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The Effect of Activin and Amyloid A in Patients with Chronic Kidney Disease

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Abstract

Background: Chronic kidney disease (CKD) is a broad term that refers to several conditions that impact the structure and function of the kidneys. Disease and management are classified according to stages of disease severity for patients with end-stage renal disease (ESRD); hemodialysis becomes a crucial therapeutic intervention to sustain life by filtering waste products and excess fluids from the bloodstream. Aim of study: This study aimed to assess the impact of hemodialysis (HD) on the levels of Activin and serum amyloid A in patients with chronic renal disease.

Materials and Methods: A study in Kirkuk City, conducted from November 2023 to April 2024, involved 70 chronic kidney disease patients undergoing regular hemodialysis at the Alamal dialysis centre. The study included 40 healthy individuals as a comparison group. Blood samples from both groups were examined for serum Activin and amyloid A levels using the Enzyme-Linked Immunosorbent Assay.

Results: The study shows that Activin level was a highly significant increase ($p < 0.01$) in Hemodialysis patients before dialysis as compared to the control group. The mean Activin level in HD patients before dialysis was 3.104±1.172ng/ml, while in the control group, it was 1.745±0.068ng/ml. Similarly, HD patients exhibited significantly elevated levels of serum Amyloid A before dialysis as compared to the control group ($p<0.01$), The mean Amyloid A level in HD patients before dialysis was 9.773±3.585ng/ml, while in the control group, it was 5.009±o.165ng/ml. The study observed a rise in serum Activin levels after hemodialysis. Specifically, the average serum Activin level before hemodialysis increased from 3.104±1.172 ng/ml to 3.670±1.255ng/ml after hemodialysis. In contrast, after hemodialysis, there was a drop in serum Amyloid A levels, with the average serum Amyloid A before hemodialysis lowering from 9.773±3.585ng/ml to 7.647±3.071ng/ml after hemodialysis.

Conclusion: HD patients have elevated Activin and serum Amyloid A levels, suggesting HD may influence the inflammatory milieu and contribute to a chronic inflammatory state in CKD. Dialysis procedure has differential effects on these biomarkers, with decreased SAA levels post-dialysis. While Activin levels still increased.

Keywords: Activin; Amyloid A; Chronic Kidney Disease

Abbreviations

CKD: Chronic Kidney Disease; ESRD: End-Stage Renal Disease; HD: Hemodialysis; GFR: Glomerular Filtration Rate; KRT: Kidney Replacement Therapy; TGF-: Transforming Growth Factor; SAA: Serum Amyloid A; HDL: High-Density Lipoprotein; COPD: Chronic Obstructive Pulmonary Disease.

Introduction

Chronic kidney disease is a broad term used to describe a diverse ailment that impacts the structure and function of the kidney. The diversity in disease manifestation is partially linked to aetiology, pathogenesis, intensity, and pace of advancement. Since the inception of the conceptual framework, definition, and classification of chronic renal disease 10 years ago [1].

Chronic kidney disease is characterized by the presence of kidney damage, specifically albuminuria, or impaired kidney function, known as glomerular filtration rate (GFR), below 60 mL/min per 1·73 m^2 for at least 3 months, regardless of clinical diagnosis [2]. The condition is classified into five phases based on the Glomerular Filtration Rate (GFR) due to its substantial influence on the development of problems.

Hemodialysis (HD) is the most prevalent method of kidney replacement therapy (KRT) globally, making up over 69% of all KRT and 89% of all dialysis procedures [3]. The main objective of hemodialysis is to re-establish the normal fluid environment found in intracellular and extracellular, which is typically seen in healthy kidney function. This is achieved by transferring substances like urea from the blood to the dialysate, and substances like bicarbonate from the dialysate to the blood. The rate of diffusion is primarily influenced by the concentration and molecular weight of the solutes [4].

Activins are a type of dimeric polypeptides that consist of two subunits of inhibin connected by a disulfide bridge. Activins are a type of growth and differentiation factor that is part of the transforming growth factor (TGF-) superfamily [5]. Five different types of subunits have been identified, and the naming of activin is based on the specific type or types of subunits that make it up. Mammals have isolated activin A (A/A), activin B (B/B), activin AB (A/B), activin C (C/C), and activin E (E/E). However, only the dimers activin A, activin B, and activin AB have clearly defined biological action [6]. Act A has a crucial role in regulating the correct development of the kidney, and its expression is easily recognized in growing fetal kidneys [7]. Expression of this factor is absent in healthy adult kidneys [8], however, its significant involvement in many renal disorders and related complications is becoming more acknowledged.

Serum amyloid A (SAA) is a significant acute-phase protein seen in different mammals, including humans [9]. Hepatocytes are the main producers of SAA synthesis, and their levels in the bloodstream rise considerably in response to inflammatory stimuli or damage to the endothelium [10]. Several studies have shown that inflammation is a significant factor in major cardiovascular events and death among patients with chronic kidney disease (CKD) [11-13]. Thus, SAA, which acts as an indicator of inflammation, has potential as a prospective predictive biomarker for CKD due to its biologically reasonable mechanism.

Material and Methods

Study Design

The cross-sectional study included 180 samples, 70 patients with chronic kidney disease and 40 controls. The first group represented a cases group consisting of 70 patients with CKD who underwent regular hemodialysis. The second group comprised a control group consisting of 40 healthy subjects.

Ethical Approval

The research protocol obtained official authority from the Scientific Committee of the Faculty of Medicine at Tikrit University, which had previously approved the approach. The Kirkuk Health Department authorized the gathering of patient samples.

Exclusion Criteria

- Patients with diabetes mellitus.
- Obesity
- Cancer
- Hepatitis
- Heart failure
- Neuromuscular disease

Sample Collection

Five ml of blood sample was collected from control groups and patients before and after the hemodialysis process in the plane tube then let stand for about (20–30) minutes to clot formation and centrifuged by using a macro centrifuge for about (15) minutes on a speed of 3000 rpm then fresh non-hemolysis serum collected in Eppendorf tubes and kept in deep freeze (- 20 Co).

Thawing of the samples allowed taking place at 25˚C for 1 hour before conducting the assay for more accurate test results to be obtained.

Statistical Analysis

The study utilized SPSS v29 and Prism GraphPad for computerized statistical analysis, with one-way ANOVA T-Test probability (P value) for comparison. A P value < 0.05 was considered statistically significant, while a P value > 0.05 was nonsignificant. The correlation coefficient was interpreted as negative or positive

Results

Table 1 showed that the mean of serum Activin before dialysis was 3.104 ng/ml, whereas, after dialysis, it increased to 3.670 ng/ml, the difference in Activin levels before and after dialysis is statistically significant at (P-value:<0.001), The mean of the control group was 1.745 ng/ml, which is statistically significant than both the before and after hemodialysis groups at (P-value:<0.001).

P Value	Mean (ng/ml)	Number	Study Group
<0.01	3.104	70	Activin before hemodialysis
<0.01	3.67	70	Activin after hemodialysis
	1.745	40	Control group

Table 1: Comparison of Serum Level of Activin in Patients with CKD before and after Hemodialysis and Control Group.

Table 2 showed that the mean of serum Amyloid A before dialysis was 9.773ng/ml, whereas, after dialysis, it decreased to 7.647ng/ml, the difference in Amyloid A levels before and after dialysis is statistically significant at (P-value:<0.01), The mean of control group was 5.009ng/ml, which is statistically significant than both the before and after hemodialysis groups at (P-value:<0.01).

P Value	Mean (µg/ml)	Number	Study Group
<0.01	9.773	70	Amyloid before hemodialysis
<0.01	7.647	70	Amyloid after hemodialysis
	5.009	40	Control group

Table 2: Comparison Serum Level of Amyloid A in Patients with CKD before and after Hemodialysis and Control Group.

Discussion

In previous study found that the Activin level increased after dialysis, The study revealed that the activin A/follistatin system is both activated and disrupted in chronic hemodialysis patients, leading to a decrease in the amount of activin A stored in tissues. The type and dosage of heparin used during hemodialysis operations have a significant impact on this multifaceted system, and can thus modify essential bodily functions and the progression of severe illnesses. The elevation of circulating activin A is caused by its displacement from the proteoglycans on the cell surface and the subsequent disintegration of the complex [14].

Another study discovered a significant increase in activin levels following hemodialysis. The study also identified several mechanisms that may contribute to the elevation of activin levels under the influence of heparin. These mechanisms include the displacement of activin from cell surfaces and extracellular matrix proteoglycans, the prolonged existence of circulating growth factors/heparin complexes, and enhanced production [15].

Also, another study discovered that the amount of activin significantly increases after hemodialysis. The researcher suggests that this occurrence is likely caused by the displacement of cell surface proteoglycans and the disintegration of the complex. Additionally, it has a crucial function in regulating the immune system by controlling the production of other proinflammatory cytokines. Consequently, inhibiting its effects may have therapeutic potential in treating inflammatory disorders. Eliminating the use of heparin during dialysis effectively inhibited the activation of activin. Enoxaparin facilitated the release and maintained stable levels of the substance [16].

In previous study observed a notable reduction in serum Amyloid A levels during hemodialysis (from 15.90 to 12.70 mg/L, $p < 0.05$). The study proposes that SAA serves as an inflammatory marker associated with HDL. Serum amyloid A (SAA) levels are elevated during inflammatory processes and are not influenced by renal function. SAA levels decrease by around 20%, possibly due to the removal of polymers or displacement of SAA caused by changes in high-density lipoprotein (HDL) levels and binding to the dialysis membrane [17].

Another study observed a significant decrease in serum levels of serum Amyloid A following Hemodialysis. The researchers propose that the utilization of hemoperfusion in conjunction with hemodialysis could assist in reducing the levels of serum Amyloid A [18]

Several studies have seen a substantial rise in serum Amyloid A levels during hemodialysis. These findings indicate that there is a temporary increase in response to the procedure, which can trigger the activation of immune cells and the release of inflammatory mediators [19,20].

Although one study did not see a significant change in the average level of serum Amyloid A (SAA) following hemodialysis, it suggests that the response of SAA to hemodialysis can differ among individuals. These variations may be driven by factors such as genetic predisposition and other inflammatory diseases [21].

Conclusion

Hemodialysis patients showed elevated levels of Activin and Serum Amyloid A, suggesting potential involvement in inflammation, metabolic processes, and renal function. These biomarkers are associated with inflammatory responses and tissue damage, suggesting that hemodialysis may influence the inflammatory milieu in chronic kidney disease patients. The dialysis procedure had differential effects on these biomarkers, with a significant reduction in serum Amyloid A levels post-dialysis. These findings contribute to understanding the pathophysiology of chronic kidney disease and emphasize the importance of monitoring Activin and serum Amyloid A levels in comprehensive patient care.

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