ABNORMAL RESPONSE OF LUTEINIZING HORMONE, FOLLICLE STIMULATING HORMONE AND TESTOSTERONE TO LUTEINIZING HORMONE-RELEASING HORMONE IN CHRONIC RENAL FAILURE

By

Koichi Hasegawa¹, Yoshiki Matsushita¹, Kenzo Hirai¹, Seima Otomo¹, Teruo Okamoto², Hirotoshi Morii² and Masahisa Wada²

ABSTRACT

Serum levels of LH, FSH, testosterone and oestradiol were measured by radioimmunoassay in 10 healthy subjects and 7 undialysed and 15 dialysed patients with chronic renal failure. The basal level of serum LH was significantly higher in patients with chronic renal failure than in healthy subjects. The basal level of serum FSH in male subjects was significantly higher in dialysed patients with chronic renal failure than in healthy subjects. Regarding testosterone secretion in male subjects and oestradiol secretion in female subjects, it was shown that the basal level of serum testosterone was significantly lower in patients with chronic renal failure than in healthy subjects, and that serum oestradiol levels were within the normal range in most of the patients with chronic renal failure. Serum levels of LH, FSH and testosterone were determined after iv injection of 100 µg of LH-RH in three groups of subjects. Responses of serum LH and FSH to LH-RH were exaggerated and prolonged in patients with chronic renal failure compared with healthy subjects. The peaks of serum LH and FSH were observed 30 min after LH-RH injection in healthy subjects while those in chronic renal failure appeared at 60 to 120 min. The levels of serum testosterone after LH-RH injection did not change within 120 min.

These findings may indicate that the pituitary gonadotrophin response to LH-RH is abnormal and that the turnover of LH, FSH and LH-RH is decreased in patients with chronic renal failure.
In recent years, various types of endocrine abnormalities, such as amenorrhoea and impotence (Maher et al. 1965), metrorrhagia (Lindsay et al. 1968), gynaecomastia (Lindsay et al. 1967), galactorrhoea (Nagel et al. 1973), goitre (Ramirez et al. 1973), exophthalmos (Schmidt et al. 1971) and abnormal secretion of GH in response to glucose loading (Samaan & Freeman 1970) have been observed in patients with chronic renal failure. These abnormalities appear to be one of the causes of the hazards in the rehabilitation of the patients.

Since it was demonstrated that responses of TSH and GH to TRH in patients with chronic renal failure were abnormal (Hasegawa et al. 1975), luteinizing hormone-releasing hormone (LH-RH) test was performed and serum LH, FSH and testosterone were determined before and after administration of LH-RH in patients with chronic renal failure.

**PATIENTS AND METHODS**

Ten healthy subjects (5 men and 5 women, ages 21 to 45 years), 7 undialysed patients (3 men and 4 women, ages 26 to 50 years) and 15 patients (8 men and 7 women, ages 22 to 50 years) with chronic renal failure undergoing haemodialysis at the Shirokita Municipal Hospital, Osaka, Japan were investigated in the study. Haemodialysis was usually performed two or three times a week. The period of haemodialysis before the test ranged from 8 to 48 months. Low protein (20 g/day), low salt (3 g/day) and high calorie (2000 cal./day) diet was prescribed for undialysed patients, and dietary protein content was 1.2 g/kg body weight per day in dialysed patients. Synthetic LH-RH was supplied by Tanabe Seiyaku Co., Ltd., Japan and administered intravenously in a dose of 100 µg, dissolved in 10 ml of saline.

Healthy subjects and patients were fasted overnight and the bed rest was maintained before and during the tests. LH-RH test was performed during the period of 12 to 30 h after haemodialysis with regard to dialysed patients and during the follicular phase in subjects during menstruation.

Serum LH, FSH and testosterone were determined before and 30, 60, 120 min after LH-RH injection, and serum oestradiol only before LH-RH injection. LH and FSH were determined by the method of double antibody radioimmunoassay (Odell et al. 1967; Midgley 1967), testosterone by the modified method of Furuyama et al. (1970) and oestradiol by the modified method of Abraham (1969). In our laboratory the minimum detectable level of both LH and FSH was 2.0 mIU/ml, and that of both testosterone and oestradiol was 20 pg/ml. While some patients under treatment with haemodialysis were given furosemide, some of the undialysed patients received furosemide, reserpine or thiazide for the treatment of hypertension.

**RESULTS**

The basal level of serum LH in both male and female subjects was significantly higher in undialysed and dialysed patients with chronic renal failure than in healthy subjects, but the level in dialysed patients with chronic renal failure was not significantly higher than that in undialysed patients. Responses
Table 1.
Effect of a 100 μg LH-RH injection on serum LH in healthy subjects and in patients with chronic renal failure. (Mean ± se).

<table>
<thead>
<tr>
<th>Sex</th>
<th>Subjects</th>
<th>No. of subject</th>
<th>LH (mIU/ml) response to LH-RH injection</th>
<th>Maximum LH (mIU/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>0'</td>
<td>30'</td>
</tr>
<tr>
<td>Healthy</td>
<td>Male</td>
<td>5</td>
<td>12.4 ± 1.3</td>
<td>111.1 ± 31.8</td>
</tr>
<tr>
<td></td>
<td>Undialysed</td>
<td>3</td>
<td>67.1 ± 23.9</td>
<td>236.0 ± 85.2</td>
</tr>
<tr>
<td></td>
<td>Dialysed</td>
<td>8</td>
<td>102.8 ± 26.7</td>
<td>240.1 ± 59.1</td>
</tr>
<tr>
<td>Healthy</td>
<td>Female</td>
<td>5</td>
<td>11.3 ± 1.4</td>
<td>35.4 ± 3.1</td>
</tr>
<tr>
<td></td>
<td>Undialysed</td>
<td>4</td>
<td>27.8 ± 3.17</td>
<td>107.4 ± 13.7</td>
</tr>
<tr>
<td></td>
<td>Dialysed</td>
<td>7</td>
<td>72.4 ± 19.57</td>
<td>175.9 ± 49.4</td>
</tr>
</tbody>
</table>

1) \( P < 0.05 \)  2) \( P < 0.02 \)  3) \( P < 0.01 \) (vs. healthy male subjects at the same time).
4) \( P < 0.05 \)  5) \( P < 0.02 \)  6) \( P < 0.01 \)  7) \( P < 0.001 \) (vs. healthy female subjects at the same time).
Table 2.
Effect of a 100 μg LH-RH injection on serum FSH in healthy subjects and in patients with chronic renal failure. (Mean ± se).

<table>
<thead>
<tr>
<th>Sex</th>
<th>Subjects</th>
<th>No. of subject</th>
<th>FSH (mIU/ml) response to LH-RH injection</th>
<th>Maximum FSH (mIU/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>0'</td>
<td>30'</td>
</tr>
<tr>
<td>Male</td>
<td>Healthy</td>
<td>5</td>
<td>11.9 ± 2.3</td>
<td>22.9 ± 4.4</td>
</tr>
<tr>
<td></td>
<td>Undialysed</td>
<td>3</td>
<td>12.5 ± 6.7</td>
<td>18.1 ± 7.6</td>
</tr>
<tr>
<td></td>
<td>Dialysed</td>
<td>8</td>
<td>45.3 ± 10.8*</td>
<td>64.2 ± 19.9</td>
</tr>
<tr>
<td>Female</td>
<td>Healthy</td>
<td>5</td>
<td>11.3 ± 1.0</td>
<td>18.4 ± 1.7</td>
</tr>
<tr>
<td></td>
<td>Undialysed</td>
<td>4</td>
<td>12.7 ± 2.0</td>
<td>15.9 ± 4.7</td>
</tr>
<tr>
<td></td>
<td>Dialysed</td>
<td>7</td>
<td>11.5 ± 0.9</td>
<td>14.8 ± 1.5</td>
</tr>
</tbody>
</table>

* P < 0.05 (vs. healthy male subjects at 0 min).
of serum LH to LH-RH were exaggerated and prolonged in patients with chronic renal failure compared with healthy subjects. The peaks of serum LH were observed at 30 min after LH-RH injection in healthy subjects while those in chronic renal failure appeared at 60 to 120 min (Table 1).

The basal level of serum FSH in male subjects was significantly higher in dialysed patients with chronic renal failure than in healthy subjects, but the level in male subjects was not significantly different between undialysed patients and healthy subjects. In female subjects there was no significant difference between the level in patients with chronic renal failure and that in healthy subjects. Responses of serum FSH to LH-RH in patients with chronic renal failure were exaggerated and prolonged compared with healthy subjects. The peaks in serum FSH were observed at 30 min after LH-RH injection in healthy subjects while those in patients with chronic renal failure occurred at 60 to 120 min (Table 2).

The basal level of serum testosterone in male subjects was significantly lower in patients with chronic renal failure than that in healthy subjects, but the difference in the basal levels was not significant between undialysed and dialysed patients with chronic renal failure. The levels of testosterone after LH-RH injection slightly increased in healthy subjects, but no change occurred within 120 min in undialysed and dialysed patients with chronic renal failure (Table 3). A significant inverse correlation was noted between the serum testosterone basal level and serum LH basal level in 6 undialysed and 10 dialysed patients (Fig. 1).

**Table 3.**
Effect of a 100 μg LH-RH injection on serum testosterone in healthy subjects and in patients with chronic renal failure. (Mean ± se).

<table>
<thead>
<tr>
<th>Subjects</th>
<th>No. of subject</th>
<th>Testosterone (ng/ml) response to LH-RH injection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0'</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy</td>
<td>5</td>
<td>5.16 ± 0.34</td>
</tr>
<tr>
<td>Undialysed</td>
<td>3</td>
<td>3.65 ± 0.28</td>
</tr>
<tr>
<td>Dialysed</td>
<td>8</td>
<td>3.05 ± 0.34</td>
</tr>
</tbody>
</table>

1) *P* < 0.05  2) *P* < 0.02  3) *P* < 0.01
4) *P* < 0.001 (vs. healthy subjects at the same time).
5) *P* < 0.01 (vs. undialysed patients at 30 min).
Correlation between serum testosterone and serum LH in male patients and serum oestradiol and serum FSH in female patients with chronic renal failure.

The serum oestradiol level in female subjects was within the normal range in all 3 undialysed patients and 4 of 7 dialysed patients. There was a significant inverse correlation between serum oestradiol basal level and serum FSH basal level (Fig. 1).

**DISCUSSION**

It was demonstrated in the present study that the basal level of serum LH was significantly higher in patients with chronic renal failure than in healthy subjects. Regarding FSH secretion, it was shown that the basal level of serum FSH in male subjects was significantly higher in dialysed patients with chronic renal failure than in healthy subjects. However, Guevara et al. (1969) reported that patients receiving intermittent haemodialysis showed higher serum levels of LH compared with normals, uraemic patients not receiving dialysis, and patients on peritoneal dialysis, while no significant alterations in FSH were observed in these groups. Stewart-Bentley et al. (1974) also reported that the baseline of serum LH was increased in the uraemic state, while FSH level was normal, and that dialysis did not significantly alter the serum immunoassayable gonadotrophin levels. Distiller et al. (1975) also demonstrated
that the mean basal LH levels in both haemodialysis and peritoneal dialysis patients were significantly elevated as compared to the control groups, and that the mean basal FSH levels were not significantly different from that of the control groups.

With regard to the higher basal levels of both LH and FSH in patients with chronic renal failure compared with healthy subjects, the possibilities of a lowered ability of renal tissue to inactivate LH and FSH, or a decreased renal excretion of LH and FSH should be considered. Kretser et al. (1973) reported that the plasma half-life of $^{131}$I-labelled LH in nephrectomized ewe maintained on haemodialysis was prolonged compared with that in the normal ewe, and that incubation of $^{131}$I-labelled LH with rat renal homogenates for 90 min failed to destroy its immunological reactivity. Christiansen (1972) reported that urinary excretion of LH ranged from 6.2 to 8.5 IU/day, and that of FSH from 5.3 to 13.7 IU/day by bioassay in normal adult men.

Since it is probable that the hypothalamic-pituitary-gonadal axis is operating in chronic renal failure in view of inverse correlations between serum testosterone and LH and between serum oestradiol and FSH, low levels of testosterone could be a factor in increasing serum LH and FSH levels. But Lim & Fang (1975) reported that male patients with chronic renal failure undergoing haemodialysis showed normal gonadotrophin (Lim & Fang 1975) and testosterone (Lim & Fang 1976) responses to clomiphene, suggesting that storage as well as release of both hypothalamic-pituitary hormones were normal.

Low levels of plasma testosterone have been reported in uraemic male subjects (Guevara et al. 1969; Lim & Fang 1975). Since a diminished number of Leydig cells and loss of libido and potency in uraemic males have been observed, it seemed important to evaluate their testosterone levels. Our data also suggest that uraemia may be associated with defective production of testosterone by the Leydig cells. Distiller et al. (1975) noted that the size of testis is closely related to FSH levels in chronic renal failure. Basal levels of serum FSH were normal in female patients. Most of the serum oestradiol levels were also within normal range in female patients with chronic renal failure.

It is possible that the procedure of dialysis may not have influenced the basal level of serum LH and FSH, while their molecular weights are 26 000 and 36 000, respectively, and may not be dialysable.

Exaggerated and prolonged responses of serum LH and FSH to LH-RH were consistent findings in patients with chronic renal failure. The peaks in serum LH and FSH were observed at 30 min after LH-RH administration in healthy subjects while those in chronic renal failure appeared at 60 to 120 min. However, Stewart-Bentley et al. (1974) reported that LH-RH caused a 2- to 3-fold rise in serum LH in 2 uraemic men on chronic haemodialysis. Schalch
et al. (1975) claimed that significant elevations in serum LH and FSH levels persisted in the patients with chronic renal failure during the second and third hours after the administration of LH-RH, although the peak levels of LH and FSH in patients with chronic renal failure were not significantly different from those in normal controls after the administration of LH-RH. Distiller et al. (1975) reported that the gonadotrophin responses to LH-RH showed a very marked LH response with a delayed return to normal in both haemodialysis and peritoneal dialysis patients, and that no significant alteration in FSH level was observed.

Regarding the prolonged effect of LH-RH, a decreased renal excretion of LH-RH and a decreased inactivation of LH-RH by renal tissue should be considered. It was shown that when [3H]LH-RH was injected intravenously into experimental animals, the majority of labelled LH-RH and its metabolic products accumulated in the liver and kidney (Redding & Schally 1973; Miyachi et al. 1973). Redding et al. (1973) reported that after an intravenous injection of [3H]LH-RH into normal subjects, no intact [3H]LH-RH was excreted in the urine whereas 73.5% of the injected radioactivity was excreted within 24 h as metabolites of LH-RH. Pimstone et al. (1977) showed that a significant prolongation of half-life and lowering of the metabolic clearance rate of gonadotrophin releasing hormone was found in patients with severely impaired renal function. A decrease in serum LH and FSH inactivation in the kidney and a decrease in the urinary excretion of LH and FSH may also have been contributory factors.

While the similar exaggerated and prolonged responses of gonadotrophin to LH-RH were reported in hypergonadotrophic patients with amenorrhoea (Keller et al. 1975), oestrogen levels were almost normal in female patients thus involving a different mechanism of abnormal responses.

REFERENCES


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