THE ENDOCRINE STATUS OF THE REGULAR DIALYSIS PATIENT

R. M. LINDSAY, I. T. BOYLE, R. G. LUKE and A. C. KENNEDY

University Department of Medicine, Glasgow Royal Infirmary, Glasgow, United Kingdom

Certain endocrine changes in the patient undergoing regular dialysis treatment (R.D.T.) for chronic renal failure have been known for some time. Depression of gonadal function is common (Maher et al., 1965; Shaldon, 1966) and abnormalities of calcium metabolism with or without hyperparathyroidism (Shaldon, 1966) are not infrequent. In addition, gynaecomastia has been observed (Lindsay et al., 1967). As far as we are aware, however, no study has been carried out that applied a wide range of endocrinological parameters to a single group of such patients.

Preliminary data from such a study are presented here.

The clinical and biochemical data of the 9 patients (5 males, 4 females) are summarised in Table I. They each receive a minimum of two ten hour haemodialyses per week using 0.9 square meter cellophane coil (Chron-a-coil, Baxter). No patient has any clinical evidence of systemic disease unrelated to the renal failure.

**TABLE I**

*Clinical and biochemical data of R.D.T. patients*

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Duration of R.D.T. (months)</th>
<th>Average pre- and post-dialysis urea (mg%)</th>
<th>Other management</th>
<th>G.R.I.* score</th>
</tr>
</thead>
<tbody>
<tr>
<td>J.C.</td>
<td>21</td>
<td>M</td>
<td>21</td>
<td>140/46</td>
<td>40 g protein 22 mEq. Na diet warfarin FE + folic acid</td>
<td>A</td>
</tr>
<tr>
<td>T.S.</td>
<td>38</td>
<td>M</td>
<td>24</td>
<td>182/66</td>
<td></td>
<td>A</td>
</tr>
<tr>
<td>J.W.</td>
<td>36</td>
<td>M</td>
<td>21</td>
<td>147/42</td>
<td></td>
<td>B</td>
</tr>
<tr>
<td>M.D.</td>
<td>28</td>
<td>M</td>
<td>18</td>
<td>118/45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S.T.</td>
<td>21</td>
<td>M</td>
<td>7</td>
<td>155/65</td>
<td>(no warfarin)</td>
<td>B</td>
</tr>
<tr>
<td>H.B.</td>
<td>35</td>
<td>F</td>
<td>4</td>
<td>134/33</td>
<td>(no warfarin)</td>
<td>A</td>
</tr>
<tr>
<td>M.McC.</td>
<td>33</td>
<td>F</td>
<td>17</td>
<td>146/36</td>
<td></td>
<td>A</td>
</tr>
<tr>
<td>M.B.</td>
<td>34</td>
<td>F</td>
<td>11</td>
<td>103/36</td>
<td>(plus methyldopa)</td>
<td>C</td>
</tr>
<tr>
<td>M.H.</td>
<td>43</td>
<td>F</td>
<td>11</td>
<td>146/56</td>
<td></td>
<td>A</td>
</tr>
</tbody>
</table>

Diagnosis: Glomerulonephritis in all patients.


The study is made under the following headings—the thyroid, the hypothalamic-pituitary-adrenal axis, calcium metabolism, glucose tolerance, growth hormone secretion and gonadal function.
THE ENDOCRINE STATUS OF THE REGULAR DIALYSIS PATIENT

THE THYROID

The serum protein bound iodine (PBI\textsuperscript{131I}) was measured immediately pre- and post-dialysis in 8 of the 9 patients by the method of Farrell and Richmond (1961) (normal range for this laboratory is 3.3–7.3 µg/100 ml). The serum thyroxine binding capacity was measured by the \(T_3\) resin sponge uptake (Triosorb: Abbott Laboratories) pre- and post-dialysis on another occasion on 6 of the patients.

Studies on thyroidal inorganic iodide metabolism were carried out on 7 of the patients using methods described by Wayne et al. (1964) and Harden et al. (1965).

25 µC of \(^{131I}\) were administered orally to the fasting patient and thyroid uptakes were measured at 1 and 2.5 hours. As there was virtually no excretion of urine no correction was made for extrathyroidal radioactivity in the neck. The plasma radioactivity was measured 105 minutes after administration of the dose and, using a modified Carlson-Crittenden cup over one parotid duct, a 30 minute saliva collection was made commencing 90 minutes after the tracer dose was given.

The thyroid clearance of radiiodine (ml per min.) =

\[
\frac{\text{Thyroid uptake 2.5 hours (\% dose)} - \text{thyroid uptake 1 hour (\% dose)}}{\text{Plasma radioactivity (\% dose per ml)} \times \text{time between 2 uptakes (min.)}}
\]

The normal range is 3–58 ml/min.

The plasma inorganic iodine (PII) can be estimated from the specific activity of parotid salivary iodine (Harden et al., 1965) using the formula:

\[
\text{PII} = \frac{\text{Salivary I \times plasma }^{131I}}{\text{Salivary }^{131I}}
\]

The normal range for the PII is 0.04–0.6 µg/100 ml.

The absolute iodine uptake (AIU) by the thyroid is then given by the formula:

\[
\text{AIU} = (\text{Thyroid clearance } \times \text{PII} \times 0.6) \mu g/\text{hour}.
\]

The normal range is 0.5–6.0 µg/hour.

Results

Seven out of the 8 patients had serum protein bound iodines within the normal range (Table II). In each case there was a significant increase in the PBI\textsuperscript{131I} after dialysis, this increase being greater than could be accounted for by water loss during the dialysis. In 5 out of 6 patients the \(T_3\) resin sponge uptake after dialysis showed a mean increase of 10% over the pre-dialysis figures—all of which were within the normal range (25–35%). Once again this seems unlikely to account for the increase in PBI\textsuperscript{131I} over the dialysis period. With one exception the 7 patients studied had high and in several cases extremely high PII’s (Table III).

<table>
<thead>
<tr>
<th>Patient</th>
<th>PBI\textsuperscript{131I} (µg/100 ml)</th>
<th>% Rise PBI\textsuperscript{131I}</th>
<th>% Fall E.C.F. wt.</th>
</tr>
</thead>
<tbody>
<tr>
<td>J.C.</td>
<td>5.6</td>
<td>53</td>
<td>12</td>
</tr>
<tr>
<td>T.S.</td>
<td>2.1</td>
<td>42</td>
<td>5</td>
</tr>
<tr>
<td>J.W.</td>
<td>6.0</td>
<td>55</td>
<td>14</td>
</tr>
<tr>
<td>M.D.</td>
<td>7.0</td>
<td>22</td>
<td>7</td>
</tr>
<tr>
<td>S.T.</td>
<td>6.7</td>
<td>77</td>
<td>15</td>
</tr>
<tr>
<td>H.B.</td>
<td>4.1</td>
<td>122</td>
<td>27</td>
</tr>
<tr>
<td>M.B.</td>
<td>5.1</td>
<td>68</td>
<td>7</td>
</tr>
<tr>
<td>M.H.</td>
<td>3.5</td>
<td>26</td>
<td>14</td>
</tr>
</tbody>
</table>
TABLE III

*Inorganic iodide metabolism in R.D.T. patients*

<table>
<thead>
<tr>
<th>Patient</th>
<th>Thyroid clearance ml/min./1.73 m²</th>
<th>PII µg/100 ml</th>
<th>AIU µg/hr</th>
<th>R.D.T. (months)</th>
<th>Last venogram (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>J.C.</td>
<td>0</td>
<td>7.9</td>
<td>0</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>T.S.</td>
<td>2.8</td>
<td>2.4</td>
<td>4.1</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>J.W.</td>
<td>7.0</td>
<td>6.0</td>
<td>25.1</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>M.D.</td>
<td>2.8</td>
<td>0.78</td>
<td>4.0</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>M.D.</td>
<td>5.7</td>
<td>10.1</td>
<td>16.6</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>M. McC.</td>
<td>3.0</td>
<td>0.78</td>
<td>2.7</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>M. B.</td>
<td>48</td>
<td>3.87</td>
<td>7.0</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>M. H.</td>
<td>7.5</td>
<td>0.53</td>
<td>15.2</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>15.2</td>
<td>128.0</td>
<td>8.1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>19.0</td>
<td>172.0</td>
<td>—</td>
<td>5</td>
<td>1 week</td>
</tr>
</tbody>
</table>

Nevertheless, the levels are lower than those generally associated with iodide goitre. Iodide containing radio-opaque media used in venograms during shunt manipulations (see Table III) may contribute toward these levels. The thyroid clearance of radio-iodine was low or in the low normal part of the normal range in all but one of the patients. These results suggest that the normal reciprocal relationship between thyroid clearance and PII is relatively intact in patients undergoing R.D.T. and the AIU (Table III) is thus often kept within normal limits. The one marked exception to this is seen in patient M.H. in whom the tests were repeated only 1 week after she had received 10 ml of Hypaque for a venogram.

All the patients have remained euthyroid and no noticeable increase in thyroid size has occurred.

**THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS**

Seven of the 9 patients were studied under standard hospital ward conditions for a period of just over three days, the period of study commencing with a routine haemodialysis.

Plasma 'cortisol' was estimated immediately before and after this dialysis and on each of the following three consecutive days at a fixed time (6.00 p.m.). Plasma 'cortisol' was also measured at 11.00 p.m. on one of these days and at 9.00 a.m. on another. One Synacthen test (the 30 minute plasma 'cortisol' response to the intramuscular injection of 250 µg synthetic B₁-28 corticotrophin—Landon, 1964; Ward, 1965; Greig, 1966) was also performed.

On 3 other patients with chronic renal failure (creatinine clearance < 5 ml/min.), but not undergoing R.D.T., plasma 'cortisol' was measured at 11.00 p.m. and 9.00 a.m. on the next day. A morning Synacthen test was also performed.

All plasma 'cortisols' were measured as 11-OHCS by the fluorimetric method of Mattingly (1962).

**Results**

Figure 1 shows the plasma 'cortisol' levels (µg/100 ml) before and after dialysis and at 6.00 p.m. on days 1, 2 and 3. None of these 'cortisols' were below 5 µg/100 ml—the lower limit of normal (Greig *et al.*, 1967). There was no constant pattern of change of 'cortisol' levels in the period of study.

Figure 2 shows in 6 of the 7 patients a well-marked diurnal variation of plasma 'cortisol', suggesting an intact hypothalamic pituitary control of adrenal cortisol secretion (Perkoff *et al.*, 1959). Figure 2 also shows that in all the patients Synacthen caused a rise in the plasma 'cortisol' showing a normal adrenocortical reserve.
Several of the 'cortisol' levels obtained in these experiments are high. It is a characteristic effect of acute or chronic illness to produce higher than basal results (Greig et al., 1967) and, therefore, such levels are not surprising in the R.D.T. patient.

Finally, the intactness of the hypothalamic-pituitary-adrenal axis would not appear to be consequent upon successful haemodialysis; a well-marked diurnal variation and a normal response to Synacthen was found in the 3 control uraemic patients who were not dialysed.

CALCIUM METABOLISM

Only two aspects of calcium metabolism are considered in this communication.

The patients have been on a diet containing about 600 mg of calcium and 50–200 units of vitamin D daily. The bath water during dialysis contains calcium in a concentration of 2.5 mEq./l.

a. A measure of calcium absorption was obtained in 5 patients by administering 5 μC of Ca$^{47}$ together with 50 mg calcium carrier as calcium chloride in 20 ml water when fasting. Blood samples were taken at 1.5, 2.5 and 3.5 hours after oral administration of the dose. The samples were counted in an automatic well type scintillation counter with counting conditions excluding the daughter isotope Sc$^{47}$.

The counts were expressed as % dose per litre serum and by multiplying these by 15% of kg body weight an approximation of the % dose in the exchangeable calcium space was obtained.

b. Limited radiological surveys of the skeleton were made at six monthly intervals.
Results

a. The absorption of calcium appeared to be much impaired when contrasted with a control group of normal patients (Fig. 3). By comparison with similar data from 4 patients with chronic renal failure, who have since gone on the programme, it would appear that R.D.T. has not appreciably improved the efficiency of calcium absorption.

b. The radiological studies revealed 3 patients with classical radiological features of osteitis fibrosa cystica and/or osteomalacia. Another 3 patients (T.S., M.D., and M.McC.) have developed a multicystic honeycombed appearance of the bone structure of at least one

![Graph showing radiocalcium (Ca⁴⁺) absorption curves.](image)

*Fig. 3.* Radiocalcium (Ca⁴⁺) absorption curves.

![X-ray image of humerus showing multicystic honeycombed appearance.](image)

*Fig. 4.* X-ray of humerus of patient M.D. showing multicystic honeycombed appearance.
humerus (Fig. 4). No adequate explanation for these latter changes is available. They may, however, be related to increased limb blood flow due to the arteriovenous shunt.

Our calcium studies lead us to favour an increase in either the dietary calcium or the calcium concentration in the bath.

**GLUCOSE TOLERANCE**

Intravenous glucose tolerance tests were carried out in 8 of the 9 patients before starting regular dialysis treatment and at 3-6 month intervals thereafter. Twenty-five grams of glucose were infused over 4 minutes after taking a fasting venous sample; further samples were taken at 10, 20, 30, 45 and 60 minutes from midpoint of the infusion. Plasma glucose was measured by a glucose oxidase method (Huggett and Nixen, 1957) and plasma insulin by the method of Hales and Randle (1963). There was no family history of diabetes in the patients studied, all patients had a diet containing at least 200 g carbohydrate for at least three days prior to the test and a 12 hour fast was instituted before the test. After dialysis treatment was begun, glucose tolerance tests were carried out either the day before or the morning before a dialysis. Glucose tolerance was assessed by calculation of a K value for each test by the method of Lundbaek (1962)*.

**Results**

Regular dialysis treatment restored glucose tolerance, which was severely impaired before dialysis treatment, to normal in all patients; the changes are highly significant (Table IV). The values for K in Table I are the latest observed, but in all patients K values were normal after 3 months' dialysis and have remained normal; in the patient observed over the longest period 5 tolerance tests carried out over a 2 year period have been well within the normal range.

Plasma insulin levels after dialysis treatment were higher at 10 and 20 minutes after glucose infusion but the changes were not significant (Table V).

**TABLE IV**

<table>
<thead>
<tr>
<th>Intravenous glucose tolerance tests in 8 patients on regular dialysis treatment for a mean period of 12 months (range 3-24 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>K value</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>Pre-dialysis</td>
</tr>
<tr>
<td>Post-dialysis</td>
</tr>
<tr>
<td>p value</td>
</tr>
</tbody>
</table>

* K value < 0.95.
** Mean ± S.E.M.

**TABLE V**

Plasma insulin values (μU/ml) during intravenous glucose tolerance tests before and after commencing R.D.T.*

<table>
<thead>
<tr>
<th></th>
<th>Fasting</th>
<th>10 min.</th>
<th>20 min.</th>
<th>30 min.</th>
<th>45 min.</th>
<th>60 min.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>31 ± 7**</td>
<td>96 ± 17</td>
<td>88 ± 18</td>
<td>87 ± 19</td>
<td>64 ± 12</td>
<td>54 ± 14</td>
</tr>
<tr>
<td>After</td>
<td>34 ± 6</td>
<td>136 ± 19</td>
<td>109 ± 13</td>
<td>84 ± 12</td>
<td>60 ± 11</td>
<td>45 ± 7</td>
</tr>
</tbody>
</table>

* Glucose tolerance tests as in Table IV.
** Mean ± S.E.M.

* K = \frac{6.693}{t_0} where t_0 = time in minutes for a blood sugar plotted logarithmically to fall by half (diabetic K is less than 0.95; non-diabetic K is greater than 1.05; mean normal K is 1.72).
Regular dialysis treatment restores glucose tolerance, commonly severely impaired in uraemia, to normal and maintains it at normal, at least in the period of observation reported in these studies. Glucose tolerance was normal by 3 months after starting dialysis treatment; Hawkes et al. (1966) have shown that this change may occur within 1–2 weeks of treatment. The statistically significant change in glucose tolerance without significant change in plasma insulin levels supports our previously stated view (Briggs et al., 1967; Luke et al., 1968) that the abnormality of glucose metabolism in uraemia is due to the accumulation of a dialysable antagonist(s) to insulin.

GROWTH HORMONE SECRETION

Five patients with chronic renal failure were studied under normal hospital conditions, 4 of these were of the 9 R.D.T. patients. The fifth was a patient about to start R.D.T. (creatinine clearance 5 ml/min.). The plasma growth hormone was measured for 5 hours at half hour intervals following a loading dose of 25 g glucose given intravenously. The patients were resting in bed during the test and had completed an overnight fast immediately prior to the administration of the glucose. In all cases at least 48 hours had elapsed since dialysis. The plasma growth hormone was measured by the method of Hunter and Greenwood (1964) and expressed in nanograms of the Raben preparation (Raben, 1959) per ml of plasma. Blood was withdrawn through an arteriovenous shunt with minimal stress to the patients.

Results

It has been shown (Roth et al., 1963) that glucose suppresses growth hormone secretion and that this suppression is followed 2 to 3 hours later by a secondary rise in plasma growth hormone levels.

Four of the 5 patients showed an abnormal response. Three of these showed no secondary rise of growth hormone following suppression by the glucose load. The fourth patient showed a rise in growth hormone immediately following the glucose. This last response is thought to represent a stress reaction since this patient’s arteriovenous shunt was leaking during the first part of the test.

The fifth patient showed a response which was within normal limits. It is interesting to note that this patient has not been dialysed whereas the other patients are all on R.D.T.

GONADAL FUNCTION

Of the 5 males, 4 have experienced return of libido and potency which was absent before R.D.T. Three patients are married and have normal sexual activity. Only one patient remains relatively impotent after 24 months of uncomplicated R.D.T. There is no evidence of testicular atrophy in these patients. They are, however, sterile. In 4 of the patients sperm examination has been carried out on at least two occasions. The greatest volume of ejaculate obtained was 0.8 ml and the greatest sperm count was $10.9 \times 10^6$/ml and in this collection only 44% were motile. All 5 have also experienced transient gynaeacomastia occurring soon after the commencement of R.D.T. It is interesting that one of these 5 had transient gynaeacomastia before R.D.T. and this has reappeared. Details of this phenomenon in these patients have been reported elsewhere (Lindsay et al., 1967).

All 4 of the female subjects show occasional vaginal bleeding for varying lengths of time. There has been no return to a regular menstrual cycle. We have, for a short time only, been observing daily basal body temperatures and performing regular vaginal cytological examinations. As yet there is no indication that ovulation takes place.

Pituitary gonadotrophins which are known to be depressed in chronic renal failure (Paulsen, 1962) do not seem to reappear. Urinary total gonadotrophins were less than 3 HMG units/24 hours in all the patients (the normal adult range being 5–23 in males, 3–30 in females by the method of Loraine and Brown, 1959).
THE ENDOCRINE STATUS OF THE REGULAR DIALYSIS PATIENT

CONCLUSIONS

It would appear that the regular dialysis patient has no clinical problem with regard to function of the thyroid gland and of the hypothalamic-pituitary-adrenal axis, although some minor abnormalities may be present at a biochemical level.

Regular dialysis treatment improves glucose tolerance. Abnormalities, however, persist with regard to gonadal function and calcium metabolism.

An abnormality in growth hormone secretion may be present.

ACKNOWLEDGEMENTS

We would like to thank the following for their continuing help and advice in this study: Dr. M. Webster (plasma growth hormone estimations); Dr. J. Mowat (plasma cortisol estimations); Dr. H. Hughes (vaginal cytology); Dr. M. T. McKiddie and Miss I. Hunter (plasma insulin estimations); Dr. M. Grant (radiology); Miss H. Mitchell and Miss J. Brown (thyroid and calcium studies); Mr. D. Hay (examination of seminal fluid); Miss O. McLeod and the nursing staff of the Renal Unit.

REFERENCES


