Interrelations Among Amenorrhea, Serum Gonadotropins and Body Weight in Anorexia Nervosa

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Abstract

Seventeen women with anorexia nervosa were studied before and during weight gain. The mean body weight was 93.8% before onset of illness, 82.9% at the beginning of amenorrhea and 61.8% at the minimum weight, each expressed as a percentage of the standard weight (SW). Basal serum LH and FSH level were significantly low in the lower weight patients, and increased with weight gain, with a linear correlation to the percent of SW. The LH response to 100 μg of LH-RH was impaired in the lower weight group, and was improved with weight gain. The LH response in those whose weight had increased to 70% or more of the SW was often excessive and the maximum levels were significantly higher than in normal women. The FSH response to LH-RH was well maintained even in the lower weight group, but the maximum response was delayed. There was a significant correlation between improvement in the LH response and weight gain, but no significant correlation was found between FSH response and body weight. Menstrual cycles were restored in some who showed 100 mIU/ml or more of the maximum LH response, but no definite relationship was found between LH or FSH response and the resumption of menstruation. Though the weights at the cessation and at the resumption of menstruation differed from case to case, the two weight levels were almost the same in each individual. These results indicate that the critical body weights for maintaining menstrual cycle are inconsistent and that the resumption of menstruation may not be accounted for only by the recovery of such a tonic regulation as seen in the responsiveness to LH-RH following weight gain but by the restoration of the individual critical weight.

Amenorrhea is one of the most prominent manifestations of anorexia nervosa. A number of studies have shown that these patients have low basal gonadotropin levels and blunted responsiveness to LH-RH (Aono et al., 1975; Frankel & Jenkins, 1975; Garfinkel et al., 1975; Halmi & Sherman, 1975; Palmer et al., 1975; Sherman et al., 1975; Warren et al., 1975; Beumont et al., 1976; Maeda et al., 1976; Travaglini et al., 1976; Vigersky et al., 1976; Hurd II et al., 1977). These gonadal dysfunctions are generally considered to be induced by hypothalamic disorders, but whether this phenomenon is simply a result of weight loss or a part of more essential and primary disorders related to this disease is still controversial. Some previous reports have shown the correlation between gonadal functions and body weight in anorexia nervosa.
nervosa (Sherman et al., 1975; Warren et al., 1975; Beumont et al., 1976; Vigersky et al., 1976) or the relationship between the occurrence of amenorrhea and body weight (Beck & Brochner-Mortensen, 1954; Kay & Leigh, 1954; Halmi, 1974; Hurd II et al., 1977). However, the results have not always been consistent. Furtheremore, very few studies have been made on the relationship between chronological changes in body weight, gonadal functions and amenorrhea, especially in individual cases.

In order to elucidate the relationship between body weight and gonadal functions or amenorrhea in anorexia nervosa, basal levels of serum gonadotropins and the responsiveness to LH-RH were studied and analyzed in various body weight groups, and they were also investigated chronologically in the same individuals.

Patients and Methods

Seventeen Japanese women, who were admitted in the metabolic ward of our medical department, were studied. They fulfilled all the following diagnostic criteria of anorexia nervosa: 1) weight loss of at least 25% of the standard weight (SW); 2) amenorrhea of at least 3 month's duration; 3) evidence of severe anorexia or abnormalities in eating behavior; 4) no evidence of organic illness or major psychiatric disorder which could account for weight loss or anorexia; 5) onset of symptoms before 25 years old. The age of the patients ranged from 14 to 28 years with mean of 20.5. The clinical features are summarized in Table 1.

Serum luteinizing hormone (LH) and follicle stimulating hormone (FSH) were measured by a double antibody radioimmunoassay method using a kit manufactured by Dai-ichi Radioisotope Laboratories (Tokyo). These reagents were provided by Carbiochem Ltd., California. The second IRP-HMG was employed as the standard. The minimum detectable amounts were 0.5 mIU/ml of LH and 1.0 mIU/ml of FSH. The mean immunologic potency of human pituitary standard, LER-907, was 255.0 mIU/ug in the LH assay and 40.5 mIU/ug in the FSH assay. The withinassay coefficient of variations in the normal female was 9.0% in the LH assay and 13.3% in the FSH assay. The between-assay coefficient of variations was 13.0% in the LH assay and 14.3% in the FSH assay (Aono et al., 1974).

LH-RH tests were performed on all 17 patients. Some cases were studied repeatedly during the weight gain. After overnight fasting, 100 μg of synthetic LH-RH (Dai-ichi Pharmaceutical Co., Tokyo or Tannabe Pharmaceutical Co., Osaka) was injected i.v.

Table 1. Clinical features of 17 cases of anorexia nervosa

<table>
<thead>
<tr>
<th>Case</th>
<th>Age yr.</th>
<th>Duration of amenorrhea prior to admission (Months)</th>
<th>Height cm</th>
<th>Body weight kg (% of standard weight)</th>
</tr>
</thead>
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<tr>
<td>No. 1</td>
<td>23</td>
<td>25</td>
<td>154</td>
<td>56 (106.7) 52 (99.0) 35 (66.7)</td>
</tr>
<tr>
<td>2</td>
<td>22</td>
<td>19</td>
<td>148</td>
<td>48 (96.6) 48 (96.6) 29 (58.4)</td>
</tr>
<tr>
<td>3</td>
<td>17</td>
<td>18</td>
<td>155</td>
<td>54 (101.9) 45 (84.9) 33 (62.2)</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>20</td>
<td>152</td>
<td>47 (91.3) 46 (89.3) 29 (56.3) 51 (99.0)</td>
</tr>
<tr>
<td>5</td>
<td>16</td>
<td>6</td>
<td>146</td>
<td>47 (97.9) 40 (83.3) 32 (66.7) 40 (83.3)</td>
</tr>
<tr>
<td>6</td>
<td>17</td>
<td>12</td>
<td>153</td>
<td>45 (86.5) 45 (86.5) 34 (65.4)</td>
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<tr>
<td>7</td>
<td>21</td>
<td>35</td>
<td>150</td>
<td>50 (99.0) 50 (99.0) 32 (63.4)</td>
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<tr>
<td>8</td>
<td>14</td>
<td>3</td>
<td>153</td>
<td>50 (96.2) 48 (92.3) 35 (67.3) 52 (100.0)</td>
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<tr>
<td>9</td>
<td>23</td>
<td>7</td>
<td>160</td>
<td>50 (89.4) 33 (59.0) 30 (53.7)</td>
</tr>
<tr>
<td>10</td>
<td>28</td>
<td>12</td>
<td>148</td>
<td>46 (92.6) 35 (70.4) 25 (50.3) 37 (74.4)</td>
</tr>
<tr>
<td>11</td>
<td>21</td>
<td>25</td>
<td>150</td>
<td>46 (91.1) 41 (81.2) 32 (63.4)</td>
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<tr>
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<td>26</td>
<td>17</td>
<td>159</td>
<td>55 (99.5) 49 (88.6) 38 (68.0)</td>
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<tr>
<td>13</td>
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<td>153</td>
<td>42 (80.8) 35 (67.3) 32 (63.5)</td>
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<tr>
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<td>21</td>
<td>50</td>
<td>159</td>
<td>54 (97.6) 43 (77.8) 33 (59.7)</td>
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<tr>
<td>15</td>
<td>17</td>
<td>3</td>
<td>156</td>
<td>55 (102.8) 44 (82.2) 38 (71.0)</td>
</tr>
<tr>
<td>16</td>
<td>22</td>
<td>5</td>
<td>149</td>
<td>38 (76.0) 36 (71.9) 27 (53.9) 38 (76.0)</td>
</tr>
<tr>
<td>17</td>
<td>18</td>
<td>9</td>
<td>154</td>
<td>46 (87.6) 42 (80.0) 32 (60.9) 43 (81.9)</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>20.5 ± 3.7</td>
<td>17.1±12.4</td>
<td>52.9±4.2</td>
<td>48.8±5.0 43.1±5.7 32.1±3.5</td>
</tr>
</tbody>
</table>
around 9:00 a.m. and blood samples were collected at 0, 15, 30, 60 and 120 min after the injection. In 5 patients whose menstrual cycles had returned during the study, LH-RH tests were performed during the early or mid-follicular phase (day 3–9).

The evaluation of the basal LH and FSH levels and the response to LH-RH was made on the basis of the value in 10 normal cyclic women aged 21 to 31 years in the follicular phase, as reported by Aono et al. (1974). The mean (±SD) of basal levels was 12.4±4.1 mIU/ml in LH, and 10.8±2.3 mIU/ml in FSH. The mean (±SD) of maximum levels was 40.4±16.2 mIU/ml at 30 min in LH and 20.3±8.5 mIU/ml at 60 min in FSH. The mean (±SD) of individual maximum responses (peak values) was 42.1±17.1 mIU/ml in LH and 21.8±9.1 mIU/ml in FSH.

When the relationship between body weight and gonadal functions was analyzed, the body weight was expressed as a percentage of the individual standard weight (SW), which referred to the average weight of Japanese female individuals of the same height and derived from the table reported by Matsuki (1974).

Results

Correlation between body weight and amenorrhea (Table 1, Fig. 1, 2)

Body weight before the onset of illness ranged from 38 to 56 kg and the mean ± SD was 48.8±5.0 kg (93.8±8.0% of SW), indicating that the patients had originally been average or slightly emaciated women. The weight at the beginning of amenorrhea ranged from 33 to 52 kg and the mean ± SD was 43.1±5.5 kg (82.9±10.7% of SW), whereas the weight at the minimum ranged from 25 to 38 kg and the mean ± SD was 32.2±3.4 kg (61.8±5.8% of SW). In contrast with the mean decrement of 16.6 kg (39.2% of SW) at the minimum weight, it was only 5.7 kg (17.1% of SW) at the cessation of menstruation.

Fig. 1 shows the chronological change in each body weight from the original to the minimum levels. The relationship between body weight and the onset of amenorrhea was different in each case, and no definite correlation was noted. However, of all 17 patients, amenorrhea occurred without any weight loss in 3 patients and with a slight weight loss of less than 5 kg in 6 patients. The occurrence of amenorrhea after a severe weight loss of more than 10 kg was seen only in 4 of 17 patients (Fig. 1).

During the present study, 6 patients recovered regular menstrual cycles. Fig. 2 shows the chronological change in their body weight. The weight at the cessation and at the resumption of menstruation varied, but both values were comparable in each individual.
Correlation between body weight and basal gonadotropin levels (Fig. 3)

Basal levels of serum LH and FSH were measured in each patient at various body weights. Some cases were studied twice or more at different body weights. Fig. 3 shows the correlation between each serum gonadotropin level and per cent of SW. Both LH and FSH levels were almost non-detectable or very low when the weight was below 59% of SW, and increased in proportion to the increase of the body weight. There were significant correlation between the degree of weight gain and basal gonadotropin levels. Two of the underweight patients who had gained weight [case 10: 26 kg (52%) to 37 kg (74%), case 16: 27 kg (55%) to 34 kg (68%)] showed extremely high basal LH levels. Except for these two cases, the mean (±SE) basal LH level for the patients below 79% of SW was significantly (p<0.001) lower than the value in the normal women (4.0±1.0 vs. 12.4±1.3 mIU/ml). Basal FSH levels showed a linear increase corresponding with the weight gain, and the coefficient of correlation was higher than that of LH (Fig. 3). The mean (±SE) basal FSH level for the patients below 79% of SW was also significantly (p<0.001) lower than the value for the normal women (4.7±1.0 vs. 10.8±0.7 mIU/ml). When body weight was more than 80% of SW, both mean (±SE) basal LH and FSH levels (17.3±4.5 mIU/ml and 11.8±1.0 mIU/ml, respectively) were slightly but insignificantly higher than the value in the normal women.

Correlation between body weight and gonadotropin responses to LH-RH (Figs. 4–6).

The response of gnadotropins to 100 μg of LH-RH was studied in various body weight groups. Some patients were studied repeatedly throughout their clinical courses. As to the response of LH to LH-RH, all patients below 59% of SW showed very poor responses. In the 60–69% weight group, 3 patients also showed a poor response or none at all, 3 other patients showed responses within normal limits but delayed and the remaining one showed an excessive response. In the last case (#16) this test was performed just after her weight had increased from 27 kg (55%) to 34 kg (68%). When body weight was more than 70% of SW, all patients showed good responses to LH-RH. Three of 7 cases in the 70–79% weight group and all 6 cases at 80% or more of SW showed an excessive response to LH-RH (Fig. 4). The mean (±SE) LH response in each weight group is shown in Fig. 5. There was a good correlation between the weight gain and the improvement in the LH response to LH-RH. The maximum LH level (mean ± SE)
Fig. 3. Correlation between body weight and the basal levels of serum LH and FSH. Body weights are expressed as a percentage of the standard weight (SW). Some data in Figs. 3-6 were obtained from a single case at different body weights.

for the group below 59% of SW was significantly (p<0.01) lower, and those for the 70-79% weight group and 80% or more weight group were significantly (p<0.05 and p<0.001, respectively) higher than in the normal women (Fig. 5). A significant correlation was noted between an increase in LH to LH-RH and body weight gain. The coefficient of correlation was 0.66 (p<0.001) (Fig. 6).

In contrast to LH, serum FSH responded constantly to LH-RH and this was unrelated to the degree of weight loss. Even though the basal FSH levels were significantly low in the group of below 59% and 60-69% of SW (p<0.001, each), the responses to LH-RH were within normal limits. The maximum FSH values (mean $\pm$ SE) for these groups (16.0$\pm$ 3.5 mIU/ml and 14.0$\pm$ 3.7 mIU/ml at 120 min, respectively) did not significantly differ from that for the normal women (20.3$\pm$ 2.7 mIU/ml at 60 min), but they were lower than those for the higher weight groups and occurred later. Both basal and maximum FSH levels for the group

Fig. 4. The response of serum LH (top) and FSH (bottom) to LH-RH in the individual cases of anorexia nervosa classified according to the percentage of the standard weight.
Fig. 5. The response of serum gonadotropins (mean±SE) to LH-RH at different body weights. The patients are grouped according to the percentage of the standard weight. The number in parentheses shows the average percent weight of each group. The shaded area indicates the response (mean ±SE) in 10 normal women.

Fig. 6. Correlation between body weight and the increase in serum LH and FSH in response to LH-RH. Body weights are expressed as a percentage of the standard weight.
Fig. 7. The chronological change in the serum gonadotropin response to LH-RH correlated with the weight gain in the individual cases. * indicates that "menstrual cycle had been restored when the test was performed".

with 70–79% of SW and 80% or more of SW were not significantly different from those for the normal women (Fig. 4 and 5). Thus, there was no significant correlation between an increase in FSH to LH-RH and body weight gain (Fig. 6).

Chronological change in gonadotropin response to LH-RH correlated with body weight gain in the individual case (Fig. 7)

The chronological change in the serum LH and FSH response to LH-RH in 5 patients is shown in Fig. 7. Each patient showed low basal LH and FSH levels, a poor or almost no LH response and a delayed FSH response to LH-RH at the time when their weights were around the minimum, but showed elevated gonadotropin levels with improved responses in proportion to the increase in their weights. In patients whose body weight was markedly increased, the LH response often became excessive but the FSH response did not show such an excessive response. Normal menstrual cycles were restored in some who showed 100 mIU/ml or more of the maximum LH level. However, no clear-cut relationship was found between the LH or FSH response and the resumption of menstrual cycles. Some patients still showed an excessive LH response even after their menstruation was resumed (e.g. case 10 and case 17), but such cases as #4 or #16 who had an excessive LH response before the resumption of menstruation showed a normal response after its resumption. No remarkable changes were noted in the FSH response before and after the resumption of menstruation.

Discussion

Low basal LH levels in severely emaciated patients have consistently been reported, but the results on basal FSH levels have not always been consistent. Many authors reported low basal FSH levels (Warren et al., 1975; Beumont et al., 1976; Vigersky et al., 1976) but Travaglini et al. (1976) showed normal FSH levels in severely emaciated patients. The present study indicates that the basal levels of both LH and FSH are well correlated with the body weight. They are significantly lower when body weight is less than 79% of SW and slightly higher or within normal limits when weight is more than 80%. Thus, an association between body weight and basal gonadotropin levels in anorexia nervosa now seems to have been established.

The LH responsiveness to LH-RH in anorexia nervosa has generally been reported to be impaired, and its correlation with body weight has also been established (Frankel & Jenkins, 1975; Halmi & Sherman, 1975; Palmer et al., 1975; Sherman et al., 1975; Warren et al., 1975; Beumont et al., 1976; Vigersky et al., 1976). Our results are
consistent with previous reports. The coefficient of the correlation between weight and the increment of LH in response to LH-RH is 0.66 ($p<0.001$) in our study, which is quite consistent with the report by Beumont et al. (1976). Though enhanced LH responsiveness during weight gain was also reported by Warren et al. (1975) or Beumont et al. (1976), such an excessive response more than 80% seen in our patients SW has not been demonstrated. Moreover, inconsistent with the result of Beumont et al. (1976), the LH response in our patients of 70–79% SW significantly greater than that in the normal women. The reason for the excessive LH responsiveness during weight gain is uncertain, but an insufficient negative feedback control due to the delay in the recovery of gonadal functions or an excessive storage of LH in the pituitary gland may be responsible for such a pituitary hyperresponsiveness.

The FSH responsiveness to LH-RH, on the contrary, was preserved even in the severely underweight patients in our study. This result is also consistent with the previous reports (Aono et al., 1975; Palmer et al., 1975; Sherman et al., 1975; Warren et al., 1975; Beumont et al., 1976; Travaglini et al., 1976; Vigersky et al., 1976). In spite of such good response in the lower weight patients, the correlation between increasing FSH response and weight gain has been reported (Sherman et al., 1975; Warren et al., 1975; Beumont et al., 1976; Vigersky et al., 1976). Though the maximum FSH level after the LH-RH stimulation was increased and the pattern of the FSH response was normalized during weight gain in our study, as the basal FSH level was markedly elevated with weight gain, the increment in FSH was not accelerated and its correlation to weight was insignificant. This finding is fairly consistent with Beumont et al. (1976). The present results, however, are inconsistent with Sherman et al. (1975) or Travaglini et al. (1976) who reported that the FSH response in the lower weight patients was greater than in the normal women. Such an excessive FSH response to LH-RH as reported by Sherman et al. (1975) or Beumont et al. (1976) was also not demonstrated in the higher weight patients in this study. An insignificant but poorly negative correlation between FSH response and weight gain was noted in this study (Fig. 6), and this may suggest that an FSH hyperresponse occurs earlier than that of LH even when patients are still emaciated and that both basal FSH levels and the responsiveness to LH-RH are normalized earlier with weight gain.

The discrepancy in the response between LH and FSH to LH-RH in the lower weight patients has also been reported and the reason for this discrepancy has been variously attributed (Palmer et al., 1975; Sherman et al., 1975; Warren et al., 1975; Beumont et al., 1976), but the reason is still not clear. A similar discrepancy has been found in prepubertal girls (Job et al., 1972; Roth et al., 1972), and it is of interest that anorexia nervosa and such sexually immature girls show a common response to LH-RH stimulation.

The correlation between weight and basal or LH-RH-stimulated gonadotropin levels suggests that the gonadal dysfunctions including amenorrhea are closely related to emaciation in anorexia nervosa. However, many authors have reported that the amenorrhea in this disease often begins before or simultaneously with the onset of weight loss (Beck & Brochner-Mortensen, 1954; Kay & Leigh, 1954; Halmi, 1974; Hurd II et al., 1977). In our study, regular menstrual cycles ceased without remarkable weight loss in 9 out of 17 patients. This suggests that the amenorrhea does not always result from the emaciation or malnutrition in anorexia nervosa and that there must be a Primary or essential hypothalamic-gonadal dysfunction independent of weight loss in
this disease.

It is well known that there are various psychiatric disorders or abnormal behavior patterns in anorexia nervosa. Thus, as a part of central nervous system disorders, some abnormality of the hypothalamic feeding center on one side and disorders of the cyclicity center or of the LH-RH releasing mechanism on another side may occur. Although both emaciation and amenorrhea are manifested coincidentally in anorexia nervosa, as the degree of hypothalamic disorders may vary among cases, it must be determined in each case whether amenorrhea begins before the onset of weight loss or vice versa. Once a patient is emaciated, a decrease in body weight may be an added factor which disturbs the maintenance of normal menstrual cycles or other gonadal functions. Fishman et al. (1975) have reported that the metabolism of estrogens is altered in emaciated girls with anorexia nervosa and that such metabolic disorders in estrogens may possibly have an effect on the hypothalamic-pituitary-gonadal system. Thus, a vicious circle may be established among hypothalamic dysfunction, anorexia, emaciation and amenorrhea.

Frisch and colleagues (Frisch & Revelle, 1971; Frisch & McArthur, 1974) have reported that a minimal body weight is necessary for the onset or the restoration of menstrual cycles, indicating that an adequate volume of fat is important for maintaining normal gonadal functions including menstrual cycles. Frisch’s data indicate that there is a common critical body weight for the maintenance of normal menstrual cycles. Our study indicates that the minimal weight for maintaining a menstrual cycle is almost consistent within individuals, because the weight at the cessation and the resumption of menstruation was found to be almost comparable (Table 1 and Fig. 2). These results suggest that the critical body weight for the normal menstrual cycle differ from case to case and that there must be individuality in this weight. It may therefore be possible to forecast the approximate time of recovery of the menstrual cycle in each patient.

From an aspect of the recovery of the hypothalamic disorders, the weight gain seems to represent an improvement in eating behavior, and this means the normalization of the hypothalamic-pituitary-gonadal system while the elevation of gonadotropin levels or the restoration of responsiveness to LH-RH seems to represent the normalization of the hypothalamic-pituitary-gonadal axis. Each factor seems to indicate the process of general recovery of the hypothalamic dysfunctions from a different side. This hypothesis may account for the parallelism between weight gain and the improvement in gonadal functions in anorexia nervosa.

Although such tonic responses as shown by the responsiveness to LH-RH are restored initially and the hypothalamic-pituitary-gonadal functions often become hypersensitive during weight gain, the resumption of normal menstrual cycles may not be accounted for by the recovery of such tonic responses alone. The resumption of menstrual cycles may depend upon complex factors such as the restoration of the hypothalamic cyclicity center, the increase in adipose tissues, the normalization of estrogen metabolism or the recovery of the receptive target tissues, as well as the excessive secretion of gonadotropins. After the normal menstrual cycle has been resumed and the ovarian functions have been normalized, such enhanced hypothalamic-pituitary functions seem to return to normal limits due to the restoration of the negative feedback mechanism.
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References


