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

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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 84 end-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 group 3: 28 non-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) and 25-hydroxyvitamin D were measured. Also, we estimate serum iPTH levels by ADVIA CENTAUR instrument using Chemiluminescence principle.

Results: Non diabetic patient on chronic hemodialysis had significantly higher values of serum 25-hydroxyvitamin D, serum iPTH more 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, iPTH level was negatively correlated with alkaline phosphatase, post prandial blood glucose, fasting blood glucose, as well as HbA1c. In patients with good glycemic control serum iPTH level was positively correlated with 25-hydroxyvitamin D, there were significant negative correlations between iPTH 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,
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 ESRD have gone up and 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, the prevalence of diabetes in adults is 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 micro and 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 ESRD on regular hemodialysis, due to low iPTH level and called Low Turnover Bone Disease (LTBD) [6].

Thus, diabetic patients on maintenance hemodialysis (MHD) are affected with alteration 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 iPTH level [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 serum levels variation in the pathogenesis of renal osteodystrophy. Therefore, the purpose of current study was to estimate serum levels of iPTH and to clarify the possible relationships between iPTH and HbA1c; which reflect glycemic control as 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 hypoparathyroidism. Ca and Vit D supplementations in ESRD may be fruitful in keeping iPTH level within target range.
Subjects and Methods: -
This study included 84 patients of 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. Patients were matched as regard age, gender, and ethnic origin. Patients were stratified into three groups: 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 Chemiluminescence principle. 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 (Ӽ2), 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 the diabetic group, 69.6% were male and 30.4% were female, their mean age was 47.73 ± 12.02 year. In the non-diabetic group, 64.3% were male and 35.7% were female, their mean 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 was 46.43 ± 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 difference regarding other 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    |
| Diastolic blood 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|
**Clinical and biochemical characteristics of diabetic groups (Table 2):** Poor glycemic control group had significantly higher values of systolic & diastolic blood pressure, PPBG, FBG, HbA1c, urea, alkaline phosphatase, TG, and cholesterol than good glycemic 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 was nonsignificant difference regarding other 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     |
|---------------------------|------------------------------|------------------------------|-------|-------|
| Systolic blood pressure (mmHg) | 140.71 ± 16.2               | 132.32 ± 13.57              | 2.10  | <0.05 |
| Diastolic blood 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               | 154.0 ± 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 ± 0.11                 | 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 (Table 3):** In diabetic patients with poor glycemic control, serum iPTH level was positively correlated with 25-Hydroxyvitamin D, on the other hand, serum iPTH level was negatively correlated with alkaline phosphatase. In diabetic 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 diabetic patients 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 | 3.132 |
|       | 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 patient on chronic hemodialysis had significantly higher values of serum iPTH (pg/ml) (371.39 ± 306.45) compared to diabetic group (65.25 ± 47.76). There was high significant elevated serum iPTH in good glycemic control group compared to poor glycemic control group (106.67 ± 31.37), (23.82 ± 10.13) respectively.

![Graph comparing serum iPTH levels among studied groups](image1)

**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 iPTH level was negatively correlated with HbA1C (r=-0.650, p<0.001), FBG (r=-0.696, p<0.001) as well as PPBG (r=-0.652, p<0.001).

![Graph showing correlation between iPTH and HbA1c](image2)

**Fig. 2a:** Correlation between iPTH and HbA1c 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 iPTH level 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. 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)

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

Worldwide, the incidence of individuals with end-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 osteodystrophias "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 shown advanced 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. Martínez-Laguna D [17] reported 20% increased risk of hip fracture in the first years following T2DM disease onset 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 study was 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 diabetic patients on hemodialysis.

This was in agreement with the findings detected by Paulo et al. [18], who reported 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 cholesterol were significantly higher than in patients with good glycemic control. Similar results had been detected by other authors Ahmed 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 patient on chronic hemodialysis had significantly higher values of serum iPTH more 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 by Ahmed 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]. Pilz S 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 iPTH level 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 iPTH and parameters of glycemic control. In diabetic patients with poor glycemic control, serum iPTH level 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 iPTH level 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 between serum 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 advised further 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 and HbA1c.

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 hypoparathyroid 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 control. 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 Ca and Vit 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.
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