Relationship Between Body Weight and Gonadotrophin Excretion in Anorexia Nervosa and Obesity

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SUMMARY

Gonadotrophin excretion in patients with anorexia nervosa or obesity was examined during dietary treatment. Patients with anorexia nervosa showed a positive correlation between weight on admission to hospital and subsequent gonadotrophin excretion. Ten out of 15 of these patients excreted detectable gonadotrophins during 50 days of treatment, although in the majority of patients gonadotrophin output was undetectable during the first week of treatment. Three obese patients became amenorrhoeic during weight reduction. Mean gonadotrophin excretion diminished during successive menstrual cycles, but the phasic pattern of excretion seemed to be unaffected by weight loss. The relationship between change in body weight and both the basal and the phasic excretion of gonadotrophin, is discussed.

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The relationship between malnutrition and amenorrhoea (arising presumably from pituitary gonadotrophin derangement) has been well established.[1-4] Studies with serial measurement of gonadotrophin excretion in cases of malnutrition or weight loss are, however, rare. Similarly, the relationship between body weight and gonadotrophin output in man has not been established.

The purpose of the present investigation was to examine the changing patterns of gonadotrophin excretion by patients while they were being treated for either excessive weight loss associated with anorexia nervosa, or obesity. Attention was paid to both the basal and the phasic excretion of the hormones. The influence of body weight change on these two funtions is of particular interest, since it is conceivable that weight change could affect one and not the other.

PATIENTS STUDIED

Two groups of patients with feeding disorders were studied. The first consisted of 15 female patients with anorexia nervosa, and a second group comprised 3 obese female patients. Both groups were treated for their weight loss or weight excess by appropriate dietary measures.[5] All patients

were cared for under skilled and specialised nursing supervision in the Metabolic Unit of the Maudsley Hospital, London.

In this study, patients with anorexia nervosa were diagnosed according to the criteria which have been fully described elsewhere.[6] All patients with obesity were at least 45% in excess of their standard body weights based on height and age.[7]

While patients were being treated by dietary measures, 24-hour urine collections were made serially over periods ranging from 50 days in the case of patients with anorexia nervosa, to 146 days in the case of patients with obesity.

HORMONE ASSAY

Total gonadotrophic activity (TGA) was extracted from 24-hour urine samples by the tannic acid method of Johnsen[8] and was measured by the mouse uterus test,[9] and the gonadotrophic potency of the extracts was expressed as mg 2nd IRP HMG (second international reference preparation of human menopausal gonadotrophin) per 24-hour urine sample.

The statistical design of the bio-assays was a 2 × 1 assay. This design posed certain problems since the evaluation of relevant reliability criteria for each assay was precluded. Also it was not possible to obtain an absolute mean value for daily gonadotrophin output during a period of time, since in a number of instances values for TGA were less than the lower limit of the assay. In a 24-hour urine extract this limit normally amounted to 0,2 - 0,25 mg 2nd IRP HMG. A range within which the mean of a number of assays must fall could, however, be calculated, e.g. >0,31, <0,40 mg 2nd IRP HMG/24 h. Thus, in this case, the mean was greater than 0,31 and less than 0,40 mg 2nd IRP HMG/24 h. An estimate of the mean could be determined by averaging the two figures obtained.

RESULTS

Patients with Anorexia Nervosa

Body weight changes during treatment: The body weights of patients with anorexia nervosa were expressed as a percentage of standard weight for age and height. On admission to hospital, the range of body weights was 47,5 - 72,9% (Table I), while 50 days later, after dietary treatment, the range was 76,3 - 92,1%.

TGA excretion patterns: Urinary TGA output, measured in 24-hour urine samples every third day, was determined in 15 patients. The over-all mean TGA, with the means for the first week, and for weeks 2 - 7 after admission to hospital, are shown in Table I. In 10 out of 15 patients urinary gonadotrophins were undetectable during the first week in hospital. This occurred during a period when the patients' body weights were lowest. Of these 10 patients, 5 had detectable TGA levels during the ensuing 6 weeks.

All 5 patients who had detectable urinary TGA levels during the first week of treatment continued to excrete normal to high amounts of TGA during the ensuing 6 weeks.

There appeared to be a relationship between the over-all mean TGA and the body weight of patients when first admitted to hospital. Patients were ranked according to their body weight on admission to hospital (Fig. 1). Patient 15 had the highest body weight (72,9% of standard) and patient 10 had the lowest body weight (47,5% of standard). When the mean TGA values for the first week

TABLE I. BODY WEIGHT CHANGE AND VARIATION IN TGA EXCRETION IN 15 PATIENTS WITH ANOREXIA NERVOSA

Patient No.	Body weight: On admission kg	Body weight: On admission % std	Body weight: After 50 days kg	Body weight: After 50 days % std	Gonadotrophin excretion (mg 2nd IRP HMG/24 h): Mean week 1	Mean weeks 2-7	Mean over-all
1	29,2	56,4	40,0	77,4	<0,22	>0,32 <0,33	>0,28 <0,31
2	29,6	57,1	43,3	76,3	<0,22	>0,09 <0,22	>0,08 <0,22
3	36,8	67,5	48,8	89,6	<0,18	>0,22 <0,31	>0,18 <0,28
4	32,5	61,9	46,1	87,8	<0,23	>0,17 <0,25	>0,08 <0,24
5	36,5	64,8	51,8	92,1	<0,20	>0,04 <0,18	>0,05 <0,18
6	37,7	62,1	52,1	85,8	<0,18	>0,37 <0,41	>0,24 <0,36
7	40,0	67,6	52,7	89,1	0,52	>0,56 <0,61	>0,56 <0,59
8	35,5	65,8	46,0	85,5	0,93	0,83	0,85
9	35,8	69,1	45,6	88,0	0,43	0,66	0,62
10	24,5	47,5	40,7	78,9	<0,17	>0,41 <0,45	>0,39 <0,42
11	27,4	55,8	40,9	83,3	<0,23	>0,21 <0,23	>0,21 <0,24
12	33,9	61,1	47,4	85,4	<0,19	>0,35 <0,41	>0,29 <0,37
13	27,6	53,5	43,1	83,5	<0,29	>0,16 <0,26	>0,19 <0,25
14	39,9	68,6	49,1	84,5	0,24	>0,47 <0,48	>0,42 <0,43
15	40,4	72,9	50,0	90,2	0,62	1,15	1,06
Means ± SD	33,8 ± 5,09	62,1 ± 6,94	46,5 ± 4,2	85,2 ± 4,7			

and for the ensuing 6 weeks were plotted below each patient's body weight value, 5 of the 6 patients whose body weight on admission exceeded 65% of standard had demonstrable levels of TGA in their urine during the first week of treatment, while all 6 patients had demonstrable TGA levels in their urine during the next 6 weeks. In contrast, all 9 patients whose body weights on admission were below 65% of standard had undetectable TGA in their urine during the first week of treatment. Four patients in this group (Nos. 1, 6, 10, 12) had detectable mean TGA concentrations during the following 6 weeks. Thus, patients who on admission had higher body weights also had a higher mean TGA output over the next 50 days ($r = 0{,}54$, $P<0{,}05$).

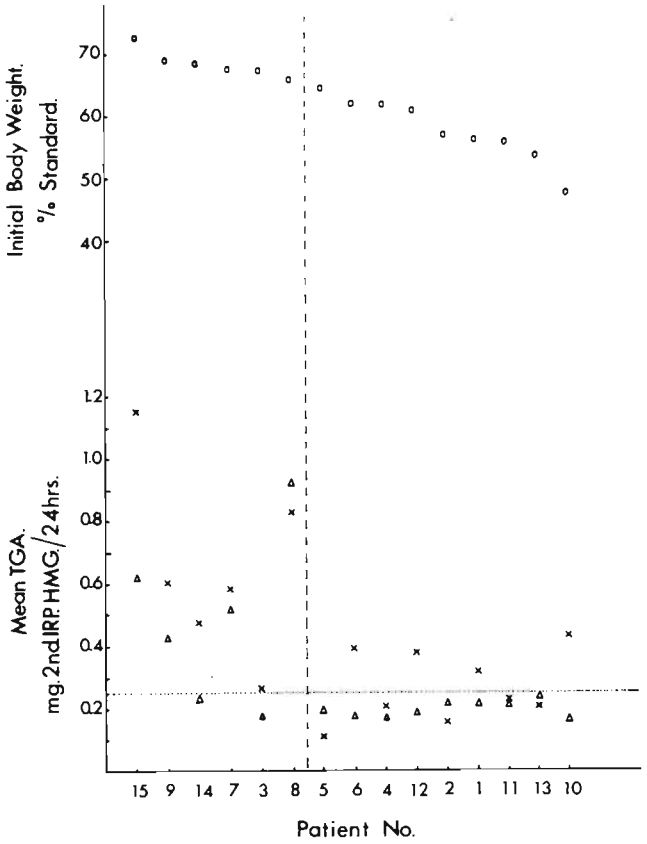

Fig. 1. The relationship between body weight (open circle) and the mean TGA output during the first week (open triangle) and the ensuing 6 weeks (cross) of dietary treatment. The vertical dashed line separates patients whose initial body weight was greater than or less than 65% of the standard. The horizontal dotted line represents the limit of sensitivity of the TGA assay.

Although all 15 patients responded to dietary treatment by gaining varying amounts of weight, several patients relapsed after discharge from hospital, and 4 of these (Nos. 2, 5, 6, 13) were readmitted to the Metabolic Unit for further treatment of their illness. An opportunity was thus afforded for the study of the same patients on two occasions. In 3 patients (Nos. 2, 6, 13) urinary TGA output was measured during both admissions on days 1 and 2, and every third day thereafter until day 50 of treatment. Patient 5 was studied in the same way, but for a period of 26 days during the second admission. TGA values on the same days after both admissions to hospital, were paired. The means of the paired differences were then compared with zero. Patients 2, 5 and 13 were between 5 and 16 kg heavier when admitted to hospital for the second time, 10 - 14 months after the first admission. Patient 6 weighed 2,3 kg less on the second admission. The difference between the paired gonadotrophin levels of the 3 patients (2, 5, 13) who weighed more the second time, was significantly different from zero (Table II) while that for patient 6, who weighed slightly less the second time, was not significantly different from zero. The TGA excretion pattern of patient 2 during both hospital admissions is shown in Fig. 2.

Rhythmical TGA output: Patient 7 showed a fluctuating TGA excretion pattern approaching normality (Fig. 3). This patient menstruated on day 62 of the study and had regular menses thereafter. Two other patients (Nos. 8 and 9) menstruated 2 - 3 months after the conclusion of the study, which suggests that phasic TGA excretion occurred at a later stage. Although both patients had TGA levels which were relatively high during the investigation, no clear-cut phasic pattern of hormone excretion was discerned at that time.

TABLE II. EFFECT OF DIETARY TREATMENT ON WEIGHT GAIN AND MEAN GONADOTROPHIN EXCRETION IN 4 PATIENTS DURING TWO CONSECUTIVE HOSPITAL ADMISSIONS

Patient No.	Hospital admission	Interval between admissions (months)	Body weight on admission (kg)	Weight gain (kg)	Mean TGA output ±SD	Difference between pairs (mean ± SD)
2	1st	12	29,6	13,7	0,22 ± ,03	0,635 ± 0,44 †
	2nd		34,7	14,0	0,86 ± ,44	
5*	1st	10	36,5	11,4	0,18 ± ,02	0,25 ± 0,18 ‡
	2nd		52,4	0,0	0,44 ± ,18	
6	1st	9	37,7	14,4	0,36 ± ,30	0,196 ± 0,52
	2nd		35,4	12,9	0,56 ± ,49	
13	1st	14	27,6	15,5	0,25 ± ,02	0,061 ± 0,090‡
	2nd		37,2	14,5	0,30 ± ,10	

* This patient was studied for a period of 26 days (10 TGA assays).
† $P < 0{,}001$.
‡ $P < 0{,}05$.

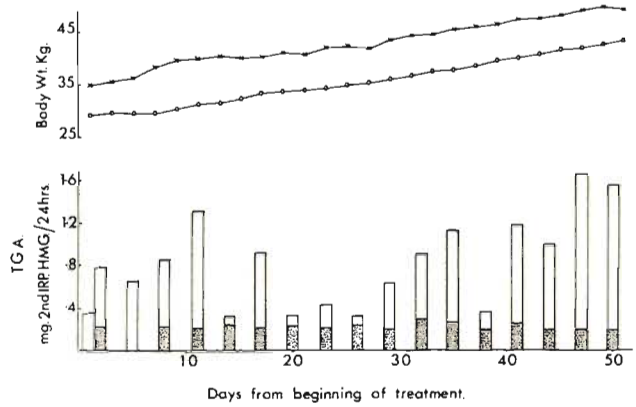

Fig. 2. Body weight and urinary TGA of patient 2 during 2 hospital admissions. o——o body weight first admission; x——x body weight second admission; stippled bars and open bars represent TGA output during first and second hospital admissions, respectively.

Of the remaining patients, TGA output was detectable in the majority at some time during 50 days of dietary treatment, but marked rhythmical variation in TGA excretion as occurs during the normal menstrual cycle was absent. Furthermore, none of the patients, except those mentioned above, had normal menses during a follow-up period of 12 months.

Patients with Obesity

Body weight changes during treatment: Weight changes in 3 obese patients on a reducing regimen are shown in Table III. Their body weights were at least 25 kg (45%) in excess of their standard weights. During the period of study, which ranged between 87 and 146 days, the 3 patients lost at least 16 kg in weight (Table III). Patient 16 had her last menstrual period after 50 days of weight loss, patient 17 after 117 days of weight loss, and patient 18 had her last period after 143 days of being on a reducing diet.

TGA excretion patterns: The output of TGA by each patient showed some variation with time and during a few menstrual cycles the mean output of TGA was near the lower limit of normality (Table IV). Thus, in patient

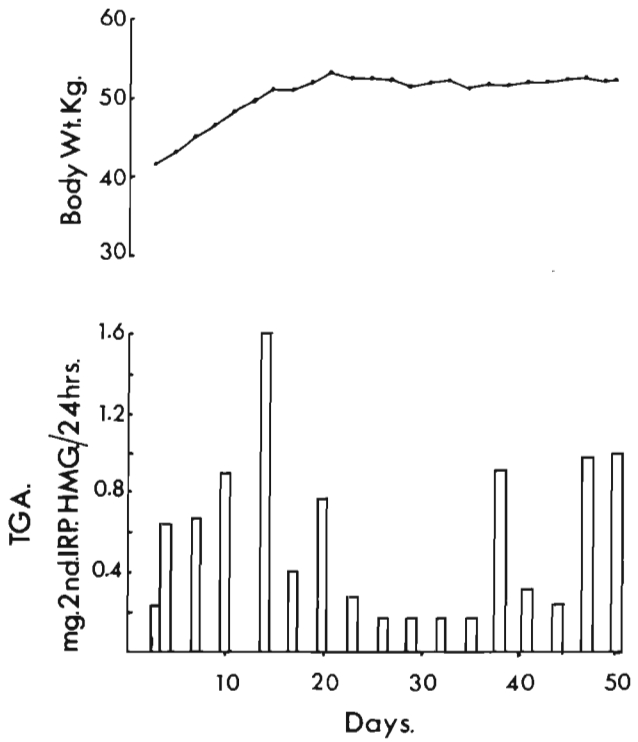

Fig. 3. Body weight changes and TGA excretion pattern of patient 7 during 50 days of dietary treatment.

16 the pattern of hormone excretion was normal until day 50 (Fig. 4). A midcycle TGA peak was apparent on day 2 of the study, followed by low levels of hormone output until day 19. During the menstrual cycle between days 20 and 50, the mean output of TGA was within the normal range (>0,70, <0,72 mg 2nd IRP HMG/24 h) and cyclicity of hormone output was apparent. During the subsequent 30 days (day 50 to day 80), rhythmic gonadotrophin excretion was still apparent, but during this period the mean output of TGA had fallen to >0,27, <0,34 mg 2nd IRP HMG/24 h. In this patient there was a diminishing mean output of TGA between the first and third menstrual cycles, while the rhythmical excretion of TGA continued until the onset of amenorrhoea. Hormone levels were then undetectable.

TABLE III. AGE, BODY WEIGHT DATA, GONADOTROPHIC HORMONE EXCRETION PATTERNS AND NUMBER OF MENSES IN 3 OBESE PATIENTS DURING WEIGHT REDUCTION

Patient No.	Age (yrs)	Duration of study (days)	Body weight (kg)		TGA excretion pattern	Menses
			Initial	Loss		
16	18	87	79	16	G: diminished R: normal	2*
17	15	120	93	20	G: diminished R: normal	5*
18	21	146	81	17	G: diminished R: normal	5*

G = mean output of TGA during successive cycles; R = rhythmicity of TGA output during successive cycles.
* Followed by amenorrhoea.

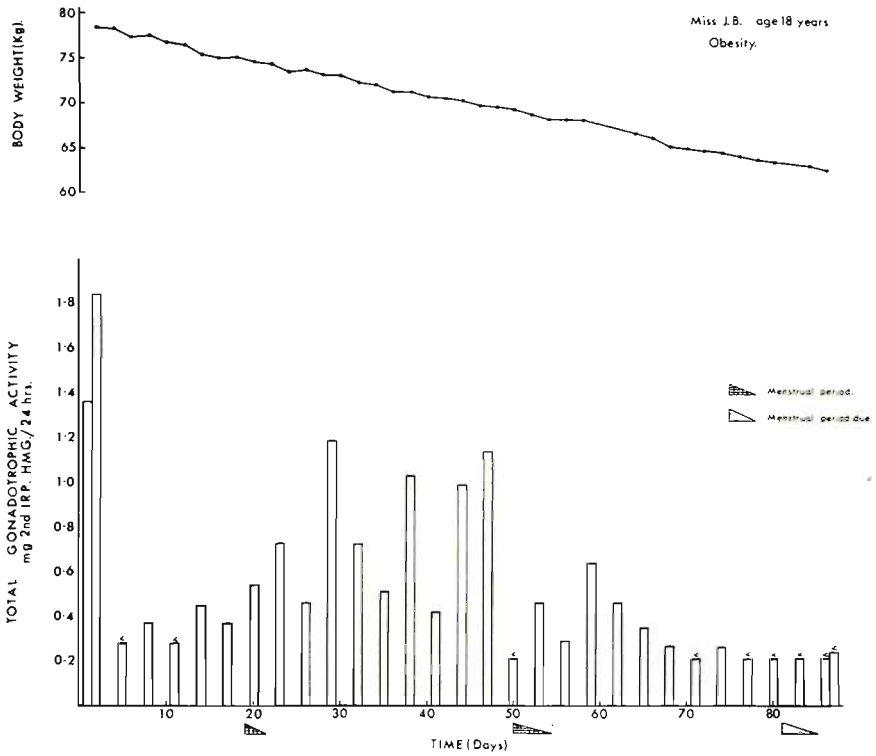

Fig. 4. Body weight change and TGA excretion pattern of patient 16 during a period of 87 days dietary restriction.

TABLE IV. MEAN TGA EXCRETION DURING SUCCESSIVE MENSTRUAL CYCLES IN 3 OBESE PATIENTS DURING WEIGHT LOSS

Patient No.	Mean TGA output during 3 successive menstrual cycles (mg 2nd IRP HMG/24 h)		
	1st cycle	2nd cycle	3rd cycle
16	>0,62 <0,70*	>0,70 <0,72	>0,27 <0,34
17	0,66	>0,32 <0,39	>0,33 <0,42
18	1,03	>0,59 <0,62	>0,54 <0,59

* Mean value during last 17 days of first cycle.

Similar observations were made on patients 17 and 18. In both cases the mean output of TGA during the third menstrual cycle was about half that of the first cycle, yet the phasic excretion of TGA was evident during all the menstrual cycles studied (Table III).

DISCUSSION

Low gonadotrophin excretion by patients suffering from malnutrition and weight loss has been well documented. The excellent review of Zubiran and Gomez-Mont[10] is perhaps the most complete work currently available on the subject. These authors showed that 80% of famine victims with malnutrition had low gonadotrophin excretion. During treatment by refeeding, however, the excretion of gonadotrophic hormones was found to increase markedly within a few weeks of treatment. Normal menstrual function returned relatively rapidly in all women who were premenopausal.

As might be expected, patients with anorexia nervosa also excrete very small or undetectable amounts of gonadotrophin when they are emaciated. While these patients invariably show increased gonadotrophin excretion during dietary treatment, phasic gonadotrophin output occurs only rarely.[11-13] In this study, 10 out of 15 patients excreted detectable gonadotrophins during 7 weeks of treatment, but only 1 of these patients exhibited a pattern of hormone excretion which may have been rhythmical. She menstruated early during treatment.

Among these patients there was a significant positive correlation between the patient's body weight on admission to hospital and subsequent mean gonadotrophin excretion during a 50-day treatment period. Additional evidence in support of this correlation was provided by repeat studies on 4 patients, 3 of whom exhibited a greater body weight when admitted to hospital for the second time. These 3 patients had a higher gonadotrophin output during their second admission when it was compared with their first.

The resumption of basal gonadotrophin excretion would thus seem to be affected by body weight level before its increase induced by diet. If body weight before treatment is below a critical point, which for patients with anorexia nervosa appears to be in the region of 65% of standard weight, gonadotrophin excretion is reduced to very low

or undetectable levels. As the pretreatment body weight nears normality, basal gonadotrophin excretion is subsequently resumed during treatment in the majority of patients. This would suggest that the pituitary gonadotrophin response to dietary treatment remains refractory in the very emaciated patient for periods greater than 50 days. On the other hand, the less severe cases of anorexia nervosa excrete normal amounts of gonadotrophin on admission to hospital and continue to do so during weight gain. None the less, a return of phasic TGA output and normal menses is limited to only a few of these patients after many months of treatment.

The loss of rhythmical gonadotrophin excretion is difficult to explain simply in terms of weight loss, since few patients displayed rhythmical hormone output after their normal body weight was restored. Dally and Sargant[14] have suggested that normal menses return in anorexic patients only after their psychological disorder has been alleviated, in addition to their maintaining a normal body weight. Morgan[15] has found a strong association between normal menstruation and normal psychiatric rating when body weight is also normal. However, when menstruation fails, psychiatric ratings tend to be lower, even though body weight may be normal. These findings suggest that a neural mechanism is in large measure responsible for the control of cyclic gonadotrophin secretion. Other clinical evidence in support of this is provided by the study of 3 obese patients on a reducing diet. Here again weight loss in obese patients resulted in a reduction of gonadotrophin excretion during successive menstrual cycles. Phasic hormone excretion, however, was unaffected by this weight reduction and continued even when basal TGA output was very low (days 50 - 80 in Fig. 4).

Evidence provided by animal studies suggests that gonadotrophin secretion is controlled by a dual mechanism[16,17] and that the regulation of its basal secretion can be separated from that of its phasic midcycle surge. The latter is to a large extent neurally mediated, although some studies suggest that oestrogen secretion may play a part as well.[18-20]

The activity of the ovaries in patients with anorexia nervosa is unclear. Hence their possible role, mediated by oestrogen secretion, in the return of phasic gonadotrophin secretion, has still to be determined.

The conclusions drawn from this study are based upon observations of consistent trends of hormone excretion. The data will not stand rigid statistical analysis, and for this reason the arguments are based upon tentative information which must await verification with the use of more refined hormone assay techniques.

CONCLUSIONS

The evidence provided by this study of female patients with anorexia nervosa or obesity, suggests that the control of gonadotrophin secretion in women occurs at two levels. The first is the basal secretion, predominantly affected by body weight changes, and the second the phasic secretion, seemingly more easily affected by psychological distress than by weight loss, which suggests an overriding neural control. These observations are supported by the extensive findings in favour of dual control of gonadotrophin secretion obtained from animal experimentation.

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