Effect of Leptin Replacement on Pituitary Hormone Regulation in Patients with Severe Lipodystrophy

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Leptin is important in regulating energy homeostasis. Severe lipodystrophy is associated with leptin deficiency and insulin resistance, hypertriglyceridemia, and hepatic steatosis. Leptin deficiency is also associated with abnormalities of the pituitary hormones in rodent models and patients with congenital absence of leptin. We inquired whether similar abnormalities are seen in patients with lipodystrophy and whether replacement of leptin will make an impact on the regulation of pituitary hormones. Seven female patients (aged 15–42 yr, all diabetic) with lipodystrophy and serum leptin levels less than 4 mg/liter were treated with recombinant methionyl-human leptin (recombinant leptin) in physiological doses in an open-labeled study. The following parameters were evaluated before and at 4 months of leptin treatment: menstrual history, pelvic ultrasonogram, LHRH, TRH, and CRH tests. While on recombinant leptin, mean serum leptin concentration increased from 1.3 ± 0.3 mg/liter to 11.1 ± 2.5 mg/liter. Only one of five patients who had intact reproductive systems was cycling normally before leptin therapy, and all five had normal menses by the fourth month of leptin therapy. Serum E2 concentrations increased (110 ± 44 pmol/liter vs. 546 ± 247 pmol/liter, P = 0.002), serum T concentrations decreased (3.5 ± 3.0 nmol/liter vs. 1.3 ± 0.7 nmol/liter, P = 0.055), and the attenuated LH response to LHRH was corrected with therapy. Serum T4 and free T3 were in the normal range before leptin therapy and did not change. However, serum TSH concentrations fell from 2.2 ± 1.1 μU/ml to 1.2 ± 0.7 μU/ml (P < 0.001). The percent increase in TSH following TRH administration was similar before (560%) and at 4 months (580%) of leptin therapy. The mean nonstimulated ACTH and cortisol concentrations were, respectively, 6.0 ± 3.4 pmol/liter and 680 ± 280 nmol/liter before leptin and did not change after 4 months of therapy (4.2 ± 1.2 pmol/liter, P = 0.11 and 453 ± 142 nmol/liter, P = 0.13, respectively). The ACTH and cortisol responses to CRH stimulation were normal both before and after therapy. Leptin replacement improved menstrual abnormalities and low E2 levels and corrected the attenuated LH response to LHRH in a group of young women with lipodystrophy and leptin deficiency. These results add to the growing body of evidence that metabolic signals such as leptin play a role in neuroendocrine regulation. (J Clin Endocrinol Metab 87: 3110–3117, 2002)

The adipocyte hormone leptin plays a central role in energy homeostasis (1). Serum leptin concentrations are directly proportional to adipocyte mass (2). In rodents, a low leptin level signals starvation and directs the body to adapt to this condition by turning on the stress response, decreasing thyroid hormone production, and turning off the gonadal activation (3). One way to gain insight into the physiological importance of leptin in humans is to study conditions associated with its absence or deficiency.

Patients with absence of leptin because of mutations in the leptin gene are morbidly obese from infancy and have a physiological and leptin deficiency. These results add to the growing body of evidence that metabolic signals such as leptin play a role in neuroendocrine regulation. (J Clin Endocrinol Metab 87: 3110–3117, 2002)

Hypertriglyceridemia and severe insulin resistance usually accompanied by diabetes mellitus (7, 8). There are several genetic and acquired forms of lipodystrophy in humans. Interestingly, leptin replacement to achieve physiological concentrations caused dramatic improvement in insulin resistance, hyperglycemia, hypertriglyceridemia, and hepatic steatosis in patients with lipodystrophy (9). In the present study, we determined the effect of leptin therapy on menstrual function and the hormonal response of the hypothalamic-pituitary-end-organ axes with respect to gonadal, thyroid, and adrenal cortical function in the patients with lipodystrophy and low serum leptin concentrations.

Materials and Methods

Patients

To be eligible for the leptin replacement trial, the patients were required to have low leptin levels (serum leptin concentrations <4.0 mg/liter in females) in association with lipodystrophy and at least one of the following metabolic abnormalities: presence of diabetes mellitus by American Diabetes Association criteria (10), fasting serum triglyceride concentrations of more than 2.2 mmol/liter, and fasting serum insulin concentrations of more than 215 pmol/liter.

Table 1 summarizes the baseline clinical characteristics of the patients treated in the study at our center and the metabolic effects of 4 months of therapy as reported previously (9). All seven patients recruited into the study were females, although the study was open to both genders. Four of the seven patients had congenital generalized lipodystrophy or

Abbreviations: TBC, T4-binding globulin.

1 Lipodystrophy is a general term encompassing lipoatrophy, lipodystrophic diabetes, and other adipocyte abnormalities. The lipodystrophy syndromes that are the subject of this study are more precisely lipoatrophy syndromes; however, for consistency with the literature, we have used the term “lipodystrophy” here.
TABLE 1. Metabolic characteristics of patients (9)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/sex/type</th>
<th>Baseline fasting insulin&lt;sup&gt;a&lt;/sup&gt; (pmol/liter)</th>
<th>Baseline leptin&lt;sup&gt;b&lt;/sup&gt; (mg/liter)</th>
<th>Baseline HbA1c (%)</th>
<th>4-month HbA1c (%)</th>
<th>Baseline triglycerides (mmol/liter)</th>
<th>4-month triglycerides (mmol/liter)</th>
<th>Fat&lt;sup&gt;c&lt;/sup&gt; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH-1</td>
<td>17/F/acquired generalized</td>
<td>221</td>
<td>&lt;0.5</td>
<td>8.6</td>
<td>7.0</td>
<td>81.6</td>
<td>13.3</td>
<td>7</td>
</tr>
<tr>
<td>NIH-2</td>
<td>17/F/congenital generalized</td>
<td>2388</td>
<td>1.0</td>
<td>9.8</td>
<td>10.0</td>
<td>6.9</td>
<td>4.5</td>
<td>17</td>
</tr>
<tr>
<td>NIH-3</td>
<td>27/F/acquired generalized</td>
<td>136</td>
<td>0.7</td>
<td>9.3</td>
<td>7.9</td>
<td>4.9</td>
<td>3.1</td>
<td>18</td>
</tr>
<tr>
<td>NIH-4</td>
<td>17/F/congenital generalized</td>
<td>1508</td>
<td>1.1</td>
<td>7.6</td>
<td>5.0</td>
<td>3.5</td>
<td>1.2</td>
<td>17</td>
</tr>
<tr>
<td>NIH-5</td>
<td>10/F/congenital generalized</td>
<td>823</td>
<td>0.8</td>
<td>9.5</td>
<td>6.1</td>
<td>10</td>
<td>1.4</td>
<td>15</td>
</tr>
<tr>
<td>NIH-6</td>
<td>37/F/congenital generalized</td>
<td>179</td>
<td>0.6</td>
<td>9.2</td>
<td>7.4</td>
<td>7.3</td>
<td>3.3</td>
<td>15</td>
</tr>
<tr>
<td>NIH-7</td>
<td>42/F/familial partial</td>
<td>286</td>
<td>3.6</td>
<td>9.5</td>
<td>6.6</td>
<td>8.8</td>
<td>2.4</td>
<td>26</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>792</td>
<td>1.2</td>
<td>9.1</td>
<td>7.1</td>
<td>17.6</td>
<td>4.2</td>
<td>16</td>
</tr>
</tbody>
</table>

<sup>a</sup> Fasting insulin; note that some patients are on exogenous insulin therapy.

<sup>b</sup> Conversion factor to nanomoles per milliliter: 0.08 X

<sup>c</sup> Measured using dual-energy x-ray absorptiometry, which gives measurements 7–8% higher than underwater weighing technique.

...
Results

Leptin replacement therapy normalized circulating leptin concentrations

The mean serum leptin concentration was 1.3 ± 0.3 mg/liter at baseline (Table 1) and increased with therapy to 2.3 ± 0.5 mg/liter, 5.5 ± 1.2 mg/liter, and 11.1 ± 2.5 mg/liter at the end of the first, second, and fourth month, respectively. Therefore, recombinant leptin administration resulted in approximately normal serum leptin levels in these patients.

Leptin therapy normalized menstrual abnormalities

All seven women in the study were of reproductive age (Table 2). Five of the seven patients had intact reproductive systems. Patient NIH-1 had first menses at age 12 yr but after the development of fat loss at age 13 yr had only one bleeding episode per year. Patient NIH-2, -4, and -5 had primary amenorrhea. Patient NIH-2 complained of hirsutism in addition to amenorrhea. Patient NIH-3 had regular periods since age 13 yr, despite having fat loss at age 10. She did not display hirsutism but had cystic acne of the face and back.

The patients who had either primary or secondary amenorrhea noted menstrual bleeding episodes starting at either the third or fourth month of leptin therapy. The patients have remained on continued leptin treatment beyond 4 months, and menses continued to be normal in patients NIH-1, -2, -4, and -5.

Two of the seven patients (NIH-6 and -7) had either total or partial hysterectomy, and hence the effect of leptin therapy on menses cannot be determined.

Ovarian ultrasounds

Ovarian ultrasonograms of patients 1 through 6 revealed the typical picture for polycystic ovarian syndrome (Fig. 1). The ovarian phenotype was similar to patients with insulin resistance and not to patients with hypogonadotropic hypogonadism.

| TABLE 2. Patients’ reproductive function and reproductive hormone levels before and after leptin therapy |
|--------------------------------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Patient      | Baseline menstrual status | 4 months menstrual status | Baseline E2 (pmol/liter) normal: 110–370 | 4 months E2 (pmol/liter) normal: 110–370 | Baseline testosterone (nmol/liter) normal: 0.7–2.6 | 4 months testosterone (nmol/liter) normal: 0.7–2.8 |
| NIH-1        | One menses/yr             | Two consecutive regular menses starting at 3 months | 59 | 352 | 2.0 | 1.1 |
| NIH-2        | Primary amenorrhea        | Two consecutive regular menses starting at 3 months | 85 | 211 | 11.6 | 2.5 |
| NIH-3        | Regular menses            | Regular menses | 181 | 722 | 1.2 | 1.0 |
| NIH-4        | Primary amenorrhea        | Menses started at 4 months | 89 | 500 | 2.8 | 1.2 |
| NIH-5        | Primary amenorrhea        | Menses started at 4 months | 118 | 603 | 2.7 | 1.6 |
| NIH-6        | S/P hysterectomy without oophorectomy | S/P hysterectomy without oophorectomy | 126 | 892 | 1.2 | 0.9 |
| NIH-7a       | S/P hysterectomy and bilateral oophorectomy | S/P hysterectomy and bilateral oophorectomy | 81 | 44 | 1.2 | 1.0 |
| Group summary | 1/5 eligible cycling regularly | 5/5 eligible cycling regularly | 110 ± 44 | 546 ± 247b | 3.5 ± 3.0 | 1.3 ± 0.7 |

The patients’ progesterone values on the day of measurements were most consistent with follicular phase of the menstrual cycle. Hence, the normal ranges in the table are given for this phase.

This patient’s data are excluded from the mean data presented in the summary column because she was postmenopausal.

b P < 0.002 when compared with baseline.
pmol/liter) and TSH (2.2 ± 1.1 μU/ml) concentrations were in the normal range (Fig. 3 and Table 3). The reverse T₃ (0.28 ± 0.05 nmol/liter) concentrations and thyroid-binding plasma proteins were also normal (23.4 ± 1.9 mg/liter for TBG and 38 ± 6 g/liter for albumin) before leptin therapy was initiated.

Although remaining in the normal range, serum TSH and T₄ concentrations decreased significantly after 4 months of leptin therapy (Table 3). T₃, reverse T₃, TBG, and albumin concentrations were unchanged after 4 months of leptin therapy (Table 3).

Despite low circulating leptin levels at the beginning of the study, the TRH stimulation test revealed a robust stimulation response (Fig. 3). Following leptin therapy, serum TSH fell and the response to TRH was attenuated, compared with the preleptin treatment values (Fig. 3, P < 0.001). The percent increase in TSH following TRH administration remained the same before leptin therapy (560%) and at 4 months of therapy (580%).

**Leptin replacement did not alter the status of hypothalamic-pituitary-adrenal axis**

The mean nonstimulated ACTH and cortisol concentrations were, respectively, 6.0 ± 3.4 pmol/liter and 680 ± 280 nmol/liter before leptin replacement therapy. Although there was a trend toward a decrease in these levels, they were not significantly different after 4 months of leptin therapy (4.2 ± 1.2 pmol/liter, P = 0.11 and 453 ± 42 nmol/liter, P = 0.13, respectively). The response to CRH stimulation was similar to the normal response (15) both before and at 4 months of leptin replacement (Fig. 4, A and B), suggesting that leptin replacement did not have a major impact on the control of hypothalamic-pituitary-adrenal axes of patients with lipodystrophy and leptin deficiency.

**Discussion**

We previously reported that leptin replacement led to clear and dramatic metabolic benefits in a group of patients with lipodystrophy and leptin deficiency, causing a 1.9 percentage point absolute reduction in hemoglobin A₁c and a 60% reduction in triglyceride levels, compared with baseline. In the present report, we studied the effects of leptin replacement therapy on the regulation of the various components of the hypothalamic-pituitary-endocrine axis. Among the three key axes tested, we observed the most remarkable effect on the hypothalamic-pituitary-ovarian axis. Four months of leptin therapy normalized menstrual abnormalities, low serum E₂ concentrations, and the attenuated LH response to LH RH stimulation. We have not observed a clinical or a key regulatory effect of leptin replacement therapy on thyroid and adrenocortical function.

Several limitations of our study are of note. The primary outcome measure of leptin replacement therapy was the amelioration of glucose and lipid control. The effects on the hypothalamic-pituitary and endocrine end-organ axes were ancillary measurements. Hence, the timing of the hormonal studies was not controlled for possible variations, such as a specific stage of the menstrual cycle. Furthermore, the number of studies that can be performed at each time point were limited by the blood volume. Therefore, we could not study diurnal variations or the pulsatility of secretory patterns.

Lastly, the patients in the study experienced dramatic improvements in their insulin sensitivity, glucose, and lipid control and hepatic steatosis as well as a remarkable reduction in caloric intake. Hence, some of the effects observed on the hypothalamic axes may be owing to improved metabolic status and may not be primary effects of leptin therapy. Despite these issues, our study is the first to evaluate the endocrinologic effects of correcting low leptin levels to the normal range in severe forms of lipodystrophy.
was turned on in leptin deficiency. Whether leptin plays a crucial role in adapting to starvation in humans is less clear. To date, there is information from only one patient with congenital absence of leptin hormone because of mutations in this gene (6).

**Role of leptin in reproductive function in severe lipodystrophy: regulation of GnRH vs. insulin sensitization or both**

Multiple studies in rodents pointed out that leptin played a critical role in permitting female mice to enter puberty by signaling that there are adequate energy stores to undertake reproduction. Starvation causes infertility in female mice; this is reversed by either refeeding or leptin (3). Replacement of leptin in ob/ob mice corrects their infertility, and leptin treatment of female prepubertal mice accelerates the onset of puberty (16–18).

In humans, a relationship between body weight and onset of puberty (19) as well as the presence of hypogonadism during times of excessive caloric deprivation, such as starvation (20) or in patients with anorexia nervosa (21), was observed. Although these observations predate the discovery of leptin, all these situations represent states of low serum leptin concentration. Prospective studies of pulsatility of leptin secretion and GnRH secretion point to the presence of a significant increase in circulating leptin concentrations immediately before puberty. This is followed by the pubertal

**TABLE 3. Thyroid function tests before and at 4 months of leptin therapy**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before leptin therapy</th>
<th>4 months of leptin therapy</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH (μU/mliter)</td>
<td>2.2 ± 1.1</td>
<td>1.2 ± 0.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(normal: 0.4–4.0)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>T3 (nmol/liter)</td>
<td>1.5 ± 0.3</td>
<td>1.7 ± 0.6</td>
<td>NS</td>
</tr>
<tr>
<td>(normal: 1.1–2.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4 (nmol/liter)</td>
<td>126 ± 27</td>
<td>92 ± 19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(normal: 55–154)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reverse T4 (nmol/liter)</td>
<td>0.28 ± 0.05</td>
<td>0.27 ± 0.04</td>
<td>NS</td>
</tr>
<tr>
<td>(normal: 0.20–0.70)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free T4 (pmol/liter)</td>
<td>1.1 ± 0.2</td>
<td>1.1 ± 0.3</td>
<td>NS</td>
</tr>
<tr>
<td>(normal: 12–27)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin (g/liter)</td>
<td>38 ± 6</td>
<td>37 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>(normal: 35–42)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBG (mg/liter)</td>
<td>23.4 ± 1.9</td>
<td>22.7 ± 3.9</td>
<td>NS</td>
</tr>
<tr>
<td>(normal: 15.0–34.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**FIG. 2.** A, Serum LH concentrations during an LHRH test at baseline (solid line and circles) and at 4 months of therapy (dashed line and triangles) are shown. Then, 100 μg of gonadorelin are administered iv at time 0 of the test. The plotted values are mean concentrations and the error bars represent the SD. The P value is derived using an ANOVA with repeated measures between the tests performed at baseline and 4 months. Data from NIH-1 to -6 are shown. B, Serum FSH concentrations during an LHRH test at baseline (solid line and circles) and at 4 months of therapy (dashed line and triangles) are shown. Then, 100 μg of gonadorelin are administered iv at time 0 of the test. The plotted values are mean concentrations and the error bars represent the SD. The P value is derived using an ANOVA with repeated measures between the tests performed at baseline and 4 months. Data from NIH-1 to -6 are shown.

**FIG. 3.** Serum TSH concentrations during a TRH stimulation test at baseline (solid line and circles) and at 4 months of therapy (dashed line and triangles) are shown. TRH is administered iv at time 0 of the test (7 μg/kg, maximum 500 μg). The plotted values are mean concentrations and the error bars represent the SD. The P value is derived using an ANOVA with repeated measures between the tests performed at baseline and 4 months after therapy. Data from NIH-1 to -7 are shown.
pattern of GnRH secretion (22). These findings suggest that leptin may play a role in determining the onset of puberty in humans.

Hypogonadotrophic hypogonadism and abnormal GnRH secretion have been reported in few humans with congenital absence of leptin because of mutations on leptin gene (4, 5). Leptin replacement in one 17-yr-old female patient lacking leptin led to normalization of GnRH secretion followed by onset of normal cyclical menstruation (6). Hypogonadotrophic hypogonadism has also been reported in a family with mutations of the leptin receptor gene and thus with absence of leptin action (23).

On the contrary, leptin does not appear to be the only factor controlling the onset of normal puberty in humans. Recently two female patients with congenital generalized lipodystrophy and leptin deficiency were reported to have a relatively normal pattern of puberty and menstruation (24). We have followed up one female patient with congenital generalized lipodystrophy and leptin concentrations below the limit of detection, who was able to have five children. Likewise, one of the patients in this study (NIH-3) has a normal-pattern menstruation despite having leptin concentrations similar to the other patients in the study who had primary or secondary amenorrhea. However, leptin replacement therapy in our study resulted in normal menstruation in four of the five female patients in whom this parameter could be evaluated. Parallel to this observation, serum E2 concentrations improved with 4 months of leptin replacement therapy. Furthermore, LH response to LHRH stimulation improved with administration of recombinant leptin. As expected, there were no differences in the FSH response before and after leptin therapy because LH appears to have a more important role in regulation of puberty.

Despite the fact that our patients had inadequate LH secretion from the pituitary, they had enlarged polycystic ovaries on pelvic ultrasonograms and elevated T concentration. Apparently the insulin resistance was sufficient to drive both the ovarian enlargement and hyperandrogenism, which is similar to observations in other patients with severe forms of insulin resistance because of mutations on the insulin receptor gene or to autoantibodies against the insulin receptor (25).

Insulin-sensitizing drugs ameliorate hyperandrogenism in common polycystic ovarian syndrome (26, 27), and troglitazone acts in a similar fashion in patients with various forms of lipodystrophy (Arioglu Oral, A., unpublished observations). Our study does not allow a clear distinction among the different regulatory pathways. It is possible that leptin corrected both the primary failure in the regulation of LH secretion and a secondary abnormality in ovarian function because of severe insulin resistance.

**Role of leptin in the regulation of thyroid hormone secretion and energy homeostasis**

In rodents a lack of leptin causes a hypothyroid state because of decreased TSH secretion (3). This leads to low circulating thyroid hormone levels and also a reduced resting energy expenditure. Starvation causes a fall in circulating leptin levels and similar effects on the hypothalamic-pituitary-thyroid axis. Prevention of the fall in leptin levels during starvation or correction of leptin deficiency with administration of leptin corrects all these abnormalities (3).

Evaluation of thyroid function appeared normal in the few humans with mutations in the leptin gene. In some of these patients, a TRH stimulation test was performed in the leptin deficient state and revealed normal TSH stimulation (5). One of these patients was reported to have primary hypothyroidism, presumably an incidental finding (5).

The thyroid function tests in our patients were in the normal range. However, we observed a small but significant
fall in the TSH concentration with leptin therapy. Yet the degree of TSH stimulation with TRH was similar before and after leptin replacement. These results suggest that the pituitary set-point for TSH secretion is altered by leptin replacement. Recently, Mantzoros et al. (28) reported that serum leptin and TSH secretion patterns follow a simultaneous diurnal pattern and that the diurnal rhythm of TSH was disrupted, and the pulsatility was disorganized in one patient with congenital absence of leptin. Because both the leptin-deficient patients (5, 28) and our patients were euthyroid before leptin therapy, it appears that either leptin is not a major regulator of TSH secretion in humans or there are compensatory mechanisms that maintain normal thyroid function despite leptin deficiency.

Role of leptin in the regulation of the hypothalamic-pituitary-adrenal axis

In the present study, we evaluated the hypothalamic pituitary-adrenocortical function with CRH stimulation. The baseline ACTH and cortisol concentrations in our patients were supranormal, but this can be observed in hospitalized patients in the normal. The patients had normal ACTH and cortisol responses to CRH stimulation before leptin therapy. There was a tendency toward decreased morning ACTH and cortisol concentrations after 4 months of leptin therapy; however, this did not reach statistical significance. Finally, the response to CRH stimulation remained normal after 4 months of therapy. These data suggest that leptin is not a major regulator of the hypothalamic-pituitary and adrenocortical axis in humans with lipodystrophy and leptin deficiency. Furthermore, it appears that increased cortisol is not an important mediator of the metabolic phenotype seen in lipodystrophy.

Conclusions

Severe lipodystrophy and congenital absence of leptin are two conditions in which leptin replacement therapy leads to a dramatic improvement. We have observed the most remarkable effect of leptin treatment on regulation of ovarian function among the three axes tested in the present study. These results are parallel to what has been observed in a patient with congenital absence of leptin and add to the evidence that leptin modulates the central regulation of gonadal function. We have also observed that circulating TSH levels are altered after leptin replacement therapy, but the biological significance of this observation is not clear because the changes seem to occur without altering peripheral thyroid hormone production. Finally, we have observed that low levels of leptin such as those seen in severe lipodystrophy do not cause elevated cortisol levels and do not inhibit ACTH or cortisol response to CRH stimulation. Although this mechanism seems a very important adaptive mechanism to starvation in rodents, it does not appear to regulate the hypothalamic-pituitary-adrenal axis in humans.

In conclusion, leptin replacement therapy has a therapeutic role in correcting both metabolic and endocrine abnormalities associated with leptin deficiency. Furthermore, this approach is instructive in elucidating the physiological role of leptin in humans.

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References

5. Ozata M, Ozdemir IC, Licinio J 1999 Human leptin deficiency caused by a nonsense mutation: multiple endocrine defects, decreased sympathetic tone, and immune system dysfunction indicate new targets for leptin action, greater central than peripheral resistance to the effects of leptin, and spontaneous correction of leptin-mediated defects. J Clin Endocrinol Metab 84:3686–3695
22. Mantzoros CS, Flier JS, Rogol AD 1997 A longitudinal assessment of hormonal and physical alterations during normal puberty in boys. V. Rising leptin levels may signal the onset of puberty. J Clin Endocrinol Metab 82:1066–1070

Massachusetts General Hospital
Reproductive Endocrine Unit

Men with hypogonadotropic hypogonadism are offered an opportunity to receive GnRH therapy and/or gonadotropins to induce fertility. The care and medications during treatment are provided at no cost as part of a NIH-funded research study under the direction of William F. Crowley, Jr., M.D.

If you have patients who could benefit from this therapy please contact: Frances Hayes, M.D., (617) 726-8434, Fhayes@Partners.org; or Nelly Pitteloud, M.D., (617) 724-1830, Npitteloud@partners.org, MGH Reproductive Endocrine Unit BHX5, 55 Fruit Street, Boston, Massachusetts 02114.