Pituitary-testicular axis in obese men during short-term fasting

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Abstract. To investigate whether short-term fasting affects the pituitary-testicular axis in obese subjects, 9 massively obese men (Body Mass Index 39.0 ± 1.3, mean ± SEM) were given two identical iv GnRH tests, the first (control) after an overnight fast, the second after 56 h of food deprivation. Short-term fasting augmented the GnRH-induced LH incremental area by 26% (1317 ± 251 vs 1661 ± 297 U · 1−1 · min−1, p < 0.05), but failed to affect the corresponding testosterone incremental area. Eight non-obese normal men (Body Mass Index 22.2 ± 0.5) were investigated for comparison. All of them were studied according to the same protocol as the obese group. Short-term fasting increased the GnRH-elicited LH response by 67% in the non-obese group (LH incremental areas 2147 ± 304 vs 3581 ± 256, p < 0.01), and the corresponding testosterone response by 180% (testosterone incremental areas 111 ± 61 vs 311 ± 49 μg · 1−1 · min−1, p < 0.01). These results imply that food deprivation affects the pituitary-testicular axis differently in obese and non-obese men.

In healthy subjects of normal weight, short-term fasting augments the gonadotropin responsiveness to iv GnRH (1–3). It is not known whether fasting has similar influence on the pituitary gonadotropes in massively obese individuals. This may not be the case, since abnormalities of the reproductive system such as a low total serum testosterone (T) level (4–7), a decreased sex hormone-binding globulin (SHBG) capacity (7–10), and elevated estrone (4, 10) and estradiol levels (4, 8, 10), have previously been found in morbidly obese men. Furthermore, Klibanski et al. have reported impaired FSH responsiveness to GnRH in obese men undergoing prolonged fasting (10 days) (11). Although Klibanski's findings may suggest different cell activity to GnRH during short-term fasting in obese and non-obese subjects, such assumption cannot be taken for granted, since pituitary gonadotropes may adjust to energy deficiency, and change reactivity in the course of a prolonged period of profound energy restriction. This hypothesis is not new. It has in fact been proposed by other investigators studying the effect of weight reduction in extremely obese men (12).

Since previous investigations have not given a clear picture of whether short-term fasting affects the pituitary-testicular axis differently in obese men compared with non-obese individuals, we decided to study that issue. For that purpose iv GnRH tests were carried out in massively obese men on two occasions: 1. after an overnight fast (8 h), and 2. after a 56-h fast. The results recorded in the obese patients were compared with those obtained in a group of healthy non-obese men given identical GnRH tests before and after a 56-h fast.

Subjects and Methods

Seventeen men were studied. Nine of them (group A) were of normal height (177 ± 2 cm) but massively obese (122 ± 4 kg). Their age ranged between 19 and 46 years (32 ± 3). In 8 subjects (group B) both height (179 ± 3 cm) and weight (71 ± 2 kg) were normal. Their age varied between 21 and 34 years (27 ± 2). The normal men in group B participated in a previous investigation (3), and were included in the present one for comparison. None was taking any medication. All were informed of the purpose of the study and gave their voluntary consent. The protocol,
Presented below, was approved by the local ethical committee in Stockholm.

Protocol

The experiments commenced at 08.00h with the participants resting in the supine position. Indwelling needles were placed in both antecubital veins and were kept patent by slow drips of normal saline. One of the needles was used for blood sampling, the other for injection of GnRH.

Group A and B. Each participant had two identical GnRH tests; the first after an overnight fast (8 h), the second after 56 h of fasting. During the fasting period food was totally withdrawn but tap water was allowed freely.

The GnRH test. At zero time, 50 μg GnRH (Relefact®, Hoechst AG, Frankfurt am Main, FRG) was injected iv. Blood samples for serum LH and T were collected before (−30, −20, −10, −1 min), and 30, 60, 90, 120, and 180 min after the GnRH injection. The mean of the 4 basal values formed a control value. In group A blood samples for determination of blood glucose, SHBG and cortisol were drawn in the control period (−10 and −1 min), and mean values calculated. One of these parameters (blood glucose) was determined in group B.

Assay procedures

Blood glucose was measured with a glucose analyzer (YSI, model 23A, Kemo-Lab, Stockholm, Sweden). An immunoradiometric assay kit from Farmos Diagnostica, Oulunsalo, Finland was used for determination of serum SHBG. Serum LH and cortisol values were measured with RIA kits provided by Farmos Diagnostica, and T with a kit from Immuchem Corp, Carson, USA. Duplicate determinations were used to calculate mean values. All samples for a specific hormone analysis in an individual subject were analysed in the same assay. The intra-assay coefficients of variation were: 7% at 10 U/l LH, 10% at 5 μg/l T, 3% at 450 nmol/l cortisol and 3% at 12 nmol/l SHBG.

Statistics

Basal values as well as values obtained in response to the GnRH tests were compared and statistically evaluated by use of Student's t-test applied on paired differences. Student's t-test was also used when comparing mean basal concentrations in the obese and non-obese subjects.

Results

Body indices

Age, body weight and Body Mass Index (BMI) recordings are shown in Table 1. The age of the participants in group A and B did not differ significantly. Obese subjects lost on an average 2.8 ± 0.3 kg during the period of short-term fasting, whereas non-obese individuals lost 2.2 ± 0.2 kg during the same time period (the difference is not significant). BMI fell significantly when food was withdrawn in both obese and non-obese participants.

Basal blood values

Basal values for blood glucose, serum LH, T, SHBG and cortisol are presented in Table 1.

| Table 1. |
| Body indices and basal blood values in 8 normal and 9 obese men studied before (control) and after a 56-h fast. |

<table>
<thead>
<tr>
<th></th>
<th>Obese men</th>
<th>Normal men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Fasting</td>
</tr>
<tr>
<td>Age (years)</td>
<td>32 ± 3</td>
<td>–</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>121.9 ± 4.3</td>
<td>119.2 ± 4.3***</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>39.0 ± 1.3</td>
<td>38.1 ± 1.2***</td>
</tr>
<tr>
<td>Basal blood values</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LH (U/l)</td>
<td>4.3 ± 0.5</td>
<td>3.8 ± 0.4*</td>
</tr>
<tr>
<td>T (μg/l)</td>
<td>4.0 ± 0.4</td>
<td>3.6 ± 0.5</td>
</tr>
<tr>
<td>SHBG (nmol/l)</td>
<td>15 ± 2</td>
<td>18 ± 3**</td>
</tr>
<tr>
<td>Cortisol (nmol/l)</td>
<td>296 ± 25</td>
<td>305 ± 40</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>5.0 ± 0.1</td>
<td>3.9 ± 0.1***</td>
</tr>
</tbody>
</table>

*p < 0.05, **p < 0.01, ***p < 0.001 (vs the control value).
Serum LH responses (increments and incremental areas) to iv injection of 50 μg GnRH. GnRH was injected before (○—○; ■) and after a 56-h fast (□—□; □) in normal and massively obese men. * p < 0.05, ** p < 0.01.

**Group A.** The blood glucose level fell from 5.0 ± 0.1 to 3.9 ± 0.1 mmol/l during short-term fasting (p < 0.001). The LH level also declined significantly from 4.5 ± 0.5 to 3.8 ± 0.4 U/l (p < 0.05). Neither the T level nor the cortisol concentration changed significantly in fasting, in contrast to the SHBG level which increased from 15 ± 2 to 18 ± 3 nmol/l (p < 0.01).

**Group B.** The basal blood glucose concentration was lower in the normal than in the obese group (4.5 ± 0.1 vs 5.0 ± 0.1 mmol/l, p < 0.01), but the blood glucose decline during fasting was almost identical in the two groups. The basal LH and T levels were higher in the normal group than in the obese (7.1 ± 1.0 vs 4.3 ± 0.5 U/l, p < 0.05, and 8.2 ± 0.8 vs 4.0 ± 0.4 μg/l, p < 0.001, respectively), but the hormone levels fell in a similar fashion in both groups.

**LH and T stimulation by GnRH**

LH and T responses to iv GnRH are demonstrated in Figs. 1 and 2.

**Group A.** The LH responsiveness to the first GnRH test, as reflected by the LH incremental area, was 1317 ± 251 (U·l⁻¹·min⁻¹). The second GnRH test resulted in a LH incremental area which was 26% larger than the first (1317 ± 251 vs 1661 ± 297, p < 0.05). The two T incremental areas were of similar magnitudes (96 ± 31 vs 107 ± 24 μg·l⁻¹·min⁻¹).

**Group B.** The LH incremental area increased by 67% during short-term fasting (from 2147 ± 304 to 3581 ± 526, p < 0.01). Also the T incremental area increased significantly from 111 ± 61 to 311 ± 49 (p < 0.01; 180%).

**Discussion**

The present investigation shows that short-term fasting augments the LH responsiveness to iv GnRH in both obese and non-obese men. The mechanism behind this finding is unknown. An enhanced central dopaminergic activity (DA), in-
duced by fasting, may contribute, since dopamine D-2 receptor blockade by metoclopramide has been found to counteract the augmentative effect of food deprivation, and return the increased LH responsiveness to normal in starving non-obese individuals (1).

It has been maintained that the central DA tone is increased in obese patients (13, 14). This might mean that several central DA neurones are working at capacity in such individuals, and hence respond poorly to additional stimulation. If so, short-term fasting should result in a more prominent LH response to GnRH in normal subjects than in obese patients. This was indeed the case in the present investigation, where fasting augmented the GnRH-induced LH response by 67% in normal, and by only 26% in obese subjects.

The well-known relationship between the LH signal and the Leydig cells makes it reasonable to expect a more powerful T response to GnRH in fasting than in fed men. This hypothesis was confirmed in the present study where the T responsiveness increased by 180% during food deprivation in normal subjects. Obese men responded differently. Their GnRH-induced T response remained unchanged in fasting. This lack of response, in spite of an increased LH signal, might have been caused by several factors such as: a. stress, b. defect stimulus-secretion coupling, and c. methodological problems.

There are several observations indicating that the Leydig cell function is inhibited by stress (15–17). It has also been maintained that hypercortisolism of endogenous or exogenous sources suppresses T secretion by a direct effect on the testis (18, 19). Consequently, it might be objected that starvation-induced stress, resulting in an increased serum cortisol level, should inhibit the Leydig cells. However, such mechanism can hardly explain the present results, since the basal T level did not fall significantly during fasting in the obese group, and the cortisol level remained unchanged.
when food was withdrawn. Hence, other mechanisms, such as defect or suppressed stimulus-secretion coupling, might be more relevant in this context. It cannot be excluded that massively obese men might have a reduced LH receptor concentration, an impaired or suppressed T synthesis, or a defect T release mechanism. Either possibility would probably result in a decreased T responsiveness despite an increased LH signal, but neither of them has, to the best of our knowledge, been studied before.

It is not necessary, however, to interpret the results in the obese subjects to mean that fasting makes the Leydig cells insensitive to stimulation. Fasting may actually augment the T responsiveness also in obese patients, but at a much later point of time than in normal men. It has been shown in rats, and also in normal rams, that iv GnRH elicits a rapid and profound increase in serum T (20, 21). In man the T response is later in onset and much less pronounced, and does not appear until 8–10 h after the GnRH administration (22). The present investigation clearly shows that food deprivation shortens the stimulus-response time in normal men, but fails to do so in massively obese subjects. Studies in which the T response curve is extended beyond 3 h have to be carried out to solve this problem.

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