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ACTA ENDOCRINOLOGICA
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# EFFECTS OF OBESITY, TOTAL FASTING AND RE-ALIMENTATION ON L-THYROXINE ($T_4$), 3,5,3'-L-TRIIODOTHYRONINE ($T_3$), 3,3',5'-L-TRIIODOTHYRONINE ($rT_3$), THYROXINE BINDING GLOBULIN (TBG), CORTISOL, THYROTROPHIN, CORTISOL BINDING GLOBULIN (CBG), TRANSFERRIN, $\alpha_2$-HAPTOGLOBIN AND COMPLEMENT C'3 IN SERUM

By

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## ABSTRACT

The effects of total fasting for 31 ± 10 days followed by re-alimentation with an 800 calorie diet on thyroid function, i.e. $T_4$,$T_3$, $rT_3$, $RT_3U$ (resin $T_3$ uptake), and TSH, and on TBG levels in serum were studied sequentially in obese hospitalized patients (N = 18). Additionally, cortisol, growth hormone, prolactin, parathyrin and free fatty acids were followed as hormonal and metabolic parameters, respectively. Further, CBG, transferrin, $\alpha_2$-haptoglobin and complement C'3 were measured as representatives of other serum proteins.

Results before fasting: $T_4$, $T_3$, TBG, cortisol, CBG, $\alpha_2$-haptoglobin and complement C'3 of the obese patients were elevated when compared with healthy normal weight controls, whereas $rT_3$, $T_4$/TBG ratio, $T_3$/TBG ratio, TSH, cortisol/CBG ratio, growth hormone, prolactin, parathyrin and transferrin of the obese group were normal. $RT_3U$ and $fT_4$ index were decreased in the obese patients.

Results during fasting: Significant decreases were observed during fasting for the following parameters – $T_3$, TBG, $T_3$/TBG ratio, transferrin, $\alpha_2$-

[1] A preliminary report was presented at the XI. Acta Endocrinologica Congress, Lausanne, Switzerland *(Scriba et al.* 1977).

haptoglobin, complement C'3. $rT_3$, $T_4$/TBG ratio, $RT_3U$, $fT_4$ index and FFA increased. $T_4$, TSH response to TRH stimulation, cortisol, CBG, cortisol/CBG ratio, parathyrin, growth hormone and prolactin did not change.
Results during re-alimentation: $T_3$, TBG, $T_3$/TBG ratio, TSH response to TRH, transferrin, $\alpha_2$-haptoglobin and complement C'3 increased. Conversely, $rT_3$, $RT_3U$, FFA, cortisol and cortisol/CBG ratio decreased, whereas the other parameters did not change.
Conclusions: 1) There is no evidence for primary hypothyroidism in obese patients during prolonged fasting and re-alimentation. 2) The rapid decrease of $T_3$ and increase of $RT_3U$ after initiation of fasting are not fully explained by the observed slower decreases in TBG. 3) The alterations of $T_3$, $rT_3$ and $RT_3U$ resemble in their kinetics the changes in FFA levels. 4) Fasting reduced the levels of only certain serum proteins, interestingly TBG, transferrin, $\alpha_2$-haptoglobin and complement C'3, all of which, except transferrin, are elevated in obesity. 5) The magnitude of the observed decreases does not suggest any clinically relevant deficiencies in serum proteins. 6) Re-alimentation reverses rapidly all observed changes.

Several recent publications have dealt with alterations of thyroid hormone metabolism in obese patients during total fasting. 3,5,3'-L-triiodothyronine ($T_3$) levels in serum were shown to decrease during fasting whereas the metabolically inactive metabolite of thyroxine 3,3',5'-L-triiodothyronine (reverse $T_3$, $rT_3$) increased (*Balsam & Ingbar* 1977; *Carlson et al.* 1977; *Croxson et al.* 1977; *Merimee & Fineberg* 1976; *Palmblad et al.* 1977; *Portnay et al.* 1974; *Vagenakis et al.* 1975, 1977) while total thyroxine ($T_4$) levels remained constant. The daily weight loss decreased during several weeks of total fasting and the basal metabolic rate (BMR) also diminished with the duration of the fasting (*Ditschuneit* 1976). This study was performed in order to evaluate the possibility that the changes in BMR could be due to thyroid hormone deficiency arising from fasting (*Hofmann et al.* 1974; *Scriba et al.* 1967; *Scriba & Hofmann* 1976).

The total thyroid hormone concentration in serum depends on the concentration of their specific transport proteins of which thyroxine binding globulin (TBG) is the most important. For this study, it had to be taken into consideration that the serum globulins transferrin, $\alpha_2$-haptoglobin and complement C'3 ($\beta_1$A-globulin) decreased during total fasting of 3 weeks duration (*Fateh-Moghadam et al.* 1977). The alterations of the TBG levels during fasting and re-alimentation had therefore to be studied for a better understanding of the thyroid function of obese patients during this procedure, also in view of the fact that an abnormally high binding of thyroid hormones to serum proteins has been reported in earlier studies (*Premachandra et al.* 1970; *Schatz et al.* 1967; *Scriba et al.* 1967).

## METHODS

### *Patients*

Treatment of alimentary obesity by total fasting of maximally 50 days duration was performed on 18 hospitalized patients, in whom other metabolic or endocrine diseases and liver or kidney diseases, respectively, had been excluded. The patients received an 800 calorie (3336 kJ) mixed diet for subsequent re-alimentation. Patients admitted to this study had no recent treatment with metabolically active drugs, in particular laxatives, diuretics, thyroid hormones or corticosteroids. In the female patients, no hormonal contraception had been practised for at least 4 weeks prior to the initiation of the fasting. The mean age of the patients was 27 years, 9 males were from 15 to 39 years old, 9 females from 16 to 46 years. The mean initial weight was 168.5 ± 20.5 % (SD) of the ideal weight in females and 166.4 ± 20.2 % in males.

### *Fasting*

The mean duration of the fasting was 31 ± 10 days, the daily weight loss was 454 ± 96 g/day in females and 547 ± 137 g/day in males. The following determinations were performed for control of the fasting and as a precaution against complications: Free fatty acids, calcium, potassium, sodium and uric acid in serum, acetone in urine and electrocardiogram at least weekly. The transaminases were controlled fortnightly. A minimal calorie-free fluid input of 2 l/day was maintained. A polyvitamin preparation lacking vitamin D was given daily, potassium was administered whenever there was a tendency for lowering of serum potassium. Allopurinol (300 mg/day) which is known to leave iodine metabolism unchanged (*Rosenkrantz et al.* 1968), was administered orally, whenever the uric acid level rose above 12 mg/100 ml. Some patients received colloidal aluminium phosphate. Blood samples were drawn between 8 and 9 a.m. at intervals indicated in Figs. 1 and 2, and before breakfast during the re-alimentation period.

### *Laboratory methods*

Triiodothyronine, $T_3$ (*Horn et al.* 1975), reverse triiodothyronine, $rT_3$ (*Meinhold et al.* 1975), thyroxine binding globulin, TBG (*Horn et al.* 1977), thyrotrophin (*Erhardt et al.* 1973), cortisol (*Horn et al.* 1975), corticosteroid binding globulin, CBG (*Bernutz et al.* 1978), parathyrin, PTH (*Wood et al.* 1978), growth hormone and prolactin (*von Werder* 1975) were determined by published radioimmunoassay (RIA) procedures. Thyroxine determinations, using competitive protein binding assay (CPBA), and $T_3$-uptake tests, $T_3U$, were performed as published (*Horn et al.* 1975). Transferrin, $\alpha_2$-haptoglobin and complement C'3 were determined by radial immunodiffusion after *Mancini et al.* (1965) and *Lamerz et al.* (1973). Free fatty acids, FFA, were analysed by a modification (*Dieterle et al.* 1968) of the colorimetric assay (*Duncombe* 1963).

### *Statistical evaluation*

Student's *t*-test was used for the comparison of pre-fasting levels of obese patients and of controls. Student's non-paired *t*-test may however not be used for the evaluation of sequential changes when more than two sampling times are involved. The sequential data during total fasting and re-alimentation are certainly not independent. Therefore, the regression of the measured values against the time and also the linearity (one way analysis of variance) were calculated (*Sachs* 1972). The significance of observed alterations could then be calculated from the correlation coefficient r and from the number of determinations N. Both, the fasting and the re-alimentation were separated into two periods in order to allow for better description of the kinetics of the observed alterations: Fasting periods I (day 1–15) and II (day 15–end); re-alimentation periods I (day 1–6) and II (day 6–30).

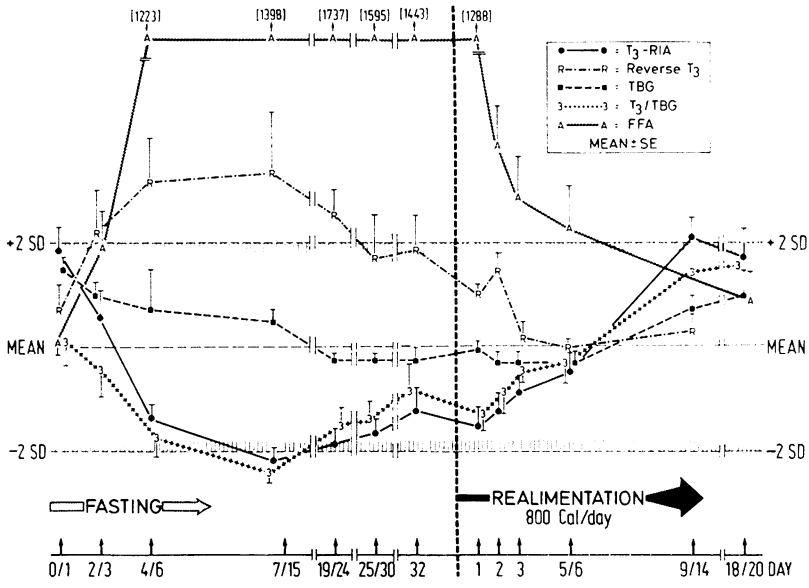


*Fig. 1.*

Triiodothyronine ($T_3$-RIA), $rT_3$, thyroxine binding globulin, $T_3$/TBG ratio, and free fatty acids before and during fasting and re-alimentation of obese patients. Superimposed normal means ± 2 standard deviations of all measured parameters correspond to the following data:

$T_3$-RIA: 116 ± 36 ng/100 ml; $rT_3$: 0.207 ± 0.184 ng/ml; TBG: 2.0 ± 0.8 ml/100 ml: $T_3$/TBG: 58 ± 36, FFA: 480 ± 250 μEq./l.

## RESULTS

### *Triiodothyronine ($T_3$)*

The initial $T_3$ levels of the obese patients (N = 18) of 141 ± 21 ng/100 ml (mean ± SD) were within the normal range but significantly ($P < 0.001$) above the mean (*Horn* 1976) of healthy normal weight controls (N = 58) of 116 ± 18 ng/100 ml (*Horn* 1976). A rapid decline of the $T_3$ levels was observed during the first 2 weeks of total fasting (Fig. 1, Table 1). The decrease was linear and significant ($r = -0.6379$; $P < 0.001$, N = 58). A linear increase was observed during the second fasting period, i.e. after the 15th day ($r = +0.3781$; $P < 0.001$, N = 50). A further increase of the $T_3$ levels was observed during the re-alimentation period, which was linear and significant during the first re-alimentation period ($r = +0.2579$; $P < 0.05$, N = 62) and non-linear but significant after the 6th day of re-alimentation ($r = +0.4138$; $P < 0.05$, n = 27).

### *Reverse $T_3$ ($rT_3$)*

The sequential $rT_3$ levels were determined in only 5 patients. The initial $rT_3$ level of these patients of 0.22 ± 0.06 ng/ml (mean ± SD) was within the

*Table 1.*

Changes in the serum levels of triiodothyronine ($T_3$), ($rT_3$), thyroxine ($T_4$), thyroxine binding globulin (TBG), $T_4$/TBG ratio, $T_3$/TBG ratio, $T_3$-uptake, free thyroxine index, free fatty acids and basal thyrotrophin, respectively TSH increase 30 min after 200 $\mu$g TRH iv, before and during fasting and re-alimentation of obese patients (mean ± SD).

| | Total fasting | | | Re-alimentation | | |
|---|---|---|---|---|---|---|
| | before | 7.–15. day | 25.–30.day | before | 5.–6. day | 15.–30.day |
| $T_3$ ng/100 ml | 141 ± 21 | 77 ± 14 | 86 ± 18 | 89 ± 24 | 107 ± 22 | 144 ± 36 |
| $rT_3$ ng/ml | 0.22 ± 0.06 | 0.38 ± 0.15 | 0.27 ± 0.10 | 0.24 ± 0.03 | 0.18 ± 0.02 | 0.20 ± 0.04 |
| $T_4$ $\mu$g/100 ml | 8.3 ± 2.4 | 8.1 ± 2.3 | 7.2 ± 1.7 | 7.4 ± 1.5 | 7.4 ± 1.2 | 8.1 ± 2.1 |
| TBG mg/100 ml | 2.6 ± 0.5 | 2.2 ± 0.3 | 1.9 ± 0.2 | 2.0 ± 0.2 | 1.9 ± 0.3 | 2.4 ± 0.6 |
| $T_4$/TBG | 3.20 ± 0.94 | 3.76 ± 1.09 | 3.70 ± 0.90 | 3.78 ± 0.9 | 3.86 ± 0.93 | 3.72 ± 1.18 |
| $T_3$/TBG | 58.1 ± 17.8 | 35.8 ± 6.0 | 45.0 ± 10.2 | 46,2 ± 12.4 | 55.3 ± 12.9 | 60.7 ± 15.0 |
| $RT_3U$ % | 31.3 ± 4.6 | 37.8 ± 5.0 | 38.7 ± 4.8 | 38.1 ± 5.9 | 36.2 ± 6.5 | 33.8 ± 7.0 |
| $fT_1$-I | 2.56 ± 0.66 | 3.04 ± 0.91 | 2.86 ± 0.64 | 2.80 ± 0.67 | 2.65 ± 0.57 | 2.64 ± 0.73 |
| FFA $\mu$Eq./l | 591 ± 108 | 1395 ± 514 | 1594 ± 636 | 1288 ± 530 | 832 ± 327 | 688 ± 207 |
| TSH basal $\mu$U/ml | 1.3 ± 0.7 | 1.4 ± 0.5 | | | | 1.4 ± 0.5 |
| $\Delta TSH_{30min}$ $\mu$U/ml | 6.8 ± 3.9 | 5.6 ± 2.1 | | | | 9.1 ± 4.7 |

normal range of 0.023–0.391 ng/ml. A significant increase of this metabolite (Fig. 1, Table 1) was observed during the first fasting period ($r = +0.5683$; $P < 0.05$, $N = 14$). A mirror image decline in $rT_3$ levels was seen during the second fasting period when compared with the $T_3$ levels. A further significant decrease of $rT_3$ was observed during the first re-alimentation period ($r = -0.5955$; $P < 0.01$, $N = 20$).

*Thyroxine ($T_4$)*

The initial $T_4$ levels (Table 1) in obese patients of $8.3 \pm 2.4$ µg/100 ml were significantly higher than the mean value of age-matched normal weight controls (*Horn* 1976; *Horn et al.* 1977) of $6.7 \pm 1.3$ µg/100 ml ($P < 0.01$). There were no significant changes of the $T_4$ levels neither during fasting nor during re-alimentation.

*Thyroxine binding globulin (TBG)*

The initial TBG levels (Fig. 1, Table 1) of obese patients of $2.6 \pm 0.6$ mg/100 ml were significantly higher than the mean of age-matched normal weight controls of $2.0 \pm 0.4$ mg/100 ml ($P < 0.001$). The TBG levels decreased significantly and linearly ($r = -0.3957$; $P < 0.001$, $N = 56$) during the first fasting period. No further change of the TBG level was observed during the second fasting period. However, a significant increase of the mean TBG level was observed during the re-alimentation period ($r = +0.3049$; $P < 0.01$, $N = 80$).

*$T_4$/TBG ratio*

Before the fasting, the mean $T_4$/TBG ratio of obese patients of $3.20 \pm 0.94$ (µg/mg; equivalent to a molar ratio of 0.249) was practically identical with the mean of age-matched normal weight controls (*Horn et al.* 1977) of $3.17 \pm 0.88$. A significant and linear increase of the $T_4$/TBG ratio ($r = +0.2567$; $P < 0.01$, $N = 102$) was observed during the complete fasting period, whereas the $T_4$/TBG ratio remained elevated during re-alimentation.

*$T_3$/TBG ratio*

The $T_3$/TBG ratio decreased from an initial value of $58 \pm 18$ (ng/mg, which is equivalent to a molar ratio of 0.021) significantly and linearly to $36 \pm 6$ ($r = -0.4904$; $P < 0.001$, $N = 56$) during the first fasting period (Fig. 1, Table 1). During the second fasting period, however, the $T_3$/TBG ratio rose already significantly and linearly ($r = +0.3429$; $P < 0.05$, $N = 50$). There was a further significant but non-linear increase of the $T_3$/TBG ratio during re-alimentation ($r = -0.3860$; $P < 0.001$, $N = 74$).

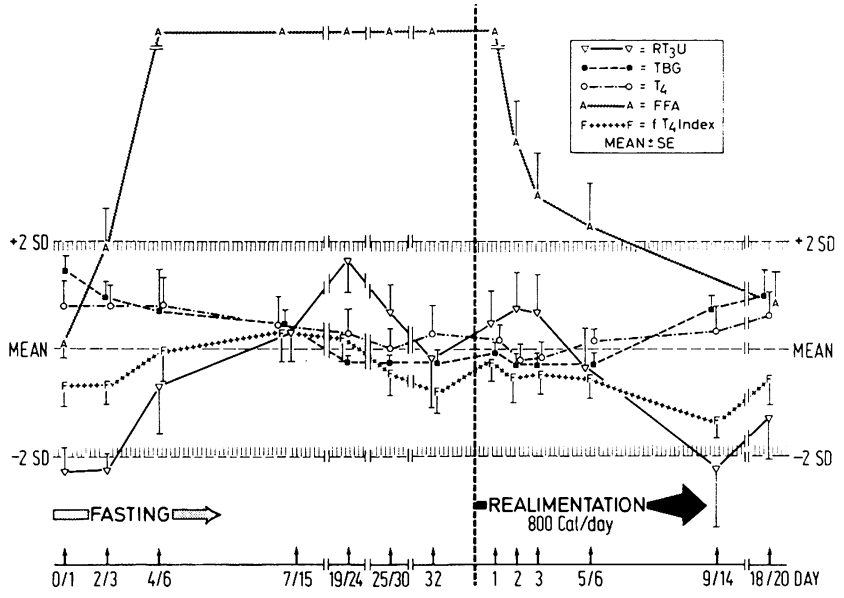


*Fig. 2.*

$T_3$-uptake ($RT_3U$), thyroxine binding globulin, thyroxine, free fatty acids, and free thyroxine index before and during fasting and re-alimentation of obese patients. Superimposed normal means ± 2 standard deviations of all measured parameters correspond to the following data:

$RT_3U$: 37 ± 5 %; TBG: 2.0 ± 0.8 mg/100 ml; $T_4$: 6.7 ± 2.6 µg/100 ml; FFA: 480 ± 250 µEq./l, $fT_4$-index: 2.9 ± 0.9.

*$T_3$-uptake test ($RT_3U$ = resin $T_3$ uptake)*

The $T_3$-uptake of the obese patients (Fig. 2, Table 1) of 31.3 ± 4.6 % was initially just below the normal range of 32–42 % (*Horn et al.* 1975) and thus significantly lower (*Scriba et al.* 1967) than in healthy normal weight controls ($P < 0.001$). There was a significant and linear increase of the $T_3$-uptake ($r = + 0.4202$; $P < 0.01$, $N = 55$) during the first 15 days of fasting. The decrease of the $T_3$-uptake during re-alimentation was again linear and significant ($r = - 0.3021$; $P < 0.001$, $N = 80$).

*Free thyroxine index ($fT_4$-index)*

The $fT_4$-index ($T_4 \times RT_3U$) was initially 2.56 + 0.66 in the obese patients and thus significantly lower than in healthy normal weight controls (Fig. 2, Table 1). A slight increment to 3.04 ± 0.91 was observed during the first fasting period ($r = + 0.2346$; $P < 0.05$, $N = 55$) with a subsequent decrease toward the initial value.

*Table 2.*

Changes in serum levels of the glycoproteins corticosteroid binding globulin, transferrin, $\alpha_2$-haptoglobin and complement C'3 ($\beta_1$A-globulin), of cortisol and of the cortisol/CBG ratio before and during fasting and re-alimentation of obese patients (mean ± SD).

| | Total fasting | | | *Re-alimentation* | | |
|---|---|---|---|---|---|---|
| | before | 7.–15. day | 25.–30. day | before | 5.–6. day | 15.–30. day |
| CBG mg/100 ml | 4.0 ± 1.1 | 4.1 ± 1.4 | 3.7 ± 0.9 | 3.5 ± 0.8 | 3.9 ± 1.5 | 3.5 ± 1.0 |
| Cortisol µg/100 ml | 19.0 ± 9.4 | 19.5 ± 9.5 | 18.0 ± 10.8 | 19.7 ± 9.8 | 17.9 ± 8.1 | 11.8 ± 4.5 |
| Cortisol/CBG ratio | 5.13 ± 2.79 | 5.95 ± 4.68 | 5.46 ± 4.00 | 5.83 ± 3.10 | 5.17 ± 2.19 | 3.41 ± 1.11 |
| Transferrin mg/100 ml | 293 ± 47 | 238 ± 67 | 221 ± 39 | 212 ± 39 | 219 ± 41 | 249 ± 46 |
| $\alpha_2$-haptoglobin mg/100 ml | 250 ± 138 | 131 ± 55 | 126 ± 69 | 155 ± 90 | 178 ± 111 | 228 ± 156 |
| Complement C'3 mg/100 ml | 131 ± 14 | 101 ± 24 | 97 ± 37 | 100 ± 32 | 104 ± 38 | 109 ± 27 |

*TSH levels before and after TRH stimulation tests*

The mean basal TSH levels of the obese patients (Table 1) and the TSH increments observed after TRH stimulation were within the normal range. Both values, however, measured in 16 patients before the initiation of the fasting, were significantly lower ($P < 0.0025$) than in healthy normal weight controls (*Erhardt et al.* 1973). The TSH increment of $5.6 \pm 2.1$ $\mu$U/ml. measured in the obese patients after 2 weeks of fasting, was not significantly lower than the initial value. However, the TSH increment after 2 weeks of re-alimentation (Table 1) was significantly higher ($P < 0.005$) than during fasting.

*Free fatty acids (FFA)*

The free fatty acids (Fig. 1, Table 1) were elevated throughout the complete fasting period. A sharp linear and significant FFA increase was observed during the first fasting period ($r = +0.6933$; $P < 0.001$, $N = 54$). A linear and significant decrease of the FFA was observed during the first 6 days of re-alimentation ($r = -0.3545$; $P < 0.01$, $N = 61$).

*Cortisol*

The obese patients had cortisol levels of $19.0 \pm 9.4$ $\mu$g/100 ml (Table 2). The mean cortisol level of the obese patients was found at the upper limit of the normal range (*Horn et al.* 1975) and was significantly higher than the mean of healthy normal weight controls of $11.1 \pm 3.7$ $\mu$g/100 ml ($P < 0.01$). Cortisol levels remained constant during fasting but a significant decrease to $11.8 \pm 4.5$ $\mu$g/100 ml was seen during re-alimentation ($r = -0.2450$; $P < 0.05$, $N = 77$).

*Corticosteroid-binding globulin (CBG)*

The mean CBG levels of the obese patients (Table 2) were initially $4.0 \pm 1.1$ mg/100 ml ($N = 18$) and thus significantly ($P < 0.005$) higher than the mean of age-matched normal weight controls of $3.4 \pm 0.5$ mg/100 ml ($N = 40$). The CBG levels remained constant during the first fasting period and showed a non-significant decline during the second fasting period ($r = -0.2404$; $P < 0.1$, $N = 50$). Likewise, there were no significant alterations of the CBG levels during re-alimentation.

*Cortisol/CBG ratio*

The cortisol/CBG ratio of the obese patients was initially $5.13 \pm 2.79$ and remained constant during the complete fasting period (Table 2). A decrease was observed at the end of the re-alimentation period which paralleled the decline of the cortisol levels ($r = -0.2628$; $P < 0.005$, $N = 76$).

*Transferrin*

The initial transferrin levels of the obese patients of 293 ± 47 mg/100 ml were not significantly different from the mean normal weight controls (*Fateh-Moghadam et al.* 1977) of 295 ± 95 mg/100 ml (Table 2). A significant and linear decrease was observed during the complete fasting period ($r = -0.6270$; $P < 0.001$, $N = 98$) with a minimum af 212 ± 35 mg/100 ml. The transferrin levels rose during re-alimentation linearly and significantly to 249 ± 46 mg/100 ml ($r = +0.3655$; $P < 0.001$, $N = 78$).

*$\alpha_2$-haptoglobin*

The $\alpha_2$-haptoglobin levels of obese patients were initially 250 ± 138 mg/100 ml and thus above the normal range of 25–220 mg/100 ml (*Fateh-Moghadam et al.* 1977). The $\alpha_2$-haptoglobin levels decreased linearly and significantly during the first fasting period (Table 2) to a minimum af 126 ± 69 mg/100 ml ($r = -0.3341$; $P < 0.05$, $N = 51$). An increase was already observed during the second fasting period ($r = +0.3375$; $P < 0.005$, $N = 50$) followed by a further linear and significant increase during the re-alimentation period ($r = +0.3162$; $P < 0.01$, $N = 78$).

*Complement C'3 ($\beta_1$A-globulin)*

The initial complement C'3 levels of the obese patients (131 ± 13.6 mg/100 ml) were higher as compared to normal weight controls (108 ± 15 mg/100 ml) (*Fateh-Moghadam et al.* 1977). There was a significant decrease (Table 2) during fasting ($r = -0.3489$; $P < 0.001$, $N = 98$), whereas during subsequent re-alimentation, the complement C'3 levels rose linearly, but not significantly, to 109 ± 27 mg/100 ml ($r = +0.1978$; $P < 0.1$, $N = 78$). The complement C'3 level did not reach the initial value during the observation period, however, the mean of normal weight controls was reached.

*Parathyrin (PTH)*

The initial mean PTH levels of obese patients were with 0.35 ± 0.31 ng/100 ml within the normal range of 0.2–1.0 ng/ml (*Wood et al.* 1978). No significant alterations were observed during fasting and re-alimentation. However, 47 of a total of 164 sera obtained for PTH determination showed a PTH level below the limit of detection of 0.2 ng/ml (28.6 %). The correct calcium balance could not be calculated in this study, but the calcium intake, chiefly through mineral water, was estimated to be 200–300 mg/day.

*Growth hormone and prolactin*

No significant alterations of the growth hormone and prolactin levels were observed during fasting and during re-alimentation, either in male or in female patients.

## DISCUSSION

### *Obese patients before fasting*

Early observations (*Scriba et al.* 1967) have shown that the protein bound iodine ($PB^{127}I$) and particularly the $T_3$-uptake were significantly lower in obese patients than in normal weight controls, although the mean values of both were within the normal ranges. The possibility of a tendency towards thyroid hormone deficiency in obesity was discussed on the basis of these studies. However, the direct determination of $T_3$ and $T_4$, and of TSH levels before and after TRH stimulation, showed that patients with alimentary obesity have higher mean $T_3$ levels than normal weight controls (*Bray et al.* 1976; *Hofmann et al.* 1974), and that the TSH levels before and after TRH stimulation are not elevated. It was concluded from the latter studies, that obese patients are euthyroid and that at least primary hypothyroidism can be excluded for this condition.

This study shows that the mean values of $T_4$, $T_3$ and TBG in obese patients are elevated but within the normal range (Figs. 1 and 2) as compared with normal weight controls. The normal $T_4$/TBG ratio and the normal TSH levels of these patients (Table 1) speak against any primary hypothyroidism in these patients.

Some serum proteins are known to be elevated in non-fasted obese patients, e.g. albumin and pseudocholinesterase (*Fateh-Moghadam et al.* 1977). In accordance with earlier observations (*Fateh-Moghadam et al.* 1977), the patients of this study were found to have elevated mean values for $\alpha_2$-haptoglobin and complement C'3. Moreover, this is the first demonstration of elevated TBG and CBG levels by direct measurement. Nothing appears to be known about the regulation of the different serum proteins in hyperalimentation of different dietary composition.

### *Effects of total fasting*

The study confirms the rapid decline of $T_3$ and the mirror image increase of $rT_3$ during fasting, as published by other investigators (*Balsam & Ingbar* 1977; *Carlson et al.* 1977; *Croxson et al.* 1977; *Merimee & Fineberg* 1976; *Palmblad et al.* 1977; *Portnay et al.* 1974; *Vagenakis et al.* 1975, 1977). This "shift" of the peripheral monodeiodination of $T_4$ from the metabolically active triiodothyronine to the inactive $rT_3$ can be interpreted as adaptation of metabolism to the reduction of energy provision from calorie-intake. The mechanism of this alteration of the hormone metabolism remains unknown (*Balsam & Ingbar* 1977; *Chopra* 1978; *Palmblad et al.* 1977). The obvious kinetic parallelism of the increases of the FFA and $rT_3$ levels and their inverse relation to $T_3$ raise the question of the regulatory effect of FFA on the monodeiodination of $T_4$. It should be noted in addition, that recently a decrease of the hepatic $T_3$ receptor binding capacity during fasting was shown (*Schussler & Orlando* 1978).

The thyroxine levels of obese patients remained constant during total fasting in accordance with the literature. (*Merimee & Fineberg* 1976; *Palmblad et al.* 1977; *Portnay et al.* 1974). Here, the long half-life of $T_4$ has to be taken into consideration.

A decrease of thyroxine binding capacity (*Schatz et al.* 1967) was observed in serum of fasting obese patients, and low TBG levels were reported in protein calorie malnutrition (*Rastogi et al.* 1974; *Chopra & Smith* 1975). This study has shown, by direct radioimmunoassay (*Horn et al.* 1977), that the TBG levels decrease during the first 2 weeks of total fasting. Interestingly similar kinetics were observed for the decrease of complement C'3, $\alpha_2$-haptoglobin and transferrin during fasting. Corticosteroid binding globulin and likewise albumin (*Fateh-Moghadam et al.* 1977), however, remained constant throughout the complete fasting period. It remains an open problem, as to why only certain serum proteins decrease rapidly during total fasting. This decrease appears to include mainly those serum proteins, which are elevated in obese patients before fasting when compared with normal weight controls. As the mean of the serum proteins does not fall essentially below the respective normal values with the duration of total fasting applied in this study, it appears unlikely that the patients are in any danger, for example of becoming deficient in immunoglobulins.

The decrease of the specific transport globulins of thyroid hormones explains only partially the known increment in $T_3$-uptake (*Schatz et al.* 1967; *Scriba & Hofmann* 1976) and decrease of total $T_3$. Comparing the kinetics of the TBG decrease and of the increase of $T_3$-uptake (Fig. 2) it can be seen that the increment of $T_3$-uptake is more rapid. The displacement of thyroid hormones from TBG by the FFA increase has been suggested (*Hollander et al.* 1967) as one explanation for the phenomenon. Further, total $T_3$ decreases more rapidly and intensively than TBG (Fig. 1), explaining the depression of the $T_3$/TBG ratio during the first fasting period. The $T_3$/TBG ratio increases already during the second fasting period in parallel to the $T_3$ levels. These results show that the most evident metabolic alterations occur within the first 2 weeks of total fasting.

An increase of the $T_4$/TBG ratio was observed in obese patients after 2 weeks of total fasting in contrast to the decrease of the $T_3$/TBG ratio when compared with the initial values. This leads to the important question as to whether obese patients are indeed euthyroid throughout the complete fasting period, particularly with respect to the known decrease of daily weight loss with longer duration of the fasting (*Ditschuneit* 1976). If one accepts the TSH response to TRH stimulation as the most sensitive parameter for the thyroid hormone status of a patient, the results of this study exclude any primary hypothyroidism. In accordance with other investigators (*Carlson et al.* 1977; *Croxson et al.* 1977; *Palmblad et al.* 1977; *Portnay et al.* 1974; *Vinik et al.* 1975), no in-

creased TSH response was observed but rather a tendency to a slightly decreased TSH increment after TRH stimulation during fasting. The possibility should be kept in mind, that these TSH levels are inadequately low. Conversely, one should realise the possibility of an alteration of hypothalamic or pituitary functions during total fasting (*Carlson et al.* 1977). Secondary endocrine disturbancies of this type have been repeatedly documented for patients with anorexia nervosa (*Travaglini et al.* 1976; *Vigersky et al.* 1976); thus some degree of thyroid hormone deficiency due to hypothalamic dysfunction cannot be excluded with certainty on the basis of current data. The latter possibility could serve as a vague rational basis for the acceleration of the weight loss of fasting obese patients, when, for example, 60 $\mu$g $T_3$ per day are given additionally (*Hofmann et al.* 1974; *Scriba & Hofmann* 1976).

*Re-alimentation*

A rapid normalisation of the free fatty acids was observed during re-alimentation with a low caloric diet, representing a normalisation of the stimulated lipolysis. $T_3$ levels were normalised within the first days of re-alimentation and reached the initially elevated mean values of obese patients during the second period of re-alimentation. Recently it was shown that glucose given orally but not intravenously normalises $T_3$ levels after 48 h fasting (*Westgren et al.* 1977). Obviously, the peripheral thyroid hormone metabolism was rapidly normalised during re-alimentation.

The increase of the TBG levels was somewhat slower, resulting in an still elevated $T_3$/TBG ratio at the end of the observed period of re-alimentation. The $T_4$/TBG ratio was increased during the complete re-alimentation period when compared with the initial value. Inspite of this, the TSH response to TRH stimulation was higher at the end of the re-alimentation than during fasting (Table 1). The increasing TBG levels probably bind more $T_4$, which can be supplied by the thyroid only at the cost of increased thyrotrophic stimulation.

Transferrin, $\alpha_2$-haptoglobin and complement C'3 increase during re-alimentation. None of these serum proteins, however, reached the initially elevated levels observed in obese patients until the end of the observed period of re-alimentation. This finding shows that there is no persisting deficiency of serum proteins after total fasting.

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