve yaşayan 102 hastadan oluşan iki grup karşılaştırıldı. Bu iki grup arasında yaş, giriş kreatinin, sodyum bikarbonat, C-reaktif protein, albümin düzeyi ve Diabetes Mellitus varlığı açısından anlamlı fark gözlendi. Sklotho değerleri açısından iki grup arasında belirgin bir fark olmamasına rağmen, ölen grupta sKlotho düzeyi daha düşük bulundu.

Sonuç: sKlotho'nun uzun dönemde üremik kardiyomiyopatiyi öngörmede uygun bir gösterge olmadığını, ancak sKlotho düzeylerinin daha geniş hasta popülasyonlu çalışmalarda mortaliteyi öngörmede yararlı olabileceğini düşünüyoruz.

Anahtar Kelimeler: Kardiyomiyopati, hemodiyaliz, sKlotho

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Received *(Geliş Tarihi)*: 08.07.2023 **Accepted *(Kabul Tarihi)*:** 11.10.2023

INTRODUCTION

Cardiovascular disease (CVD) is one of the main causes of mortality in routine hemodialysis patients. The CVD mortality rate in patients on routine hemodialysis is 10-20 times higher than in the general population.[1] In chronic kidney disease (CKD), soluble klotho (sKlotho) has a significant role in cardiovascular disease and death.[2-4]

sKlotho is a single transition transmembrane protein with a long extracellular body and short cytoplasmic tail that seems to regulate senility process.[5] Overexpression of the Klotho gene extends lifetime, while defective Klotho proteins are related with early death.[6,7] Moreover, serum sKlotho likely plays a role in identify the risk of cardiovascular disease or death in some populations and animal experiments.[4,8]

Serum sKlotho is reduced in the early stages CKD due to the effects of uremic toxins on DNA methyltransferase protein expression, which withdraws Klotho by hypermethylation.[19 This is why CKD or dialysis patients generally are disposed to to have lower sKlotho amounts than healthy individuals.[10-12]

Serums Klotho has been related with cardiovascular diseases and mortality in the general population and several subpopulations (i.e. the geriatric or client with diabetes).[13,14] On the other hand related research in CKD patients are inconsistent. The inconsistencies between studies in patients receiving hemodialysis treatment also aroused curiosity about the role of sKlotho in this patient group.

In this study, the relationship between sKlotho levels and echocardiographic parameters after 18 months of follow-up and mortality at 30 months of follow-up in routine hemodialysis patients was investigated.

MATERİAL AND METHOD

In this study, 136 routine hemodialysis patients aged between 18-80 years who were treated in the hemodialysis unit from December 2019 to February 2020 were included. 56 of these patients with echocardiographic results at the beginning and 18 months later were included in the research to define the long-term relationship between sKlotho and uremic cardiomyopathy and echocardiographic parameters. In addition, 136 patients were included in the study to evaluate the relationship between sKlotho and all-cause mortality by being followed up from our hemodialysis center and system. Patients who did not have an echocardiography at the beginning or after 18 months, who left our hemodialysis center, who died, who have a malignancy, under the age of 18, who have an autoimmune disease, who have a mitral valve disease, who have coronary artery disease, who have severe heart failure (New York Heart Association Class III or IV), who have a history of primary cardiomyopathy and who have active infection were removed from the research.

Initial sKlotho values and echocardiographic results at the beginning and after 18 months were recorded for all patients. General information, age, time of dialysis admission, underlying CKD etiology and comorbidity status of all patients were also enrolled. The systolic blood pressure (SBP) and diastolic blood pressure (DBP) measured before hemodialysis in the middle of the week were recorded. The blood results of all patients within the scope of the study were recorded, including the laboratory values at the beginning and after 18 months were simultaneously measured in 3-month periods sodium (Na), potassium (K), calcium (Ca), phosphorus (P), parathormone (PTH), hemoglobin (Hg), creatinine, albumin, C-reactive protein (CRP), ferritin, uric acid. Blood sample for sKlotho was received into standard biochemistry tubes. The peripheral venous blood samples were centrifuged at 3000g for 5 minutes, their serums were split and maintained at -20'C until the working day. Serums were melted on the day of study and all samples were analized on the same day.

The delta (Δ) difference values of the beginning and after 18-months laboratory values and echocardiography results of the patients were obtained. Values at the beginning and after 18 months were compared. Patients who died were enrolled to investigate the relationship between sKlotho and mortality based on 30-month follow-up.

Patients were separated into two groups as sKlotho value ≥1.24 ng/ml and <1.24 ng/ml according to the median value at the beginning. In addition, according to the median age at the beginning, it was separated into two groups as <54 years and ≥54 years. Initial patients were divided into two groups as deceased and surviving patients.

Echocardiographic Examination

Comprehensive echocardiography was implemented to patients in the cardiology clinic with a Philips Epiq 7G device (Philips, The Netherlands). Ventricular wall thick, ejection fractions, left atrium, M mode aorta systole and diastole diameter were measured

The left ventricular mass (LVM) was estimated through the Devereux equation: Left ventricular mass (gram)=0.8{1.04[(LVEDD+IVST+PWT)3_(LVEDD)3]}+0.6.[15] Surface area of the body was estimated with the Mosteller formula: Surface area of the body (m^2): (body weight x height/3600)1/2.[16]

Left ventricular mass index was estimated as:(LVMI)=(LVM/ body surface area) LVEDD: The end of the left ventricular end diastole diameter IVST: inter-ventricular septum thick PWT: left ventricular posterior area thick, VA: body weight, LA: Left atrial diameter, LVSF: Left ventricular systolic failure.

Echocardiographic measurements (Δ) values of the patients at baseline and after 18 months were calculated.

Statistical Analysis

Statistical analyses were made with the SPSS 22.0 (IBM) package program. Kolmogorov Smirnov and Shapiro Wilk tests were used for normality analysis. T-test was applied for determination of normally distributed parameters in pairwise comparisons and Mann-Whitney U test was used for non-normally distributed parameters. Spearman Correlation Test was used to detect correlation and cox-regression analysis to detect independent parameters. Values were given as the mean for those with regular distribution, and as the median (minimum-maximum) for those not normally distributed. Two groups with sKlotho rates ≥1.24 ng/ml and <1.24 ng/ml were compared. Statistics were made among the separated groups by separating them two groups with respect to age as <54 years and ≥54 years. In order to determine its relationship with all-cause mortality, patients were separated two groups as living and non-living patients. Parameters with P<0.05 were considered significant in paired comparisons.

RESULTS

There was no considerable distinction in the ΔSKB, ΔCa, ΔP, ΔPTH, ΔAlbumin, ΔHCO₃, ΔHgb parameters between the two groups divided with respect to the Sklotho <1.24 and ≥1.24 values of the 56 patients included in the study (**Table 1**). In the cox-regression analysis performed on parameters with P<0.1 to detect the presence of independent parameters, the presence of DM was found to be independently related with sKlotho levels. In addition, no significant difference was found between the ΔLA, ΔLVMI, ΔLVM, ΔLVEF, ΔIVST-PWT and Kt\V parameters calculated between the two groups (**Table 2**). While a significant difference was found between the two groups in terms of ΔSBP in the pairwise comparison according to age (<54 and ≥54 years), no considerable distinction was determined in the ΔCa, ΔP, ΔPTH, ΔAlbumin, ΔHCO₃, and ΔHgb parameters (**Table 1**). In addition, no significant difference was found between the ΔLA, ΔLVMI, ΔLVM, ΔLVEF, ΔIVST-PWT and Kt\V parameters calculated between the two groups (**Table 2**). According to the results of Spearman Correlation Analysis, it was determined that there is a correlation between ΔLVM and ΔCa, ΔLVEF with ΔSKB and ΔPTH, and ΔLA and ΔPTH. In order to determine the association between sklotho and all-reason mortality in 136 patients followed for 30 months, two groups of 34 patients who died and 102 patients who survived were compared (**Table 3**). A significant difference was observed between these two groups in terms of age, entry creatinine, HCO₃, CRP, albumin level and existence of DM (**Table 3**). However there was no considerable distinction in the two groups with regard to sklotho values, the sklotho level was found to be lower in the deceased group (P:0.084) (**Table 3**). In addition, P:0.057 was found to be the borderline value in terms of LVEF values between the two groups, and it was found to be lower in the deceased group. Age, CRP and HCO₃ levels were higher in the group of patients who died. Albumin, entry creatinine and sklotho were found to be lower (**Table 3**).

Table 1. Biochemical and demographic parameters

Parameters	sKlotho ≥ 1.24 ng/ml (n:30)	sKlotho < 1.24 ng/ml (n:26)	P	Age < 54 groups (n:35)	Age ≥ 54 groups (n:21)	P
Gender male female	 17 (57 %) 13 (43 %)	 13 (50 %) 13 (50 %)	0,261	 15 (42.9%) 20 (57.1%)	 9 (43 %) 12 (57 %)	0.174
Δ SBP (mm/Hg)	5.3±21.6	3.6±16.8	0.761	2.9±32.5	20.9±30.1	0.043
Δ DBP (mm/Hg)	0 (-20 - 20)	0 (-20 - 20)	0.627	0 ((-20)- 80)	10 ((-10) - 80)	0.060
Δ Kt/V urea	0.04 (-1.5-1.4)	1.70±0.26	0.331	0.08(1.52-2.0)	0 ((-1.28)-1.4)	0.175
Δ Calcium (mg/dl)	0.2±0.7	0.2±0.6	0.927	0.3±0.6	0.5±2.0	0.516
Δ Phosphorus (mg/dl)	-0.3±1.5	-0.2±1.4	0.756	-0.2±1.6	-0.1±1.7	0.859
Δ PTH (ng/ml)	-67.6±324.7	-139±444	0.506	-97.9±403	-62.8±316.8	0.735
Δ Albumin (g/dl)	0.3±0.3	0.3±0.4	0.763	0.4±0.5	0.4±0.9	0.853
Hb (g/dl)	0.5±1.5	0.2±1.6	0.404	0.4±3	0.7±1.8	0.720
Δ HCO₃ (mEq/L)	4.4±3.5	4.8±3.4	0.641	4.2±3.4	6.2±6.0	0.132

SBP: Systolic blood pressure DBP: Diastolic blood pressure Kt/V: Measure dialysis adequacy PTH: Parathroid hormone Hb:Hemoglobine HCO₃: Bicarbonate Δ:delta

Table 2. Comparison of echocardiographic parameters of sclotho and age groups

Parameters	sKlotho ≥ 1.24 ng/ml (n:30)	sKlotho < 1.24 ng/ml (n:26)	P	age < 54 groups (n:35)	age ≥ 54 groups (n:21)	P
Δ LA (cm)	0 ((-0.80)-1.2)	0.05 ((-0.6)-1.4)	0.867	0.1((-0.8)-1.4)	-0.1 ((-0.6)-1.2)	0.486
Δ LVMI (g/m²)	-14.9((-1962)-26.8)	0.02((-56)-55.9)	0.185	0 ((-119.9)-56)	-15.3((-1962)-18.8)	0.256
Δ LVEF (%)	0 ((-44.5)-25)	0 ((-5)-21)	0.560	0 ((-44.5)-25)	0 ((-22)-25)	0.696
ΔIVST/PWT	0 ((-0.11)-1.1)	0 ((-0.9)-0.20)	0.637	0 ((-0.1)-0.1)	0.01 ((-0.18)-107)	0.202

LVM: Left ventricular mass LVMI: Left ventricular mass index was IVST: inter-ventricular septum thick PWT: left ventricular posterior wall thick, LA: Left atrial caliber LVEF: Left ventricular ejection fraction

Table 3. Comparison of groups according to mortality status.

Parameters	Mortality group n:34	Living group n:102	P
sKlotho (ng/ml)	0.99 (0.7-7.5)	1.33 (0.65-21.9)	0.084
Age (year)	63.3±12.3	50.8±18.2	<0.001
BMI (g/m²)	26.9±6.2	25.5±5.9	0.295
Creatinine before dialysis (mg/dL)	6.7±2.0	7.8±2.3	0.019
Phosphorus (mg/dl)	4.5±1.5	4.9±1.6	0.270
Potassium (mmol)	5.1±0.9	5.3±0.7	0.355
HCO_3 (mEq/L)	20.2±3.1	18.8±2.9	0.016
Uric acid (mg/dl)	5.4±1.1	5.6±1.2	0.119
Gender Male Female	 18 (47.1%) 16 (52.9%)	 51 (50%) 51 (50%)	0.461
DM Yes No	 21 (61.8%) 13 (38.2%)	 29 (28.4%) 73 (71.6%)	0.001
Duration dialysis (month)	35 (3-108)	34.5 (3-271)	0.656
SBP (mmHg)	130 (90-160)	120 (90-160)	0.214
DBP (mmHg)	80 (60-100)	75 (60-100)	0.307
CRP (mg/dl)	11.3 (3.02-90.8)	4.25 (3.02-206)	<0.001
Ca (mg/dl)	8.5 (6.8-10.4)	8.6 (5.4-10.3)	0.687
Na (mEq/L)	137 (128.143)	136 (130-142)	0.360
Ferritin (ng/mL)	571.6 (6.1-1406.8)	513.7 (16.5-1922.9)	0.784
Albumin (g/dl)	3.5 (2.6-4.2)	3.8 (1.75-4.4)	<0.001
Hb (g/dl)	10.4 (5.13.3)	10.6 (6.4-14.5)	0.242
PTH (ng/mL)	300 (56.6-2000)	383.8 (4.9-2000)	0.341
LA (cm)	3.8 (2.9-5.5)	3.6 (2.2-5.3)	0.173
LVEF (%)	55 (25-65)	57 (25-69)	0.057
IVST (mm)	1.2 (0.9-1.6)	1.2 (0.8-4.7)	0.481
PWT (mm)	1.2 (0.9-1.4)	1.2 (0.8-1.7)	0.173
Kt/V urea	1.68 (1.16-2.32)	1.68 (1.16-2.36)	0.822

BMI: Body mass index HCO_3: Bicarbonate DM: Diabetes Mellitus CRP: C-reactive protein Ca: Calcium Na: Sodium IVST: inter-ventricular septum thick PWT: left ventricular posterior wall thick, LA: Left atrial caliber LVEF: Left ventricular ejection fraction

DISCUSSION

In this research, we found that sKlotho was not an appropriate indicator for predicting uremic cardiomyopathy during the 18-month follow-up period in chronic renal failure patients receiving hemodialysis treatment, and it was not significant in demonstrating all-cause mortality in the 30-month follow-up. Edip et al. and our study showed that sKlotho is neither a cardiac pathological marker nor a marker to be used in terms of cardiac protection. According to the results of the study of Edip et al. no significant correlation was found between instant Klotho and uremic cardiomyopathy and echocardiographic parameters.[17]

In this study, the similar results were found when we compared the sKlotho and echocardiographic parameters at the beginning and after 18 months surveillance. In the 30-month surveillance of 136 patients, no significant relationship was found between all-cause mortality and sKlotho, but sKlotho level was found to be lower in the group that resulted in mortality compared to the living group. There are studies supporting these results in our study. In a study by Zhang et al. in 105 patients, there was a considerable association in the sKlotho and IVST, but no considerable association was determined with LVEF, LA and LVMI.[18]

Seiler et al. noticed that sKlotho was not significantly associated with cardiovascular events and mortality in patients with CKD stages 2-4. In this study, a univariate analysis of 444 patients observed for a median of 2.6 years found that sKlotho was unable to prognosticate cardiovascular events or mortality and decompensated heart failure or mortality.[19,20]

In a late study by Buiten et al., it was found that serum sKlotho in dialysis patients was not detached related with the existence of coronary artery disease, but patients with low serum sKlotho showed a high rate of cardiovascular disease and left ventricular failure.[21] Another research by Nowak et al. also reported that sKlotho was not related in death in hemodialysis patients. In this research conducted with 239 hemodialysis patients, no correlation was found between sKlotho and all-cause mortality in cox-regression analysis.[22] In our analysis of mortality, it was found that sKlotho was not significant in showing all-cause mortality, but the sKlotho value was lower in the group of non-living (P:0.084).

In clinical studies in rodents, s-Klotho has been shown to protect for calcifications in blood vessel, while higher amounts of sKlotho in person who has not chronic kidney disease are related with fewer mortality and fewer incidence of coronary artery disease.[8,23]

In the research by Hong Cai et al. it was determined that low sKlotho was related with a higher CVD mortality rate.

It was found that lower sKlotho concentration could predict cardiovascular mortality in hemodialysis patients with no calcification or mild calcification.[24] In a study of 63 patients followed for 65 months by Naoko et al., serum Klotho levels of non-living group were numerically lower than in living group. In addition to, it showed that without cardiovascular event survival and death ratio was similar, while the cumulative survival rate was significantly lower in the low sKlotho group.[25] It is seen that these studies vary according to the numerical differences of the patients included in the study, the differences in the comorbidities of the patients and the follow-up periods. In addition, the differences in primary diseases and residual renal functions of the patients included in the study may cause these studies to yield different results. Disproportionately high sKlotho levels have been determined in recent studies of hemodialysis patients.[22,26,27] In this context, circulating sKlotho level may not necessarily reflect Klotho expression detected at the tissue level, especially in patients with late stage CKD. This may lead to different results in studies.

Studies showing that low serum albumin is related with mortality in elderly people support our results in our research.[28-30]

In the research of Lijie Ma et al. low albumin and high CRP were related with mortality.[31] In another study, high albumin/crp ratio was found to be significant in terms of mortality.[32] This study, which was conducted to determine the relationship between low albumin and mortality, supports our study.

In our study, a significant difference was found in terms of CRP and albumin when the patient group of non-living and the patient group of living were compared.[33] In the group of non-living, CRP was higher and albumin value was lower. Our study shows how important it is in terms of stabilizing the inflammation and nutritional status of hemodialysis patients and reducing the mortality risk of the patients.

From this point of view, it is necessary to seriously consider the dietary status and inflammation status of the patients. In the study conducted by Rajaa et al. it was determined that the age of the non-living group was higher in the comparison between living and non-living group in chronic hemodialysis patients.[34] These results are the same as those in our study. As age increases, comorbidity increases and patients' mortality risks increase. At the same time, as age increases, the immune system mechanism becomes more vulnerable and the risk of mortality increases.

In a meta-analysis including 220689 patients and 35 studies conducted to investigate the effect of diabetes mellitus on mortality, 33 studies showed that diabetes mellitus increased mortality.[35]

In our study, when the two groups were compared, it was significant and higher in the group of non-living. Microvascular and macrovascular complications of DM rise the risk of mortality. Microvascular and macrovascular complications of DM rise the risk of mortality. In addition, diabetes mellitus increases inflammation and immunosuppression, which increases mortality.

CONCLUSION

As a result, it has been seen that sKlotho is not an indicator to be used to determine and predict uremic cardiomyopathy both in the short and long term. At the same time, although it was not found to be a significant parameter in terms of mortality, the P value was found close to the limit value in terms of significance. It may be meaningful to use it as a mortality determining parameter in studies to be conducted with larger patient populations. In our study, it has been shown that CRP, which we have used for a long time to determine, predict and prevent mortality, and which is more cost-effective, may be more useful. This study, which we conducted in the Turkish patient population, is the first to show the long-term relationship of sKlotho with echocardiographic parameters and mortality.

ETHICAL DECLARATIONS

Ethics Committee Approval: The ethics committee confirmation of the research was obtained by the Hamidiye Scientific Research Ethics Committee of the University of Health Sciences with the decision dated 31.03.2021-23746 (no: E-46418926-050.01.04—23746).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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