

Serum α -Klotho Level in the Patients Subjected to Hemodialysis in Association with Lipid Profile

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Abstract

Background: Klotho, is a protein associated with life extension plays a important role in kidney disease progression, anti-aging, anti-oxidation, modulation of ion transport, and development of disturbed mineral metabolism. The aim of the study was to measure Soluble α -Klotho(SAKL) levels in chronic kidney disease(CKD) patients before and after dialysis in relation with Lipid profile. Methods: This short-prospective hospital-based study was done in the Department of Chemistry and Biochemistry, College of medicine, Tikrit University, Tikrit, Iraq. The study was carried out for 30 patients subjected to Hemodialysis recruited from Tikrit Teaching Hospital, hemodialysis unit between 1st December,2018 and 1st April,2019. The study also included 30 adult persons looks healthy with no prior medical or family history of CKD as a control participated in this study.The levels of SAKL and lipid profile were measured in the serum of 30 patients, before and after Hemodialysis and compared with controls. Results: The study revealed increased in the SAKL level in CKD patients before dialysis compared to healthy control group, and decreased in group of CKD after dialysis compared to control group. Furthermore, there was a significant positive correlation of SAKL level with serum Triglyceride and Very low density lipoprotein cholesterol(VLDL-C) in CKD patients before dialysis. Conclusions: There was a highly significant relation of SAKL with lipid abnormality in CKD patients under hemodialysis.

Keyword: Soluble α -Klotho; chronic kidney disease; hemodialysis; Lipid profile.

Introduction

Chronic kidney disease (CKD) describes abnormal kidney function and/or structure. It is common, frequently unrecognized and often exists together with other conditions such as cardiovascular disease(CVD) and diabetes (1). CKD is a global health burden estimated to affect up to 15% of adult populations and is independently associated with increased CVD risk similar to the risk of diabetes mellitus or coronary heart disease(2). This risk increases as CKD advances and is evidenced by worsening excretory function, usually manifest as declining glomerular filtration rate, and increasing proteinuria(3). The increased cardiovascular risk associated with end-stage renal disease(ESRD) has been well established, and estimated cardiovascular mortality rates are 10- to 100-fold higher among dialysis patients than age- and sex-matched individuals in

the general population. Hemodialysis(HD) should be starting when indicated by the impact of symptoms of uraemia on daily living, or biochemical measures or uncontrollable fluid overload, or at glomerular filtration rate (GFR) of around 5-7 mL/min/1.73 m² if there are no symptoms.This syndrome leads to death unless the toxins are removed by renal replacement therapy, using dialysis or kidney transplantation(2,4).

Dyslipidemia is a major risk factor for cardiovascular morbidity and mortality and is common among patients with CKD. Lipid profiles vary widely in these patients, reflecting the level of kidney function and the degree of proteinuria. Several factors contribute to the development dyslipidemia associated with chronic renal impairment(5).Patients with CKD have a reduction in the activity of lipoprotein lipase and hepatic triglyceride lipase. Hypercholesterolemia in nephrotic syndrome

is thought to be a result of increased production and decreased catabolism of lipoproteins(6).

Klotho exists in both membrane-bound and secreted(S.Klotho) forms, the latter of which may exert vasculoprotective effects. It enhances endothelial nitric oxide production and thereby improves endothelium-dependent vasodilatation and it is an endogenous inhibitor of vascular calcification, as shown in recent studies in vitro and in CKD mice in vivo(7). So, the aim of the study was to measure SAKL level in CKD patients before and after dialysis in relation with Lipid profile.

Patients and Method

This short-prospective hospital-based study was done in Tikrit city-Iraq between 1st December,2018 and 1st April,2019. The study included 30 adult patients with chronic kidney disease who underwent Kidney dialysis unit at Tikrit Teaching Hospital and their age range were between 18-80 years. They were clinically diagnosed by nephrologist as ESRD patients (on hemodialysis), based on their history, clinical examination, renal function tests and other laboratory tests, undergoing hemodialysis twice weekly. The study also included 30 adult persons looks healthy with no prior medical or family history of CKD as a control participated in this study. Blood samples were collected from CKD patients before dialysis and 4 hours after dialysis. All blood samples were centrifuged and the obtained sera were aspirated and labeled for determination of serum Klotho were measured by enzyme-linked immunosorbent assay (ELISA) kit supplied by (MYBIOSOURCE, USA), and lipid profile including Total cholesterol, Triglyceride, High density lipoprotein cholesterol(HDL) were measured by colorimetric method using kits provided by Biolabo (France) according to the manufacturer manual instruction. Furthermore, Very low density lipoprotein(VLDL) and LDL levels were assessed using the following equation:

$$\text{VLDL-C (mg/dl)} = (\text{Triglycerides} / 5)$$

$$\text{LDL-C (mg/dl)} = [\text{Total cholesterol}] - [\text{HDL-C}] + [\text{TG}]/5$$

Statistical Analysis

Computerized statistically analysis was performed using SPSS Software version 23.3 statistic program. Comparison was carried out for determination of the P. value (P<0.05: significant).

Finding

Relation of SAKL and lipid profile in CKD patients before and after hemodialysis and control group.

Results presented in Table 1 shows increased in the SAKL (pg/ml) level in CKD patients before dialysis compared to healthy control group. While the decrease in SAKL level was recorded in group of CKD after dialysis compared to control group, although the result was non-significant (p>0.05). Our study showed that the higher mean level of Total cholesterol was recorded in the control group (168.60±46.03 mg/dl), followed by CKD patients before dialysis and patients after dialysis (131.94±75.44 and 98.23±54.25 mg/dl) respectively with significant differences among the groups, Also the higher mean level of TG was documented in the control group (158.50±74.92 mg/dl), followed by CKD patients before dialysis and patients after dialysis (95.43±50.48 and 87.77±44.51 mg/dl) respectively with significant differences among the groups.

The study showed that the higher mean level of HDL-cholesterol was recorded in the control group (65.60±34.16 mg/dl), followed by CKD patients after dialysis and patients before dialysis (33.80±19.93 and 31.87±11.67 mg/dl) respectively with significant differences among the groups, Also the higher mean level of VLDL-cholesterol was recorded in the control group (31.70±15.05 mg/dl), followed by CKD patients before dialysis and patients after dialysis (19.13±10.12 and 16.97±8.89mg/dl) respectively with significant differences among the groups (P<0.05).Furthermore current study showed that the higher mean level of LDL-cholesterol was found in CKD patients before dialysis (81.93±73.41mg/dl), followed by the control group (74.63±48.25 mg/dl) and the lowest mean level was in patients after dialysis (54.23±51.06 mg/dl). Although there were no significant differences among the groups (P>0.05).

			Good	Poor		
Age	<30	Count	3	43	46	0.24
		%	6.5%	93.5%	100.0%	
	≥30	Count	2	9	11	
		%	18.2%	81.8%	100.0%	
Residence	Urban	Count	2	44	46	0.04
		%	4.3	95.7%	100.0%	
	Rural	Count	3	8	11	
		%	27.3	72.7%	100.0%	
Marital status	Single	Count	0	22	22	0.35
		%	.0%	100.0%	100.0%	
	Married	Count	4	26	30	
		%	13.3%	86.7%	100.0%	
	Others	Count	1	4	5	
		%	20.0%	80.0%	100.0%	
Length of experience	≤5	Count	4	30	34	0.63

Pa: P value between control group and before dialysis, Pb : p value between control group and after dialysis. SAKL: Soluble α -klotho, T.Ch: Total cholesterol, TG: Triglycerides, HDL: High-density lipoprotein cholesterol, VLDL: Very low-density lipoprotein cholesterol, LDL: Low-density lipoprotein cholesterol, SD: Standard deviation.

Correlation between SAKL and parameters of CKD patients before and after hemodialysis

The study showed no correlation between SAKL

and cholesterol in CKD patients before dialysis (Figure 1) and no correlation with cholesterol after dialysis.

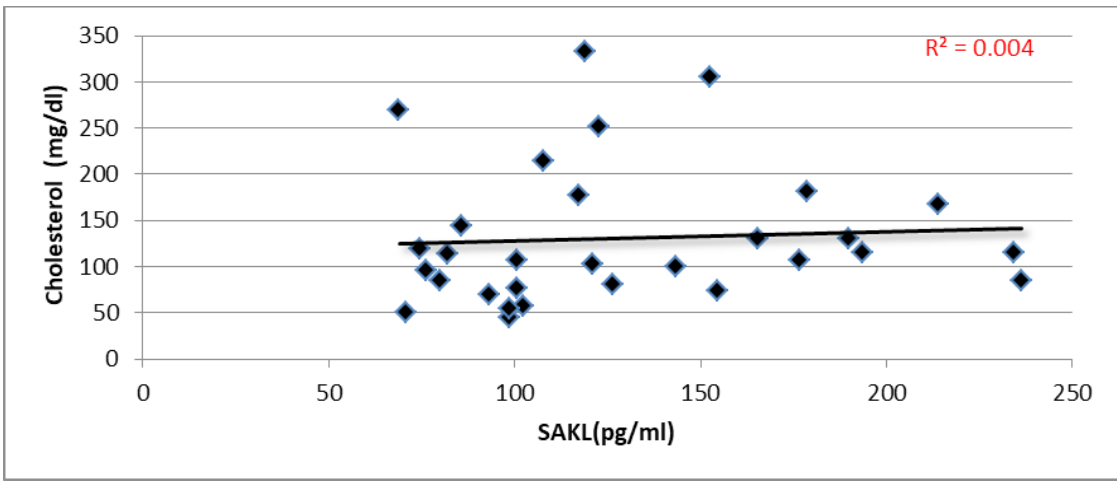


Figure 1: Correlation between SAKL and Total cholesterol in CKD patients before hemodialysis.

Current study showed a positive correlation of SAKL with S. TG in CKD patients before dialysis (Figure 2) and negative correlation with TG after dialysis.

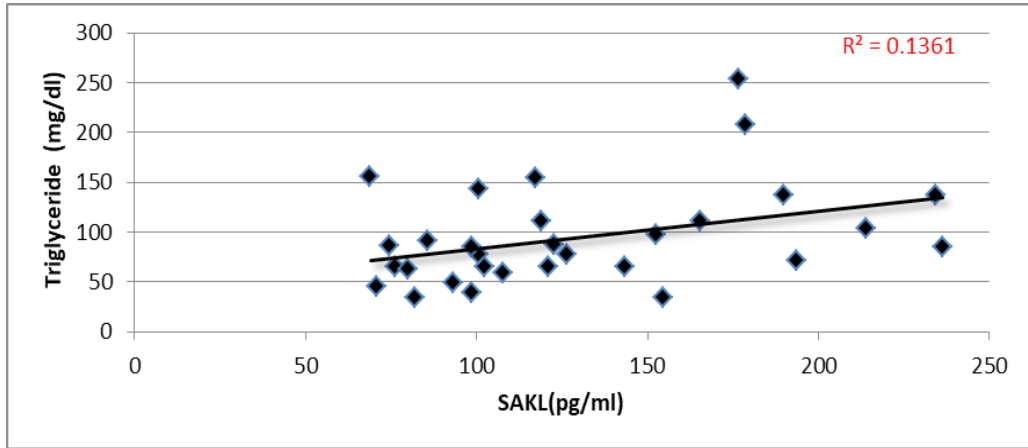


Figure 2: Correlation between SAKL and S. TG in CKD patients before dialysis.

The study showed a negative correlation of SAKL with HDL-C in CKD patients before dialysis and no correlation with HDL-C after dialysis .

Our study showed a positive correlation of SAKL with VLDL-C in CKD patients before dialysis (Figure 3) and negative correlation with VLDL-C after dialysis.

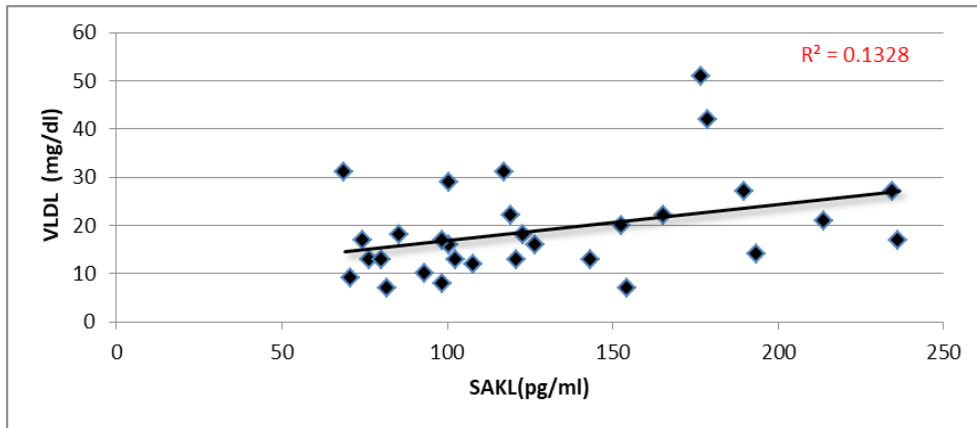


Figure 3: Correlation between SAKL and VLDL-C in CKD patients before dialysis.

The study showed no correlation of SAKL with LDL-C in CKD patients before and after dialysis.

Discussion

Soluble α -Klotho

In recent years, emerging evidence suggests that the SAKL could serve as an early biomarker for CKD (8). In agreement with our findings in studying the elevation of SAKL in CKD patients before dialysis, Devaraj et al (9) registered an elevated level of SAKL in patients with CKD before dialysis when comparing with control group. Also, Shimamura et al (10) reported higher levels of SAKL in stage 5 CKD compared with healthy individuals. Akimoto et al (11) and Hage et al (12) also agreed with our current findings and reported that SAKL level was significantly higher in patients with CKD as comparing with healthy control.

The study was disagreed with studies done earlier by Seiler et al (13) and Hu et al (14), who indicated that SAKL levels had no elevation in pre-hemodialysis CKD patients. Although this difference from our results may be due to the difference in the stage of CKD which showed a different levels of SAKL (low level in 1st stage and high level in the 5th stage of CKD) (9). The decreased level of klotho may be due to its downregulated after kidney injury and intensive renal damage (12).

In the present study, reduction in SAKL level was recorded in group of CKD after hemodialysis compared to control group. In agreement with this findings, study done by Asai et al (15) demonstrated that SAKL was reduced in CKD patient after dialysis. Also, Shimamura et al (10), Koh et al (16) and Sakan et al (17) agreed with our result, they revealed a reduced α -Klotho in CKD patients specially after dialysis, and indicated a reduced production of klotho in human chronic renal failure kidney patients with CKD after hemodialysis. Furthermore, Golembiewska et al (18) and other studies agreed with our findings, reported that reduced SAKL in plasma of CKD and ESRD patients on hemodialysis when comparing with elevated SAKL in pre-dialysis patients.

On the other hand, the current result was disagreed with some studies with contradictory results showed that soluble α -Klotho levels were not differed in CKD patients (12,13).

The decreased of SAKL in CKD patients after dialysis have some explanations. Kidney is a major organ to maintain soluble Klotho homeostasis by two ways, One is to cleavage membrane-bound α -Klotho

in the renal tubular epithelial cells and release into circulation and the second is to eliminate redundant and unnecessary soluble α -Klotho from circulations into the urinary lumen through renal proximal tubules by transcytosis (16). This mechanism clarify the reduction of SAKL after HD in same patients who have elevated SAKL before HD. In addition, there are indications that urinary Klotho measurement is more closely linked to residual renal nephrons and that the significance of serum and urine measurement should be investigated. Therefore, there are still few reports indicating whether Klotho levels can be used as prognostic factors for CKD (19).

Correlation of SAKL with Lipid Profile

It is well known that patients with impaired renal function exhibit significant alterations in lipoprotein metabolism resulting in the development of severe dyslipidemia and this is attributed to the non-traditional risk factors in patients with ESRD, such as, inflammation, oxidative stress, anemia, malnutrition and endothelial dysfunction that have been proposed to play a central role in lipid metabolism abnormalities. The lipid abnormalities often accompany and aggravate the renal disease, thereby favoring the acceleration of atherogenesis and progression of cardiovascular disease (1,6).

The study showed that there was positive correlation of SAKL with Triglyceride and VLDL-C in CKD patients before dialysis and negative correlation with HDL-C in CKD patients before dialysis. Furthermore a negative correlation of SAKL with TG and HDL-C in CKD patients after dialysis and no correlation of SAKL with cholesterol and LDL-C after dialysis. There were very few studies on the relation between SAKL and lipid profile. From these studies, Seiler et al (13) studied that the level of SAKL in patients with chronic kidney disease and found that there was positive correlation of SAKL with LDL-C. Yu et al (20), showed that no correlation occurred of α -Klotho with Total cholesterol and LDL-C in CKD patients. In pathological conditions, including CKD, renal tubular epithelial cells may be exposed to ox-LDL. Oxidized modified lipoproteins have been identified in human kidney tissues, injurious actions of ox-LDL include induction of inflammation, oxidation and apoptosis, all of them processes associated with progression of renal disease. Studies in hypercholesterolemic animal models showed that renal injury was accompanied by increased oxidative

stress and inflammation, changes that may decrease Klotho expression, as previously reported(21). On the other hand, Pan et al (22) showed positive correlation of SAKL with LDL and negative correlation with HDL in patients with diabetes mellitus.

Conclusions

There was a highly significant relation of SAKL with lipid abnormality in CKD patients under hemodialysis.

Conflict of Interest: None

Source of Findings: Self

Ethical Clearance: Nil

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