Parathyroid Hormone: Effects on Glucose Homeostasis and Insulin Sensitivity in Chronic Renal Failure Patients on Regular Hemodialysis

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Abstract
Objective
To look into the relation between parathyroid hormone and abnormal glucose homeostasis in chronic renal failure patients on regular hemodialysis.

Methods
41 subjects, with chronic renal failure, and on regular hemodialysis (28 male, 13 female; age range 19-64 years). Full history and clinical examination were taken for every patient. In addition, ten age and sex matched healthy persons were selected randomly as control group. Informed consent was obtained. All patients were investigated to determine serum creatinine, calcium, phosphorus, alkaline phosphatase, parathyroid hormone, fasting glucose, and fasting insulin. Homeostasis module assessment of insulin resistance was calculated as a measure of insulin resistance, Homeostasis module assessment of beta cell was calculated as a measure of pancreatic beta cell function. The uremic patients were classified into two groups: group A included 24 patients with plasma parathyroid hormone levels < 450 pg/ml and group B included 17 patients with plasma parathyroid hormone level !450 pg/ml.

Results
There is a marked increase in fasting insulin level in all patients versus control associated with increased homeostasis module assessment of insulin resistance, an index for insulin resistance. Significant negative correlation is found between parathyroid hormone and fasting insulin and homeostasis module assessment of insulin resistance in uremic patients. Patients with severe hyperparathyroidism have relatively more impaired pancreatic beta cell function in comparison to those with mild hyperparathyroidism. The pulsed dose of intravenous 1-cholecalciferol is associated with low parathormone level and high serum calcium.

Conclusion
Insulin resistance is a constant feature of chronic renal failure patients under hemodialysis therapy, while secondary hyperparathyroidism is linked negatively to beta cell function. Intermittent pulsed intravenous alphacalcidol is an effective method of lowering high serum parathyroid hormone and is associated with improvement of beta cell function without significant effect on insulin resistance.

Key words: Secondary hyperparathyroidism, one alpha therapy, parathormone, insulin sensitivity, hemodialysis

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Introduction

Chronic renal failure is a major health problem in Egypt, and the number of patients on regular hemodialysis is increasing nowadays. At the same time, its different lines of therapy (conservative, dialysis, and transplantation) open wide hopes for long term survival of uremic patients.

Increased secretion of parathyroid hormone (PTH) is common in patients with chronic renal failure, and the excess blood levels of PTH could be deleterious to many organ systems. A variety of symptoms and signs including encephalopathy, neuropathy, dialysis dementia, reduced left ventricular ejection fraction, impaired insulin secretion, glucose intolerance, hyperlipidaemia, soft tissue calcification, bone resorption, pruritis, immunological disturbances, and sexual dysfunction are encountered in patients with uremia. These manifestations contribute to the uremic syndrome and at least part of their pathogenesis has been attributed to PTH as a uremic toxin, and it is thought that such actions of PTH are mediated by an increase in intracellular calcium. Uremic patients are thought to be insulin resistant and about half of them were found to have impaired glucose tolerance. The insulin resistance is a characteristic feature of uremic patients; a problem that could be partially ameliorated both by hemodialysis and by the chronic ambulatory peritoneal dialysis.

Some evidences suggest a role for PTH in the pathogenesis of deranged beta cell function of uremia. Early studies reported that PTH has a role in the problem of insulin resistance. Subsequent investigations using clamp techniques demonstrated that the development of glucose intolerance in uremic dogs could be prevented by parathyroidectomy. Administration of PTH to rats with normal renal function increased the resting cytosolic calcium, decreased the ATP content and impaired insulin release through ATP-dependent K-channels. Pancreatic islets are apparently a PTH target; PTH stimulates cAMP production and possibly also protein kinase C in a calcium-dependent fashion. Also, it was suggested that uremic patients with elevated serum PTH were found to be severely insulin resistant and hyperinsulinemic and intravenous vitamin D treatment led to a significant reduction of serum PTH levels and to complete normalization of insulin sensitivity in hemodialysis patients.

However, the exact effect of hyperparathyroidism on different parameters of glucose homeostasis, and the effect of lowering serum PTH by one alpha hydroxycholecalciferol therapy still need further evaluation. It is theoretically possible that the deficiency of 1,25 (OH)2D3 commonly encountered in patients with CRF plays a role in the impaired insulin secretion encountered in these patients. The aim of the study is to look into the relation between serum PTH and parameters of glucose homeostasis and to analyze the effect of lowering PTH on these parameters.

Materials and Methods

The present study was conducted on forty one subjects suffering from chronic renal failure due to different intrinsic renal causes.
who were on regular hemodialysis sessions. Their ages range from 19 to 64 years. They were 28 Males and 13 females. They were selected randomly from inpatient and outpatient clinics of Internal Medicine Department of Mansoura University Hospital Cairo Egypt.

Full history was taken for every subject including name, age, sex, duration of dialysis therapy, cause of the original kidney disease, dry weight, number of sessions per week, duration of session, type of the dialyzer used, associated complications during the sessions, associated medical disorders (IHD, hypertension, DM), and medications received. Cases with diabetes mellitus, cases with impaired glucose tolerance, and cases taking any medications that affect carbohydrate metabolism were excluded.

In addition, 10 healthy volunteers age and sex matched selected randomly as a reference (control) group. Informed consents were obtained from all subjects (patients and control) in the study. All persons of the study were subjected to full laboratory investigation to determine serum creatinine, calcium, phosphorus, alkaline phosphatase, PTH, blood hemoglobin, fasting glucose, and fasting insulin. HOMA-IR was calculated as a measurement of insulin resistance, also HOMA-B was calculated as a measurement of pancreatic beta cell function.

The patients were classified into two groups according to plasma PTH level. Group A; included patients with plasma PTH level less than 450 pg/ml. This group included 24 patients 15 males and 9 females. Group B; included patients with plasma PTH level more than 450 pg/ml. This group included 17 patients 13 males and 4 females.

Ten patients from those of group B have been selected randomly to receive pulsed doses of one alpha-cholecalciferol in the form of 1 microgram I.V. thrice weekly at the end of the hemodialysis session for four consecutive months. After the termination of the pulsed dose of one alpha-cholecalciferol, the patients were returned back to their oral dose of 1 α-cholecalciferol.

Complete laboratory investigations were performed for all the patients and the control at the beginning of the study, and four months later after termination of the pulsed dose of 1 α-cholecalciferol for all patients who received the pulsed dosage of 1 α-cholecalciferol.

Insulin resistance was measured using HOMA-IR test, while, pancreatic beta cell function was measured using HOMA-B test which were measured according as follows12:

HOMA-IR = (fasting insulin x fasting glucose in mmol/L) / 22.5
HOMA-B = (20 x fasting insulin) / (fasting glucose in mmol/L – 3.5)

Statistical analysis: The statistical analysis of the present work was done by IBM personal computer using EXCEL statistical program, accepted level of significance for Probability value is 0.05.

Chi square (X2) test with Yates correction or fisher, S exact test tested difference in prevalence, where applicable. Student t-test or Mann-Whitney test analyzed continuous variables expressed as mean and standard deviation, where applicable.

**Results**

The detail of the results recorded in this study is outlined in Tables 1-5. Further interpretation of the results and data comparison is mentioned in the discussion.

**Discussion**

Abnormal glucose homeostasis has been a well known feature of uremic patients for many years. Several studies demonstrated the presence of insulin resistance and impaired glucose tolerance in uremic patients 13, 14. Others demonstrated pancreatic beta cell dysfunction in uremia 14, 15. The problem of abnormal glucose homeostasis may be responsible for the increased incidence of atherosclerosis and cardiovascular morbidity in uremic patients 16, which can account for high mortality rates in these patients.

Patients with chronic renal failure (CRF) in
Table 1: Clinical data and anthropometric measurements for the patients versus controls and group A (PTH level < 450 pg/ml) versus group B (PTH level > 450 pg/ml)

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>Sex</th>
<th>Age (years)</th>
<th>HD (ys) Duration</th>
<th>BMI</th>
<th>SBP</th>
<th>DBP</th>
<th>IHD</th>
<th>HTN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control N = 10</td>
<td>M: 7(70%) F: 3(30%)</td>
<td>36.9±5.8</td>
<td>------</td>
<td>23.7±3.1</td>
<td>126.4±10</td>
<td>73.5±8.2</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>All patients N= 41</td>
<td>M: 28(68%) F: 13(32%)</td>
<td>51±10.5</td>
<td>5.2±3.7</td>
<td>25.6±4.6</td>
<td>127±23</td>
<td>76.5±13</td>
<td>9</td>
<td>13</td>
</tr>
</tbody>
</table>

Statistical analysis:

- Chi square = 0.011
- p = 0.9
- P < 0.0001*
- P = 0.04*
- P = 0.56
- P = 0.48

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>Sex</th>
<th>Age (years)</th>
<th>HD (ys) Duration</th>
<th>BMI</th>
<th>SBP</th>
<th>DBP</th>
<th>IHD</th>
<th>HTN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A N = 24</td>
<td>M: 15(62%) F: 9(38%)</td>
<td>50.7±12.3</td>
<td>4.2±3.1</td>
<td>24.5±3.3</td>
<td>129.5±19</td>
<td>77.9±11.4</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Group B N= 17</td>
<td>M: 13(76%) F: 4(23%)</td>
<td>51.2±8</td>
<td>6.5±4.2</td>
<td>27.2±5.7</td>
<td>124±27.4</td>
<td>74.7±15</td>
<td>2</td>
<td>6</td>
</tr>
</tbody>
</table>

Statistical analysis:

- Chi square = 0.89
- p = 0.34
- #P = 0.87
- P = 0.07
- P = 0.07
- P = 0.07
- P = 0.48
- p = 0.41
- p = 0.41

*Chi square = 0.488. P value: Probability value

Table 2: Laboratory data for the patients versus controls and group A (PTH level < 450 pg/ml) versus group B (PTH level > 450 pg/ml)

<table>
<thead>
<tr>
<th>Features</th>
<th>Creat. mg/dl</th>
<th>Ca mg/dl</th>
<th>P mg/dl</th>
<th>AP KAu/dl</th>
<th>PTH Pg/ml</th>
<th>Hb gm/dl</th>
<th>FBG Mg/dl</th>
<th>FSI I.U/ml</th>
<th>HOMA -IR</th>
<th>HOMA-B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control  (n=10)</td>
<td>1.1±0.2</td>
<td>10.7±0.3</td>
<td>3±0.5</td>
<td>5.5±1.4</td>
<td>31±3.7</td>
<td>14±1.2</td>
<td>96±7</td>
<td>6.6±0.9</td>
<td>1.5±0.3</td>
<td>76.7±18.5</td>
</tr>
<tr>
<td>Patients (n=41)</td>
<td>10.1±3.4</td>
<td>8.8±1.5</td>
<td>7±1.6</td>
<td>14±6.1</td>
<td>539±647</td>
<td>10.4±0, 9</td>
<td>93±12</td>
<td>10.5±6. 7</td>
<td>2.5±1.7</td>
<td>140.2±100</td>
</tr>
<tr>
<td>P value P1</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td>0.001*</td>
<td>&lt;0.001*</td>
<td>0.001*</td>
<td>0.46</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td>0.08</td>
</tr>
<tr>
<td>Group A (n=24)</td>
<td>9.6±2.8</td>
<td>9.3±1.2</td>
<td>6.4±1.3</td>
<td>12.7±5</td>
<td>137±86</td>
<td>10.3±1</td>
<td>92±10</td>
<td>12±6.2</td>
<td>2.8±1.6</td>
<td>157±76.2</td>
</tr>
<tr>
<td>Group B (n=17)</td>
<td>10.6±4</td>
<td>8±1.6</td>
<td>7.8±1.6</td>
<td>15.9±7</td>
<td>1107±672</td>
<td>10.4±0, 9</td>
<td>95±14</td>
<td>8.6±7.2</td>
<td>2.1±1.8</td>
<td>116.2±125</td>
</tr>
<tr>
<td>P value P2</td>
<td>0.4</td>
<td>0.004*</td>
<td>0.004*</td>
<td>0.1</td>
<td>0.001**</td>
<td>0.9</td>
<td>0.4</td>
<td>0.12</td>
<td>0.08</td>
<td>0.01**</td>
</tr>
</tbody>
</table>

* T-test ** Mann-Whitney test. P value: Probability value
P1: comparison between patients versus control. P2: comparison between patients with PTH level above versus below 450 pg/ml.

The mean levels of serum PTH, creatinine, phosphate, alkaline phosphatase, fasting insulin are higher in the uremic patients than control and low levels of hemoglobin & serum calcium in uremic patients. HOMA-IR is significantly higher in uremic patients than control.

In comparing the fasting serum insulin, glucose, HOMA-IR, and HOMA-B in between patients with severely elevated (group B) and those with moderately elevated serum PTH (group A), there is no significant difference in fasting glucose, fasting insulin and HOMA-IR. While HOMA-B is significantly lower in severe HPT.
Table 3: Comparison between patients with moderate anemia ((Hb<10.5 gm/dl) and patients with mild anemia (Hb>10.5 gm/dl) as regard insulin sensitivity for all patients

<table>
<thead>
<tr>
<th>Features</th>
<th>Fasting Insulin IU/ml</th>
<th>Fasting glucose mg/dl</th>
<th>HOMA-IR</th>
<th>HOMA-B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mildly anemic patients</td>
<td>11 ± 7</td>
<td>89 ± 11.8</td>
<td>2.5 ± 1.8</td>
<td>156.2±96.6</td>
</tr>
<tr>
<td>N= 21</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderately anemic patients</td>
<td>10 ± 6.2</td>
<td>96 ± 10.6</td>
<td>2.4± 1.6</td>
<td>123.3±103</td>
</tr>
<tr>
<td>N=20</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.7</td>
<td>0.05</td>
<td>0.5</td>
<td>0.2</td>
</tr>
</tbody>
</table>

* T-test, **Mann-Whitney test.  P value: Probability value

Table 4: Correlation between laboratory indices glucose homeostasis and some laboratory data in hemodialysis patients (n = 41)

<table>
<thead>
<tr>
<th>Features</th>
<th>Calcium</th>
<th>Phosphorus</th>
<th>Alk. Phosphatase</th>
<th>Creatinine</th>
<th>Hemoglobin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting insulin r</td>
<td>0.5</td>
<td>-0.1</td>
<td>-0.24</td>
<td>-0.04</td>
<td>0.04</td>
</tr>
<tr>
<td>p</td>
<td>0.003</td>
<td>0.5</td>
<td>0.12</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>Fasting glucose r</td>
<td>0.03</td>
<td>-0.02</td>
<td>0.004</td>
<td>-0.15</td>
<td>0.3</td>
</tr>
<tr>
<td>p</td>
<td>0.85</td>
<td>0.99</td>
<td>0.9</td>
<td>0.3</td>
<td>0.06</td>
</tr>
<tr>
<td>HOMA-IR r</td>
<td>0.43</td>
<td>-0.13</td>
<td>-0.2</td>
<td>-0.06</td>
<td>0.08</td>
</tr>
<tr>
<td>p</td>
<td>0.006</td>
<td>0.4</td>
<td>0.2</td>
<td>0.72</td>
<td>0.6</td>
</tr>
<tr>
<td>HOMA-B** rs</td>
<td>0.41</td>
<td>-0.05</td>
<td>-0.24</td>
<td>0.03</td>
<td>0.02</td>
</tr>
<tr>
<td>p</td>
<td>0.008</td>
<td>0.5</td>
<td>0.13</td>
<td>0.8</td>
<td>0.3</td>
</tr>
</tbody>
</table>

There is no significant correlation between hemoglobin level and any of the parameters of glucose homeostasis. There is significant negative correlation between serum PTH and fasting insulin, HOMA-B (a marker of B cell function). this correlation does not reach the level of statistical significance (p = 0.07). but; there is a significant negative correlation between PTH and HOMA-IR index, a marker of insulin resistance.

Table 5: Laboratory data of the studied patients (10 patients) before and after 4 months intravenous pulsed dose of one alpha cholecalciferol

<table>
<thead>
<tr>
<th>Features</th>
<th>Creatinine mg/dl</th>
<th>Ca mg/dl</th>
<th>P mg/dl</th>
<th>AK KAU/dl</th>
<th>PTH Pg/ml</th>
<th>FBG mg/dl</th>
<th>FSI IU/ml</th>
<th>HOMA-IR</th>
<th>HOMA-B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before M±SD</td>
<td>13.7±1.6</td>
<td>8.1±0.5</td>
<td>8.3±1.7</td>
<td>15.6±6.4</td>
<td>125±597</td>
<td>93±14</td>
<td>7.5±5.5</td>
<td>1.7±1.2</td>
<td>106±117</td>
</tr>
<tr>
<td>After M±SD</td>
<td>12.3±1.3</td>
<td>9.5±0.6</td>
<td>7.2±1.1</td>
<td>13.2±2.6</td>
<td>827±202</td>
<td>88±7</td>
<td>12.6±4.7</td>
<td>2.8±1.2</td>
<td>181±48</td>
</tr>
<tr>
<td>P value</td>
<td>0.041*</td>
<td>0.002*</td>
<td>0.3</td>
<td>0.24</td>
<td>0.09</td>
<td>0.49</td>
<td>0.18</td>
<td>0.18</td>
<td>0.02**</td>
</tr>
</tbody>
</table>

* T-test, **Mann-Whitney test.  P value: Probability value

This table shows the effect of lowering serum PTH by intravenous pulsed alphacalcidol on glucose homeostasis data. There is significant increase in serum calcium and non-significant decrease in serum PTH and significant increase in beta cell function (measured by HOMA-B).

The current work have significantly lower serum calcium, and significantly higher serum phosphorus than that of the control group. These changes reflect well-known problems in CRF that were previously reported[17]. This denotes that although these patients were under hemodialysis therapy, they were far from being ideally controlled. The predialysis serum creatinine was greatly increased. The higher serum PTH in the uremic patients indicates the well known major
problem affecting these patients which is a secondary hyperparathyroidism in CRF patients. Since the reduced PTH degradation and clearance affect mainly the inactive PTH fragments, it is unlikely to cause alternation in the intact PTH steady state concentration. Therefore, uremic hyperparathyroidism is mainly due to an increase in bioactive PTH synthesis and a release by the parathyroid gland. The stimulatory factors of parathyroid hormone synthesis and secretion include hypocalcaemia, hyperphosphatemia, and vitamin D3 metabolic abnormalities. Thus, there are additional factors that may contribute to hyperparathyroidism in chronic renal failure as acidosis and uremic toxins. Increased fasting insulin in uremic patients can be attributed to decrease in the metabolic clearance of insulin. Impaired degradation of insulin in non-renal tissues (liver and muscle) may also contribute to the prolonged half life of insulin in uremic patients. This increase in fasting insulin is not associated with any significant change in fasting blood glucose that may give an impression of resistance to the action of insulin. Moreover, the higher HOMA-IR value in CRF documents the presence of insulin resistance in CRF patients in the present work. These results are consistent with the study of Tuzeu et al., who demonstrated that mean insulin level is significantly elevated in uremic patients versus control group, and also, demonstrated insulin resistance in the uremic patients of the study using HOMA-IR as a measurement of insulin resistance. Also, these results are in accord with those of Sechi et al. who reported that the problem of insulin resistance is found in uremic patients and even in early renal impairment; alternation of glucose metabolism became evident only when creatinine clearance was < 50ml/min. A multitude of many previous studies reported insulin resistance in uremic patients. Many factors contribute to the problem of insulin resistance in uremia. Accumulation of some uremic toxin(s) may be responsible...
for decreased insulin sensitivity. When uremic serum was incubated with tissues from normal animals, glucose utilization and oxidative phosphorylation were inhibited.

Mak and his coworkers demonstrated that, glucose tolerance and insulin sensitivity were improved significantly after protein restriction, or dialysis, thus, insulin resistance in uremia can be improved by dialysis or a low-protein diet. This may suggest that, accumulation of dialyzable toxins from protein metabolism is responsible for impaired glucose tolerance and decreased insulin sensitivity in uremic patients.

Anemia can be attributed to shortened erythrocyte survival, blood loss, and failure of the bone marrow to enhance red cell production to compensate their increased demand. Several studies demonstrated that anemia is a major pathogenic factor behind insulin resistance in chronic renal failure. Spaia and his co-workers proved the beneficial effect of EPO treatment on insulin resistance in dialysis patients. Tuzeu and his co-workers demonstrated that correction of anemia using erythropoietin normalized insulin sensitivity in uremia. Furthermore, they demonstrated that improvement in insulin sensitivity is positively correlated with duration of EPO therapy.

Plasma cell differentiation antigen 1 (PC-1) is an inhibitor of insulin receptor tyrosine kinase and it is thought to be one of the factors behind insulin resistance in uremia. Stevanovic and his co-workers found increased lymphocyte PC-1 activity in uremic patients over the control, and two months after EPO therapy, lymphocyte PC-1 activity decreased significantly, suggesting that an effect of PC-1 expression could be implicated in the amelioration of insulin resistance in uremic patients.

The uremic patients have more insulin resistance in moderate anemia than mild anemia. This may be due to the fact that some of them have been under EPO therapy while others received frequent blood transfusion. Moreover, in contrast to the previous study of Mak, there is no significant correlation between hemoglobin level and any of the parameters of glucose homeostasis in the present work. This may be attributed to the observation that many patients were already receiving EPO therapy and that the degree of anemia is much less than that reported in the previous studies before correction.

Lindall and his co-workers reported that uremic patients on hemodialysis with normal PTH levels had a normal insulin response to I.V glucose, while those with hyperparathyroidism showed disturbed insulin responses which was normalized after parathyroidectomy.

The negative correlation between serum PTH and fasting insulin and HOMA-B (an indicator of beta cell function) and HOMAIR index (a marker of insulin resistance), denote that PTH has an ameliorating effect on insulin resistance or, in other words, it is at least not linked to the worsening of insulin resistance. This is in obvious contrast with previously cited researches demonstrating the role of PTH in the problem of insulin resistance.

The patients with severe hyperparathyroidism (HPT) have significantly low HOMA-B than those patients with moderate HPT. This may denote that the higher PTH level may have a deleterious effect on beta cell function.

In our study, the intravenous pulsed alphacalcidol thrice weekly resulted in significant increase in serum calcium and improve the beta cell function (measured by HOMA-B). Whether these changes were due to lowering the PTH or an intrinsic effect of alphacalcidol or increased serum calcium level is open to speculations.

Lindall, Prager, Amend, and their co-workers studied insulin resistance using insulin tolerance tests in six stable uremic patients with secondary hyperparathyroidism prior to and after subtotal parathyroidectomy, the authors found that parathyroidectomy per se had no significant effect upon glucose utilization, or the resistance of the peripheral tissues to the action of exogenous insulin. This agrees with the finding of the present work of absence of significant improvement of
insulin resistance after lowering PTH with I.V. alphacalcidol.
Mak 35, Akmal 8, and their co-workers studied the effect of PTH on glucose homeostasis using the hyperglycemic clamp technique in eight uremic children, and they found that lowering of PTH using high-dose phosphate binders and dietary restriction of phosphate led to improvement in pancreatic beta cell function and was not associated with any improvement in insulin resistance of the uremic children.

Also, Mak and his co-workers 28 used the hyperglycemic clamp studies to study insulin sensitivity in eight uremic patients. They demonstrated a negative correlation between glucose metabolic rate (a measure of insulin sensitivity) and PTH level, but this was possibly ascribed to the effect of changing the GFR with serum PTH level. The authors also, demonstrated that correction of hyperparathyroidism by subtotal parathyroidectomy did not improve the problem of insulin resistance in the parathyroidectomized uremic patients. Moreover, lowering of PTH by subtotal parathyroidectomy was associated with increased insulin secretion from pancreatic beta cells with amelioration of glucose tolerance 27, which is consistent with the results of the present study. Furthermore, the observation of negative relation between PTH and beta cell function is consistent with the study of Fadda and his co-workers 37 demonstrated that, excess PTH is responsible for the decreased insulin secretion by pancreatic beta cells. They found that, insulin secretion in parathyroidectomized uremic rats was better than the control uremic rats. They also demonstrated that PTH administration to non uremic normal rats decreased insulin release by the islets.

Available data indicate that pancreatic beta cells have a specific receptor protein for 1, 25(OH)2D3 41. They found, in the chick, that the pancreatic islets possess receptor proteins for 1, 25(OH)2D3 through which it interacts with the pancreatic islets and modulates their insulin secretion. Likewise, it is still premature to confirm whether PTH modulation and vitamin D3 has a role in insulin resistance or insulin secretion and whether it acts through lowering PTH or through another different mechanism inherent to this molecule 42,43.

In conclusion, hyperparathyroidism, insulin resistance, and beta cell dysfunction are common problems in CRF patients on hemodialysis. The excess PTH is significantly associated with CRF patients on hemodialysis. The excess PTH is significantly associated with beta cell dysfunction. Effective lowering of serum PTH by intravenous pulsed one alpha cholecalciferol or subtotal parathyroidectomy can achieve better beta cell
function but may not help the problem of
insulin resistance. It is recommended that all
CRF patients are investigated regarding
glucose intolerance, insulin resistance, and
beta cell function. Any drugs or chemicals
that may deteriorate glucose tolerance
should be avoided if possible. Using drugs
that may improve insulin resistance and
beta cell function can be beneficial to some
cases; but this awaits further longitudinal
studies.

References

1. Ringoir S. An update on uremic toxins. 
Kid Int 1997; 52: 52-54
2. Lazarus JM, and Brenner BM. Chronic
renal failure, In Fauzi AS, Braunwald A, 
Isselbacher J et al (eds): Harrison’s
Principles of Internal Medicine. 16th
edition, Vol.3, New York, Mc-Grow-
Hill 2005: 1513-1520
Mechanisms through which parathyroid
hormone mediates its deleterious effects
on organ function in uremia. Semin 
Nephrol 1994; 14: 219-231
4. Kobayashi S, Maejima S, Ikeda T, 
Nagase M. Impact of dialysis therapy on
insulin resistance in ESRD: comparison
of hemodialysis and CAPD. Nephrol 
5. El-Baiomy A., Ehsan M., El-Kanashy 
M., El-Sayed S, Hypertriglyceridemia
interrelation to circulating insulin, PTH, 
and calcitriol in nonobese non diabetic
CRF men. Mansoura Medical Journal 
6. Mak RHK and DeFronzo RA. Glucose
and insulin metabolism in uremia. 
Nephron. 1992; 61: 377-382
7. Lindall A, Carmena R, Cohen S: Insulin
hypersecretion in patients on chronic 
hemodialysis; role of PTH. J Clin 
Endocrinol 1971; 32:653-658
8. Akmal M, Massry SG, Goldstein DA, 
Fanti P, Weisz A, DeFronzo RA. Role of
parathyroid hormone in glucose
intolerance of chronic renal failure. J 
Clin Invest 1985; 75:1037-1044
9. Perna AF, Fadda GZ, Zhou XJ, Massry 
SG. Mechanisms of impaired insulin
secretion after chronic excess of
parathyroid hormone. Am J Physiol 
1990; 259:F210-F216
10. Fadda GZ, Akmal M, Lipson LG, 
Massry SG. Direct effect of PTH on
insulin secretion from pancreatic
Intravenous calcitriol normalizes insulin
sensitivity in uremic patients. Kid Int. 
1995; 74: 200-206
12. Matthews DR, Hosker JP, Rudenski AS,
Maylor BA, Turner RC. Homeostasis
model assessment, insulin resistance
and beta cell function from fasting
insulin and fasting plasma glucose
levels. Diabetologia 1985; 28: 412-419
Am J Kid Dis, 2001; 38: 749-56
14. Tuzeu A, Bahceci M, Yilmaz E, Bahceci 
S. The comparison of insulin sensitivity
in non-diabetic hemodialysis patients
treated with and without recombinant
human erythropoietin. Horm Metab 
Res 2004; 36: 716-720
15. Fadda GZ, Massry SG. Impaired
glucose-induced calcium signal in
pancreatic islets in chronic renal failure. 
16. De Fronzo RA, Smith D. Is glucose
intolerance harmful for the uremic
patient. Kid Int.1985; 28: S88
17. Oh HY, Fadda GZ, Smogorzewski M, 
Liou HH, Massry SG. Phosphate
depletion impairs leucine-induced
insulin secretion. J Am Soc Nephrol 
1994; 5:1259-1265
18. Gallieni M, Cucciniello E, D’Amaro E. 
Calcium, phosphorus and PTH levels in 
the hemodialysis population: A multi
M, Amar M.. Hyperparathyroidism
secondary to renal insufficiency. 
Physiology, clinicoradiological aspects
55: 147-158


