Effects of Protein-Sparing Modified Fasting on Obese Japanese Patients

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(Received August 9, 1986)

Summary A protein-sparing modified fasting diet containing 240 kcal per day with supplemental nutrients was used for weight reduction of 15 Japanese patients with obesity. The effects of this treatment on glucose and lipid metabolism, uric acid and hormone levels, and body weight loss were investigated. The rate of body weight reduction was about 500 g per day in the first week, and 300 g per day thereafter. The average weight loss after 4 weeks was 12% of the initial relative weight obtained from standard body weight. Glucose tolerance was improved, and no significant alterations in the measured variables were observed except positive ketonuria, a slight increase in plasma uric acid during the first 2 weeks, and a decrease in the T_3 level.

Key Words: protein-sparing, obesity, Japanese, modified fasting

Obesity is an important risk factor because it can lead to hypertension [1], hyperlipidemia [2], ischemic heart disease [3], atherosclerosis [3], diabetes mellitus [4], and gout [5]. There are many treatments for simple obesity, such as diet, exercise, drugs [6-8] and surgical removal of part of the intestine [9]. Dietary treatments such as semistarvation or total starvation are tried in Western countries to reduce the body weight of obese individuals [10, 11]. However, serious cardiovascular complications [12] and even death [13] have been observed on administration of liquid-protein diet or total starvation. On the other hand, adequately supplemented semistarvation diets have been recently reported [10, 13]. In Japan, supplemented semistarvation therapy has not been used. Therefore, we performed semistarvation therapy using Modifast[®] for Japanese patients with simple obesity, and examined the effects of this treatment on protein and lipid metabolism and hormonal levels. The value of semistarvation therapy for Japanese is discussed.

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SUBJECTS AND METHODS

Patients and procedure of protein-sparing modified fasting using Modifast. Obesity was defined by a body weight of 120 percent or more of the standard body weight according to Broca's method modified for Japanese by Katsura ($\{\text{height (cm)} - 100\} \times 0.9 \text{ kg}$) [14]. Six obese males of 13 to 52 years of age with body weights of 141 to 181 percent (mean 163.0%) of the standard values and nine obese females of 16 to 47 years of age with body weights of 133 to 210% (mean 163.4%) of the standard values were studied. After confirming the diagnosis of obesity, having excluded secondary obesity, we initiated semistarvation therapy on the patients, all of whom were hospitalized. One adolescent boy (T.Y., 13 years old) had obesity accompanied with Pickwickian syndrome, and thus weight reduction was urgent. One girl (S.N., 16 years old) was already mature and very nervous about her obesity; therefore she was eager to take the semistarvation diet. The patients received instructions from clinical dieticians, and no medication was permitted either before or during the study. Each patient received Modifast in powder form (dissolved in 300 ml of water) three times a day, as well as more than 2.5 liters of water per day.

The dietary treatment consisted of the successive intake of a 1,300 kcal, 1,000 kcal, and 700 kcal regular diet (3 days for each); and then the modified protein-sparing diet (Modifast therapy). Control data for values during Modifast therapy were obtained during the first stage of the 1,300 kcal intake.

Composition of Modifast. Three packs of Modifast provided 240 kcal per day and contained a total of 33.0 g of protein, 0.7 g of fat, and 25.5 g of carbohydrate. The contents of vitamins and trace elements in 3 packs of Modifast were as follows: vitamin A, 0.9 mg; D, 2.5 μg ; E, 12 mg; B₁, 16 mg; B₂, 20 mg; B₆, 1.8 mg; C, 75 mg; nicotinic acid, 15 mg; pantothenic acid, 8 mg; folic acid, 0.4 mg; sodium, 1.0 g; potassium, 1.0 g; chloride, 0.8 g; calcium, 0.8 g; magnesium, 0.26 g; phosphate, 0.8 g; and iron, 25 mg. Modifast was kindly supplied by Wander Co., Netherlands.

Measurements of body weight and blood sampling. Patients were weighed every morning wearing a hospital gown and after voiding urine. Venous blood samples were taken after overnight fasting before the patients got out of bed.

Assay of post-heparin lipolytic activity. Post-heparin plasma was obtained 10 min after injection of 10 U/kg of heparin into patients. Total lipase activity was measured using tri[1-¹⁴C]oleoylglycerol emulsified with Triton X-100 in the presence of 2 μg apolipoprotein CII. Released [¹⁴C]oleic acid was determined as described previously [15]. Hepatic lipase activity was assayed in the presence of 1 M NaCl [16] and lipoprotein lipase activity was calculated as the difference between the value for total lipase activity and that for hepatic lipase activity.

Clinical laboratory test. Routine clinical laboratory tests were performed in the Central Laboratory of Chiba University Hospital.

Results are presented as mean $\pm$ SD. Statistical analyses were performed using Student's *t*-test for paired data [17].

RESULTS

Characteristics of the patients studied and their obesity indices are shown in Table 1.

Body weight reduction

The changes in body weight of the individual subjects during Modifast therapy are shown as changes in the obesity index in Fig. 1. All the patients lost weight. The mean obesity index just before Modifast therapy was $163 \pm 24\%$, and the indices at weeks 2, 4, and 6 were 153 ± 23 , 151 ± 20 , and $146 \pm 23\%$, respectively. Figure 2 shows the time course of average body weight reductions per day. The reduction was about 500 g/day in the first week of therapy and then about 300 g/day.

Glucose metabolism

Table 2 shows results on glucose metabolism just before and after Modifast therapy for at least 6 weeks. The fasting plasma glucose levels tended to decrease

Table 1. Data on obese patients.

Name	Sex	Age (years)	Height (cm)	Body weight (kg)	Obesity index (%)
T.Y.	M	13	157	94	181
F.K.	M	21	166	89	153
M.M.	M	32	157	86	170
A.T.	M	37	160	88	164
K.Y.	M	48	166	99	169
S.H.	M	52	161	77	141
S.N.	F	16	163	78	137
T.H.	F	19	157	83	162
W.K.	F	22	155	94	189
H.S.	F	23	157	97	193
K.K.	F	23	143	69	161
N.T.	F	23	165	128	210
S.S.	F	33	161	82	149
S.M.	F	43	155	68	138
H.T.	F	47	158	69	133
Average	M=6	34 $\pm$ 11	161.2 $\pm$ 4.1	88.8 $\pm$ 7.5	163.0 $\pm$ 14.1
	F=9	28 $\pm$ 11	157.4 $\pm$ 6.9	85.3 $\pm$ 19.1	163.5 $\pm$ 27.8
Total	15	30 $\pm$ 13	158.9 $\pm$ 6.0	86.7 $\pm$ 15.2	163.4 $\pm$ 24.0

The Obesity index is the body weight as a percentage of the standard body weight. The standard body weight was calculated by the modified method of Broca [14] for Japanese (Katsura's method, {height (cm) - 100} $\times$ 0.9 (kg)).

Fig. 1. Effect of Modifast therapy on relative body weight.

Fig. 2. Average daily weight loss during Modifast therapy. Daily weight losses during weeks 2-6 were significantly lower than those during the significantly different from the value during week 1. * $p < 0.001$; ** $p < 0.02$.

during therapy, but remained within the normal range. C-Peptide excretion also decreased (Table 2-A), being significantly lower by the 6th week. Results of glucose tolerance tests are shown in Table 2-B. Glucose intolerance, observed initially, improved greatly during treatment. Immunoreactive insulin (IRI) secretion was decreased by the treatment, but the $\Delta\text{IRI}/\Delta\text{glucose}$ ratio [18] at 30 min. ($\Delta\text{IRI} = \text{IRI at 30 min} - \text{IRI initially}$, $\Delta\text{glucose} = \text{plasma glucose at 30 min} - \text{plasma glucose initially}$) remained unchanged (0.89 before and 0.91 after treatment).

Table 2. Glucose metabolism during Modifast therapy.

(A) Fasting plasma glucose levels and urinary C-peptide concentrations during protein sparing, modified fasting.

Week	0	2	4	6
Fasting plasma glucose (mg/dl)	89±17	78±13	74±9	77±7
Urine C-peptide (μg/day)	55±21	—	—	33±25*

* $p < 0.02$ compared with value at week 0.

(B) Oral glucose tolerance test (75 g) during protein sparing, modified fasting.

Min		Modifast therapy	
		Before	After
0	Plasma glucose ^a	107±35	75±11**
	IRI ^b	16±7	10±4
30	Plasma glucose	172±55	112±32***
	IRI	74±43	44±19
60	Plasma glucose	194±103	119±46*
	IRI	64±37	40±18
90	Plasma glucose	194±94	118±61*
	IRI	76±35	37±9
120	Plasma glucose	196±92	117±50*
	IRI	79±31	35±8**

Mean±SD ($n=6$); ^a mg/dl; ^b μU/ml. * $p < 0.05$; ** $p < 0.02$; *** $p < 0.01$.*Lipid metabolism*

Table 3 shows changes in serum lipids. The levels of total cholesterol, low-density lipoprotein (LDL)-cholesterol, and high-density lipoprotein (HDL)-cholesterol tended to decrease during therapy, but the decreases were not significant. Very low density lipoprotein (VLDL)-triglyceride also decreased. The level of free fatty acids increased from week 2 to 6. The activities of lipoprotein lipase (LpL) and hepatic triglyceride lipase (HTGL) in postheparin plasma were high before Modifast therapy (LpL, 4.8 ± 2.9 μmol/ml/h, HTGL, 10.4 ± 6.2 μmol/ml/h) and both activities decreased to almost normal levels during treatment.

Hormonal changes accompanying Modifast therapy

Results on plasma and urinary hormone concentrations are shown in Table 4. Modifast therapy decreased the T_3 level to below normal. Increase in reverse T_3 (rT_3) and free T_4 were observed, but were not significant. The T_4 level decreased, but also not significantly. Other hormones remained within normal ranges.

Routine examinations

Table 5 shows hematological and biochemical data obtained from routine examinations during Modifast therapy. Values were within the normal ranges, except the uric acid level, which increased significantly at weeks 2 and 4 of therapy,

Table 3. Effect of Modifast therapy on plasma lipid and post-heparin lipolytic activities.

Weeks	0	2	4	6
Total cholesterol (mg/dl)	203±46	183±45	164±23*	182±33
LDL-Cholesterol (mg/dl)	141±35	127±31	115±28	126±9
HDL-Cholesterol (mg/dl)	42±9	37±5	38±7	36±6
Triglyceride (TG) (mg/dl)	102±40	89±22	91±18	90±18
VLDL-TG (mg/dl)	81±35	68±14	46±14	51±15
FFA (μ Eq/liter)	1,069±436	1,224±343	1,498±695	1,402±115
LpL (μ mol/ml/h)	4.8±2.9	—	—	2.9±1.0*
HTGL (μ mol/ml/h)	10.4±4.2	—	—	4.6±3.0*

Values are Mean±SD. Normal range: LpL, 3.4±1.6 μ mol/ml/h; HTGL, 5.5±1.1 μ mol/ml/h.

* p <0.01 compared with value at week 0.

Table 4. Effect of Modifast therapy on hormone levels and routine laboratory data on plasma and urine.

	Normal range	Modifast therapy	
		Before	After
Adrenaline (urine)	3.0–15.0 μ g/day	6.1±3.3	9.3±1.7
Noradrenaline (urine)	26–121 μ g/day	70.6±20.0	57.4±9.2
Plasma cortisol	4.5–20 μ g/dl	9.3±3.2	13.9±6.2
17 OHCS (urine)	2.4–6.4 mg/day	7.4±2.6	6.7±1.9
17 KS (urine)	3.0–8.0 mg/day	6.4±0.5	3.7±2.2
GH	<5 ng/ml	2.9±1.6	3.3±3.5
TSH	<5 μ U/ml	1.4±0.3	1.3±0.3
Somatomedin-C	0.64–2.22 U/ml	0.80±0.44	0.80±0.35
Glucagon	40–180 pg/ml	81±48	55±20
T ₃	1.1–2.25 ng/ml	1.11±0.39	0.77±0.37*
T ₄	4.5–12.0 μ g/dl	7.09±2.00	5.23±0.68
Free T ₄	0.80–2.30 U/ml	1.25±0.20	1.56±0.38
Reverse T ₃	190–375 pg/ml	378±43	566±343
TBG	15–28 ng/ml	21.5±4.6	16.3±5.7

17OHCS, 17-hydroxycortisol; 17KS, 17-ketosteroid; GH, growth hormone; TSH, thyroid-stimulating hormone; TBG, thyroid-binding globulin. * p <0.01.

but returned to the pre-therapy level by week 6. As shown in Fig. 3(a), urinary uric acid excretion per day decreased when the amount of urinary ketone bodies was increased; and as shown in Fig. 3(b), the plasma uric acid level was inversely correlated with urinary uric acid excretion.

DISCUSSION

Semistarvation therapy has been used for treatment of morbid obesity in Europe and the United States [10, 11]. In Japan, such therapy had not been evaluated here to fore, primarily because the incidence and grade of obesity have been less in Japan than in Western countries. But recently, the incidence of obesity

Table 5. Laboratory findings.

	Normal range	0	2	4	6 weeks
Hemoglobin	12–18 g/dl	14.2±1.5	14.3±2.0	14.1±1.7	12.9±1.4*
WBC	4,000–9,000/mm ³	5,200±1,600	5,600±1,500	4,800±1,600	3,700±800**
RBC	375–500×10 ⁴	478±60	482±61	468±69	435±71*
Platelets	12–35×10 ³ /mm ³	22.1±5.0	22.7±2.7	20.1±4.6	18.4±5.9
Total protein	6.5–8.2 g/dl	7.3±0.6	7.3±0.5	7.1±0.5*	6.8±0.5**
BUN	10–20 mg/dl	12±3.5	11.9±4.3	9.4±2.1	9.6±4.1
Uric acid	2.5–8.0 mg/dl	6.6±1.7	8.9±2.4*	7.7±1.2	6.8±0.6
Na	135–145 mEq/liter	139±2.5	138±1.2	139±1.6	139±2.2
K	3.6–5.0 mEq/liter	4.3±0.2	4.1±0.6	4.3±0.6	4.0±0.3
GOT	7–40 mU/ml	36±19	38±15	47±30	44±20
GPT	7–40 mU/ml	46±36	43±26	51±38	49±36
Ch-E	2.0–6.0×10 ³ IU/liter	5.8±1.5	5.6±1.1	4.7±1.1**	4.7±1.4**

Mean±SD. BUN, Blood urea nitrogen; Ch-E, choline esterase. * $p<0.05$ compared with value at week 0; ** $p<0.01$ compared with value at week 0.

among Japanese has been increasing because of westernization of the diet [19]. Therefore, an increased need for this type of therapy has resulted. Semistarvation therapy using Modifast for patients with simple obesity was effective in our hospital for reducing body weight (Fig. 1). The body weight decreased 500 g per day in the first one week and then 300 g per day in the following weeks. The effectiveness of this treatment was almost the same as that reported from Europe [10, 11, 20]. Two adolescent patients were included in this therapy, and its effect on their body weight was the same as in adults. Merritt *et al.* [20, 21] reported that obese adolescents treated with the protein-sparing, modified fasting demonstrated its clinical efficacy and minimum side effects as determined by standard biochemical determination [21]. Adequate semistarvation is considered to be safe and effective for the treatment of childhood or adolescent obesity.

Glucose intolerance was observed before treatment, but improved during treatment. After semistarvation, insulin secretion decreased (Table 2), but the Δ IRI/ Δ glucose insulin index at 30 min [18] which is thought to indicate the responsiveness of insulin secretion from β -cells, was unchanged. These results suggest that the effectiveness of insulin was improved by semistarvation therapy.

The FFA level was increased during treatment, suggesting that lipid mobilization from adipose tissue was enhanced. The post-heparin LpL and HTGL activities of the patients were initially higher than those of control subjects, but decreased to almost the normal ranges during Modifast therapy. These results are consistent with the idea that the adipose tissue mass was reduced. These phenomena might be a reflection of a decrease in insulin over-secretion, because lipoprotein lipase production is known to depend on insulin [22].

The levels of all hormones examined except thyroid hormones remained within normal ranges during therapy (Table 4). As for thyroid hormones, a decrease in the T_3 level and increase in rT_3 and free T_4 were observed. The T_3 concentration is reported to be affected by the nutritional status [23]. Kaptein *et al.* [24] reported

Fig. 3. (a) Relationship between urinary excretion of uric acid and urinary ketone bodies. Amounts of urinary ketone bodies are shown as follows: +, 15 mg/dl; ++, 40 mg/dl; +++, 80 mg/dl; +++++, 160 mg/dl. Urinary ketone bodies were measured every morning before patients received Modifast. The hatched area indicates the normal range (mean $\pm 2 \times$ SD). (b) Correlation between uric acid in plasma and urinary excretion of uric acid in the presence and absence of urine ketone bodies. The hatched area indicates the normal range (mean $\pm 2 \times$ SD).

an increase in rT_3 and free T_4 and a reduction in the T_3 concentration during protein-supplemented weight reduction. And they speculated that those changes may facilitate conservation of visceral protein and reduce muscle protein turnover. The variation in magnitude of those changes was thought to depend on individual differences in nitrogen economy. No clinical signs or symptoms indicating thyroid functional abnormality were observed.

In routine laboratory examinations, the WBC count at the end of week 6 was below the normal range, but returned to the normal range following the change to an ordinary diet.

Uric acid was increased in the first two weeks, as previously reported by others [25]. As shown in Fig. 3(a), urinary uric acid secretion was decreased when urinary excretion of ketone bodies increased during semistarvation. Furthermore, an increase in plasma uric acid was observed when uric acid excretion was decreased, suggesting that increase in the former during semistarvation might be partly due to decreased excretion of uric acid. These results also suggest that ketone bodies might directly inhibit the excretion of uric acid from the kidney, which is consistent with Drenick's observation [26]. The excessive accumulation of uric acid is thought to result from accelerated protein breakdown during the initial period of fasting [27] and from impairment of renal uric acid clearance [28, 29]. Aside from the evaluation in uric acid level, the Modifast diet gives a protein intake below the recommended dietary allowance (RDA) level and thus will invariably lead to unnecessary loss of lean tissue. Therefore diet formulae containing higher level of protein are needed to solve these problems.

The Japanese diet is different from that in Europe, especially in salt content, taste, and protein composition. So, the intake of the Modifast is not so familiar but can be tolerated by the Japanese. But in order for the protein-sparing modified fasting to become more familiar and to be widely acceptable for the Japanese, improvement in taste will be required.

Overall, semistarvation therapy using Modifast for obese Japanese was effective almost to the same extent as for European, and showed no serious side effects except minor subjective complaints.

Further studies are now in progress on the value of Modifast therapy.

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