Effect of Mazindol on Body Weight and Insulin Sensitivity in Severely Obese Patients after a Very-Low-Calorie Diet Therapy

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Abstract. The present investigations were performed in order to clarify the effects of mazindol on body weight and insulin sensitivity in patients with morbid obesity who had already been treated with a very-low-calorie diet containing 480 kcal food (VLCD) with various amino acids. We attempted to study whether a further decrease in body weight would be achieved by the administration of mazindol, because it is difficult to obtain sufficient and continuous reduction of body weight after VLCD therapy. Thirteen female severely obese subjects were 51.0 ± 13.9 years old (25-73 years old), with a mean height of 154.7 ± 5.6 cm (146.0-160.5 cm), mean weight of 84.5 ± 9.4 kg (69-98 kg) and a mean body mass index (BMI) of 35.3 ± 3.6 kg/m² (29.2-41.0 kg/m²). Their mean body weight decreased to 76.7 ± 2.2 kg (net decrease: 6.3 ± 0.9 kg) after VLCD therapy for 2-4 weeks. Then they were treated by the administration of mazindol with diet restriction (1000-1200 kcal/day). Mazindol administration resulted in a further weight reduction of 2.9 ± 0.5 kg after 4 weeks, 4.9 ± 0.5 kg after 8 weeks and 6.9 ± 0.9 kg after 12 weeks. Their blood pressure was not changed after mazindol treatment. The responses of blood glucose and insulin levels in a 75 g oral glucose tolerance test (OGTT) were not significantly different before and after mazindol administration. The blood glucose area calculated from the data obtained during OGTT for 120 min did not significantly differ before and after mazindol administration, while the insulin area significantly decreased after mazindol treatment (from 98.0 ± 12.1 before administration to 70.1 ± 7.8). The mean M value reflecting insulin sensitivity in the whole body determined by euglycemic glucose clamping was increased significantly after mazindol treatment (from 4.92 ± 0.30 mg/kg/min to 6.36 ± 0.43 mg/kg/min). The results demonstrated that mazindol administration with diet restriction further reduced body weight in the morbidly obese subjects after treatment with VLCD, with an increase in the M value and a decrease in insulin release. The results suggest that mazindol is useful for reducing body weight as well as improving insulin sensitivity.

Key words: Mazindol, Very-low-calorie diet, Severe obesity, Insulin sensitivity, Euglycemic glucose clamping

OBESE patients are frequently associated with impaired metabolism of carbohydrates and lipids, often resulting in cardiovascular disorders such as hypertension and ischemic heart disease [1, 2]. A negative energy balance is therefore essential for the treatment of obese patients in order to prevent those complications. But some psychological factor(s) and behavioral pattern(s), including eating habits, make long-term dietary therapy extremely difficult in obese patients, and therapy by administering anorexic agents is sometimes recommended as a supplementary treatment with diet restriction.

Mazindol (Sanorex®) is the only anorexigenic
agent available in Japan. It exerts an anorexigenic action through a central action in the hypothalamus [3, 4], and has been reported to be effective for simple obesity [5, 6]. Severely obese patients subjected to the present investigations were given mazindol after a very-low-calorie diet (VLCD) therapy. It has been reported that severely obese patients possess insulin insensitivity which is known to be one of the greatest risk factors in atherosclerotic changes leading to coronary and other artery diseases [1, 2].

We therefore tried to examine whether mazindol therapy could augment weight reduction and whether it could maintain weight loss resulting from VLCD therapy. The effect of mazindol administration on insulin sensitivity was also observed. The aim of these studies is to clarify exactly further effects of mazindol on body weight and insulin sensitivity in patients with morbid obesity after VLCD therapy.

**Subjects**

We studied 13 severely obese female patients who agreed to participate in a weight reduction program explained in detail by each doctor belonging to the Division of Endocrinology and Metabolism, Department of Medicine, Yokohama Rosai Hospital. The profiles of the patients are shown in Table 1. Their average age was 51.0 ± 13.9 years old (range 25 to 73 years old), average height was 154.7 ± 5.6 cm (range: 146.0 to 160.5 cm), average weight was 84.5 ± 9.4 kg (range 69.0 to 98.0 kg) and average body mass index (BMI) was 35.3 ± 3.6 kg/m² (range: 29.5 to 41.0 kg/m²). Among these subjects, 4 patients were diabetic, 5 were complicated with hyperlipidemia, and 6 had hypertension (Table 1). None of them was treated with insulin nor oral hypoglycemic agents. Six of the 13 patients had hypertension. Of these, 2 were treated with calcium antagonist, and another two with angiotensin converting enzyme inhibitor and β-blocker.

In the present study, concomitantly administered drugs and dosage were not changed.

**Methods**

VLCD therapy of 480 kcal/day was performed for 2–4 weeks at the inpatient clinic, and was followed by one week of conventional dietary therapy (1000 to 1200 kcal/day). Administration of one tablet (taken 30 to 60 min before lunch) of 0.5 mg mazindol was then started and continued daily. In cases in which there was an insufficient effect on weight loss and a reduction in caloric intake without any side effects of mazindol, its dose was increased gradually every 2 weeks (maximum dose

| Table 1. Profiles of all subjects in the present study |
|-----------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| Patient         | 1       | 2       | 3       | 4       | 5       | 6       | 7       | 8       | 9       | 10      | 11      | 12      | 13      |
| Sex             | F       | F       | F       | F       | F       | F       | F       | F       | F       | F       | F       | F       | F       |
| Age (years old) | 50      | 59      | 55      | 43      | 61      | 54      | 73      | 25      | 32      | 46      | 50      | 72      | 43      |
| Height (cm)     | 160.0   | 154.5   | 155.0   | 160.5   | 146.0   | 146.0   | 157.0   | 159.5   | 155.0   | 160.2   | 146.0   | 152.0   | 159.0   |
| Body weight (kg)| 82.9    | 97.9    | 86.8    | 97.4    | 78.5    | 78.0    | 72.0    | 77.2    | 92.3    | 83.0    | 69.2    | 79.5    | 83.3    |
| Body mass index (kg/m²) | 32.4   | 41.0    | 36.1    | 37.8    | 36.8    | 36.6    | 29.2    | 30.3    | 38.4    | 32.3    | 32.5    | 34.4    | 32.9    |
| Systolic blood pressures (mmHg) | 138    | 140    | 170    | 150    | 142    | 132    | 120    | 150    | 160    | 162    | 152    |
| Diastolic blood pressure (mmHg) | 60    | 86    | 100    | 100    | 70    | 70    | 72    | 90    | 100    | 100    | 82    | 68    |
| Total cholesterol (mg/dl) | 360    | 186    | 178    | 133    | 227    | 269    | 144    | 207    | 185    | 246    | 190    | 225    | 206    |
| Triglyceride (mg/dl) | 221    | 143    | 81    | 76    | 74    | 123    | 65    | 136    | 118    | 73    | 56    | 65    | 119    |
| High density lipoprotein (mg/dl) | 34.8   | 37.7   | 53.5   | 52.4   | 46.5   | 40.6   | 33.1   | 41.3   | 60     | 47.8   |
| Fasting plasma glucose (mg/dl) | 180    | 143    | 94    | 88    | 94    | 92    | 92    | 93    | 86    | 88    | 94    | 90    | 82    |
| Plasma glycohemoglobin A1c (%) | 11.3   | 11.7   | 7.7   | 16    | 11.6  | 5.3   | 4.6   | 10.9  | 4.7   | 6.4   | 7.7   | 9.0   |
| Immunoreactive insulin (µU/ml) | (+)    | (+)    | (−)   | (−)   | (+)   | (−)   | (−)   | (−)   | (+)   | (−)   | (−)   | (−)   | (−)   |
| Blood c-peptide (ng/ml) | (+)    | (+)    | (−)   | (−)   | (+)   | (−)   | (−)   | (−)   | (−)   | (−)   | (−)   | (−)   | (−)   |

These parameters were examined before VLCD therapy.
Mazindol was administered for 12 weeks to those patients who were observed at the out-patient clinic every 2 or 4 weeks. Body weight, blood pressure, and blood levels of glucose and lipids were measured every 2 or 4 weeks. A venous blood sample was taken in the morning after a 12 h fast. The plasma glycohemoglobin AIC (HbAIC), blood glucose and serum insulin concentrations in a 75 g oral glucose tolerance test (OGTT) were measured before and after mazindol administration. The area of the glucose curve and the time axis (values before glucose loading, at 30 min, 60 min, and 120 min) and that of the insulin curve and the time axis were calculated and designated as the glucose area and insulin area, respectively. Insulin sensitivity was also measured quantitatively by a euglycemic glucose clamp method. Euglycemic glucose clamping was performed in each subject with an artificial pancreas apparatus STG-22 (Nikkiso, Tokyo, Japan), according to the method of Zuniga-Guajardo et al. [1]. In euglycemic glucose clamping, regular insulin (Novolin®, Novonordisc Co., Denmark) was infused at 4.48 mU per minute for 90 min. The rate of infusion of a 20% glucose solution for up to 70 to 90 min to maintain a constant blood glucose level of 100 mg/dl was taken as the M value which indicates insulin sensitivity in peripheral tissues of the whole body, and the M value is expressed as mg/kg body weight/min.

During these studies, the administration of drugs other than mazindol and anti-hypertensive drugs was completely avoided, after permission was obtained from each patient. The serum immunoreactive insulin (IRI) concentration was determined with a double antibody enzyme-linked immunoassay kit (Boehringer Mannheim Co.) HbAIC was determined by high performance liquid chromatography. Plasma glucose and serum concentrations of cholesterol and triglycerides were analyzed in a Nippon Densi autoanalyzer (JCA-RX20, Tokyo, Japan). HDL-cholesterol was measured by heparin-manganese methods. LDL-cholesterol was calculated with the following formula:

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\text{LDL-cholesterol} = (\text{total cholesterol}) - (\text{HDL-cholesterol}) - (\text{triglycerides}/5).
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Statistical analyses

Data were expressed as the mean ± SD. Continuous variables were compared by unpaired Student’s t-test. A computer program (SAS) was used in all the analyses. Results were considered statistically significant when P values were less than 0.05.

Results

Before the experiment, the average body weight of the patients was 84.5 ± 9.4 kg and the BMI was 35.3 ± 3.6 kg/m². A weight reduction of 6.3 ± 0.9 kg was achieved with the VLCD therapy and one week of conventional dietary therapy (1000 to 1200 kcal/day). The average body weight at the start of mazindol administration was 76.7 ± 2.1 kg and the BMI was 32.1 ± 0.9 kg/m². A further weight reduction of 2.9 ± 0.5 kg was observed after 4 weeks of mazindol administration, 4.9 ± 0.5 kg after 8 weeks and 6.9 ± 0.9 kg after 12 weeks (Fig. 1). All thirteen patients achieved weight loss in the 3 to 13.1 kg range after 12 weeks of administration compared with the pre-administration weight.

The blood pressure changes in all 13 patients are shown in Fig. 2. Both the systolic and diastolic pressures were significantly reduced (P<0.05), when those at the beginning of VLCD therapy were compared with those at the start of mazindol administration, but no changes were observed after 12 weeks of mazindol administration.

The blood concentrations of glucose and insulin in 75 g OGTT before and after mazindol administration are shown in Fig. 3. No significant change in the OGTT glucose curve was observed after mazindol administration. Although the insulin concentration at each time point tended to be higher before mazindol administration, no significant difference was observed between the values before and after the administration of mazindol. The glucose area was 294.4 ± 13.7 before mazindol administration and 294.7 ± 13.1 after, with no significant difference (Fig. 3A); whereas the insulin area decreased significantly after administration (P<0.05) (from 98.0 ± 12.1 before administration to 70.1 ± 7.8) (Fig. 3B).

The M values determined quantitatively by the euglycemic glucose clamp technique (Fig. 3C) and several parameters in the serum are shown in Table 2. The average M value was 5.1 ± 0.3 mg/kg/min before mazindol administration and in-
Increased significantly (P<0.05) to 6.3 ± 0.5 mg/kg/min after mazindol administration. There were no significant differences between serum lipid, glucose and insulin values before and after the administration of mazindol (Table 2).

Discussion

Recently, a semi-starvation therapy or a very-low-calorie diet (VLCD) has been established in the treatment of severely obese patients [7]. However, severely obese subjects are often very reluctant to take very low calorie formulated powdered food (Optifast®, Sandoz), and many of them cannot always maintain this diet therapy especially when treated at the outpatient clinic. On the other hand, mazindol acts directly on the hypothalamus by means of an anorexigenic effect [3, 4, 8, 9], and it has also been reported to suppress the secretion of the salivary glands and of gastric juice [10], resulting in a reduction in the overall energy intake, and improvement of obesity.

In our present study, we initially attempted to treat inpatients with a VLCD for 2 to 4 weeks. To achieve long-term maintenance of the weight loss, we conducted nutritional guidance individually to ensure nutritional imbalance and correct knowledge of calorie intake, and prescribed a conventional dietary therapy restricted to 1000–1200 kcal per day. As a result of the VLCD and one week of dietary therapy at 1000 to 1200 kcal, an average weight reduction of 6.3 ± 0.9 kg was achieved. A further weight loss of 6.9 ± 0.9 kg was attained after 12 weeks of mazindol administration.
Mazindol therefore enhanced the weight reducing effect of conventional dietary therapy after the treatment with a VLCD, and prevented default from treatment.

Reduced insulin sensitivity in obese subjects is usually observed [1, 11]. The present data demonstrated that the M values estimated by the euglycemic glucose clamping were significantly increased and integrated insulin output during the oral glucose tolerance test was significantly decreased after mazindol administration. The present study clearly demonstrated that the mazindol-induced body weight reduction improved insulin sensitivity.
It was reported that there was a significant correlation between body mass index and insulin sensitivity in non-diabetic subjects [11], suggesting that decreasing body weight in obese patients may induce an improvement in insulin resistance. For this reason, the intention to reduce body weight is essential in improving insulin sensitivity in obese patients. It was also reported that insulin resistance is partially due to decreased insulin receptors and insulin receptor kinase activity in the muscle of obese humans [12]. This is similar to most studies in human adipocytes [13, 14]. Reducing body weight therefore seems to improve those abnormalities in adipocytes and muscles in obese subjects. Moreover, Nagai et al. [15] had reported an enhancing effect of mazindol on glucose uptake in skeletal muscle. It is suggested that decreasing body weight by restricting diet and administering mazindol can mostly improve insulin sensitivity and also that mazindol itself may partly improve insulin sensitivity in the muscles of obese patients.

On the other hand, it was reported that impaired insulin sensitivity or associated hyperinsulinemia can depress the activity of the Na-K pump [16], augment Na-H exchange [17], and impair Ca-AT-Pase [18], suggesting that resistance to insulin-stimulated glucose uptake and hyperinsulinemia are involved in the etiology and clinical course of hypertension [2, 19]. Blood pressure in the present subjects was decreased to normal by VLCD therapy, but there was no difference between blood pressure before and after mazindol therapy. It is therefore suggested that blood pressure does not seem to be changed by mazindol administration even though it induces a significant improvement in insulin sensitivity.

The effect of mazindol in treating severe obesity may be produced by exerting an anorexigenic effect that facilitates the maintenance of dietary therapy, thus motivating the patient to continue treatment. This drug is expected to be effective in improving obesity and other pathologic conditions which accompany obesity, such as insulin resistance associated with hyperinsulinemia.

In conclusion, mazindol is apparently useful for further reduction of body weight after a VLCD therapy. Moreover, mazindol increases insulin sensitivity while reducing body weight, possibly resulting in protecting severely obese patients from complications such as atherosclerotic changes in blood vessels.

References


