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**RESEARCH ARTICLE**

**THE EFFECT OF IRON AND ERYTHROPOIETIN TREATMENT ON THE HBA1C OF  
 HEMODIALYSIS PATIENTS WITH DIABETES.**

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**Abstract**

**Background & Aims:-** The aim of this thesis is to validate the effect of iron and erythropoietin treatment on the HbA1c of hemodialysis patients with diabetes.

**Methods:-** This study was conducted on 50 HD patients with type-2 diabetes. All patients were selected from those under going regular HD in nephrology and dialysis unit in Banha University Hospitals.

.the diagnosis of diabetes will be based on a history of diabetes or on the ADA criteria. The patients will be classified into two groups (each consists of 25 patients). The first group (group A) are patients selected for iron therapy according to clinical need. The second group (group B) consisted of patients who were those needing ESA treatment. Glycemic control in both patient groups will be assessed using HbA1c in the month leading up to treatment and once again for a 4-week period 4 months after therapy. The main values of the three-monthly measurements of casual.

**Results:-** A1C value falls after four months of therapy in both groups (iron and ESA group) compared to before therapy. This change was independent on glycemic control.

**Conclusions:-** A1c is the most widely accepted and used method of assessing chronic glycemia in patients with diabetes. This study showed that iron and ESA treatments result in a fall in A1C, which is independent of glycemic changes in patients with diabetes and CKD.

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**Introduction:-**

A1c is the most widely accepted and used method of assessing chronic glycemia in patients with diabetes. It is formed by the irreversible binding of glucose to hemoglobin over the lifespan of the erythrocytes (Goldstien et al, 2004). Patients with Chronic kidney disease (CKD) are commonly anemic due to a variety of reasons, including functional or absolute iron deficiency and erythropoietin insufficiency. Treatment of anemia in patients with CKD using iron replacement therapy and erythropoietin-stimulating agents (ESAs) has resulted in significant improvements to quality of life and the correction of anemia without the need for blood transfusions (Nissenson et al, 1999).

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### Material and Methods:-

This study was conducted on 50 HD patients with type-2 diabetes. All patients were selected from those undergoing regular HD in nephrology and dialysis unit in Banha University Hospitals. The diagnosis of diabetes was based on a history of diabetes or on the ADA criteria. Information collected from participants included demographic data, height, weight (dry weight in HD patients), duration of diabetes and duration of HD.

**Inclusion criteria:-** Patients with type 2 DM who fulfil the following criteria; regular HD, anemia due to CKD, Patients with diabetes were restricted to those with stable blood glucose and whose diabetes treatment had not been altered during the preceding 6 months before the determination of HbA1c.

**Exclusion criteria:-** Patients with hemoglobinopathy, anemia due to causes other than CKD, patients who had a history of overt blood loss or who received a blood transfusion 4 months prior to the study, patients with evidence of scurvy, evidence of hepatic disorders, inflammatory disease or thyroid disease, who had been previously treated with ESA on renal replacements, or with previous transplantation were excluded from the study. The patients will be classified into two groups (each consists of 25 patients). The first group (group A): serum ferritin values  $<200\mu\text{g/l}$  these patients were candidate for iron therapy. The second group (group B): serum ferritin value  $>200\mu\text{g/l}$  these patients were candidate for ESA therapy. Glycemic control in both patient groups was assessed using HbA1c in the month leading up to treatment and once again for a 4-week period 4 months after therapy. Blood was drawn without overnight fasting, immediately before the session of HD. Blood was drawn from the dialyzer circuit prior to the initiation of dialysis or administration of anticoagulants. Blood samples were divided into 5 ml sent for HbA1c and 5 ml centrifuged with the serum frozen at  $80\text{ }^{\circ}\text{C}$  for measurement of GA, 8 ml will be analyzed for total protein, albumin, blood urea nitrogen and creatinine and 2 ml on EDTA for CBC. All the patients selected for iron therapy had either absolute or functional iron deficiency as evidenced by serum ferritin values  $<200\mu\text{g/l}$ . All patients had hemoglobin  $\leq 10.5\text{ g/dl}$ . Patients in this group were not on previous or concurrent ESA therapy and were vitamin B12 and folate replete. Intravenous iron was given as a single dose in the form of low-molecular weight iron dextran dependent on the patient's body weight. This will be delivered as an initial intravenous test infusion of 100 mg of iron over 1 h followed by the remaining dose over the next 2-4 h. All patients receiving ESA therapy had hemoglobin  $<$  or  $=10.5\text{ g/dl}$  and were considered iron, vitamin B12, and folate replete prior to initiation. Patients were considered iron replete following a serum ferritin value  $>200\mu\text{g/l}$  or having received intravenous iron at least 6 weeks prior to ESA therapy. The dose of ESA will be titrated monthly to achieve target hemoglobin 10.5-12 g/dl.

### Statistical analysis:-

The collected data were tabulated and analyzed using SPSS version 16 software (Spss Inc, Chicago, ILL Company) and. Categorical data were presented as number and percentages while quantitative data were expressed as mean  $\pm$  standard deviation, and range. Categorical variables were analyzed using Chi square test ( $\chi^2$ ) and Fisher's exact test (FET). Quantitative data were tested for normality using Shapiro-Wilks test, assuming normality at  $P>0.05$ . Student's t test was used to analyze the difference between 2 independent groups regarding normal variables, non-parametric variables were analyzed using Mann-Whitney U test (MWU) for 2 independent groups and Friedman test which was used to test the differences between matched variables considering P value significant at 0.05. Significant Friedman test was followed by post hoc multiple comparisons using Bonferroni adjusted Wilcoxon test to detect the significant pairs at adjusted  $P=0.017$ .

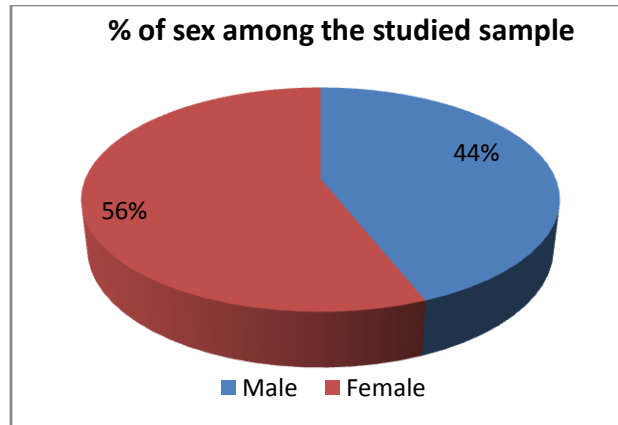
### Results:-

**Table 1:-** Socio-demographic characters of the studied groups.

Variable		No. (n=50)	% (100.0)
Group	Group A (S. ferritin $<200$ , iron therapy)	25	50.0
	Group B (S. ferritin $>200$ , ESA therapy)	25	50.0
Sex	Male	22	44.0
	Female	28	56.0
		Mean $\pm$ SD	Range
Age (ys)		56.3 $\pm$ 5.7	40-65

Weight (kg)	79.8±17.8	56-110
Height (cm)	162.2±8.05	150-175
BMI (kg/m <sup>2</sup> )	30.07±5.1	23.2-40.2

50 studied patient group (A):25 patients and Group(B):25 patients Among 50 studied patient 22patients were male, 28 patients were female Mean age(ys):56.3 of range from 40 to 65 years Mean weight(kg):79.8 of range from 56 to 110 kg Mean height (cm):162.2 of range from150 to 175 cm Mean pmi(kg/m):30.07 of range from 23.2 to 40.2 kg/m



**Fig. 1:-** % of sex among the studied groups.

**Table 2:-** Comparison of the studied groups regarding socio-demographic characters.

Variable		Group A (N=25)		Group B (N=25)		Test of significance	P
		No.	%	No.	%		
Sex	Male	8	32.0	14	56.0	X <sup>2</sup> = 2.92	0.09 (NS)
	Female	17	68.0	11	44.0		
Age (ys)	Mean ± SD (Range)	57.1±3.2 (52-60)		55.6±7.4 (40-65)		St."t"= 0.95	0.34 (NS)
Weight (kg)	Mean ± SD (Range)	75.4±17.4 (56-103)		84.0±17.5 (60-110)		St."t"= 1.74	0.09 (NS)
Height (cm)	Mean ± SD (Range)	159.8±6.2 (152-170)		161.2±9.6 (150-175)		St."t"= 0.59	0.55 (NS)
BMI (kg/m <sup>2</sup> )	Mean ± SD (Range)	29.4±5.9 (23.2-40.2)		30.7±5.1 (25.0-36.75)		St."t"= 0.96	0.34 (NS)

Among studied groups Group A formed from 8 male and 17 female patients Group B formed from 14 male and 11 female patients in group A mean age 57.1 and in groupB mean age 55.6 which statistically non significant ( p=.34) in group A mean weight was 75.4 and in groupB mean weight was 84 which statistically non significant ( p=.09) in group A mean height was 159.8 and in groupB mean height was 161.2 which statistically non significant ( p=.55) in group A mean BMI was 29.4 and in groupB mean BMI was 30.7 which statistically non significant ( p=.34)

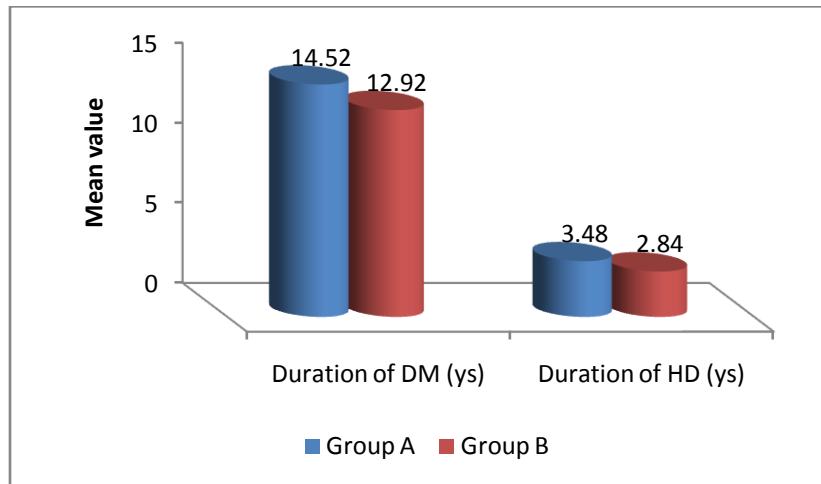
**Table 3:-** Comparison of the studied groups regarding duration of DM and hemodialysis.

Variable	Group A (N=25)			Group B (N=25)			St. 't'	P
	Mean	± SD	Range	Mean	± SD	Range		
Duration of DM (ys)	14.52	5.12	10-25	12.92	5.75	4-25	1.04	0.3 (NS)
Duration of HD (ys)	3.48	2.44	1-8	2.84	1.69	1-6	1.08	0.28 (NS)

**Among studied groups:-**

In group A mean duration of DM was 14.52 and in group B mean duration of DM was 12.92 which statistically non significant( p=.3)

In group A mean duration of HD was 3.48 and in group B mean duration of HD was 2.84 which statistically non significant( p=.28)



**Fig. 2:-** Duration of DM and HD among groups

**Table 4:-** Comparison of the studied groups regarding type of treatment.

Group		Total			
Group A	Group B				
TTT	Premix insulin	Count	13	11	24
		% within Group	52.0%	44.0%	48.0%
	Life style, diet	Count	12	14	8
		% within Group	48.0%	56.0%	16.0%
Total		Count	25	25	50
		% within Group	100.0%	100.0%	100.0%

FET was used

P=0.81 (NS)

This table show regimen for glycemc control for both groups.

**Table 5:-** Comparison of the studied groups regarding laboratory findings before treatment.

Variable	Group A (N=25)			Group B (N=25)			MWU test	P
	Mean	± SD	Range	Mean	± SD	Range		
S. Ferritin	85.1	52.54	27-167.4	1039.9	607.30	292.5-2000	6.08	<0.001 (HS)
HbA1C	6.7	0.64	6.2-8.3	6.42	0.77	4.5-7.1	0.029	0.98 (NS)
PPG	176.7	90.91	130-375	162.1	27.13	130-200	0.26	0.79 (NS)
T. protein	6.57	0.35	6.2-7.3	6.53	0.22	6.1-6.9	0.36	0.72 (NS)
Albumin	3.37	0.22	3.1-3.7	3.42	0.30	3-3.7	0.60	0.54 (NS)
BUN	125.2	57.99	26-212	134.1	36.39	84-197	0.31	0.76 (NS)
Creatinine	6.1	3.0	1.8-9.7	7.11	2.17	3.5-11.4	1.29	0.19 (NS)
Hb%	8.8	1.39	6.6-10.5	9.2	1.32	6.6-10.5	1.34	0.18 (NS)

In studied groups

In group A mean serum ferritin before treatment was 85.1ng/dl compared with group B mean serum ferritin before treatment was 1039.9ng/dl wich statistically highly significant ( $p < .001$ )

HA1C,PPG,T.protein, albumin, BUN, creatinine, Hb% before treatment in group A compared with group B were non significant

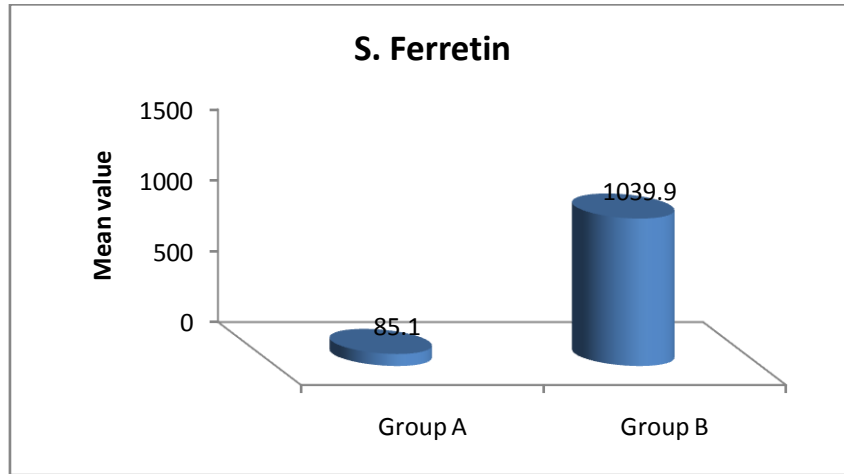


Fig. 3:- S .ferritin among studied groups before treatment.

Table 6:-Comparison of serum ferritin before and after treatment among the studied groups.

Serum ferretin	Group A (N=25)				Group B (N=25)				MWU test	P
	Mean	± SD	Min.	Max.	Mean	± SD	Min.	Max.		
Before intervention	85.18	52.54	27.00	167.40	1039.9	607.30	292.50	2000.0	6.08	<0.001 (HS)
1 month later	515.77	210.68	320.00	921.00	885.0	528.48	250.00	1650.0	2.38	0.017 (S)
4 months later	360.73	116.28	229.50	550.00	950.3	570.58	245.00	1650.0	4.75	<0.001 (HS)
Friedman test	39.1				31.0					
P	<0.001 (HS)				<0.001 (HS)					
Sig pairs	Before ≠ 1m Before ≠ 4m				Before ≠ 1m Before ≠ 4m					

Among studied groups

In group A mean serum ferritin before treatment 85.18 µg /l compared with one month later 515.77 µg /l and four months later 360.73 µg /lwich was highly significant( $p < 0.001$ )

In group B mean serum ferritin before treatment 1039.9 µg /l compared with one month later 885 µg /l and four months later 950.3 µg /lwich was highly significant(  $p < 0.001$ )In group B mean values of serum ferretin were significant high compared with group A in whole duration of study ( $p < 0.001$  )

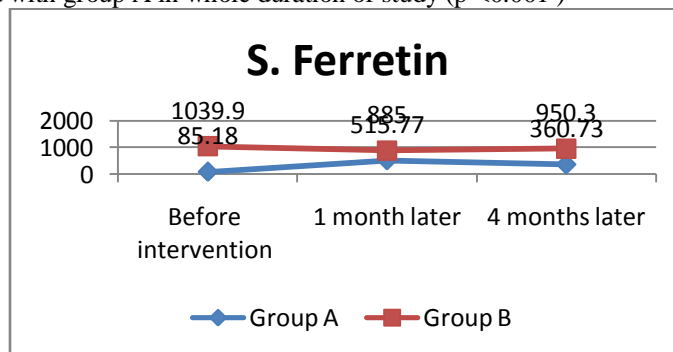


Fig 4:- S.Ferritin among groups during treatment.

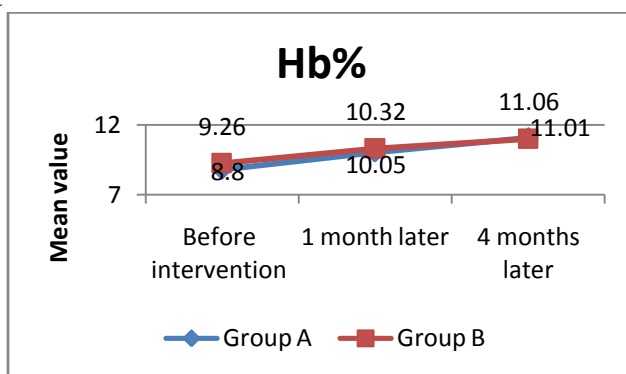
**Table 7:-** Comparison of hemoglobin before and after treatment among the studied groups.  
Among studied groups

Hb%	Group A (N=25)				Group B (N=25)				MWU test	P
	Mean	± SD	Min.	Max.	Mean	± SD	Min.	Max.		
Before intervention	8.80	1.39	6.6	10.5	9.26	1.32	6.6	10.5	1.34	0.18 (NS)
1 month later	10.05	1.03	8.6	11.0	10.32	0.75	9.0	11.2	1.21	0.22 (NS)
4 months later	11.06	0.75	10.5	12.7	11.01	0.51	10.3	12.0	0.43	0.67 (NS)
Friedman test	46.8				48.6					
P	<0.001 (HS)				<0.001 (HS)					
Sig pairs	Before ≠ 1m Before ≠ 4m 1m ≠ 4m				Before ≠ 1m Before ≠ 4m 1m ≠ 4m					

In group A mean value of Hb% before treatment 8.8% compared with one month later 10.05% and four months later 11.06% which was highly significant (p<0.001)

In group B mean value of Hb% before treatment 9.26 % compared with one month later 10.32% and four months later 11.01 which was highly significant (p< 0.001)

In group B mean value of Hb% before treatment and one month later and four months later compared with that of group A was non significant



**Fig. 5:-** Hb% value among groups during treatment

**Table 8:-** Comparison of fasting blood glucose before and after treatment among the studied groups.

Fasting blood glucose	Group A (N=25)				Group B (N=25)				MWU test	P
	Mean	± SD	Min.	Max.	Mean	± SD	Min.	Max.		
Before intervention	101.6	27.5	80.0	150.0	90.8	13.00	73.0	110.0	0.519	0.6 (NS)
1 month later	102.0	27.1	81.0	149.0	95.8	31.79	74.0	176.0	1.8	0.07 (NS)
4 months later	101.6	27.6	80.0	151.0	90.2	12.85	74.0	111.0	0.517	0.61 (NS)
Friedman test	3.8				5.34					
P	0.16 (NS)				0.069 (NS)					
Sig pairs	-----				-----					

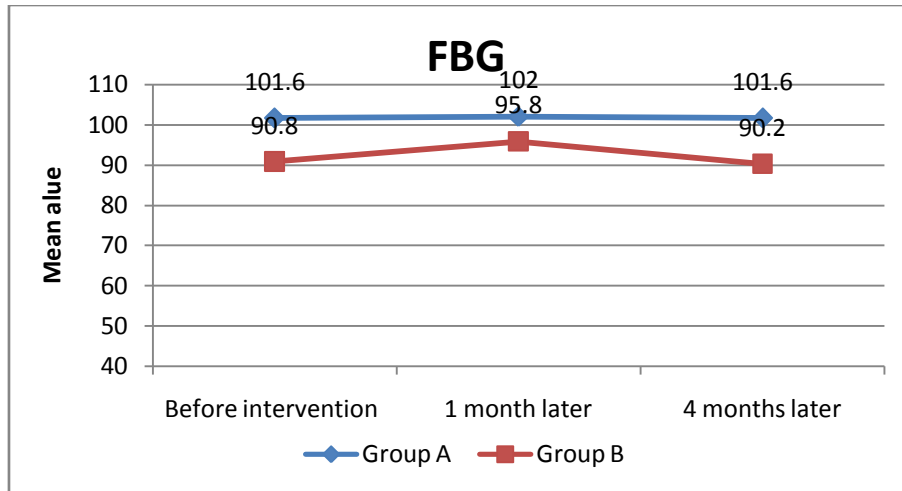


Fig 6:- FBG among the studied groups during course of treatment

Table 9:- Comparison of PP blood glucose before and after treatment among the studied groups.

PP blood glucose	Group A (N=25)				Group B (N=25)				MWU test	P
	Mean	± SD	Min.	Max.	Mean	± SD	Min.	Max.		
Before intervention	176.7	90.91	130.0	375.0	151.7	22.59	130.0	200.0	1.02	0.31 (NS)
1 month later	178.4	81.4	120.0	340.0	146.40	17.41	125.0	170.0	0.55	0.58 (NS)
4 months later	174.1	81.98	125.0	365.0	140.31	12.76	120.0	160.0	0.61	0.54 (NS)
Friedman test	5.10				5.37					
P	0.1 (NS)				0.07 (NS)					
Sig pairs	-----				-----					

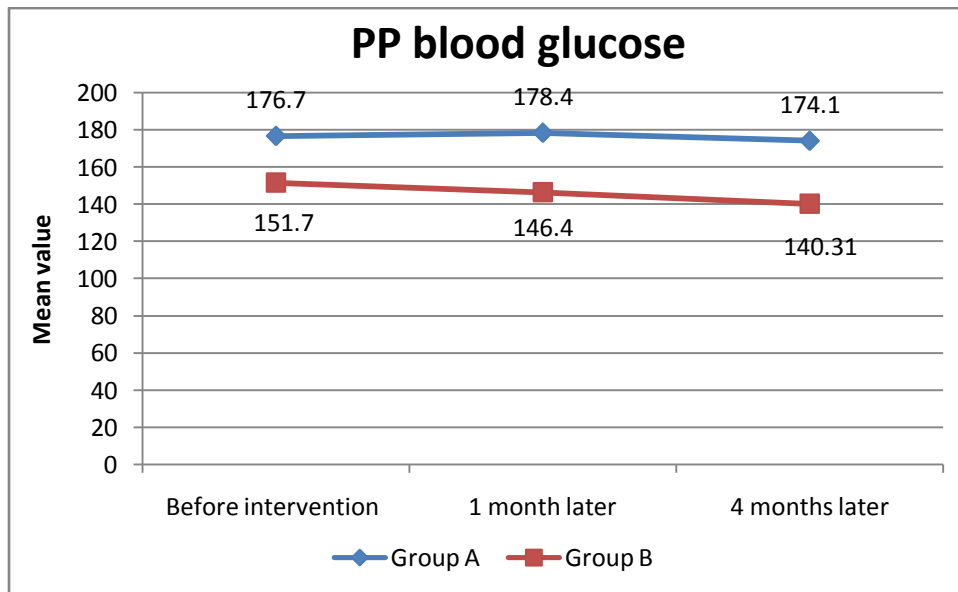


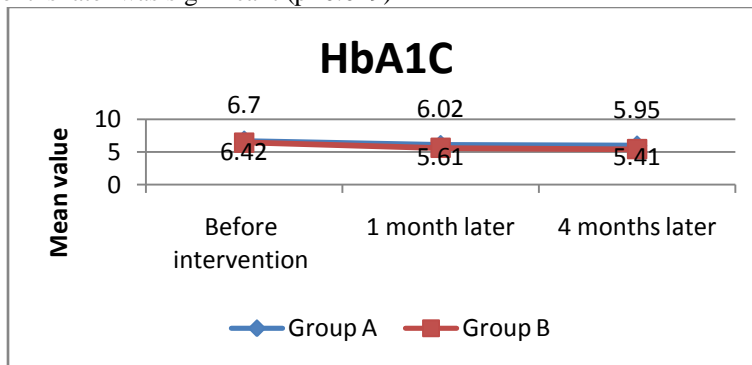
Fig 7:- PP blood glucose among studied groups

**Table 10:-** Comparison of HbA1C before and after intervention among the studied groups.

HbA1C	Group A (N=25)				Group B (N=25)				MWU test	P
	Mean	± SD	Min.	Max.	Mean	± SD	Min.	Max.		
Before intervention	6.70	0.64	6.20	8.30	6.42	0.77	4.50	7.10	0.029	0.98 (NS)
1 month later	6.02	0.94	5.00	8.10	5.61	0.82	4.50	6.90	1.72	0.084 (NS)
4 months later	5.95	0.76	5.00	8.00	5.41	0.91	4.30	7.00	2.35	0.019 (S)
Friedman test	13.9				20.5					
P	0.001 (HS)				<0.001 (HS)					
Sig pairs	Before ≠ 1m Before ≠ 4m				Before ≠ 1m Before ≠ 4m					

Among studied groups

In group A mean value of HbA1C before treatment 6.7% compared with one month later 6.02% and four months later 5.95% which was highly significant (p=0.001). In group B mean value of HbA1C before treatment 6.42 % compared with one month later 5.61% and four months later 5.41 % which was highly significant (p<0.001). In group B mean value of HbA1C before treatment and one month later compared with that of group A was non significant but four months later was significant (p=0.019)



**Fig 8:-** HA1C among groups during treatment.

**Table 11:-** Correlation between HbA1c and FBG, PP blood glucose.

With	HbA1c (before intervention)			
	Group A		Group B	
	rho	P	rho	P
FBG	0.242	0.24 (NS)	0.14	0.49 (NS)
PP bl glucose	0.311	0.015 (NS)	0.329	0.11 (NS)
	HbA1c (1 m after intervention)			
FBG	0.016	0.93 (NS)	0.11	0.61 (NS)
PP bl glucose	0.42	0.84 (NS)	0.31	0.16 (NS)
	HbA1c (4 m after intervention)			
FBG	0.07	0.74 (NS)	0.13	0.52 (NS)
PP bl glucose	0.29	0.16 (NS)	0.21	0.32 (NS)

This table showed non significant Correlation between HbA1c and FBG, PP blood glucose.

**Table 12:-** Comparison of total protein before and after intervention among the studied groups..

Total protein	Group A (N=25)				Group B (N=25)				MWU test	P
	Mean	± SD	Min.	Max.	Mean	± SD	Min.	Max.		
Before intervention	6.57	0.35	6.20	7.30	6.53	0.23	6.10	6.90	0.36	0.71 (NS)
1 month later	6.71	0.45	6.00	7.40	6.58	0.22	6.30	7.00	1.04	0.29 (NS)



4 months later	6.83	0.42	6.50	7.50	6.70	0.26	6.30	7.30	0.02	0.98 (NS)
Friedman test	3.1				5.1					
P	0.21 (NS)				0.1 (NS)					
Sig pairs	-----				-----					

Among studied groups, mean values of T. Protein in group A and group B along course of treatment were non significant.

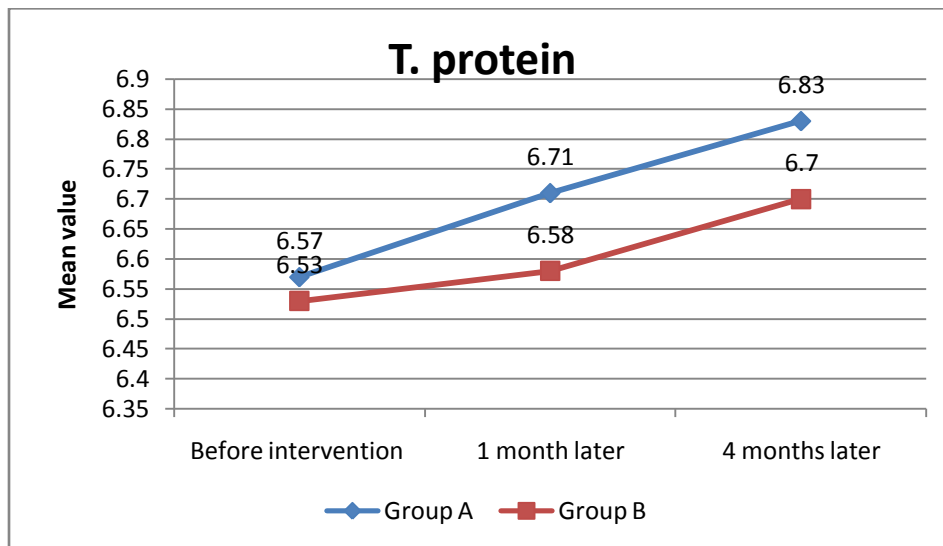


Fig 9:- T.Protein value among groups during treatment

Table 13:- Comparison of albumin before and after treatment among the studied groups.

Albumin	Group A (N=25)				Group B (N=25)				MWU test	P
	Mean	± SD	Min.	Max.	Mean	± SD	Min.	Max.		
Before intervention	3.37	0.22	3.10	3.7	3.42	0.30	3.0	3.7	0.60	0.54 (NS)
1 month later	3.53	0.19	3.20	3.8	3.46	0.28	3.1	3.9	1.09	0.27 (NS)
4 months later	3.66	0.22	3.40	4.0	3.53	0.18	3.2	3.8	1.61	0.11 (NS)
Friedman test	5.04				4.97					
P	0.061 (NS)				0.08 (NS)					
Sig pairs	-----				-----					

Among studied groups

Mean values of albumin in group A and group B along course of treatment were non significant.

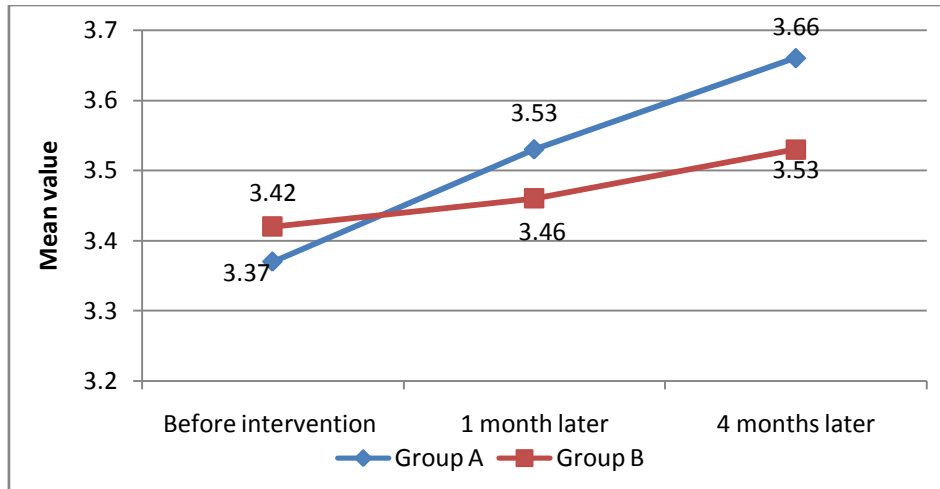


Fig.10:- Albumin value among groups during treatment

Table 14:- Comparison of Creatinine before and after treatment among the studied groups.

Creatinine	Group A (N=25)				Group B (N=25)				MWU test	P
	Mean	± SD	Min.	Max.	Mean	± SD	Min.	Max.		
Before intervention	6.14	3.07	1.80	9.70	7.11	2.17	3.50	11.40	1.29	0.19 (NS)
1 month later	5.91	2.88	1.80	9.50	6.31	1.85	3.50	9.50	0.84	0.41 (NS)
4 months later	7.59	3.74	2.50	14.10	6.79	2.27	3.60	10.50	0.44	0.66 (NS)
Friedman test	3.2				4.93					
P	0.19 (NS)				0.09 (NS)					
Sig pairs	-----				-----					

Mean values of creatinine in group A and group B along course of treatment were non significant.

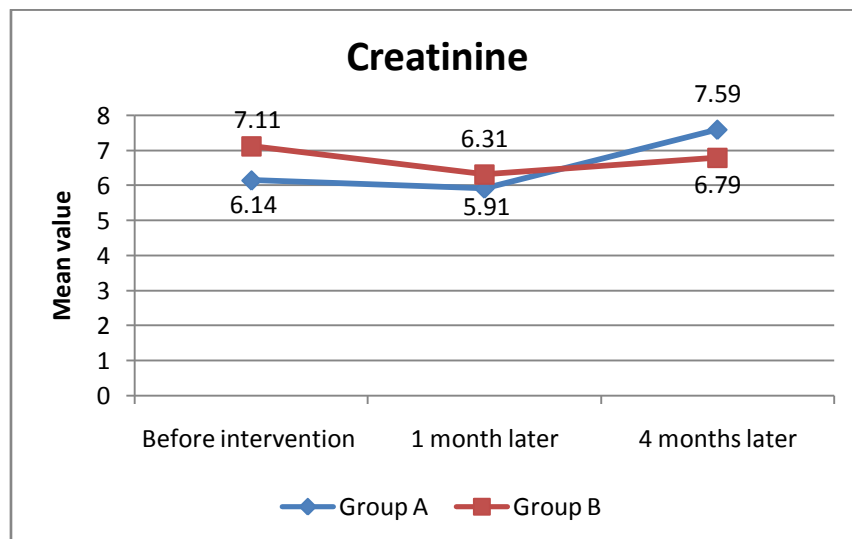
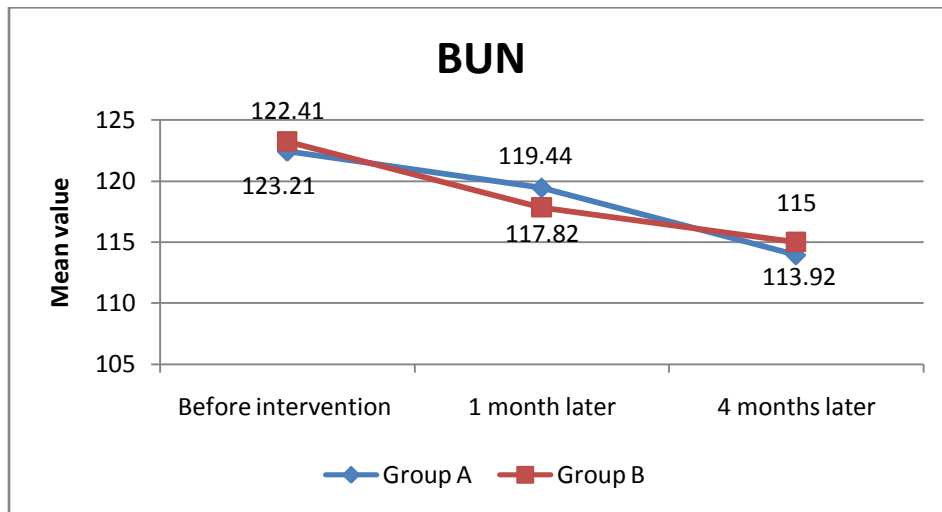


Fig 11:- Creatinine value among groups during treatment

**Table 15:-** Comparison of Blood urea nitrogen before and after treatment among the studied groups.

BUN	Group A (N=25)				Group B (N=25)				MWU test	P
	Mean	± SD	Min.	Max.	Mean	± SD	Min.	Max.		
Before intervention	122.41	43.39	26.0	212.0	123.21	37.85	84.0	197.0	0.92	0.34 (NS)
1 month later	119.44	53.48	40.0	210.0	117.82	35.92	80.0	195.0	0.87	0.38 (NS)
4 months later	113.92	48.30	50.0	200.0	115.00	34.03	85.0	190.0	0.44	0.66 (NS)
Friedman test	4.63				3.84					
P	0.092 (NS)				0.15 (NS)					
Sig pairs	-----				-----					



**Fig 12:-** BUN value among groups during treatment.

**Discussion:-**

A1c is the most widely accepted and used method of assessing chronic glycemia in patients with diabetes. It is formed by the irreversible binding of glucose to hemoglobin over the lifespan of the erythrocytes (Goldstien et al., 2004).

Patients with Chronic kidney disease (CKD) are commonly anemic due to a variety of reasons, including functional or absolute iron deficiency and erythropoietin insufficiency (Gotloib et al., 2006). Treatment of anemia in patients with CKD using iron replacement therapy and erythropoietin-stimulating agents (ESAs) has resulted in significant improvements to quality of life and the correction of anemia without the need for blood transfusions (NCCCCA, et al., 2006, and Nissenon et al., 1999).

ESAs and intra venous iron are commonly used therapies in the management of anemia in patients with CKD. Patients with both diabetes and CKD have a higher prevalence of severe anemia compared with patients with CKD alone (Thomas et al.,2003).

For the purpose of detecting new cases of diabetes, in those with an initial A1C <6.0%, rescreening at intervals shorter than 3 years identifies few individuals (~≤1%) with an A1C ≥6.5%. At A1C ≥6%, rescreening even at a 1-year interval would be reasonable strategy to identify disease. ( Osamu et al., 2016)

One of categories of increased risk for type2 diabetes (Prediabetes )(ADA 2016 Guidelines)was A1C equal 5.7-6.4%(39-46 mmol/mol)

**The aim of this thesis was to evaluate:-**

The effect of iron and erythropoietin treatment on the HbA1c of hemodialysis patient with diabetes.

This study was conducted on 50 HD patients with type-2 diabetes. All patients was chosen from those attending Banha University Hospitals. The diagnosis of diabetes was based on a history of diabetes or on the ADA criteria. Information collected from participants included demographic data, height, weight (dry weight in HD patients), duration of diabetes and duration of HD. Patients with diabetes was restricted to those with stable blood glucose and whose diabetes treatment had not been altered during the preceding 6 months before the determination of HbA1c.

The patients was classified into two groups (each consists of 25 patients).

The first group (group A): It included patients selected for iron therapy with serum ferritin values  $<200 \mu\text{g/l}$ . All patients had hemoglobin  $\leq 10.5 \text{ g/dl}$ . Patients in this group were not on previous or concurrent ESA therapy and were vitamin B12 and folate replete. Intravenous iron was given as a single dose in the form of low-molecular weight iron dextran dependent on the patient's body weight. This was delivered as an initial intravenous test infusion of 100 mg of iron over 1 h followed by the remaining dose over the next 2-4 h.

The second group (group B):It consisted of patients who needed ESA treatment with serum ferritin value  $>200 \mu\text{g/l}$ . All patients receiving ESA therapy had hemoglobin  $< \text{ or } =10.5 \text{ g/dl}$  and were considered iron, vitamin B12, and folate replete prior to initiation. Patients were considered iron replete following a serum ferritin value  $>200 \mu\text{g/l}$  or having received intravenous iron at least 6 weeks prior to ESA therapy. The dose of ESA was titrated monthly to achieve target hemoglobin 10.5-12 g/dl.

All patients were subjected to complete history taking( age, sex , type of diabetes ,medications and duration of HD ) , complete physical examination investigated for HA1C, rondon blood glucose, S.Ferretin, T.Protein, albumin,BUN, creatinine before treatment, one month later and four month later.

The result of this work were tabulated and statistically analysed using suitable statistical tests.

The results of this study were that, in group A patients, parentral iron administration was attended with a significant rise of serum ferretin after four months.in group B, serum ferretin showed a significant fall four months after ESA therapy. Table(6)Fig(4).

In this study, there was significant improvement in haemoglobin level in both groups( in group A mean hemoglobin after four months 11.06% compared with before therapy 8.85% ( $p<0.001$ ), in group B mean hemoglobin after four months 11.01% compared with before therapy 9.26% ( $p<0.001$ ) ) with treatment and a decrease in the number of patients requiring blood transfusions. Table(7)Fig(5).

The other results came in coordination with,(**Thomas et al.,2003**) who reported that anemia of CKD was improved by ESAs and intra venous iron, (**Muñoz et al.,2008**)who reported that administration of ESAs and iron managed the anemia of CKD and achieved target haemoglobin level, and (**Lucia et al.,2016**)who reported that anemia in CKD was managed primary with ESAs and iron therapy.

In our study, the dose of ESA was titrated monthly to achieve target hemoglobin of 10.5-12gm/dl and this resulted in correction of anemia and improvement of quality of life. In agreement with our study, several studies have demonstrated that the correction of anemia in patients with chronic kidney disease improves the quality of life and exercise tolerance while reducing the need for transfusion.(**Al-Khoury et al., 2007**),( **Teehan.,1991**)

The 2006 NKF KDOQI-recommended target Hb concentration is  $> 11-12 \text{ g/dl}$ , with recommendations against routinely maintaining Hb concentrations of  $> 13 \text{ g/dl}$  in patients with CKD (**National Kidney Foundation, 2006**).

On the other hand, the CHOIR trial studied the outcomes of anemia treatment in over 1400 CKD patients who had a hemoglobin  $< 11 \text{ g/dl}$  at entry. Enrolled subjects were randomly assigned to EPO therapy treatment protocols designed to achieve a target hemoglobin levels of either 13.5 (n=715) or 11.3 g/dl (n= 717). The study was terminated prematurely due to higher mortality rates adverse events in the group with higher targeted Hb levels (**Singh et al., 2006**), (**Teehan and Benz.,2011**).

(**Pfeffer et al., 2009**) reported that despite the increased usage of ESA agents, his findings had shown that the correction of anemia to levels of hemoglobin in excess of 12.5 g/dl in patients with type 2 diabetes using this therapy had not led to an improvement in mortality but rather an increased risk of stroke. This study showed that iron and

ESA treatments result in a significant fall in A1C in patients with diabetes and CKD, the change was independent of glycemic changes. Table (11). In group A mean value of HbA1C before treatment was 6.7% compared with HbA1C four months after which was 5.95%. In group B the mean value of HbA1C before treatment was 6.42% whereas HbA1C after four months was 5.41%. Table (10) Fig(8). This study showed no significant change occur in fasting and post prandial levels among groups during course of treatment. Table (8,9) Fig (6,7). This study showed non significant Correlation between HbA1c and FBG, PP blood glucose among groups during the course of the study. Table (11). This results came in coordination with **(Sunil et al., 2010)** who achieved a similar study and reported that despite a lack of change of glycemic control in the both groups, A1C concentrations fell significantly ( $P < 0.001$  and  $0.013$ , respectively, for groups A and B). The effect of the lowering of the A1c values following either treatment has been postulated to be secondary to the formation of new erythrocytes in the blood stream, causing a change of proportion of young to old cells, and also from an alteration in the red-cell glycation rates **(Brooks et al, 1980, and Kim et al, 2006)**. Discordantly high A1C values compared with glucose readings have been reported in previous studies and case reports on non diabetic patients with iron deficiency and in patients with type 1 diabetes in childhood and pregnancy **(Hashimoto, 2008, Brooks et al, 1980, and Kim et al, 2006)**. Hemolytic anemia as well as recovery from acute blood loss seem to have the opposite effect to iron deficiency by reducing HbA1c in affected individuals. Reports have shown that abnormally low HbA1c levels may be associated to conditions such as hereditary spherocytosis, elliptocytosis, autoimmune or drug-induced hemolytic anemia, and anemia due to chronic renal failure. These conditions are characterized by reduced red cell survival and therefore by a reduction in the availability of hemoglobin for glycation **(Jiao et al., 1998, Herranz et al., 1999, Liew and Cheah, 2003, Kutter and Thoma, 2006 and Lum, 2010)**. High levels of urea in the blood can lead to formation of carbamylated hemoglobin that can interfere with some methods of HbA1c measurement. However, carbamylated hemoglobin does not present an analytical interference in most modern methods of measurement **(Weykamp et al., 1993)**. The correction of the iron deficiency in all patient groups led to a significant fall in A1C values in our study.

Several studies have also shown a fall in A1C concentrations following ESA treatment in patients with diabetes undergoing hemodialysis **(Inaba et al, 2007, Nakao et al., 1998)**. **(Nakao et al., 1998)** reported a fall in A1C in non diabetic patients with CKD on hemodialysis following ESA therapy.

Good glycemic control in patients with diabetes and CKD has been shown to be associated with better survival rates **(Morioka, 2001)**.

The results of our study showed statistically significant falls in the A1C following iron and ESA treatment (mean 5.95% following iron and 5.41% following ESA) in the absence of a change in glycemic control. It showed that A1C can be unreliable and can fall following treatment with both iron and ESA therapy.

**(Sunil et al., 2010)**. Fluctuations of A1C that can occur in this patient group (patients with diabetes and CKD who were treated with iron or ESA therapy) so alternative methods for measuring glycemic control such as capillary glucose testing and CGM should be used, and therapy should not be based on the A1C value alone.

It has been shown that 62% of the population variance in HbA1c level is genetically determined **(Jeffcoate, 2004)**.

**(Inaba et al., 2007)**. Glycated albumin has been suggested as an alternative marker to represent glycemic control, as it was noted to be similar (in contrast to A1C, which was higher) in patients with iron deficiency and pre-ESA compared with patients post therapy

It is known that glycation among various proteins is increased in diabetic patients compared with non-diabetic subjects. Currently, among these glycosylated proteins, glycosylated hemoglobin (HbA1C) is used as the gold standard index of glycemic control in clinical practice for diabetes treatment. However, HbA1C does not accurately reflect the actual status of glycemic control in some conditions where plasma glucose changes during short term, and in patients who have diseases such as anemia and variant hemoglobin. In comparison, another index of glycemic control, glycosylated albumin (GA), more accurately reflects changes in plasma glucose during short term and also postprandial plasma glucose. Although GA is not influenced by disorders of hemoglobin metabolism, it is affected by disorders of albumin metabolism. Some diseases and pathological conditions where GA measurement is useful. These include the status of glycemic control changes during short term, diseases which cause postprandial hyperglycemia, iron deficiency anemia, pregnancy, chronic liver disease (liver cirrhosis), chronic renal failure (diabetic nephropathy), and variant hemoglobin **(Masafumi and Soji, 2010)**.

This study managed to show that A1C values fell significantly both with iron and ESA. This change in A1C was independent of changes in glycemic control. Intravenous iron and ESA are increasingly common therapies used in the management of anemia in patients with CKD and diabetes. The present study has been able to confirm that reported changes in A1C following these treatments are independent of changes in glycemic control; therefore, caution is warranted in the interpretation of A1C and management of glycemia when based on A1C alone.

At a time when self monitoring of blood glucose is being discouraged, especially in non-insulin treated patients Regular capillary glucose measurements, and the concurrent use of CGM if available, seems essential in order to accurately assess glycemic control in this group of patients. (Simon et al., 2008).

This study showed no significant change occur in T. Protein, albumin, BUN, and creatinine levels among groups during course of treatment. Table (12,13,14,15) Fig (9,10,11,12). This study showed no significant value of duration of diabetes and duration of hemodialysis. Table (3) Fig (2).

### Conclusion:-

A1c is the most widely accepted and used method of assessing chronic glycemia in patients with diabetes. This study to showed that iron and ESA treatments result in a fall in A1C, which is independent of glycemic changes in patients with diabetes and CKD.

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