RESEARCH ARTICLE

FUNCTIONAL HYPOPARATHYROIDISM AMONG TYPE 2 DIABETIC PATIENTS ON HEMODIALYSIS: IMPACT OF GLYCEMIC CONTROL.

Mohamed M. M. Hassaan[1], Nearmeen M. Rashad[1]*, Ashraf A. Hammam[1], Hoda G. Bakr[1], Tarek M. H. Ibrahim[1], Hazem M. Ghazal [1] and Samy H. Mohamed[2].

1. Internal Medicine Department, Faculty of Medicine, Zagazig University, Egypt.
2. Medical Biochemistry Department, Faculty of Medicine, Zagazig University, Egypt.

……………………………………………………………………………………………………....

Manuscript Info

……………………….

Abstract

……………………………………………………………………………

Background: End-stage renal disease has become a public health concern worldwide. Type 2 diabetes is associated with significantly accelerated rates of diabetic nephropathy. There are controversies about the role of intact parathyroid hormone (iPTH) in the pathogenesis of osteodystrophy among diabetic patients on regular hemodialysis.

We aimed to estimate serum levels of iPTH, 25-hydroxyvitamin D and to clarify the possible relationships between iPTH and HbA1c ;which reflect the glycemic control as well as other clinical and biochemical parameters in end-stage renal disease patients on regular hemodialysis.

Subjects and methods: A case-control study of 84end-stage renal disease patients on maintenance hemodialysis thrice weekly.Patients were stratified into three groups;group1:28 diabetic patients with good glycemic control(HbA1c < 7), group 2:28 diabetic patients with poor glycemic control(HbA1c >7), and group3:28non diabetic patients, In all studied participants,blood urea, serum creatinine , calcium, phosphorus, albumin, alkaline phosphatase, lipid profile, HbA1c, fasting blood glucose (FBG),post prandial blood glucose (PPBG) and25-hydroxyvitamin Dwere measured.Also, we estimate serum iPTHlevels by ADVIA CENTAUR instrument using Chemiluminescence principle.

Results: Non diabetic patienton chronic hemodialysis had significantly higher values of serum 25-hydroxyvitamin D,serum iPTHmore than diabetic group, moreover diabetic patients with poor glycemic control had significantly lower values of serum 25-hydroxyvitamin D and serum iPTH, compared to good glycemic control.In diabetic patients with poor glycemic control,iPTHlevel was negatively correlated with Alkaline phosphatase,post prandial blood glucose, fasting blood glucose, as well as HbA1c. In patients with good glycemic control serum iPTHlevel was positively correlated with25-hydroxyvitamin D., there were significant negative correlations betweeniPTH level and creatinine, alkaline phosphatase, phosphorous, albumin, post prandial blood glucose, fasting blood glucose, as well as HbA1c.Stepwise linear regression analysis showed that, serum iPTH levels were independently correlated with 25-hydroxyvitamin D with diastolic blood pressure,

Corresponding Author:-Nearmeen M. Rashad.
Address:-Internal Medicine Department, Faculty of Medicine, Zagazig University, Egypt.

serum phosphorus, albumin, alkaline phosphataseFBG, PPBG and HbA1c.

Conclusion: Non diabetic patienton chronic hemodialysis had significantly higher values of serum 25-hydroxyvitamin D and iPTHmore than diabetic group.Moreover,in diabetic patients with poor glycemic control, serum iPTHlevel and 25-hydroxyvitamin D were significantly lower than good glycemic control patients .

………………………………………………………………………………………………....

Introduction:-

End-stage renal disease (ESRD) has become a public health concern worldwide. According to the United States Renal Data System annual report (USRDS); it is high in Taiwan patients, Japan and USA and low in Philippines, Bangladesh and Russia [1].Anand et al. [2] predicted an annual incidence of 239 pmp in people with diabetes and hypertension who live in sub-Saharan Africa,where renal replacement therapy (RRT) use correlated with regional income, with most patients unable to access RRT. Liyanage et al. [3] estimated that at least 432 000 people in Africa require RRT but are not receiving it.Regarding developing countries such as Egypt, the prevalence of ESRDhave gone upand increased from 225 pmp in 1996 to 483 pmp in 2004. The main cause of ESRD in Egypt is hypertension, followed by diabetes, and still unknown causes represent about 15% of the cases [4].

Diabetes is a chronic metabolic disease,415 million people have diabetes in the world and more than 35.4 million people in the MENA Region (the Middle East and North Africa region), by 2040 this will rise to 72.1 million. In Egypt,theprevalence of diabetes in adults are 14.9% and 7.8 million cases of diabetes were estimated in Egypt in 2015 according to International Diabetes Federation (2015). Type 2 diabetes (T2D) is associated with accelerated rates of microand macro vascular complications [5].

There was great evidence that, the higher incidence of osteodystrophy among the diabetic patients on regular hemodialysis was attributed to high intact parathyroid hormone (iPTH) level (150-300 pg/ml),osteodystrophy due to high iPTH level is called High Turnover Bone Disease (HTBD)[6].

Interestingly, recent studies suggested that, there were another type of osteodystrophy in type 2 diabetic patients with ESRDon regular hemodialysis ,due to low iPTH level and called Low Turnover Bone Disease (LTBD) [6].

Thus, diabetic patients on maintenance hemodialysis (MHD) are affected withalteration of iPTH level in opposite direction. Consequently, renal osteodystrophy can be of two types. High Turnover Bone Disease (HTBD) due to high iPTH level and Low Turnover Bone Disease (LTBD) due to comparatively low iPTHlevel[7]. It has been revealed in some studies that, usually diabetic ESRD patients on MHD have lower iPTH level than non-diabetic ESRD patients on MHD [8-10].Increasing evidence suggests that,in both diabetic and non-diabetic haemodialyzed patients, impaired iPTH secretion appears to be the main determinant responsible for decreased bone turnover and 'adynamic bone disease [11].

There are controversies about the mechanisms of renal-related bone disease,and the actual role of iPTH serumlevels variation in thepathogenesis of renal osteodystrophy.Therefore, the purpose of current study was to estimate serum levels ofiPTHand to clarify the possible relationships betweeniPTH andHbA1c;which reflect glycemic controlas well as other clinical and biochemical parameters in ESRD patients on regular hemodialysis.

iPTH level was decreased in poor glycemic control diabetic patients on hemodialysis, moreover it was negative correlated to measures of blood glucose, as well as biochemical parameters of end stage renal disease. Considering the controversy about the level of iPTH in diabetic patients on hemodialysis and its correlation with HbA1c and other biochemical parameters; our findings revealed the favorable effect of good control of blood glucose on iPTH. Furthermore, tight metabolic control of the diabetic patients is mandatory to avoid hypoparathyroidim. Ca and Vit D supplementations in ESRD may be fruitful in keeping iPTH level within target range.

Subjects and Methods:-

This study included 84 patientsof end-stage renal disease on maintenance hemodialysis thrice weekly; 4 hours each session for more than 3 months.Patients recruited from Hemodialysis and Endocrinology units of Internal Medicine Department of Zagazig University Hospitals, Egypt.Patientswere matched as regard age, gender, and ethnic origin. Patients were stratified into threegroups;group 1(n=28); diabetic patients with good glycemic control with HbA1c <7, group 2;diabetic patients with poor glycemic control with HbA1c > 7 (n=28) and group 3(n=28) non diabetic patients . All patients were subjected to thorough medical history and full clinical assessment.Patients suffering from any acute infection,acute renal failure, liver disease, cardiac disease, acute illness, parathyroidectomy,any endocrine disorder except diabetes mellitus,those who were taking hormone replacement therapy, bisphosphonates, aluminium hydroxide and steroids were excluded from the study. The ethical committee of Faculty of Medicine, Zagazig University approved our study protocol, and all participants assigned written informed consent.

Blood sampling:-

Blood samples were drawn from all subjects after an overnight fasting and divided into 3 portions: and HbA1c; 1 ml of whole blood was collected into evacuated tubes containing fluoride for fasting blood glucose. Serum was separated immediately from remaining part of the sample and stored at −20 °C until analysis.

Biochemical measurements :-

We determined fasting blood glucose using the glucose oxidase method (Spinreact, Girona, Spain). Total cholesterol and triglycerides were measured by routine enzymatic methods (Spinreact, Girona, Spain). HDL cholesterol was determined after precipitation of the apoB-containing lipoproteins. LDL cholesterol was calculated using the Friedewald formula (12). Biochemical parameters including serum levels of blood urea nitrogen (BUN), calcium, phosphorous, alkaline phosphatase, uric acid, creatinine, and albumin were measured with standard techniques by an automatic analyzer. Serum 25(OH) D levels tested by a high-performance liquid chromatography (HPLC).Serum iPTH was measured by ADVIA CENTAUR instrument using Chemiluminescenceprinciple.The serum samples were immediately frozen at -70˚C until analysis.

Statistical analysis:-

Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (version 22.0; SPSS Inc., Chicago, IL, USA). Data were expressed using descriptive statistic (mean ± standard deviation)and were analyzed statistically by Chi-squared test (X2), paired T test. Pearson correlation coefficient was used to assess the association between iPTH, clinical, biochemical tests and other studied metabolic parameters in patients with hemodialysis. A linear regression analysis was performed to detect the main predictors of iPTH levels in hemodialysis patients. P-values were considered significant if <0.05.

Results:-

Among patients on chronic hemodialysis,in thediabetic group,69.6 % were male and 30.4% were female, their mean age was 47.73 ± 12.02 year. In thenon-diabetic group,64.3% were male and 35.7% were female , theirmean age was 45.25 ± 14.45 year . Diabetic and nondiabetic patients were matched for age and gender.

Patients with poor glycemic control(PGC),67.8 % were male and 32.2% female, their mean age was 49.04 ± 11.28 year. In patients with good glycemic control(GGC),71.4% were male and 28.6% were female,their mean age was46.43 ± 12.79 year. Both diabetic groups were matched for age and gender.

Clinical and biochemical characteristics of the studied groups are summarized in Table 1: Diabetic patient on chronic hemodialysis had significantly higher values of PPBG, FBG, HbA1c,LDL,TG,TC,PO4,albumin and Alkaline phosphatase thannon diabetic group (p < 0.05), and there was non-significant differenceregardingother parameters, (p > 0.05).

Table 1:-clinical and biochemical characteristics of the studied groups .

Variable	Diabetic (*n*=56)	Non-diabetic (n=28)	T	p
Systolic blood pressure (mmHg)	136.5 ± 15.43	131.25 ± 18.14	1.39	NS
Diastolicblood pressure(mmHg)	74.20 ± 9.90	70.71 ± 9.10	1.56	NS
Pulse (beat/min)	80.75 ± 2.99	81.1 ± 3.86	0.47	NS
FBG(mg/dL)	113.5 ± 19.4	76.18 ± 3.08	10.09	<0.001[*]

PPBG(mg/dL)	213.8 ± 67.9	119.6 ± 5.17	7.30	<0.001*
HbA1c (gm%)	8.22 ± 1.59	5.43 ± 0.35	9.19	<0.001*
LDL (mg/dl)	89.9 ± 15.5	76.32 ± 6.18	4.93	<0.001*
HDL (mg/dl)	41± 4.20	40.64 ± 3.19	0.40	NS
TG (mg/dl)	196.8±68.6	163.14 ± 3.5	3.27	<0.01*
Cholesterol (mg/dl)	166.9 ± 34.8	142.00 ± 10.6	3.68	<0.001*
Ca (mg/dl)	9.20 ± 0.97	9.00 ± 0.39	1.09	NS
PO4 (mg/dl)	5.17 ± 1.46	4.29 ± 0.83	2.98	<0.01*
Albumin (g/dl)	3.72 ± 0.10	3.89 ± 0.15	6.129	<0.001*
Alkaline phosphatase (IU/L)	159.2 ± 50.04	105.6 ± 17.3	5.49	<0.001*
Creatinine (mg/dl)	9.14 ± 1.00	9.00 ± 0.84	0.67	NS
Urea (mg/dl)	135.9 ± 14.6	132.2 ± 10.7	1.18	NS
25-Hydroxyvitamin D (ng/ml)	17.1 ±7.7	19.7±7.3	2.4	NS

HDL-C; high-density lipoprotein-cholesterol,TG ;triglycerides, LDL-C; low-density lipoprotein-cholesterol, PPBG; postprandial blood glucose, FBG; fasting blood glucose, HbA1c; hemoglobin A1c.* P <0.05 .

Clinical and biochemical characteristics of diabetic groups (Table 2): Poor glycemic control grouphad significantly higher values of systolic& diastolic blood pressure, PPBG, FBG, HbA1c ,urea,alkaline phosphatase, TG, and cholesterolthan goodglycemic control group (p < 0.05).On the other hand, there were significant lower levels of 25-Hydroxyvitamin D in poor glycemic group compared to good glycemic control group .There wasnonsignificant difference regardingother parameters(p > 0.05).

Table 2:-clinical and biochemical characteristics of both diabetic groups .

Variable	Poor Glycemic Control (*n*=28)	Good Glycemic Control (n=28)	T	p
Systolicblood pressure (mmHg)	140.71 ± 16.2	132.32 ± 13.57	2.10	<0.05*
Diastolicblood pressure (mmHg)	77.32 ± 10.41	70.07 ± 8.43	2.47	<0.05*
Pulse (beat/min)	80.96 ± 2.95	80.54 ± 3.09	0.53	NS
FBG(mg/dL)	129 ± 14.83	98.00 ± 6.93	10.02	<0.001*
PPBG(mg/dL)	273.2 ± 41.40	154.40 ± 18.95	13.81	<0.001*
HbA1c (gm%)	9.66 ± 0.9	6.79 ± 0.23	16.16	<0.001*
LDL (mg/dl)	92.90 ± 17.33	88.11 ± 10.95	1.24	NS
HDL (mg/dl)	41.11 ± 5.17	40.89 ± 3.05	0.19	NS
TG (mg/dl)	221.1 ± 82.40	183.21 ± 19.14	2.37	<0.05*
Cholesterol (mg/dl)	177.9 ± 41.81	155.75 ± 21.57	2.50	<0.05*
Ca (mg/dl)	9.43 ± 1.09	8.98 ± 0.79	1.78	NS
PO4 (mg/dl)	5.38 ± 1.41	4.97 ± 1.51	1.05	NS
Albumin (g/dl)	3.70 ± 0.1	3.75 ± 0.12	1.94	NS
Alkaline phosphatase (IU/L)	196.25 ± 42.1	122.11 ± 21.94	8.27	<0.001*
Creatinine (mg/dl)	9.10 ± 0.95	9.18 ± 1.07	0.30	NS
Urea (mg/dl)	140.1 ± 16.45	131.57 ± 11.18	2.28	<0.05*
25-Hydroxyvitamin D (ng/ml)	13.9± 5.5	20.1 ±8.4	6.27	<0.01*

HDL-C; high-density lipoprotein-cholesterol,TG ;triglycerides,LDL-C; low-density lipoprotein-cholesterol, PPBG; postprandial blood glucose, FBG; fasting blood glucose,HbA1c;hemoglobin A1c.* P <0.05 .

Pearson correlations between serum iPTH (pg/ml),clinical and biochemical characters among both diabetic groups on hemodialysis(Table3): In diabeticpatients with poor glycemic control,serum iPTH level was positively correlated with25-Hydroxyvitamin D, on the other hand, serum iPTHlevel was negatively correlated with alkaline phosphatase. Indiabetic patients with good glycemic control,serum iPTH level was positively correlated with 25-Hydroxyvitamin D, on the other hand there were significant negative correlations between serum iPTH level and creatinine, alkaline phosphatase, phosphorous and albumin, there were non-significant correlation between iPTH and other clinical and biochemical characters in both groups.

Table 3:-correlation between iPTH (pg/ml),clinical and biochemical characters among both diabetic groups on hemodialysis.

Variable	Poor Glycemic Control (*n*=28)		Good Glycemic Control (n=28)	
	r	P	r	p
Sex (gender)	0.147	0.454	0.111	0.573
Age (year)	0.031	0.875	0.128	0.517
Diastolic blood pressure	-0.176	0.370	-0.068	0.733
Systolic Blood Pressure	-0.260	0.182	-0.087	0.658
Ca	-0.257	0.187	-0.236	0.227
PO4	-0.243	0.213	-0.465	<0.01*
Albumin	-0.110	0.578	-0.530	<0.001*
Alkaline phosphatase	-0.574	<0.001*	-0.599	<0.001*
Creatinine	-0.099	0.615	-0.442	<0.05
Urea	-0.-301	0.119	-0.088	0.654
25-Hydroxyvitamin D	0.787	<0.001**	0.940	<0.001**
LDL	0.106	0.590	-.304-	0.116
HDL	0.152	0.440	0.042	0.831
Cholesterol	-0.514-	.005*	-0.288-	0.138
Triglyceride	-0.528-	.004*	-0.233-	0.233

Linear regression analyses in diabetic patients on hemodialysis (n=56) : stepwise linear regression analysis was done to assess the main independent parameters associated with serum iPTH.Our results showed that, serum iPTH levels were independently correlated with 25-Hydroxyvitamin D , diastolic blood pressure, serum phosphorus ,albumin,alkaline phosphatase,post prandial blood glucose, fasting blood glucose, hemoglobin A1c. (p< 0.001) (**Table 4**).

Table 4:-Linear regression analyses in diabeticpatients on hemodialysis to test the influence of the main independent variables against serum iPTH (pg/ml) levels (dependent variable).

Model		Unstandardized Coefficients		Standardized Coefficients	T	P	95.0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	229.952	173.140		1.328	0.195	585.205	125.301
	Diastolic blood pressure	1.148	.401	.884	2.865	<0.001*	.326	1.970
	Systolic blood pressure	.321	.183	.477	1.756	0.090	.696	.054
	Albumin	250.53	311.300	.149	.805	<0.001*	885.439	384.363
	Urea	11.828	8.863	.505	1.335	0.192	6.248	29.904
	25-Hydroxyvitamin D	2.444	.327	.393	7.475	.000	1.788	3.101
	Serum calcium	27.909	60.620	.068	.460	0.648	95.726	151.543
	Serum phosphorus	80.760	34.748	.399	2.324	<0.001*	9.892	151.629
	Creatinine	52.277	41.303	.197	1.266	0.215	136.515	31.962
	LDL	5.087	4.033	.213	1.261	0.217	3.138	13.312
	HDL	9.631	8.919	.117	1.080	0.289	8.559	27.821
	TG	.291	2.200	.022	.132	0.896	4.777	4.196
	TC	1.814	2.520	.130	.720	0.050	6.953	3.326
	Pulse	2.597	15.549	.036	.167	0.868	34.310	29.117
	Alkaline phosphatase	2.069	2.822	.173	.733	<0.001*	7.824	3.686
	PPBG	4.025	4.013	.353	1.003	<0.001*	12.210	4.160
	FBG	13.929	6.470	.671	2.153	<0.001*	27.124	.735
	HbA1c	136.764	108.640	.404	1.259	<0.001*	84.808	358.337

HDL-C; high-density lipoprotein-cholesterol, LDL-C; low-density lipoprotein-cholesterol, PPBG; post prandial blood glucose, FBG; fasting blood glucose, HbA1c; hemoglobin A1c. * P < 0.05

Comparison of serum iPTH(pg/ml) levels among the studied groups (Fig.1): Non diabetic patienton chronic hemodialysis had significantly higher values of serum iPTH (pg/ml) (371.39 ± 306.45) compared todiabetic group (65.25 ± 47.76). There was high significant elevated serum iPTH ingood glycemic control group compared topoor glycemic control group(106.67 ± 31.37), (23.82 ± 10.13)respectively.
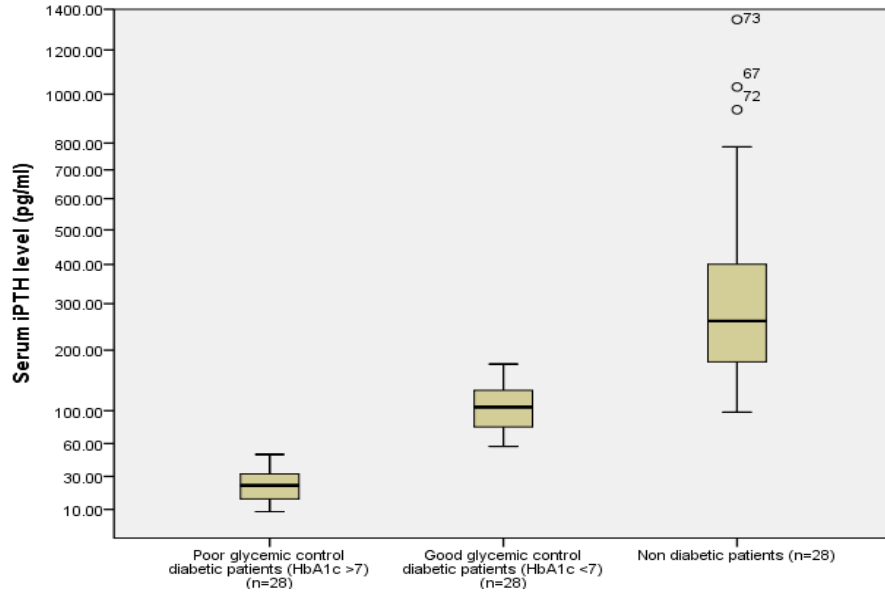

Fig .1:- Comparison of serum iPTH(pg/ml) levels among the studied groups

Correlations between iPTH(pg/ml),glycemic parameters among poor glycemic control group on hemodialysis(Fig.2 a,b and c): In diabetic patients with poor glycemic control, serum iPTHlevel was negatively correlated withHbA1C(r=-0.650,p<0.001),FBG (r=-0.696,p<0.001)as well as PPBG(r=-0.652,p<0.001).
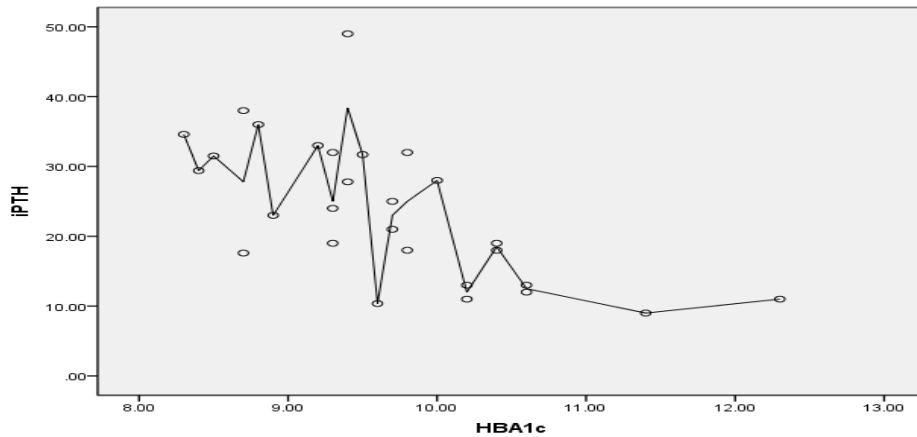
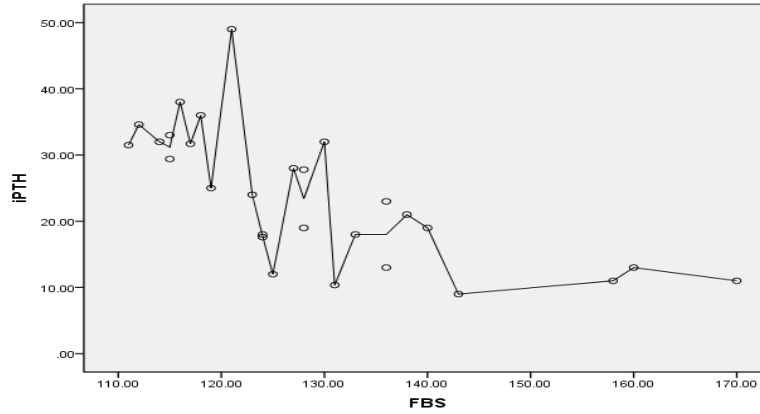**Fig. 2a:-**Correlation between iPTH and HbA1c in diabetic patients (poor glycemic control group)

Fig. 2b:- Correlation between iPTH and FBG in diabetic patients (poor glycemic control group)
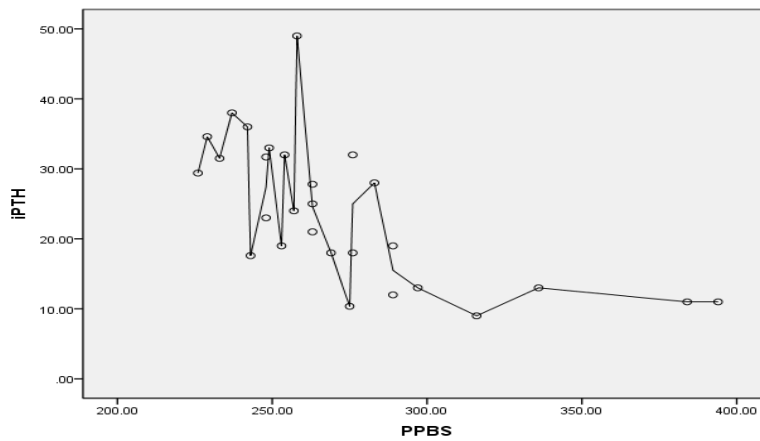

Fig. 2c:- correlation between iPTH and PPBG in diabetic patients (poor glycemic control group)

Correlations between iPTH(pg/ml),glycemic parameters among good glycemic control group on hemodialysis (Fig.3 a,b and c): In diabetic patients with good glycemic control, serum iPTHlevel was negatively correlated with HbA1C(r=-0.649,p<0.001),FBG (r=-0.634,p<0.001),as well as PPBG(r=-0.631,p<0.001).
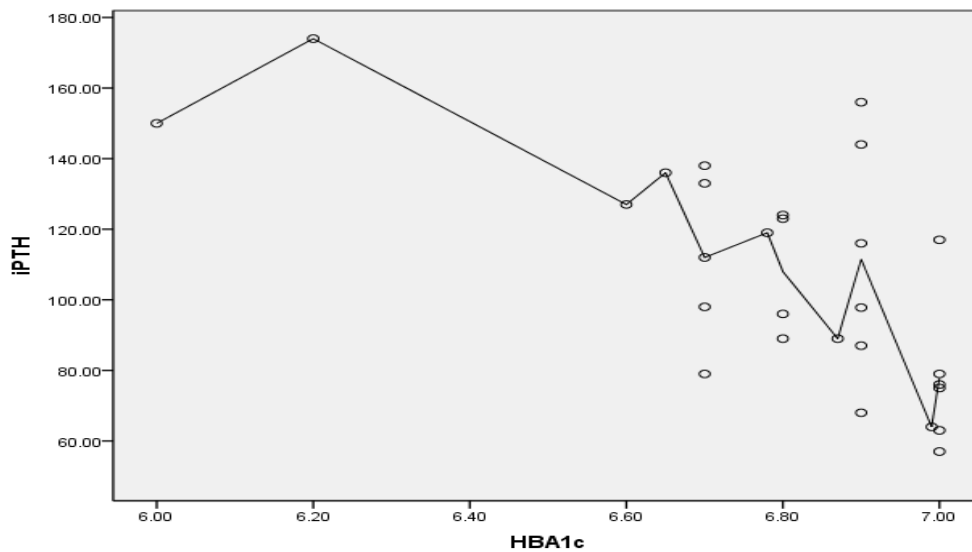

Fig. 3a:- Correlation between iPTH and HbA1C in diabetic patients (good glycemic control group)
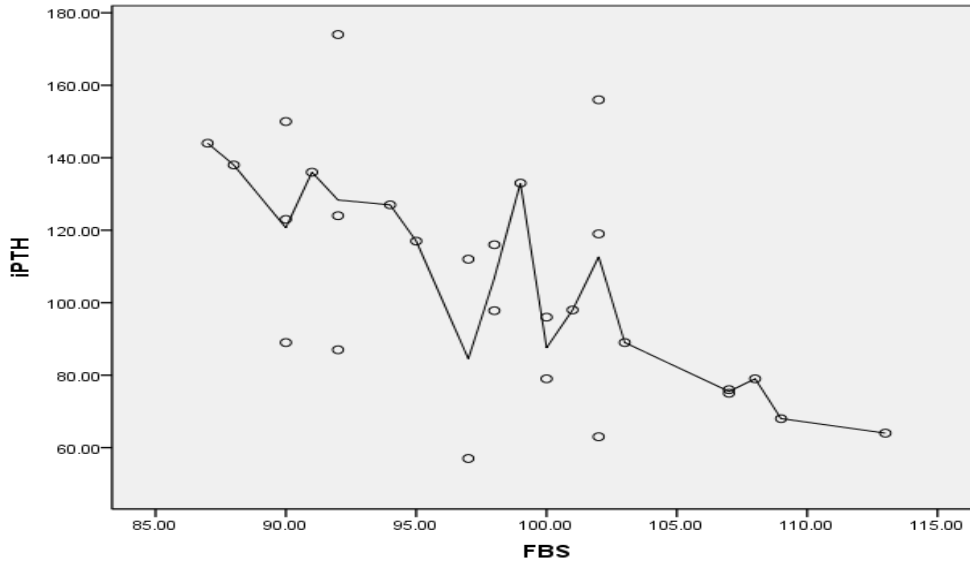
Fig. 3b:- Correlation between iPTH and FBG in diabetic patients (good glycemic control group)
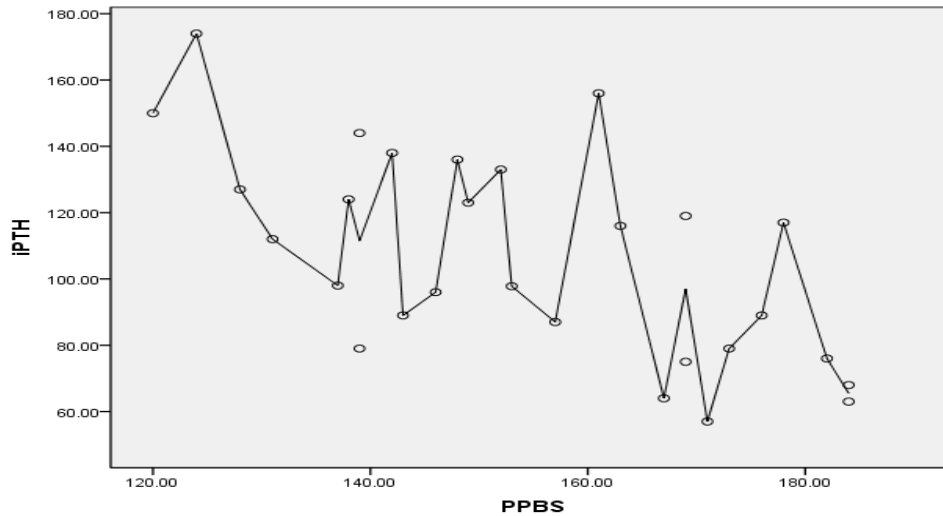

Fig. 3c:- correlation between iPTH and PPBG in diabetic patients (good glycemic control group)

Discussion:-

Worldwide, the incidence of individuals withend-stage renal disease (ESRD)has increased markedly over the past decades and imposes a major social and economic burden for healthcare systems [12].

Diabetes Mellitus (DM) is the main cause of chronic kidney disease (CKD). Given the prevalence of DM is estimated to increase from 366 million patients in 2011 to 552 million patients in the year 2030.Furthermore, it is well established that diabetic nephropathy particularly from type 2 diabetes and hypertensive nephrosclerosis are the leading causes of ESRD in developed and developing countries possibly because of increasing prevalence of obesity, diabetes and hypertension [13].

Numerous reports have described renal osteodystrophyas "the silent crippler"; affected patients may be completely asymptomatic. Nonetheless,if symptoms developed it observed in the late stages of the disease, these symptoms including bone and joint pain as well as bone deformity and fractures. Adynamic bone disease is a severe state of renal osteodystrophy characterized by low levels of PTH, lack of bone cell activity and a low bone turnover [14]. The excessive suppression of PTH can lead to adynamic bone disease (currently the most common osteodystrophy), mainly because of low bone turnover [15].

Previous studies have shownadvanced glycation end products (AGEs) which produced in diabetic state play an important role in the pathogenesis of both impaired secretion of iPTH and decreased bone formation. Furthermore, (AGEs) inhibit hypersecretion of PTH in response to low serum calcium [16].Data on the association between T2DM and osteoporotic fractures is controversial. Martinez-Laguna D [17] reported 20% increased risk of hip fracture in the first years following T2DM diseaseonset compared to matched non-diabetic patients.

Nonetheless, numerous reports have linked the higher incidence of osteodystrophy among the diabetic patients on regular hemodialysis to high intact parathyroid hormone (iPTH) level, thus, the objective of the present studywas to estimate the serum levels of iPTH and to clarify the possible relationships between iPTH serum levels and HbA1c ;which reflect the glycemic control as well as other clinical and biochemical parameters in ESRD patients on regular hemodialysis.Our study revealed clear evidence that, diabetic patient on chronic hemodialysis had significantly higher values of PPBG, FBG,HbA1c, LDL , TG,TC, PO4, albumin and Alkaline phosphatase, compared to non diabeticpatients on hemodialysis .

This was in agreement with the findings detected by **Paulo et al.,**[18],whoreported a statistical significant difference regarding fasting blood sugar, phosphorus and glycated hemoglobin in diabetic group compared to non diabetic group.Likewise **,Takeshi et al., [19],** reported a high statistical significant difference between all groups regarding glycated hemoglobin. These results were in agreement with the study of **Ahmed R. et al., [20],** they reported a statistical significant difference between all diabetic and non-diabetic patients regarding HbA1c , fasting blood sugar ,serum albumin and phosphate .

Regarding the influence of hyperglycemia on clinical and biochemical parameters, our results revealed that in poor glycemic control group, systolic & diastolic blood pressure, FBG, PPBG,HbA1c ,urea, alkaline phosphatase, TG, and cholesterolwere significantly higher than in patients with good glycemic control.Similar results had been detected by other authorsAhmed R. et al.,[20] they reported a statistical significant difference between controlled diabetic and uncontrolled diabetic patients regarding fasting blood sugar and glycated hemoglobin.

The main finding of our study, non diabetic patienton chronic hemodialysis had significantly higher values of serum iPTHmore than diabetic group,moreover, patients with good glycemic control had significantly higher levels of serum iPTH and 25 Hydroxyvitamin D compared to poor glycemic control group .

These findings are in a close agreement with results reported byAhmed R. et al., [20],who have also determined that serum iPTH levels in diabetic patients on hemodialysis were lower when compared with those in non-diabetic patients, also poor glycemic control further reduced levels of serum iPTH , also good glycemic control was associated with higher levels of serum iPTH, while no statistical difference of serum levels of iPTH between controlled diabetic patients and non- diabetic patients, suggesting that proper glycemic control could eliminate the effects of diabetic state on serum iPTH level.

Previous studies also have shown that, despite the fact that serum iPTH levels are considered important for the understanding of the mechanisms leading to renal related bone disease, changes in iPTH biological action play a significant role in the pathogenesis of renal osteodystrophy[21]. Both high and low circulating iPTH levels have been linked respectively to high and low bone turnover osteodystrophy or adynamic bone disease in patients on hemodialysis [14, 22].PilzS et al;2011 [23] showed low 25(OH)D concentrations in patients with CKD . Molina P et al 2014[24] have reported that cholecalciferol decreases albuminuria and improves iPTH levels

Our study demonstrated that, in diabetic patients with poor glycemic control, serum iPTH level was positively correlated with 25-Hydroxyvitamin D,on the other hand, serum iPTHlevel was negatively correlated with Alkaline phosphatase. In good glycemic control,serum iPTH level was positively correlated with 25-Hydroxyvitamin D, but there were significant negative correlations between serum iPTH level and creatinine, alkaline phosphatase, phosphorous and albumin, there were non-significant correlation between iPTH and other clinical and biochemical characters in both groups.Regarding correlation between serum iPTHand parameters of glycemic control .In diabetic patients with poor glycemic control, serum iPTHlevel was negatively correlated with post prandial blood glucose, fasting blood glucose, as well as HbA1C.

These results were in agreement with the studies of**Wasan et al.,** [25]and**Dan S et al.,** [26],they observed that in diabetic poor glycemic control group ,there was a significant inverse correlation between serum iPTH and serum

alkaline phosphatase, cholesterol, triglycerides, fasting blood sugar, postprandial blood sugar and glycated hemoglobin.

Also our results revealed that diabetic patients with good glycemic control, serum iPTHlevel was negatively correlated with post prandial blood glucose, fasting blood glucose, as well as HbA1C. Similarly the study of **Dan S et al.,**[26]observed that,in the diabetic good glycemic control group there was a significant positive correlation between serum iPTH and serum albumin and creatinine, while there is a significant inverse correlation between serum iPTH and serum phosphate, alkaline phosphatase, fasting blood sugar, postprandial blood sugar and glycated hemoglobin.

These results were supported previously by **Murakami et al.,** [10], who reported that there was an inverse correlation betweenserum iPTH levels and glycemic control. Specifically, diabetic patients with poor glycemic control were characterized by low circulating iPTH, which is conversely found at higher levels in diabetic patients with good glycemic control. Atmaca et al [27] reported that, impaired blood glucose regulation in subjects with type II DM leads to functional hypoparathyroidism and advisedfurther investigation for the effect on bone loss and fragility. Also Polymeris et al [28] revealed reduction in parathyroid hormone which was inversely correlated with elevated blood glucose during oral glucose tolerance test in non diabetic postmenopausal women.

Our study explored that, In diabetic patients on hemodialysis, stepwise linear regression analysis showed that, serum iPTH levels were independently correlated with 25-Hydroxyvitamin D,diastolic blood pressure, serum phosphorus, albumin, alkaline phosphatase FBG, PPBG andHbA1c .

Also, **Paula et al.,** [18],found that serum HbA1c levels were independent correlated with the serum iPTH levels in diabetic group .The inverse correlation noted between blood glucose and parathyroid hormone suggest that hyperglycemia may have an inhibitory action on the synthesis and secretion of parathyroid hormone and it is attractive to speculate that hyperglycemia together with an insulin deficit may lead to a hypoparathyriod state and a downregulation of PTH receptors[25].

Paula et al.,[18]detected the inhibitory effects of insulin on both the secretion and the action of iPTH in both primary and secondary hyperparathyroidism. however, it is still unclear as**Procopio M and Borretta G**[29] studies suggest that poor metabolic control per se, could inhibit low calcium-mediated iPTH secretion.**Guh et al.,[30]**detected the protective effect of diabetic process on the development of hyperparathyroidism and development of an adynamic bone lesion. In contrast,the uncontrolled hyperglycemia is parallel with increased risk of vascular calcification and increased cardiovascular mortality .

Also, **Gnudi et al.,[31]** reported that low bone turnover osteodystrophy represents a risk factor for accelerated peripheral vascular disease in patients on hemodialysis. While low blood levels of intact PTH strongly suggest the presence of adynamic bone, a high PTH level does not exclude this possibility. Histological studies have found adynamic bone in patients on hemodialysis despite PTH values above 44.0 pmol/L. This may be related to limitations of the PTH assay due to accumulation of inhibitory PTH fragments [32].Despite the fact that K-DOQI[33] guidelines recommend keeping glycated hemoglobin below 7% in diabetic patients undergoing dialysis, this recommendation is not based on clinical trials for the population undergoing renal replacement therapy (RRT), and the target range might be challenged due to the lack of nationwide studies related to this issue, making way for an individualized approach for these patients [34].

Conclusion:-
Non diabetic patient on chronic hemodialysis had significantly higher values of serum 25-hydroxyvitamin D and intact parathyroid hormone (iPTH) more than diabetic group.Moreover,in diabetic patients with poor glycemic control, serum iPTH level and 25-hydroxyvitamin D were significantly lower than diabetic patients with good glycemic.Thus,tight metabolic control of the diabetic process is very important to avoid hypoparathyroidism and low bone turnover in these patients. Alongside, individual titration of CaandVit D supplementations in ESRD patients on hemodialysis may be fruitful in keeping iPTH level within target range. Further studies should be done to investigate whether targeting iPTH and other determinants involved in renal bone disease in dialysis patients may prevent or delay the development of vascular calcifications.

References:-

1. US renal data system, USRDS 2005 Annual data report: Atlas of end-stage renal disease in the United States, national institute of health, national institute of diabetes and digestive and kidney disease, Bethesda, MD, 2005. Am J Kidney Dis 2006;47:S1.
2. Anand S, Bitton A, Gaziano T. The gap between estimated incidence of end-stage renal disease and use of therapy.PLoS One 2013; 8: e72860.
3. Liyanage T, Ninomiya T, Jha V, et al. Worldwide access to treatment for end-stage kidney disease: a systematic review. Lancet 2015; 385: 1975–1982
4. AAfifi, et al. Annual reports of the Egyptian renal registry; 1996-2008
5. Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. Diabetes.2005;54(6):1615–1625.
6. Gal-MoscoviciA,Popovtzer MM. New worldwide trends in presentation of renal osteodystrophy and its relationship to parathyroid hormone levels.*ClinNephrol.* 2005;63: 284-89.
7. Coen G. Adynamic bone disease: an update and overview. *J Nephrol.*2005;18: 117-22.
8. Vincenti F, Hattner R, Amend WJ Jr*et al*. Decreased secondary hyperparathyroidism in diabetic patients receiving hemodialysis. *JAMA* 1981; 245: 930-933.
9. InabaM OS, Nagasue K, et al. Impaired secretion of parathyroid hormone is coherent to diabetic hemodialyzed patients. *Am J Kidney Dis.* 2001; 38:139-42.
10. Murakami R, Murakami S, Tsushima R, Ueda C, Mikami K, Ebina T, et al. Glycaemic control and serum intact parathyroid hormone levels in diabetic patients on haemodialysis therapy. *Nephrol Dial Transplant.*2008; 23:315-20.
11. InabaM, Nagasue K, Okuno S *et al*. Impaired secretion of parathyroidhormone, but not refractoriness of osteoblast, is a major mechanismof low bone turnover in hemodialyzed patients with diabetes mellitus.*Am J Kidney Dis* 2002; 39: 1261–1269.
12. BeladiMousavi SS, Alemzadeh Ansari MJ, Cheraghian B (2011): Outcome of Patients on Hemodialysis in Khuzestan, Iran. NDT Plus: 4:143-4.
13. BeladiMousavi SS, Alemzadeh Ansari MJ, Alemzadeh Ansari MH, BeladiMousavi M (2012): Long-term survival of patients with end-stage renal disease on maintenance hemodialysis a multicenter study in Iran. IJKD.;6: 452-6.
14. Coen G, Ballanti P, Bonucci E et al. (1998): Bone markers in the diagnosis of low turnover osteodystrophy in hemodialysis patients. Nephrol Dial Transplant; 13: 2294–2302
15. Andress DL (2008):Adynamic bone in patients with chronic kidney disease. Kidney Int; 73: 1345–54.
16. Yamamoto T, Ozono K, Miyauchi A (2001): Role of advanced glycationendproducts in adynamic bone disease in patients with diabetic nephropathy. Am J Kidney Dis.; 38:S161–S64
17. Martinez-Laguna D1, Tebe C, Javaid MK, Nogues X, Arden NK, et al .Incident type 2 diabetes and hip fracture risk: a population-based matched cohort study.Osteoporos Int. 2015 Feb;26(2):827-33
18. Paula FJ, Lanna CM, Shuhama T, Foss MC (2001): Effect of metabolic control on parathyroid hormone secretion in diabetic patients. *Braz J Med Biol Res*; 34:1139-45.
19. Takeshi O, Masanori E, Tsutomu T, Tomoaki M, Yoshihro T, Hideki T, Tetsuo S, Yoshiki N (2006):Impact of Glycemic Control on Survival ofDiabetic Patients on Chronic RegularHemodialysis. *Diabetes Care* 29:1496–1500
20. Ahmed Ramadan Ali, Ahmed AlsayedEmam,Heba S. Assal, Alaa B. Abbas (2010): Intact Parathyroid Hormone in Egyptian Type 2 Diabeticswith Chronic Hemodialysis: Impact of Glycemic Control. Kidney; 19:17–22.
21. LuigiGnudi (2008):Serum intact parathyroid hormone in diabetic patients on hemodialysis: what is the treatment goal? Nephrol Dial Transplant; 23: 24–26.
22. Gal-Moscovici A &Popovtzer MM (2005): New worldwide trends in presentation of renal osteodystrophy and its relationship to parathyroid hormone levels. *ClinNephrol*; 63: 284-89.
23. Pilz S, Iodice S, Zittermann A, Grant WB, Gandini S. Vitamin D status and mortality risk in CKD: a meta-analysis of prospective studies. Am J Kidney Dis. 2011;58:374–382.
24. Molina P, Górriz JL, Molina MD, Peris A, Beltrán S, Kanter J, Escudero V, Romero R, Pallardó LM. The effect of cholecalciferol for lowering albuminuria in chronic kidney disease: a prospective controlled study. Nephrol Dial Transplant. 2014;29:97–109.
25. WasanAbdulkareem Abbas, Mohammed A. Al-Zubaidi, SundusKh. Al-Khazraji (2012): Estimation of serum calcium and parathyroid hormone (PTH) levels in diabetic patients in correlation with age and duration of disease.Iraqi J. Comm. Med., Apr. (2).

26. Dan S,Aditya P,Samanta M, Jothimalar R,Soundarajan P (2014): Effect of Glycemic Control on Intact Parathyroid Hormone Level in End Stage RenalDisease Patients on Maintenance Hemodialysis.*Diabetes Research and Clinical Practice*,S0168-8227(14)00180-6.

27. Murat Atmaca, IsmailAcar,EnginGonultas, Ismet Seven et al (2014).Type 2 diabetes mellitus and functional hypoparathyroidism.Turk Jem;18:116-120.

28. Polymeris AD,Doumonchtsis KK, Giagourta I ,Karga H.(2011). Effect of oral glucose load on PTH,25OHD3,calcium and phosphorous homeostasis in postmenopausal women.EndocrRes ;36:45-52.

29. Procopio M, Borretta G (2003): Derangement of glucose metabolismin hyperparathyroidism. J Endocrinol Invest.;26:1136–42.

30. Guh JY, Chen HC, Chuang HY, Huang SC, Chien LC, Lai YH (2002):Risk factors and risk for mortalityof mild hypoparathyroidism inhemodialysis patients. Am J Kidney Dis.;39:1245–54

31. Gnudi L (2008): Serum intact parathyroid hormone in diabetic patientson hemodialysis: what is the treatment goal? Nephrol DialTransplant;23:24–6.

32. National Kidney Foundation (2003): Am J Kidney Dis. 2003;42:S1–202.

33. KDOQI (2003): Clinical Practice Guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis*; 42 Suppl 3:S2

34. Kovesdy CP, Sharma K, Kalantar-Zadeh K (2008): Glycemic control indiabetic CKD patients: where do we stand? Am J Kidney Dis ;52(4):766-77