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The Association between Hypoalbuminemia and Intradialytic Hypotension in Heamodialysis Patients

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ABSTRACT

Background: hypoalbuminemia is an important risk factor of hypotension during hemodialysis and progressive left ventricular hypertrophy in patients with chronic kidney disease (CKD). **Aim of the study**: this study was done to evaluate the relationship between serum albumin and intradialytic hypotension (IDH) and cardiac functions. **Patients and Methods**: forty patients on regular hemodialysis (HD) were included in the present study. They have been divided into two groups; Group **1**: Patients of this group developed recurrent attacks of IDH and Group **2**: Patients of this group not developed IDH. The patients have been classified again according to serum albumin level into two groups; Group **A**: Hypoalbuminemic patients and Group **B**: Non-hypoalbuminemic patients. Data collected from each patient included: (1) Demographic features (age, gender) and clinical features (blood pressure changes during session, ultrafiltration rate, cardiothoracic ratio, duration of dialysis and Kt/V); (2) Blood chemistry (creatinine, urea, hemoglobin, hematocrit value, total proteins, albumin, triglycerides, cholesterol, AST, ALT, Kt/V, and fasting blood sugar); and (3) Echocardiographic assessment of left ventricular geometry. **Results**: there was a significant negative correlation between serum albumin and Delta BP in HD patients. Also we found no significant changes in cardiac functions among different studied groups. **Conclusion**: We concluded that there was a relationship between low serum albumin and intradialytic hypotention and cardiac functions in CKD patients undergoing HD. **Recommendations**: Regular assessment of serum albumin is mandatory for all HD patients.

Key words: Heamodialysis, Hypoalbuminemia, Risk factor, Intradialytic hypotension.

INTRODUCTION

The association between blood pressure changes and death rate is higher in hemodialysis patients than in general population.[(1)] Intra-dialytic hypotension (IDH) was found to be an independent and negative predictor of long-term fistula outcome.[(2)]

Intradialytic hypotension continues to be a leading problem, especially in elderly and cardiovascular compromised patients.[(3)] The sensitivity of patients for IDH may not be a stable condition. Many patients were found to have large differences in the incidence of IDH over a 24-month period.[(4)]

Rapid ultrafiltration especially in elderly patients may cause a premature drop in blood pressure during hemodialysis before they reach dry weight.[(3)] Hypoalbuminemia is an important risk factor of hypotension during hemo-dialysis.[(5)] Also, hypoalbuminemia was an important risk factor for progressive left ventricular hypertrophy in patients with end stage renal disease (ESRD).[(6)]

AIM OF THE STUDY

The aim of the study is to identify the relationship between serum albumin and intradialytic hypotention and cardiac functions in patients with chronic kidney disease (CKD) on regular hemodialysis.

PATIENTS AND METHODS

Study groups:

This study was done in the nephrology and dialysis unit at Bab-Eshearea University Hospital on 40 patients with CKD on regular hemodialysis (HD). They were divided into 2 groups according to BP changes during HD:

Group 1: This group included 20 patients with CKD on regular HD for at least 6 months, 3 times /week, duration of each session was 4 hours, 11 of them were males, 9 were females, their age ranged between 17 and 63 years with a mean of 47.1±2.72. Also, their serum albumin ranged between 2.4 and 4.7 g/dl with a mean of 3.55±0.15. Blood access was through arteriovenous fistula. The duration of HD ranged between 1 and 12 years with a mean of 5.8±0.89. The criteria for inclusion in the study were that patients had recurrent episodes of intradialytic hypotension (IDH) and interdialytic normal BP. Among these twenty

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patients in group 1, 9 were hypoalbuminemic (<3.5 mg/dl) and 11 were non-hypoalbuminemic (≥3.5 mg/dl).

The dialyzer used was Fresenius Polysulfone F6 and F7 models, for single use only with surface area suitable for each patient.

We used bicarbonate dialyzing concentrate with a final concentration of diluted solution in mEq/Litre as following:

Na^+	135 mEq/l	Cl^-	106.5 mEq/l
K^+	2.5 mEq/l	Mg^{2+}	1.5 mEq/l
Ca^{2+}	3.5 mEq/l	CH_3COOH	8.5 mEq/l

During dialysis the patient received heparinization with 10,000 units as a maximum dose. Erythropoietin was taken for each patient according to body weight (100-150 IU/kg/week). The blood flow rate was suitable for each patient. The dialysate flow rate was 500 ml/min for all patients.

Group 2: This group included 20 patients with CKD on regular HD, not developed IDH (as control group), for at least 6 months, 3 times/week, duration of each session was 4 hours, 12 of them were males, 8 were females, their age ranged between 22 and 62 years with a mean of 45±3.01, their serum albumin ranged between 3.3 and 4.9 g/dl with a mean of 4.03±0.088. Blood access was through arterio-venous fistula. The duration of HD ranged between 1 and 11 years with a mean of 4.37±0.68. The criteria for inclusion in the study were that patients had no episodes of IDH. The dialyzer, dialyzate solution, heparinization, and erythropoietin dose were the same as for patients in group1.

The patients have been classified again according to serum albumin levels into two groups:

- **Group A**: A Hypoalbuminemic patients, their number was 11 patients.
- **Group B**: Non-hypoalbuminemic patients, their number were 9 patients.

All patients were subjected to the following: (1) History taking and clinical examination; (2) Blood chemistry investigations (Serum creatinine, serum urea, hemoglobin, hematocrite value, total proteins, serum albumin, serum triglycerides, serum cholesterol, AST, ALT, Kt/v, and fasting blood sugar); and (3) Echocardiographic assessment of left ventricular geometry.

(1) Clinical and dialysis criteria: Age (years); gender (male or female); weight (Kg); body mass index (kg/m^2); ultrafiltration rate (ml/hour); plain x-ray chest and heart for calculation of cardiothoracic ratio (CTR); duration of dialysis (years); blood flow rate (BFR); dialyzer surface area (DSA); blood pressure changes during session [Systolic blood pressure before session (SBPBS), diastolic blood pressure before session (DBPBS); lowest systolic blood pressure (LSBP); and lowest diastolic blood pressure (LDBP)].

Delta systolic blood pressure (Delta SBP) was calculated as:

Delta systolic blood pressure= Systolic BP before dialysis session - Lowest systolic BP during session. Delta SBP increase denotes more drop of systolic BP which may predispose to IDH.

(2) Blood chemistry:

Specimen collection: Ten CC venous blood sample was drawn from each patient after an overnight fasting and divided in tubes as follows: 1) Plain tubes in which blood samples were centrifuged and serum aliqouted where routine investigations were done. 2) Tubes containing EDTA for blood picture.

Biochemical investigations: Total proteins and serum albumin, serum creatinine and blood urea, hemoglobin (Hb) and hematocrite (hct) values, serum triglycerides (TG) and serum cholesterol, aspartate transaminase (AST) and alanine transaminase (ALT) enzymes, fasting blood sugar (FBS), estimation of serum Sodium (Na) and Potassium (K), and Kt/V:

The dose of HD can be expressed as $(K_{urea} \times t_d)/V_{urea}$ (abbreviated as Kt/V), where K_{urea} is the effective (delivered) dialyzer urea clearance in milliliters per minute integrated over the entire dialysis, T_d is the time in minutes measured from beginning to end of dialysis, and V_{urea} is the patient's volume of urea distribution in milliliters.

- Kt/V is a good indicator of adequacy of dialysis it should be more than 1.4.

(3) Echocardiographic assessment of left ventricular geometry and systolic function:

M-mode echocardiography was performed by a single experienced echocardiographer, who was blinded to the results of the other study

parameters, with all patients were examined in the left lateral decubitus position.

M-mode measurements included: Interventricular septal thickness (IVST), left ventricular posterior wall thickness (PWT), left ventricular end-systolic diameter (LVESD), left ventricular end-diastolic diameter (LVEDD), left ventricular mass (LVM), left ventricular fractional shortening (FS), and ejection fraction (EF).

- Left ventricular hypertrophy (LVH) was defined as: LVMI >131 g/m^2 in males and > 100 g/m^2 in females.
- Systolic dysfunction was defined as: Ejection fraction less than 50.0%.

Statistical analysis:

Data were analyzed using SPSS program version 13. Results were expressed as mean ± standard deviation (SD) for normally distributed data, and percentages for categorical data. Comparison between the means was carried out with the t- student's test, while comparison between the groups was carried out with chi square (χ^2) test. In correlation study, data were analyzed using Pearson's correlation; degree of the association was expressed as (r) (correlation co-efficient). Significance level for t, χ^2, correlation was accepted at P-value < 0.05.

RESULTS

As regard age and gender, table **(1)** shows comparison between group 1 (patients with IDH) and group 2 (patients not developed IDH), there was no significant difference between the two groups.

As regard mean blood pressure changes **(table 2)**; before the dialysis session, there was no significant difference between the 2 groups as regard diastolic BP, but there was a significant difference as regard systolic BP; mean systolic BP was lower in group 1. Meanwhile, there were significant differences between the 2 groups as regard lowest systolic and diastolic BP during the dialysis session; patients in group 1 were more hypotensive than patients in group 2 for both lowest- SBP and DBP. Lastly, Delta SBP was significantly higher among patients in group 1. As regard ultrafiltration rate (UFR), it was significantly higher among patients in group 2. Meanwhile, mean cardiothoracic ratio (CTR) was significantly higher among patients in group 1. As respect duration of hemodialysis, it was insignificantly higher among patients in group 1.

As respect the laboratory data of the studied groups **(table 3)**; there were no significant differences between the 2 groups except for mean serum albumin, which was significantly lower in group 1 than in group 2.

Regarding echocardiographic parameters of the studied groups **(table 4)**; there were no significant differences between the 2 groups.

As respect mean blood pressure changes among hypoalbuminemic (group A) and non-hypoalbuminemic (group B) patients **(table 5)**, before the dialysis session, there was no significant difference between the 2 groups as regard diastolic BP, but there was a significant difference as regard mean systolic BP; it was higher in group A. While, there were significant differences between the 2 groups as regard lowest systolic and diastolic BP during the dialysis session; patients in group A were more hypotensive than patients in group B for both lowest- SBP and DBP. Also, Delta SBP was significantly higher among patients in group A. Meanwhile, mean CTR was significantly lower among patients in group A.

As regard echocardiographic parameters of the studied groups **(table 6)**; there were a significant difference between the two groups as regard mean LVMI, LVEDD, and LVPWT as they are higher in group A than in group B. Meanwhile, other echocardiographic parameters were statistically insignificant between the 2 groups.

Respecting correlations between serum albumin level and study parameters **(table 7)**; there were significant positive correlations between serum albumin and ultrafiltration rate, BMI, Kt/V, hematocrit value, and hemoglobin. Meanwhile, there were significant negative correlations between serum albumin and Delta BP, CTR, LVMI, IVST, LVPWT, LVEDD, and LVESD. On the other hand, there were insignificant negative correlations between serum albumin and age, LVEF, and LVFS.

Regarding correlation between serum albumin and LVMI **(figure 1)**, there was significant negative correlation. Regarding correlation between serum albumin and Kt/V **(figure 2)**, there was a significant positive correlation.

DISCUSSION

In view of the possibility that changes in serum albumin in HD patients could contribute to impaired cardiac functions as well as development of IDH and deterioration of residual renal function and inadequate dialysis, we studied serum albumin and cardiac function as potential risk factors in hypoalbuminemic and non-hypoalbuminemic normotensive HD patients with recurrent episodes of IDH, who were well maintained on regular HD and not developed IDH.

Hypoalbuminemia and dialysis efficacy have been shown repeatedly to be perhaps the most critical predictors of outcomes in patients with end stage renal disease. The relationship between hypoalbuminemia and mortality was especially strong; each 1 gm/dl decrease in mean serum albumin is associated with the development of de novo and recurrent cardiac failure, de novo and recurrent ischemic heart disease, cardiac mortality and overall mortality.[7]

In the present work, the mean CTR in hemodialyzed patients who developed IDH (group 1) was significantly higher than that of hemodialyzed patients not developed IDH (group 2). The difference was statistically significant, moreover, CTR was found to be higher in hemodialyzed patients with hypoalbuminemia (group A) than non-hypoalbuminemic (group B) patients who developed IDH. This could be attributed to volume overload and/or anemia induced LV dilatation and compensatory LV hypertrophy. So, hypoalbuminemia can contribute in the pathogenesis of hypervolemia and enlargement of the cardiac size. Also, this result was consistent with Parfrey and Foley [8] who found that CTR was significantly increased in hypotensive patients than normotensive patients. They suggested that there is pathophysiological role of hypervolemia in increased cardiac size.

In the current work we found that LVEDD is more evident in group A than in group B denoting increased cardiac size caused by over hydration in hypoalbuminemic patients. We also found a significant negative correlation between serum albumin and LVEDD. Kurast *et al*.[9] cleared that LVEDD is one of the important markers of hypervolemia.

Capuano *et al*. [10] reported that the incidence of IDH is higher in old age than in younger patients, this difference could be attributed to relatively younger patients in their study.

Delta blood pressure is a very important indicator of change of systolic blood pressure during dialysis session.[5] The increase of Delta SBP indicates more declines in blood pressure and consequently increase incidence of IHD. In the present work, we found a significant negative correlation between serum albumin and Delta BP. Also, Delta BP was more evident in group A (hypoalbuminemic) than group B (non-hypoalbuminemic), these results denote significance of serum albumin as a factor for occurrence of IDH. So, hypoalbuminemia could be a factor, which accelerates IHD in those patients. Also, this finding is in agreement with Nakamoto *et al*.[5] who found that hypo-albuminemia is a major risk factor of IHD and they suggested that it leads to hypervolaemia due to decreased oncotic pressure. This lead to decreased plasma refills and causes premature drop in BP leading to IDH. However, we found that IDH was absent in 2 patients in group 2 in spite of the presence of low serum albumin (3.4 and 3.4 g/dl).

Diabetic neuropathy is one of the important factors that cause IDH through impairment of vascular reactivity. Our results showed that many patients among group 1 who are not hypoalbuminemic but they are diabetics and developed IDH, this can be explained by autonomic neuropathy caused by diabetes mellitus. This result is consistent with Sato *et al*.[11] who found that the presence of autonomic neuropathy (including diabetic neuropathy) is a risk factor for IDH.

Despite advances in the dialysis therapy, cardiovascular disease (CVD) remains the most important cause of death in patients receiving maintenance dialysis therapy. CVD accounts for almost 44.0% of overall mortality in long-term dialysis patients. Hemodialysis patients are predisposed to cardiomyopathy and athero-sclerosis when compared with age and gender matched persons with normal kidney function.[12]

Diastolic dysfunction is frequently present in dialysis patients. The abnormal ventricular filling in ESRD results from increased LV stiffness caused by intramyocardial fibrosis and delayed relaxation. It is highly likely that patients with concentric

LVH or LV dilatation have diastolic dysfunction.[8]

In the present work the result showed eight patients in group 1 who were non-hypoalbuminemic but have left ventricular hypertrophy and developed IHD. This finding is similar with result obtained by Ritz *et al*.[13] who found that left ventricular hypertrophy predispose to IHD.

Hypoalbuminemia is a well known risk factor for development of left ventricular hypertrophy. In the current work, we reported a significant negative correlation between serum albumin and LVMI. Also we showed that LVMI is more evident in hypoalbuminemic (group A) than non-hypoalbuminemic (group B) patients, this observation suggests that the adverse effect of hypoalbuminemia might be mediated via cardiac disease. Also, these observations compatible with Robert *et al*.[14] who cleared that hypoalbuminemia is a major risk factor for left ventricular hypertrophy.

Hypoalbuminemia is known to be a marker of malnutrition in HD patients. Malnutrition is a common complication among HD patients despite apparent adequate protein intake, and absence of increased energy. Also, malnutrition is a predictor of survival.[15] Meanwhile, patient who can be assessed by BMI is also a marker of malnutrition in HD patients.[16]

In the current work, there was a significant negative correlation between serum albumin and BMI. Also, hypoalbuminemia was evident in group 1 (hypotensive). The explanation of these findings that recurrent hypotensive episodes leads to insufficient dialysis, which in turn increase the probability of malnutrition, so hypoalbuminemia not only a cause but may be also a result of IDH. These results correspond with Bergstrom[17] who found that inadequate dialysis leads to anorexia and poor nutritional intake followed by the development of hypoalbuminemia. So, adequate dialysis is a very important determinant of the dialysis outcome and can be assessed by calculation of Kt/V.[18]

In this study, we found significant positive correlation between serum albumin and hematocrit value. Our result is in agreement with Sean *et al*.[19] who found significant positive correlation between serum albumin and hematocrit value. Also, lower hematocrit and albumin levels may be co-dependent on inflammatory mechanisms that contribute to erythropoietin resistance and decreased albumin synthesis, respectively.[20]

Anemia, which has many complications, is a common complication in HD patients. Left ventricular hypertrophy is one of the complications caused by anemia. In the current study, we showed significant positive correlation between serum albumin and hemoglobin. Our result is consistent with Locatelli *et al*.[21]

CONCLUSIONS

There was a significant positive correlations between serum albumin and Kt/V, ultrafiltration rate, hemoglobin, hematocrit value, and BMI. Meanwhile, there were significant negative correlations between serum albumin and Delta BP, CTR, LVMI, LVPWT, IVST, LVESD, and LVEDD. Also, patients with recurrent episodes of IDH had increased CTR and Delta systolic BP than patients not developed IDH. So, we conclude that there was a relationship between serum albumin and intradialytic hypotention and cardiac functions.

RECOMMENDATIONS

Low serum albumin is an important factor for occurrence of IDH and cardiac morbidity. Regular assessment of serum albumin is mandatory for all HD patients. Further studies are necessary to study the therapeutic effect of albumin infusion in treatment of IDH.

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Table (1): Demographic characteristics of patients in group 1 (patients with IDH) and group 2 (patients not developed IDH) as regard age and gender

Variables	Group 1 (n=20)		Group 2 (n=20)		t*-value χ^2-value	P-value
	No.	%	No.	%		
Age (year): Mean± SD	47.1±2.72		45.0±3.01		0.570*	0.576
Gender:						
Male	11	55.0	12	60.0		
Female	9	45.0	8	40.0	0.1	0.749

Table (2): Mean± standard deviation (SD) of the studied patients in group 1 and 2 according to blood pressure, ultrafilteration rate, cardiothoracic ratio, and duration of hemodialysis

Variables	Group 1 (n=20) patients with IDH	Group 2 (n=20) patients with no IDH	t-value	P-value
	Mean± SD	Mean± SD		
Blood pressure before the dialysis session				
Systolic	123.5±2.43	132.0±1.86	-12.422	0.007*
Diastolic	80.0±1.62	83.0±1.63	-5.838	0.186
Lowest blood pressure during the dialysis session				
Systolic	78.0±2.47	119.5±1.23	-67.261	0.0001*
Diastolic	47.0±1.93	77.0±1.05	-61.063	0.0001*
Delta systolic blood pressure (SBP)				
Delta SBP	45.5±2.45	13.0±1.93	-46.6	0.0001*
Ultrafiltration rate (UFR)				
UFR	456.25±26.08	606.25±26.9	-17.9	0.0001*
Cardiothoracic ratio (CTR)				
CTR	55.85 ±0.68	48.5 ±0.43	-40.85	0.0001*
Duration of hemodialysis (years)				
Duration (year)	5.8±0.89	4.37±0.68	1.16	0.257

*= Significant

Table (3): Mean± standard deviation (SD) of the studied patients in group 1 and 2 according to laboratory results

Variables	Group 1 (n=20) patients with IDH	Group 2 (n=20) patients with no IDH	t-value	P-value
	Mean± SD	Mean± SD		
Kt/V	1.03±0.08	1.16±0.1	-1.168	0.257
Urea	112.4±12.18	117.45±10.46	-0.367	0.718
Creatinine	6.37±0.95	5.86±0.40	0.954	0.352
Hematocrit	29.42±1.32	29.99±1.24	-0.328	0.746
Hemoglobin	8.98±0.45	8.96±0.38	0.037	0.970
Triglycerides	185.15±24.27	173.9±16.33	0.348	0.731
Cholesterol	123.1±5.19	111.05±2.31	1.956	0.065
FBS	130.65±9.37	113.85±4.24	1.686	0.108
AST	28.8±2.32	29.5±2.96	-0.225	0.824
ALT	31.55±3.23	34.4±3.96	-0.615	0.546
Albumin	3.55±0.15	4.03±0.088	-2.218	0.039*
Total proteins	5.29±0.09	5.4±0.1	0.438	0.667

*= Significant

Table (4): Mean± standard deviation (SD) of the studied patients in group 1 and 2 according to echocardiographic parameters

Variables	Group 1 (n=20) patients with IDH	Group 2 (n=20) patients with no IDH	t-value	P-value
	Mean± SD	Mean± SD		
Left ventricular mass index (LVMI)	152.45±6.15	150.28±8	0.198	0.848
Left ventricular ejection fraction (LVEF)	52.32±1.82	58±2.56	-1.931	0.069
Left ventricular fractional shortening (LVFS)	27.62±0.98	30.45±1.45	-1.819	0.085
Left ventricular end-diastolic diameter (LVEDD)	5.0±0.08	5.02±0.13	0.237	0.815
Left ventricular end-systolic diameter (LVESD)	3.66±0.09	3.36±0.18	1.340	0.196
Interventricularseptal thickness (IVST)	1.21±0.03	1.13±0.04	1.461	0.160
Left ventricular posterior wall thickness (LVPWT)	1.22±0.044	1.09±0.04	1.868	0.077

Table (5): Mean± standard deviation (SD) of the studied patients in group A and B (with- and without hypoalbuminemia) according to blood pressure and cardiothoracic ratio

Variables	Group 2 patients with no IDH (n=20)		t-value	P-value
	Group A Hypoalbuminemia (n=11)	Group B No hypoalbuminemia (n=9)		
	Mean± SD	Mean± SD		
Blood pressure before the dialysis session				
Systolic	130.0±3.3	126.89±1.93	-2.625	0.04*
Diastolic	82.72±2.37	81.0±1.34	2.041	0.276
Lowest blood pressure during the dialysis session				
Systolic	79.08±5.63	105.5±3.56	-12.756	0.005*
Diastolic	50.9±4.75	65.86±2.78	-8.77	0.005*
Delta systolic blood pressure (SBP)				
Delta SBP	41.5±1.95	13.5±2.43	-27.97	0.001*
Cardiothoracic ratio (CTR)				
CTR	3.55±0.15	4.03±0.08	-2.22	0.039*

*= Significant

Table (6): Mean± standard deviation (SD) of the studied patients in groups A and B (with- and without hypoalbuminemia) according to echocardiographic parameters

Variables	Group 2 patients with no IDH (n=20)		t-value	P-value
	Group A Hypoalbuminemia (n=11)	Group B No hypoalbuminemia (n=9)		
	Mean± SD	Mean± SD		
Left ventricular mass index (LVMI)	176.63±9.91	141.81±4.73	3.321	0.008*
Left ventricular ejection fraction (LVEF)	51.13±2.32	56.72±2.0	-0.563	0.586
Left ventricular fractional shortening (LVFS)	26.95±1.31	29.82±1.11	-0.545	0.598
Left ventricular end-diastolic diameter (LVEDD)	5.3±0.1	4.94±0.09	2.620	0.026*
Left ventricular end-systolic diameter (LVESD)	3.87±0.08	3.37±0.13	2.166	0.056
Inter ventricular septal thickness (IVST)	1.26±0.06	1.13±0.02	2.058	0.067
Left ventricular posterior wall thickness (LVPWT)	1.18±0.31	1.02±0.01	3.068	0.044*

*= Significant

Table (7): Correlation co-efficient between serum albumin level and the study parameters among the studied patients

Variables	r	P
Age	-0.099	0.273
Delta blood pressure (BP)	-0.670	0.0001*
Ultrafiltration rate (UFR)	0.361	0.011*
Cardiothoracic ratio (CTR)	-0.618	0.0001*
Body mass index (BMI)	0.323	0.042*
Kt\V	0.402	0.005*
Hematocrit (Hct)	0.283	0.038*
Hemoglobin (Hb)	0.320	0.022*
Left ventricular mass index (LVMI)	-0.555	0.0001*
Left ventricular ejection fraction (LVEF)	0.266	0.97
Left ventricular fractional shortening (LVFS)	0.259	0.107
Left ventricular end-diastolic diameter (LVEDD)	-0.341	0.031*
Left ventricular end-systolic diameter (LVESD)	-0.344	0.030*
Inter ventricular septal thickness (IVST)	-0.435	0.005*
Left ventricular posterior wall thickness (LVPWT)	-0.435	0.003*

*= Significant

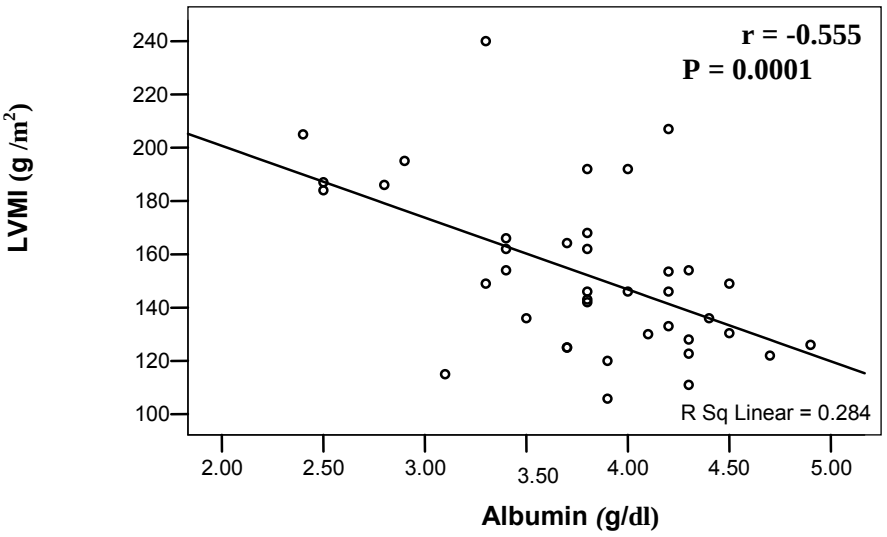

Figure (1): Correlation co-efficient between serum albumin and LVMI

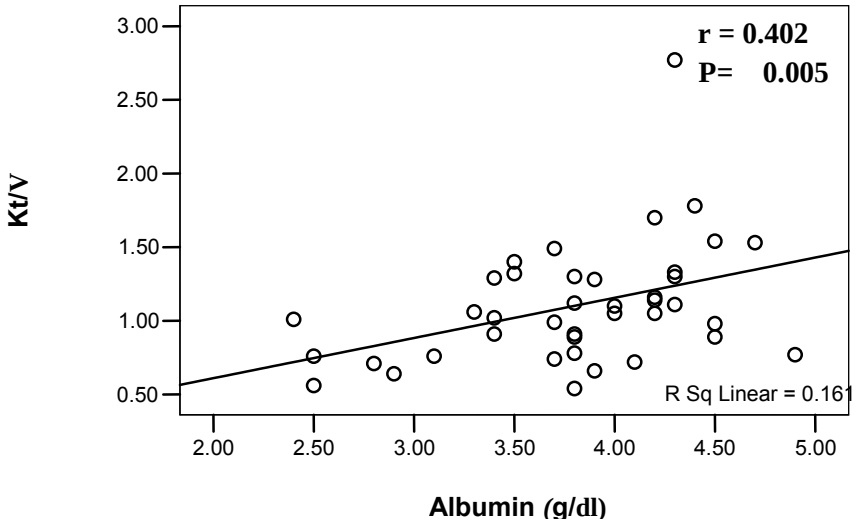

Figure (2): Correlation co-efficient between serum albumin and Kt/V