

## Relation of Serum Albumin Level and C- reactive Protein to Hypotensive Episodes during Hemodialysis Sessions

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### ABSTRACT

**Background:** Intradialytic hypotension (IDH) remains the most common complication of hemodialysis (HD) with potentially devastating consequences despite the technological advances regarding the hemodialysis techniques of the last decades. The increasing number of advanced-age patients, diabetics and patients with cardiovascular comorbidities undergoing hemodialysis emphasizes the need on implementation of new IDH avoidance tactics. **Aim of the Work:** Our work aimed to evaluate serum albumin (Alb) level and C-reactive protein level in hemodialysis patients and their correlation with dialysis-induced hypotension (DIH).

**Patients and Methods:** This prospective study was conducted based on data collected from HD patients treated at Aswan University Hospital, dialysis unit, in a period from 1/1/2017 to 30/5/2017. It included 40 chronic HD patients with no history of endocrine tumors, diabetes mellitus, liver failure, heart failure, or unstable coronary artery disease. Patients with hemoglobin less than 9 mg/dL, feverish patients, and patients with any source of apparent infection were excluded. The age of the patients ranged from over 18 to less than 75 years. **Results:** : the mean value of serum albumin level in group (A) was ( $2.97 \pm 0.71$ ) with the highest serum albumin was 4.4 and the lowest serum albumin was 2.1, while in Group (B) the mean value of serum albumin level was ( $4.53 \pm 0.74$ ) with the highest serum albumin was 5.5 and the lowest serum albumin was 2.8. There was a significant decrease in serum albumin level in patients in group (A) who had developed hypotensive episodes during hemodialysis ( P value < 0.001), in group (A) also there were 18 patients had positive C-reactive protein (90 %) and 2 patients had negative C-reactive protein (10 %) with a mean value ( $15.67 \pm 13.27$ ), while in group B : there were 2 patients had positive C-reactive protein level (10 %) and 18 patients had negative C-reactive protein level ( 90 %) with a mean value ( $2.07 \pm 1.48$ ) , So, there was a significant increase in C-reactive protein level in patients in group (A) who had developed hypotensive episodes during dialysis ( P value < 0.001). **Conclusion:** Serum Alb. levels and high levels of CRP may predict an increased risk of DIH in regular HD patients and this was the main issue for our study, however we also found that there were some other biochemical markers, which can come inbetween with our two main markers, which confirm our results. **Recommendations:** Further studies on a larger scale of patients are needed to confirm these results.

### INTRODUCTION

Chronic kidney disease (CKD), also known as chronic renal disease, is a progressive loss in kidney function over a period of months or years. The symptoms of worsening kidney function are not specific, and might include feeling generally unwell and experiencing a reduced appetite. Often, chronic kidney disease is diagnosed as a result of screening of people known to be at risk of kidney problems, such as those with high blood pressure or diabetes and those with a blood relative with CKD. This disease may also be identified when it leads to one of its recognized complications, such as cardiovascular disease, anemia, pericarditis or renal osteodystrophy<sup>(1)</sup>.

CKD is a long-term form of kidney disease; thus, it is differentiated from acute kidney disease (acute kidney injury) in that the reduction in kidney function must be present for over 3 months. CKD is an internationally recognized public health problem affecting 5–10% of the world population<sup>(2)</sup>. Hypotensive episodes are a major complication

of hemodialysis. Hypotension during dialysis (DIH) could be directly related to a reduction in blood volume or to a decrease in cardiovascular activation as a response to decreased cardiac filling<sup>(3)</sup>.

Dialysis-induced hypotension (DIH) is a very serious clinical problem. It is one of the most frequent complication in renal replacement therapy which diminish patient's quality of life, and increases mortality in the dialyzed population. The main mechanism of DIH is rapid reduction of blood volume owing to ultrafiltration and decrease in extracellular osmolarity during the dialysis session. Coexisting illnesses, especially cardiovascular diseases, particularly common in older and diabetic patients, have an essential meaning in the episodes of dialytic hypotension<sup>(4)</sup>.

Intradialytic hypotension is a well-recognized HD complication, occurring in 10–70% of treatments, depending on the definition. Patient and clinical characteristics associated with intradialytic hypotension include older age, female sex, longer dialysis vintage, diabetes, lower pre-

dialysis BP, lower albumin and higher body mass index <sup>(5)</sup>.

The National Kidney Foundation (NKF), Kidney Disease Outcomes Quality Initiative (KDOQI) and European Best Practices Guidelines define Intradialytic hypotension (IDH) as a decrease in systolic blood pressure by  $\geq 20$  mm Hg or a decrease in mean arterial blood pressure (MAP) by 10 mm Hg associated with symptoms that include: abdominal discomfort, yawning, sighing, nausea, vomiting, muscle cramps, restlessness, dizziness or fainting, and anxiety. Dialysis-induced hypotension (DIH) observed in 20-33% of hemodialysis (HD) patients, and the pathogenesis is multifactorial <sup>(6)</sup>.

Over the last two decades the increase in the number of dialysis patients has been seen globally although to varying degrees. Certain trends in end stage renal disease (ESRD) epidemiology have been observed. The annual increase in number of patients undergoing hemodialysis has been around 8%. The National Kidney Foundation Dialysis Outcomes Quality Initiative (DOQI) practice guidelines, was first established in 1997 to create standards for dialysis care <sup>(7)</sup>.

Protein-energy malnutrition and wasting are frequent complications among patients with ESRD <sup>(8)</sup>. Moreover, considerable evidence has accumulated over several years that malnutrition is associated with cardiac co-morbidity, inflammation and poor survival in ESRD patients <sup>(9)</sup>.

Malnutrition of visceral proteins often occurs in many chronic illnesses such as chronic renal failure, protracted infections and cancer <sup>(10)</sup>. Clinical assessment of malnutrition is most commonly done by biochemical indicators of nutrition <sup>(11)</sup>. Serum albumin is a well-known marker of nutrition in ESRD patients. There is a linear increase in death rate with declining serum albumin levels in the dialysis patients <sup>(12)</sup>. Low serum albumin levels may reflect poor nutrition. Presence of an inflammatory reaction, old age and degree of hydration could also cause hypoalbuminemia <sup>(13)</sup>.

Hypoalbuminemia is a strong predictor of mortality and morbidity among HD patients, and is associated with increased risk of infection in dialysis patients <sup>(14)</sup>. Hypoalbuminemia is a major risk factor of hypotension during HD and can result from protein malnutrition, increased dialysate protein loss, systemic illness, and inflammatory disorders <sup>(15)</sup>.

Although several approaches have been used to assess nutrition, serum albumin is probably still the most commonly used nutritional marker in ESRD patients. Several studies have shown that

inflammation is another cause of problems attributed to malnutrition <sup>(9)</sup>. The sources of inflammation in these patients are not clear. Of the variety of circulating inflammatory markers, C-reactive protein (CRP), the major acute phase response (APR) protein is elevated in hemodialysis patients <sup>(16)</sup>.

CRP is used as a marker of infection or ongoing inflammatory disease in ESRD patients <sup>(17)</sup>. CRP is also considered as a biomarker of chronic, systemic inflammation as well as a predictor or atherosclerosis <sup>(17)</sup>. The severity of inflammation could be estimated by the levels of circulating CRP <sup>(18)</sup>.

## AIM OF THE STUDY

Our work aimed to evaluate serum albumin level and C-reactive protein level in hemodialysis patients and their correlation with dialysis-induced hypotension (DIH).

## PATIENTS AND METHODS

This is a prospective study based on data collected from HD patients treated at Aswan University Hospital, dialysis unit, in a period from 1/1/2017 to 30/5/2017.

We recruited 40 chronic HD patients with no history of endocrine tumors, diabetes mellitus, liver failure, heart failure, or unstable coronary artery disease. Patients with hemoglobin less than 9 mg/dL, feverish patients, and patients with any source of apparent infection were excluded. The age of the patients ranged from over 18 to less than 75 years of age.

We divided the patients into two equal groups:

- 1- Group with DIH, including 20 patients and
- 2- Group without DIH, including the other 20 patients.
- 3-

## Subject selection and study design

### Eligibility criteria

#### Inclusion criteria

Patients age ranges from (18-75) years on standard maintenance hemodialysis for at least 3 months before entering this study.

#### Exclusion Criteria

- 1- Patients with history of endocrine tumors.
- 2- Patients with liver cell failure.
- 3- Patients with heart failure or coronary artery disease.
- 4- Patients with hemoglobin less than 9 mg/dl.
- 5- Patients with infection or fever.
- 6- Patients with fluid overload.

Blood pressure was measured with an automatic sphygmomanometer every 30 minutes during every hemodialysis session, and dialysis induced hypotension (DIH) were defined as a

decrease in the systolic BP of more than or equal 20 mm Hg of the basal value of each patient.

All the patients were dialyzed for at least three months before entering the study. They were dialyzed three times a week for 4 hours each time on Fresenius 4008B machines and low flux synthetic polysulfone membrane dialyzers. Dialysate temperature, sodium and calcium concentration were also kept constant. In all patients, we used bicarbonate-based dialysate fluid that contained sodium 136 mmol/L, potassium 2 mmol/L, magnesium 1 mmol/L, and calcium 1.25 mmol/L, and those settings were the same for all the patients during the HD session. Blood and dialysate flow rates were 250-300 and 500 mL/min, respectively.

The ultrafiltration rate was fixed over the course of a dialysis session with meticulous adjustment of dry weight. The administration of any drugs that could influence blood pressure (BP) was strictly avoided during dialysis sessions.

Blood samples from HD patients in a fasting state were collected from the arterial line immediately before the midweek dialysis session before heparin administration, and they were centrifuged and frozen at  $-70^{\circ}$  C before the measurements.

**Assessed parameters**

Data was collected by follow-up regular clinical examination, measuring blood pressure, and the following laboratory tests were measured regularly over the study period in the same laboratory, which is the laboratory of Aswan University Hospital:

- Serum albumin level.
- C-reactive protein level.
- Lipid profile (total cholesterol, LDL, HDL, triglycerides, and VLDL).
- Blood urea nitrogen (BUN) level.
- Serum creatinine level.
- Hemoglobin level.

- Serum calcium level.
- Serum phosphorus level.
- Serum sodium level.
- Serum potassium level.

Normal range of CRP was defined  $\leq$  3.3mg/dL., Hypoalbuminemia was defined as Alb  $<$  4 g/dL (NFK-DOQI guidelines).

Electrocardiogram was performed before and after dialysis sessions.

DIH episodes were treated conventionally by decreasing the ultrafiltration volume or administering hypertonic salt solution. All patients signed written informed consents.

**Statistical methods**

Date entry and data analysis were done using SPSS version 19 (Statistical Package for Social Science). Data were presented as number, percentage, mean, standard deviation. Fisher Exact test was used to compare between qualitative variables. Mann-Whitney test was used to compare between two quantitative variables in case of non-parametric data. Spearman correlation was done to measure correlation between quantitative variables. P-value considered statistically significant when  $P < 0.05$ .

**Ethical Considerations**

This study follows all the regulations of the ethical committee of the faculty of medicine at Aswan University. There was a formal consent that had all the required information about this study for the patients. Only those who signed the consent were enrolled in this study. Participants had the entire right to withdraw from this study at any time without giving any reason. **The study was approved by the Ethics Board of Aswan University Hospital.**

**Study location:** Aswan University Hospital.

**RESULTS**

**Table (1):** Albumin and C-reactive protein levels in the studied groups

	Group A (n= 20)		Group B (n= 20)		P-value
<b>Albumin: (g/dl)</b>					<0.001*
Mean $\pm$ SD	2.97 $\pm$ 0.71		4.53 $\pm$ 0.74		
Range	2.1 - 4.4		2.8 - 5.5		
<b>C-reactive protein (mg/dl)</b>					
Mean $\pm$ SD	15.67 $\pm$ 13.27		2.07 $\pm$ 1.48		<0.001*
Range	2.3 - 48.0		0.3 - 6.0		
<b>C-reactive protein level</b>					<0.001*
Positive	18	90.0	2	10.0	
Negative	2	10.0	18	90.0	

**Biochemical parameters**

**Albumin level:** As shown in table (1) and fig. (1):

- Group A: the mean of albumin level was  $(2.97 \pm 0.71)$  with the highest serum albumin was 4.4 and the lowest serum albumin was 2.1
- Group B: the mean of albumin level was  $(4.53 \pm 0.74)$  with the highest serum albumin was 5.5 and the lowest serum albumin was 2.8

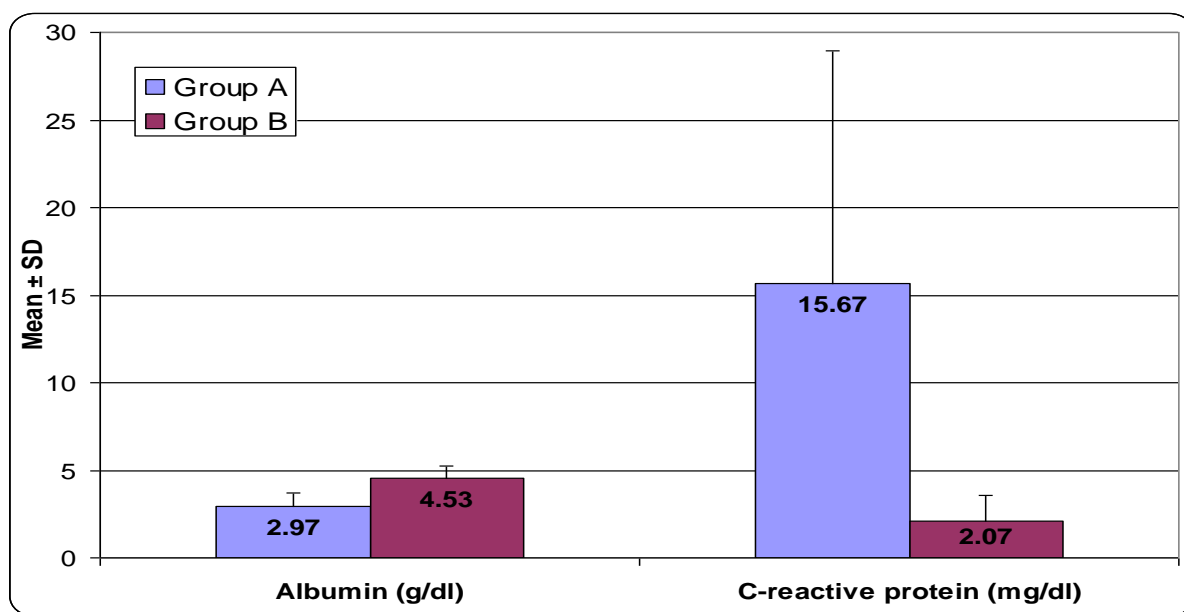
Where there is a significant decrease in serum albumin level in patients in group (A) who developed hypotensive episodes during dialysis ( $P < 0.00$ ).

**C-reactive protein level:** As shown in table (1) and fig. (1):

Group A: there is 18 patients have positive C-reactive protein level (90 %) and 2 patients have negative C-reactive protein level (10 %) with the mean was  $(15.67 \pm 13.27)$ .

Group B: there is 2 patients have positive C-reactive protein level (10 %) and 18 patients have negative C-reactive protein level (90 %) with the mean was  $(2.07 \pm 1.48)$ .

So, there is a significant increase in C-reactive protein level in patients in group (A) who developed hypotensive episodes during dialysis ( $P$  value 0.000).



**Table (2):** Correlation of albumin level with and personal, clinical and laboratory investigations

	Albumin (g/dl)	
	r-value	P-value
Age (years)	-0.234	0.320
Duration of dialysis (years)	-0.020	0.934
Total cholesterol (mg/dl)	-0.161	0.498
LDL (mg/dl)	0.273	0.244
HDL (mg/dl)	0.042	0.859
Triglycerides (mg/dl)	-0.209	0.376
VLDL (mg/dl)	0.061	0.797
Blood urea nitrogen (BUN) (mg/dl)	0.048	0.841
S. creatinine (mg/dl)	0.035	0.883
Hemoglobin (mg/dl)	-0.108	0.651
S. calcium (mg/dl)	<b>0.632</b>	<b>0.003*</b>
S. phosphorus (mg/dl)	0.312	0.181
S. sodium (meq/l)	<b>0.684</b>	<b>0.001*</b>
S. potassium (meq/l)	0.143	0.549

As shown in table (2):

- There was a strong correlation between the decrease in s. calcium level and the decrease in s. albumin level among the patients in both groups which was statistically significant (P value 0.003, r-value:0.632).
- There was a strong correlation between the decrease in s. sodium level and the decrease in s. albumin level among the patients in both groups which was statistically significant (P value 0.001, r-value:0.684).
- There was no correlation between the age and s. albumin level among the patients in both groups.
- There was no correlation between the duration of dialysis and s. albumin level among the patients in both groups.
- There was no correlation between lipid profile (total cholesterol, LDL, HDL, VLDL and Triglycerides) and s. albumin level among the patients in both groups.
- There was no correlation between kidney function tests (BUN and s. creatinin) and s. albumin level among the patients in both groups.
- There was no correlation between hemoglobin level and s. albumin level among the patients in both groups.
- There was no correlation between s. phosphorous and s. albumin level among the patients in both groups.
- There was no correlation between s. potassium and s. albumin level among the patients in both groups.

## DISCUSSION

Hypoalbuminemia is a strong predictor of mortality and morbidity among HD patients, and is associated with increased risk of infection in dialysis patients<sup>(19)</sup>. Two to four liters of fluid needs to be removed during a regular session, equivalent to 40–80% of the blood volume. It is therefore not surprising that hypotension occurs so often especially in HD patients prone to it<sup>(20)</sup>.

In our study we found that there was a positive association between serum albumin level and intradialytic hypotension (IDH) with significant p-value (<0.001). In some but not all studies, a positive association between serum Alb concentration and BP, which turned out to be a prime risk factor for stroke and coronary heart disease<sup>(21)</sup>. Whitfield *et al.*<sup>(22)</sup> demonstrated a strong correlation between BP and plasma Alb., Hostmark *et al.*, showed that systolic BP and diastolic BP increased with increasing serum Alb concentration up to the physiological range<sup>(23)</sup>. Some authors have suggested that the observed

effect of serum Alb on BP might be actually due to serum Ca. level<sup>(21)</sup>.

In our study we found that there was a positive association between serum albumin level with serum calcium level (P value 0.003, r-value:0.632) and between serum albumin level with serum sodium level (P value <0.001, r-value:0.684). There was also a positive association between intradialytic hypotension and both s. calcium and sodium levels with p value < 0.001, and 0.004 respectively, which means that intradialytic hypotension is accompanied by a decline in serum albumin, serum calcium and serum sodium levels (directly proportional relationship). However, another study has found no association between ionized Ca. and BP<sup>(24)</sup>. The association of serum Alb concentrations and BP could result from increased hydrostatic pressure producing hemoconcentration<sup>(25)</sup>.

Our study come in line with Zhai *et al.*<sup>(26)</sup> who identified that dialysate sodium profiling, compared to regular dialysate sodium status, effectively decreases intradialytic ABP and use of antihypertensive medication. Another study<sup>(27)</sup> similarly to ours showed that low-sodium dialysate can reduce morning and night ABP over a period of 6 months. Inrig *et al.*<sup>(28)</sup> conducted a randomized study, comparing hemodialysis patients receiving low- and high-sodium dialysate for 3 weeks, and found that low-sodium dialysate leads to a mean 9-mmHg decrease in systolic BP, consistent with our study findings. Is *et al.*<sup>(29)</sup> in agreement with our study, stated that hypotension may reflect both the severity of disease (ischemic heart disease and/or cardiomyopathy), and the intensity of therapy used to treat the disease.

There was also a close correlation observed between diastolic blood pressure and serum albumin level. Nakamoto *et al.*<sup>(15)</sup> compared background characteristics of hypotensive patients during HD and showed that serum Alb. in the DIH group was significantly lower compared with the normotensive group. Our results were consistent with those found by Nakamoto *et al.* in which Alb. in the DIH group was significantly lower compared with the non DIH group with P-value:<0.001. However, some studies as Walker *et al.*<sup>(30)</sup> failed to demonstrate an association between Alb and BP.

In our study, about 90% of the patients who had intradialytic hypotension had also positive and high results of CRP with a mean of (15.67 ± 13.27), on the other hand, the negative and low results of CRP were in the other group of patients who didn't had hypotension during dialysis with a mean of (2.07 ± 1.48). So CRP appears to be significantly higher in patients who had hypotensive episodes

during dialysis (P value < 0.001). Tomita et al. <sup>(31)</sup> in consistent with our results examined the relationship between HD- induced immune activation and DIH, using the acute phase reactant, serum CRP as a surrogate for immunogenic activation. The maximum percent change in the mean arterial pressure was correlated significantly with CRP (r=0.67, P< 0.05) in nine patients with a history of symptomatic DIH. Immune activation mediated by interleukine-6, CRP and other cytokines played also a role in pathogenesis of DIH in some patients.

## CONCLUSION

The present study concluded that low serum Alb. levels and high levels of CRP may predict an increased risk of DIH in regular HD patients and this was the main issue for our study, however we also found that there are some other biochemical markers, which can come inbetween with our two main markers, and this confirms our results. These biochemical markers include serum sodium and calcium levels, as hyponatremia and hypocalcemia accompanied hypoalbuminemia in patients experienced hypotensive episodes during hemodialysis sessions.

These findings might help us in our future adjustment of hemodialysis treatment and dose, putting in consideration these serum electrolytes and their relation to DIH in patients prone to. We also concluded that acute phase response occurs in the majority of ESRD patients. We believe that measuring CRP as a marker of inflammation can be helpful in managing these patients. Our findings have important implications for clinical practice. More important, the study recommended that ESRD patients with low albumin and/or high CRP levels should receive close follow up and all sources of malnutrition and inflammation should be controlled.

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