Nagoya J. Med. Sci. **49.** 61 ~ 69, 1987

# THE RELATIONSHIP BETWEEN INSULIN SENSITIVITY AND WEIGHT REDUCTION IN SIMPLE OBESE AND OBESE DIABETIC PATIENTS

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## ABSTRACT

Tissue sensitivity to exogenous insulin was determined in 10 obese diabetic patients, in 15 patients with simple obesity, and in 28 non-obese controls. Eight of the obese diabetics and five of the patients with simple obesity underwent dietary restriction (1,000–1,600 kcal/day) and physical training for eight weeks. Insulin sensitivity was evaluated by the euglycemic insulin clamp technique for 120 min. The amount of infused glucose (glucose metabolism: GM) is a measure of the overall tissue sensitivity to insulin. Differences in fasting blood glucose levels were adjusted by calculation of the glucose metabolic clearance rate (MCR). GM and MCR in the obese diabetics and in the patients with simple obesity were significantly ($P<0.001$) lower than in the controls. Inverse correlations existed between BMI and GM, between BMI and MCR, and also between fasting plasma insulin levels and both GM and MCR, respectively. After physical training, significant weight reduction was obtained, while MCR increased from $2.70\pm0.26$ ml/kg/min to $5.47\pm0.88$ ml/kg/min. Further significant correlation existed between reduction of BMI and increases in insulin sensitivity (GM and MCR). These results suggest that a combined program of physical training with caloric restriction would decrease body weight and increase peripheral insulin sensitivity, and would therefore be especially appropriate for the treatment of simple obese and obese diabetic patients.

Key Words: simple obese subjects, obese diabetic patients, insulin sensitivity, euglycemic insulin clamp technique, physical exercise.

## INTRODUCTION

Increased physical exercise has long been considered important for the management of diabetes mellitus[1], and has been recommended in medical textbooks and in teaching programs for patients with diabetes[1]. However, evidence supporting the long-term beneficial therapeutic effect of exercise programs remains limited[3-5]. In a previous study, we[5] found that glucose metabolism (GM) determined by the euglycemic insulin clamp technique directly correlates with maximal oxygen uptake ($\dot{V}O_2max$) and that this technique provides a reliable estimate of training effects. Studies comparing the insulin sensitivity in obese subjects with that in trained athletes have provided evidence that GM in obese subjects is significantly lower than in controls, but that GM in athletes is significantly higher than in controls[4]. An inverse correlation between GM and Broca's index was

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Received for Publication February 20, 1987

also demonstrated[4]. In addition, it has been shown that physical training for one month improves insulin sensitivity in non-obese control subjects[5]. However, these studies do not address the issue of the therapeutic benefits of exercise on glucoregulation in simple obese and obese diabetic patients. Limited investigation[6] has shown that physical training increases insulin sensitivity in obese subjects and in patients with type II diabetes, although a long-term improvement in glucose tolerance was not consistently evident[2]. The present study was undertaken to document the long-term effects of exercise in simple obese and obese diabetic individuals.

## MATERIALS AND METHODS

*Subjects*

*In vivo* tissue sensitivity to exogenous insulin was evaluated in 15 simple obese subjects (Body Mass Index: $31.7 \pm 1.1$ age: $24.8 \pm 2.7$ yr), in 10 obese non-insulin-dependent (type II) diabetic patients ($29.3 \pm 1.0$, $41.0 \pm 3.0$ yr), and in 28 non-obese healthy controls ($20.7 \pm 0.3$, $19.5 \pm 0.3$ yr) using the euglycemic insulin clamp technique[3,7]. Five of the simple obese subjects and eight of the obese diabetic patients underwent dietary restriction (1,000～1,600 kcal/day) and a daily physical exercise program consisting of 20 min of aerobic exercise and walking over 10,000 paces for an average of eight weeks. They were examined before and after the eight-week training program. The purpose and potential risks of the study were carefully explained to all subjects before receiving their voluntary consent.

*Euglycemic insulin clamp study*

Since this method has been previously described[3-5,8], only the general procedure will be outlined. After an overnight fast, a primed intravenous infusion of insulin (Novo Industri A/S, Denmark) (800 mU over 10 min) was followed by a constant infusion at 40 $mU/m^2/min$ for 110 min. Basal plasma glucose levels were maintained by determination of plasma glucose concentration every 5 min and by adjustment of a variable infusion of a 20% glucose solution. Under these steady-state conditions of euglycemia, the rate of glucose infusion provides the total body glucose turnover, because insulin at this dose level has been shown to inhibit hepatic glucose production[8]. In order to compare *in vivo* insulin action of subjects with different basal plasma glucose levels, the glucose metabolic clearance rate (MCR) was calculated by dividing GM by the mean plasma glucose[9].

*Analytical procedures*

Plasma glucose was measured by the glucose oxidase method. Plasma insulin concentration was measured by a modified double-antibody radioimmunoassay technique[10].

*Statistical methods*

All data were presented as the means $\pm$ SEM. Statistics were analyzed by paired and unpaired Student's t-test, and by correlation coefficients.

## RESULTS

Insulin and glucose levels in the basal state and during the euglycemic insulin clamp procedure are shown in Table 1. The basal plasma insulin concentrations of the simple obese and

Table 1. Insulin and glucose levels in the basal state and during euglycemic insulin clamp procedure

| | Insulin | | Glucose | | | |
|---|---|---|---|---|---|---|
| | Basal plasma insulin | Steady-state plasma insulin | Basal plasma glucose | Steady-state plasma glucose | Glucose metabolism (GM) | Glucose metabolic clearance rate (MCR) |
| | μU/ml | | mg/dl | | mg/kg/min | mℓ/kg/min |
| Controls (28) | 7.2±0.7 | 87.7±4.3 | 82.5±2.1 | 80.2±2.4 | 7.40±0.21 | 9.54±0.40 |
| Simple Obestities (15) | 20.7±2.6*** | 100.1±6.1 | 83.7±2.8 | 89.3±4.9 | 3.88±0.48*** | 4.52±0.62*** |
| Obese Diabetics (10) | 14.4±1.5*** | 101.1±14.1 | 127.1±16.8** | 117.5±11.5* | 3.50±0.30*** | 3.19±0.38*** |

Values are given as the means±SEM

* $p<0.05$
** $p<0.01$
*** $p<0.001$

the obese diabetic patients were significantly higher than those of the controls ($P<0.001$). Basal plasma glucose ($P<0.01$) and steady-state plasma glucose during the insulin clamp procedure ($P<0.05$) in the obese diabetic patients were significantly higher than those of the controls. Glucose metabolism and MCR of the simple obese and obese diabetic patients were significantly ($P<0.001$) lower than those of the controls. Inverse correlations existed between fasting plasma insulin levels and both GM ($P<0.001$, Fig. 1) and MCR ($P<0.001$, Fig. 2). Inverse relationships were also observed between BMI and GM ($P<0.001$, Fig. 3) and between BMI and MCR ($P<0.001$, Fig. 4). After dietary restriction and physical training, body weight significantly ($P<0.001$) decreased from an average 87.3±3.6 kg to 77.6±2.7 kg.

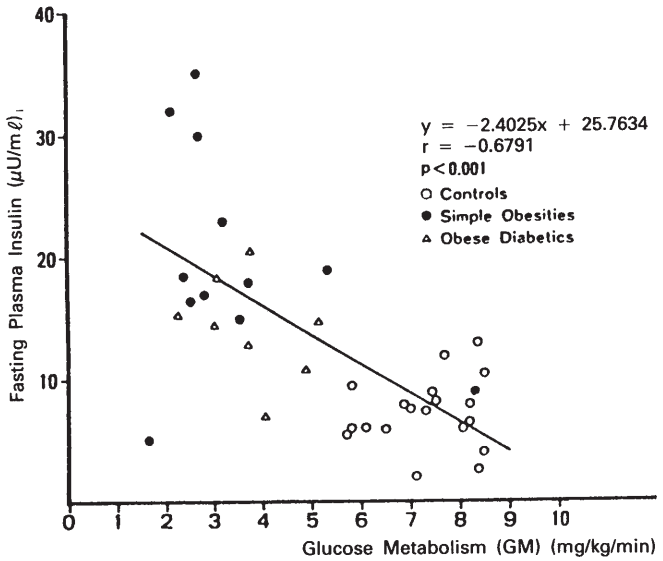


Fig. 1 Correlation between fasting plasma insulin and glucose metabolism (GM)

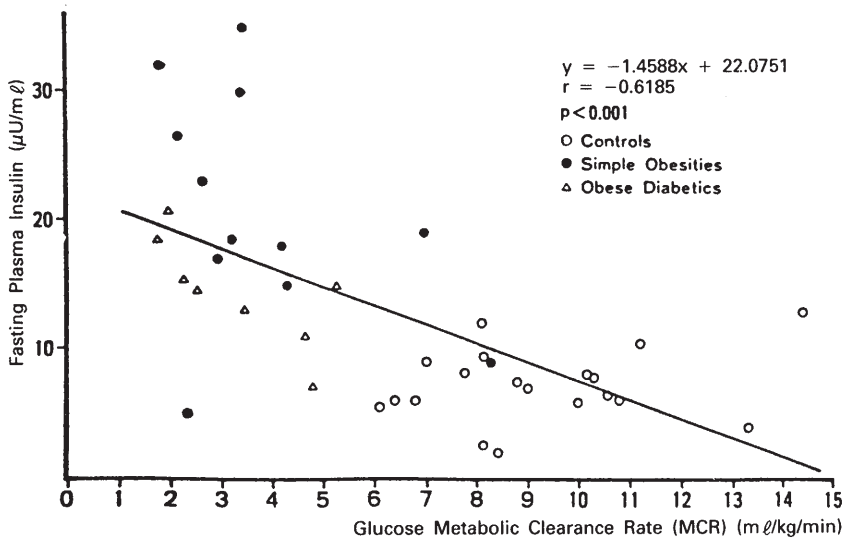


Fig. 2 Correlation between fasting plasma insulin and glucose metabolic clearance rate (MCR)

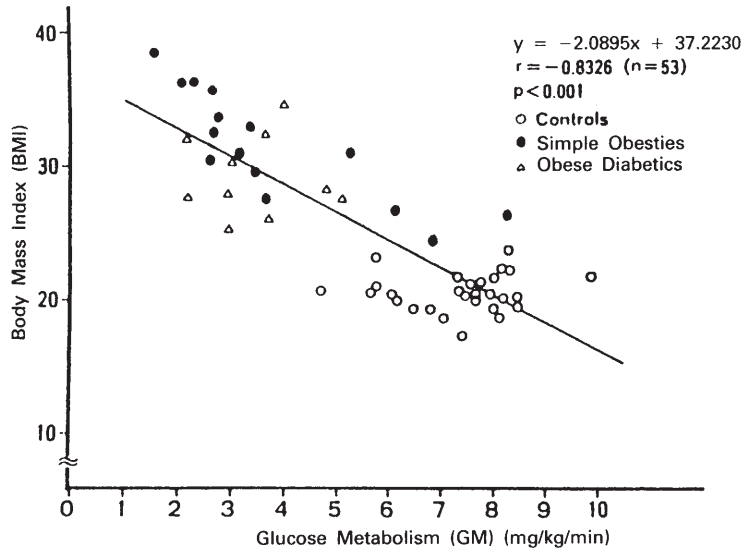


Fig. 3 Correlation between body mass index (BMI) and glucose metabolism (GM)

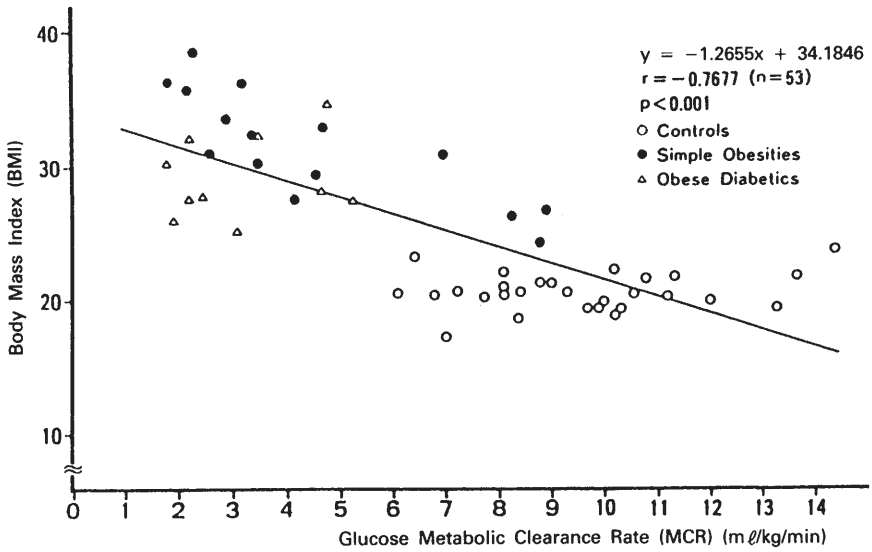


Fig. 4 Correlation between body mass index (BMI) and glucose metabolic clearance rate (MCR)

After weight reduction (10.2±2.4 kg), BMI decreased from 31.8±1.1 to 28.2±0.9 ($P<0.001$), while MCR increased from 2.70±0.26 ml/kg/min to 5.47±0.88 ml/kg/min ($P<0.01$) as shown in Fig. 5. Fig. 6 and Fig. 7 illustrate follow-up results of BMI and GM, and BMI and MCR in each patient, respectively. Close correlations existed between the magnitude of reduction of BMI (△BMI) and the degree of increase in insulin sensitivity (△GM, $r=0.778$, $P<0.01$ and △MCR, $r=0.703$, $P<0.01$) in each patient.

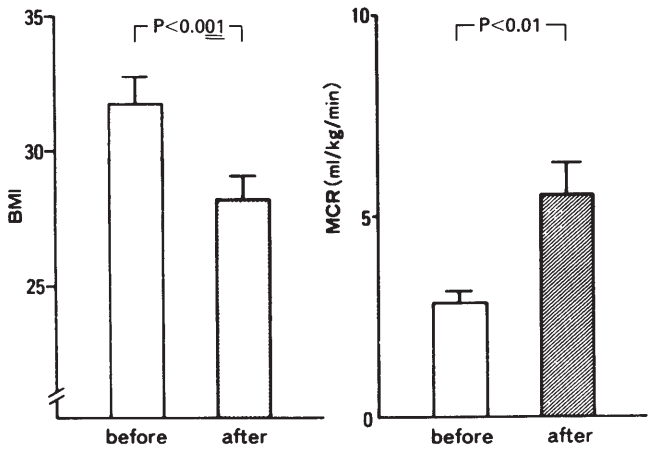


Fig. 5 Comparison of body mass index (BMI) and glucose metabolic clearance rate (MCR) before and after physical training

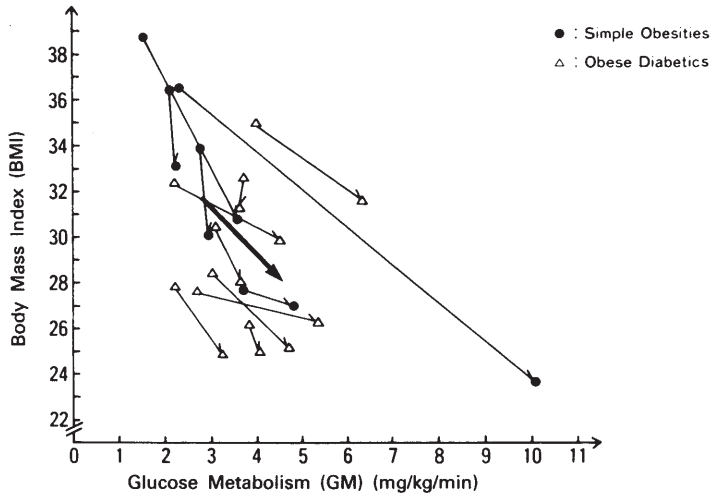


Fig. 6 Follow-up results of body mass index (BMI) and glucose metabolism (GM) in each patient
● (before) → ● (after)
The bold arrow represents the mean value of the individual data.

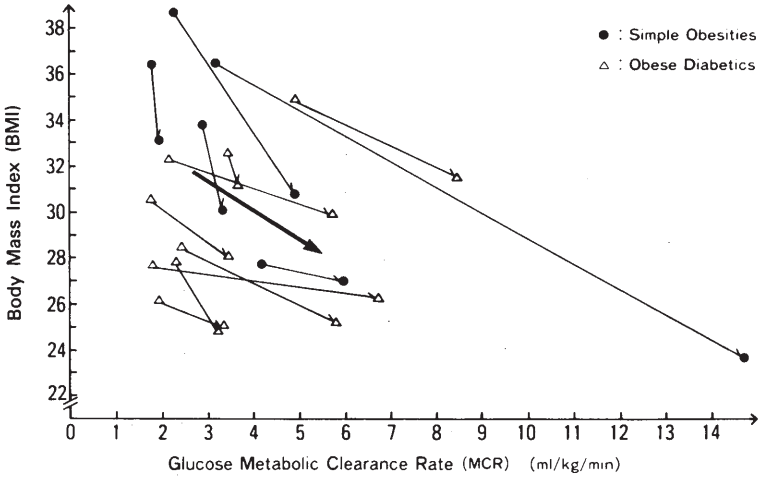


Fig. 7 Follow-up results of body mass index (BMI) and glucose metabolic clearance rate (MCR) in each patient
● (before) → ● (after)
The bold arrow represents the mean value of the individual data.

## DISCUSSION

DeFronzo et al[7] demonstrated that the euglycemic insulin clamp technique provides a more reliable estimate of tissue sensitivity to exogenous insulin. Maintaining the basal glucose level after insulin infusion not only prevents the discomfort and potential hazard of hypoglycemic reactions, but also the complex neuroendocrine response to hypoglycemia. Insulin resistance is a characteristic feature of human obesity[11]. Using the insulin clamp technique, the present study clearly comfirmed the above findings. In Japan, we used to apply Broca's index as a clinical index for obesity[12]. Recently, BMI has been employed because of its better correlation with percent fat[13]. Previous studies in our laboratory demonstrated that an inverse relationship exists between GM and Broca's index[4]. However, Ho et al[14] reported that in non-insulin-dependent diabetes, MCR correlated only with fasting plasma glucose (FPG) levels, and not with BMI; whereas in non-diabetics, MCR did not correlate with either FPG or BMI. We found inverse correlations between BMI and GM ($r = -0.833$, $P < 0.001$), and between BMI and MCR ($r = -0.768$, $P < 0.001$). Inverse relationships were also observed between FPG and GM ($r = -0.296$, $P < 0.05$), and between FPG and MCR ($r = -0.515$, $P < 0.001$), but the correlations between BMI and GM, and between BMI and MCR were more apparent. Therefore the obesity index (Broca's index and BMI) was inversely related to insulin sensitivity (GM and MCR).

In the present study, there were some differences in average age among the simple obese subjects, obese diabetic patients, and control subjects. DeFronzo[15] demonstrated that impaired tissue sensitivity to insulin is the primary factor responsible for the glucose intolerance observed with advancing age. We analysed the relationship between insulin sensitivity and age in the 10 obese diabetic patients and in the 15 simple obese subjects, but no correlation could be found between age and insulin sensitivity. Since there were only two patients over 50 years of age, the failure to observe such a correlation might not be surprising. However, age-matched study is needed; therefore further study of older subjects is in progress.

In the present study, insulin sensitivity correlated with degree of obesity, but not with the presence of diabetes. Thus, we analysed the individual data, before and after the training program, for eight obese diabetic patients and five simple obese subjects combined into one group. After the dietary restriction and physical training, a 10.2 kg average weight reduction was obtained, and insulin sensitivity increased to 202% of pretraining levels. Furthermore, $\triangle$ body weight and $\triangle$BMI significantly correlated with improvement in insulin sensitivity ($\triangle$GM and $\triangle$MCR). Since sensitivity to insulin is directly related to muscle mass and inversely proportional to adiposity[16], one would anticipate that a decrease in adipose tissue after physical training could account, at least in part, for the increase in sensitivity to insulin. On the other hand, previous studies in man[17] and in rats[18] have noted that muscle tissue characteristics may be of considerable importance in the increased insulin sensitivity after exercise training. This conclusion is supported by recent studies of James et al[19] on exercise-trained rats showing that the marked increase in whole body insulin sensitivity is due mainly to increased glucose oxidation in skeletal muscle. Previous studies in our laboratory have also shown that physical training for one month improves insulin sensitivity not only in glucose metabolism but also in lipid metabolism[5]. Our physical training program was not vigorous. Kemmer et al[20] stated that physical training of mild intensity, which would not necessarily improve cardiopulmonary capacity, might nevertheless be sufficient to improve metabolic parameters. Factors that may mediate the enhanced glucose uptake after physical training or weight loss are derived from the increase in muscle enzyme activity, the increased capillary supply in muscle tissue, and the augmented insulin binding to receptors[16,18]. Thus, the increase in insulin sensitivity found in the present study may have been mediated by an increased insulin sensitivity in skeletal muscle after physical training and by a decrease in adipose tissue[16,19].

Dietary regulation is also important in the treatment of simple obese and obese diabetic patients[21,22]. Wallberg-Henriksson et al[21] demonstrated that physical training in insulin-dependent diabetic patients results in increased peripheral insulin sensitivity, in a rise in muscle mitochondrial enzyme activities, and in unchanged blood glucose control. LeBlanc et al[22] likewise reported that the beneficial effect of exercise is greatly reduced if trained subjects are inactive for three days while eating *ad libitum*.

As insulin resistance is a characteristic feature of obesity as well as of non-insulin-dependent diabetes mellitus[11], an increase in insulin sensitivity would be most desirable in patients with such insulin-resistant state[20]. In addition, recent evidence indicated that hyperinsulinism might play an important role in the occurrence and the development of diabetic macroangiopathy[23]. Thus, a combined treatment of physical training with caloric regulation would increase periperal insulin sensitivity and, therefore, be more appropriate, from the pathophysiological point of view, than the use of betacytotrophic agents[1,20].

## ACKNOWLEDGEMENTS

This study was supported, in part, by Grants-in-Aid for Scientific Research from the Japanese Ministry of Education, Science and Culture (00548315, 58482006). The authors wish to thank Ass. Prof. S. Hayamizu of Aichi Prefectural University for invaluable assistance in performing this study, M. Miyao, MD, of the Department of Public Health, Nagoya University School of Medicine, for calculation of statistical significance of the present data, and Miss Y. Asano for typing the manuscript.

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