Hypothalamo-pituitary-thyroid function in anorexia nervosa: influence of weight gain

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Summary and conclusions

The functional state of the hypothalamo-pituitary-thyroid axis was assessed in 14 women and girls with anorexia nervosa when at low body weight and again in 12 cases after they had gained weight. Mean serum thyroxine concentrations were low before and after weight gain. Mean serum triiodothyronine (T3) concentrations were substantially reduced at low weight and doubled after weight gain, the absolute values being linearly correlated with body weight expressed as a percentage of the ideal. Concentrations of reverse T3 were greatly increased in some patients initially and fell with weight gain. Basal concentrations of thyroid-stimulating hormone (TSH) were unchanged after weight gain but the TSH response to thyrotrophin-releasing hormone was significantly augmented; delayed patterns of response were found in seven out of 12 patients tested before and three out of 12 patients tested after weight gain.

Changes in the hypothalamo-pituitary-thyroid axis are common in anorexia nervosa and probably represent both peripheral and central adaptations to the altered nutritional state.

Introduction

Anorexia nervosa is characterised by severe weight loss and amenorrhoea associated with refusal to eat.¹ There may be various abnormalities of endocrine function, and controversy persists about whether these are of pituitary or hypothalamic origin.² Thyroid function is usually regarded as normal³ despite features suggestive of hypothyroidism, such as low basal metabolic rate,⁴ sinus bradycardia, and prolonged ankle reflex relaxation time.⁵ Recently serum triiodothyronine concentrations were reported to be low in anorexia.⁶ Thus hypothyroidism may be more common than has been thought.

We have studied a group of patients with anorexia nervosa to define their thyroid state and examine the relation between body weight and thyroid function during refeeding.

Patients and methods

Fourteen women and girls with typical anorexia nervosa⁷ but no clinical evidence of thyroid disease were studied (table I). All were treated with an increased energy intake, reinforced by rewards for reaching target weights, together with continuing psychotherapy. No psychotropic drugs were given. The patients were first investigated

shortly after admission to hospital while still at low body weight. Twelve were reinvestigated, some during and all after a period of weight gain, either while still in hospital or, in two cases, eight months after treatment was started while they maintained a stable weight as outpatients. No patient resumed menstruation during the study.

The patients were fasted overnight and an indwelling cannula was inserted into a forearm vein between 9 and 10 am and kept patent with heparinised saline. An initial blood sample was taken for estimation of thyroid and pituitary hormones. A mixture of 200 µg thyrotrophin-releasing hormone (TRH) and 100 µg luteinising hormone/ follicle-stimulating hormone-releasing hormone was given by rapid intravenous injection and further blood samples were taken 20 and 60 minutes later.

TABLE I—Age, weight on presentation, and percentage of ideal body weight at times of first and final tests

Case No	Age (years)	Weight on presentation (kg)	% Ideal body weight	
			Initial	Final
1	14	40.2	81.2	88.0
2	12	31.6	70.1	
3	23	36.5	79.5	96.3
4	14	33.8	71.3	95.4
5	17	21.5	51.2	95.7
6	19	29.5	65.8	88.8
7	16	35.9	81.9	98.5
8	16	39.3	79.8	89.6
9	18	35.5	71.3	85.5
10	16	31.1	62.2	86.6
11	41	24.4	57.4	86.9
12	22	31.9	59.9	
13	25	32.6	63.9	96.7
14	19	34.4	66.2	86.7

3,5,3'-Triiodothyronine (T3) and thyroxine (T4) were measured by radioimmunoassay using 8-anilino-naphthyl-1-sulphonic acid to displace the hormones from serum binding protein and charcoal-methylcellulose to separate bound and free fractions. Thyrotrophin (TSH) was measured by a double antibody radioimmunoassay with guinea-pig antihuman TSH, the WHO first IRP 68/38 being used as standard. All TSH specimens were measured in the same assay. Reverse T3 (3,3',5'-triiodothyronine; rT3) was kindly estimated in some samples by Dr W Ratcliffe, Glasgow Royal Infirmary, by radioimmunoassay.⁸ Prolactin and gonadotrophin measurements will be reported elsewhere.

The data were analysed with reference to body weight as a percentage of the ideal for each patient's age, height, and frame derived from the tables of the Metropolitan Life Insurance Company.

Results

THYROXINE

Before refeeding the mean total T4 concentration was $87.7 \pm SE 8.5$ nmol/l (range 51-134) (6.8 ± 0.7 µg/100 ml; range 4.0-10.4), while after weight gain it was 87.0 ± 5.7 nmol/l (range 53-131) (6.7 ± 0.4 µg/100 ml; range 4.1-10.2) (table II). There was no significant difference between these means, though both were significantly lower ($P=0.005$ and $P=0.003$ respectively) than the mean in a group of 23 healthy male and female medical students (109.9 ± 4.2 nmol/l, range 70-153; 8.5 ± 0.3 µg/100 ml, range 5.4-11.9). The normal reference range for our laboratory is 70-160 nmol/l (5.4 - 12.4 µg/100 ml). Four of the 14 values were frankly subnormal before weight

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TABLE II—Serum concentrations of thyroxine (T4), triiodothyronine (T3), and reverse triiodothyronine (rT3) before and after weight gain (results in some patients tested at intermediate weights not shown). Concentrations in nmol/l

Case No	Before weight gain			After weight gain		
	T4	T3	rT3	T4	T3	rT3
1	119	1.2		80	2.1	0.14
2	87	0.8				
3	62	1.6	0.18	53	2.1	0.03
4	75	0.8		78	2.05	0.16
5	78	0.3	0.61	100	2.3	0.07
6	93		0.84	100	1.8	0.16
7	76	2.0	0.05	88	2.25	
8	51			63		
9	102	1.1		94	1.2	
10	60	0.96	0.18	89	1.1	0.08
11	65	0.9	0.24	78	2.6	
12	112	0.73	1.39			
13	134			90	2.4	0.06
14	114	1.7		131	2.1	
Mean ± SE	87.7 ± 8.5	1.10 ± 0.15	0.54 ± 0.19	87.0 ± 5.7	2.00 ± 0.14	0.10 ± 0.02

Conversion: SI to traditional units—Serum T4: 1 nmol/l ≈ 0.08 µg/100 ml. Serum T3 and rT3: 1 nmol/l ≈ 0.65 ng/ml.

gain, as were two out of 12 after weight gain. There was no correlation between T4 and body weight.

TRIIODOTHYRONINE

Before refeeding the mean total T3 concentration was 1.10 ± 0.15 nmol/l (range 0.3–2.0) (0.7 ± 0.09 ng/ml; range 0.2–1.3), rising to 2.0 ± 0.14 nmol/l (range 1.1–2.6) (1.3 ± 0.09 ng/ml; range 0.7–1.7) after weight gain, this difference being highly significant (P < 0.001). Six out of 11 patients tested initially had values below the lower limit of our normal range (1.08–2.61 nmol/l; 0.7–1.7 ng/ml), while all 11 tested after weight gain were within the normal range. All nine patients for whom paired results were available showed a rise in T3 (P < 0.001). There was a highly significant correlation between serum T3 concentration and body weight expressed as a percentage of the ideal (r = 0.79; P < 0.001—fig 1).

THYROXINE/TRIIODOTHYRONINE RATIO

The mean T4/T3 ratio fell from 98.8 ± 18.9 to 48.1 ± 5.7 after weight gain (P = 0.018). There was a highly significant inverse correlation between the T4/T3 ratio and the percentage of ideal

body weight (r = -0.71; P < 0.001), though this was slightly weaker than that for T3 alone.

REVERSE TRIIODOTHYRONINE

There was a wide scatter of results for rT3 concentrations before weight gain (fig 2, table II), with three out of seven well above the normal range of 0.15–0.42 nmol/l (0.09–0.27 ng/ml) (mean 0.27 ± 0.01 nmol/l; 0.18 ± 0.007 ng/ml). The one subnormal value of 0.05 nmol/l (0.03 ng/ml) was obtained on the sixth hospital day, when the patient's T3 was 2.0 nmol/l (1.3 ng/ml). After weight gain five out of seven patients tested had subnormal rT3 values, with two others at the lower limit of normal. Four patients tested both before and after weight gain showed a fall in rT3. There were significant inverse correlations between rT3 and percentage of ideal body weight r = -0.61; P = 0.025) and between rT3 and T3 (r = -0.55; P = 0.028).

FIG 2—Serum reverse triiodothyronine (rT3) concentrations before and after weight gain. Normal range shaded.
Conversion: SI to traditional units—Serum rT3: 1 nmol/l ≈ 0.65 ng/ml.

THYROTROPHIN

One patient (case 11) had mildly raised basal TSH concentrations (4.5–8.0 mU/l) throughout the study (normal < 4.0 mU/l) (table III). Eight of the other 12 patients tested had initial TSH concentrations at or below the detection limit of the assay (1 mU/l), while after weight gain this was true of five out of 11 patients tested. There was no correlation between basal TSH values and weight.

Table IV shows the mean TSH concentrations before and after TRH injection in the 11 patients tested both before and after weight gain. With undetectable TSH concentrations being taken as 0.5 mU/l there was no significant difference between basal values, whereas TSH increments were significantly increased after weight gain at both 20 minutes (P = 0.016) and 60 minutes (P = 0.035), as was the maximal TSH increment (P = 0.012). Comparison of the 20-minute and 60-minute TSH values by the Wilcoxon ranked pairs test also showed a significant increase after weight gain (P < 0.01 for both values). There was no correlation between post-TRH values of TSH or TSH increments and body weight.

Patterns of response were variable. The patient (case 11) with a raised basal TSH concentration showed delayed responses on the three occasions on which she was tested (the 60-minute TSH value being equal to or greater than the 20-minute value). Before weight gain five of the other patients showed normal patterns of response, and six delayed patterns, four of which were also impaired (TSH increment < 5 mU/l). After weight gain a normal response was characteristic,

FIG 1—Correlation between serum triiodothyronine (T3) concentrations and percentage ideal body weight.
Conversion: SI to traditional units—Serum T3: 1 nmol/l ≈ 0.65 ng/ml.

TABLE III—Serum concentrations of thyrotrophin (TSH), maximal TSH increment after TSH-releasing hormone (TRH) (Max Δ TSH), and pattern of response to TRH (N=normal, D=delayed) before and after weight gain (results in some patients tested at intermediate weights not shown)

Case No	Before weight gain			After weight gain		
	TSH (mU/l)	Max Δ TSH	Response	TSH (mU/l)	Max Δ TSH	Response
1	2.0	11.0	N	<1.0	10.5	N
2	1.0	24.0	D			
3	<1.0	6.7	N	<1.0	11.5	N
4	<1.0	4.9	N	2.0	5.0	N
5	<1.0	2.2	D	<1.0	25.5	N
6	1.1	0.9	D	1.0	5.4	N
7	<1.0	3.5	D	<1.0	5.9	N
8	<1.0	7.5	N	4.0	8.0	D
9				1.7	22.3	N
10	2.6	13.4	D	3.0	21.5	D
11	6.0	18.0	D	8.0	31.0	D
12	<1.0	2.3	D			
13	2.2	8.7	N	3.8	21.2	N
14	<1.0	10.5	N	3.0	15.0	N

TABLE IV—Mean ($\pm$ SE) thyrotrophin (TSH) concentrations in 11 patients before and after weight gain, and effect on TSH increments (Δ TSH) during TSH-releasing hormone tests. Concentrations in mU/l. Basal values below 1 mU/l assumed to be 0.5 mU/l

	Time in minutes					
	0	20	60	Δ 20	Δ 60	Max Δ
Before	1.5 $\pm$ 0.5	8.3 $\pm$ 1.5	8.5 $\pm$ 2.0	6.7 $\pm$ 1.2	6.9 $\pm$ 1.5	7.9 $\pm$ 1.5
After	2.4 $\pm$ 0.7	16.8 $\pm$ 3.2	13.8 $\pm$ 3.2	14.4 $\pm$ 2.7	11.4 $\pm$ 2.7	14.6 $\pm$ 2.7
P	>0.05	<0.01	<0.01	0.016	0.035	0.012

being found in nine cases; the other two patients had delayed responses.

Discussion

It is well established that T3 concentrations may be reduced in many severe and chronic non-thyroidal illnesses.⁹ Anorexia nervosa is no exception, and reduced T3 associated with an increased T4/T3 ratio is well documented.^{6,10} When patients with anorexia are given a sub-replacement dose of oral T3 a greater reduction in their ankle reflex relaxation time than in normal controls has been observed, suggesting a tissue hormone deficiency.¹⁰ Circulating T3 is largely derived from peripheral deiodination of T4, but in systemic illness there may be preferential conversion of T4 to the inactive isomer rT3.¹¹ We found a raised rT3 concentration in some of our patients, which fell to within or below the normal range on refeeding. Such an increase in the metabolically inactive rT3 associated with reduced T3 may represent an adaptive process to limit catabolism and has also been described in protein-energy malnutrition¹² and in fasted obese subjects.¹³ In anorexia nervosa the T3 concentration increases on refeeding.¹⁰ We found this increase to be linearly correlated with the percentage of ideal body weight, in agreement with Vigersky *et al.*¹⁴ Mean T4 concentrations, however, remained low throughout.

The lack of increase in basal TSH despite low T3 and T4 concentrations has been noted before^{9,14} and, if rT3 itself is assumed to play no part in the feedback inhibition of TSH release, must be due to an alteration in the "set-point" at which the pituitary thyrotroph cells are inhibited by thyroid hormones. This effect may be mediated via central dopaminergic pathways. Levodopa reduces TSH concentrations in hypothyroidism,¹⁵ and metoclopramide, a centrally acting dopamine receptor antagonist, increases TSH concentrations in normal¹⁶ and hypothyroid subjects,¹⁷ suggesting dopaminergic inhibitory control of TSH secretion. In our patients the pituitary TSH reserve was reduced at low body weight, which has also been shown for prolactin.¹⁸ This accords with the theory that there is excessive dopaminergic activity at central receptors in anorexia nervosa.¹⁹

It remains uncertain whether such an effect occurs mainly in the thyrotroph cells or is mediated indirectly via the hypo-

thalamus. Evidence of hypothalamic dysfunction in anorexia nervosa, however, is found in the impaired diurnal variation of thyroidal iodide release,¹⁰ and in the delayed TSH response to TRH²⁰ shown in some patients by ourselves and others.¹⁰

We conclude that changes in the hypothalamo-pituitary-thyroid axis in anorexia nervosa are common and probably represent both peripheral and central adaptations to the altered nutritional state. Apart from the low mean T4 concentrations these changes are rapidly reversed on refeeding and weight gain.

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