Combination Therapy of Exercise and Angiotensin-Converting Enzyme Inhibitor Markedly Improves Insulin Sensitivities in Hypertensive Patients With Insulin Resistance

Manabu Kinoshita, MD; Yutaka Nakaya, MD*; Nagakatsu Harada, BS*; Akira Takahashi, MD*; Masahiro Nomura, MD**; Shigenobu Bando, MD

The contraction of muscle enhances the release of bradykinin (BK) and improves glucose uptake by the muscle. Angiotensin-converting enzyme inhibitors (ACEI) slow the breakdown of BK, thus the effect of BK is augmented in the presence of ACEI. The present study investigated whether the combination of exercise (increased production of BK) and ACEI (delay in breakdown of BK) might further improve insulin sensitivity in hypertensive patients with insulin resistance (HOMA-R>1.8). Patients were assigned either to increased walking distance (Walking group) or taking 2 mg temocapril, an ACEI daily (ACEI group) for 8 weeks. Then both interventions were given to all patients for 8 weeks (ACEI+Walking group). Blood concentrations of triglycerides were slightly lower in the ACEI+Walking group than at baseline, although there were no significant differences in total cholesterol or high density lipoprotein-cholesterol among the 2 groups. Blood glucose was not significantly different with each treatment, but blood concentrations of insulin and HOMA-R were significantly lower in the Walking and ACEI groups compared with the Control group. The combination of walking and ACEI further lowered blood concentrations of insulin and HOMA-R, which suggests that this treatment is beneficial for hypertensive patients with insulin resistance. (Circ J 2002; 66: 655–658)

Key Words: Bradykinin; Insulin resistance; Temocapril; Walking

Insulin resistance is a risk factor for hypertension, and it has been shown to be improved by lifestyle modifications, including exercise and by pharmacotherapy. Angiotensin-converting enzyme inhibitors (ACEI) have a beneficial effect on insulin resistance, although the precise mechanism is still unknown. Kininase 2, another name for angiotensin-converting enzyme, degrades bradykinin (BK). Kishi et al and Miyata et al found that BK facilitates glucose utilization, and its involvement in ACEI-mediated improvement of glucose metabolism has been well demonstrated. During contraction, skeletal muscle releases BK and the enhanced glucose uptake observed with exercise training might be partly mediated by a BK-dependent pathway. However, BK is broken down rapidly by kininase 2, so we hypothesized that if inhibition of kininase 2 by ACEI leads to a further accumulation of BK after exercise, further improvement of insulin sensitivity could be expected. Therefore, we investigated the combined effect of ACEI and exercise training on insulin sensitivity in hypertensive patients.

Methods

Study Group

The study consisted of 36 hypertensive patients with insulin resistance (HOMA-R>1.8) but without previous treatment for hypertension or diabetes. Those who showed high fasting blood concentrations of glucose (>8 mmol/L) were excluded because they may show decreased insulin secretion, which is considered inappropriate in an evaluation of insulin resistance by homeostasis model assessment (HOMA-R). After an overnight fast from 22.00 h, and abstention from drugs, the patients attended Tokushima University Hospital or Kagawa Prefectural Shiratori Hospital at 09.30 h. Height and weight were recorded before subjects rested supine and acclimatized to a controlled environmental temperature of 20–24°C. After 20 min, a 20-ml venous blood sample was obtained and blood pressure (BP) was recorded with a cuff manometer. Insulin resistance was estimated using HOMA-R from the fasting blood glucose and insulin concentrations (HOMA-R = fasting immunoreactive insulin (IRI) (pmol/L) × fasting glucose (mmol/L)/135). The patients were assigned to one of 2 groups of 18 patients each: temocapril 2 mg per day (protocol-1) or walking (protocol-2). In protocol-1, the patients were initially given temocapril 2 mg per day for 8 weeks, and then instructed to walk more than 10,000 steps a day (or increase their walking by >3,000 steps from baseline), using a pedometer (Calorie Counter Suzuken, Nagoya, Japan), at least 3 days a week in addition to the temocapril treatment. The patients were asked to record their daily steps at baseline and in the 8th week of each treatment. The average numbers of steps were calculated from the 3 days on which they walked. We included only those who walked more than 10,000 steps per day or those who walked 3,000 steps more than baseline at least 3 days: 3 patients in protocol-1 and 8 patients in protocol 2 did not walk enough steps. In addition, 2 patients in protocol-1 complained of nonproductive cough after 8 and 10 weeks, respectively.
Baseline characteristics were not significantly different between the 2 patients groups: body mass index (BMI) (protocol-1 23.9±3.0kg/m² vs protocol-2 23.6±2.8kg/m²); systolic BP (156.2±12.3mmHg vs 165.0±14.0mmHg); diastolic BP (85.6±10.7mmHg vs 81.0±8.9mmHg); total cholesterol (23.1±9.3mmol/L vs 19.9±3.1mmol/L); triglyceride (16.4±6.5mmol/L vs 15.9±5.2mmol/L); and HDL-cholesterol (4.6±5.4mmol/L vs 4.8±3.5mmol/L). As in Table 1, body weight was not altered significantly by either treatment. Patients walked 5,721±1,425 and 5,119±1,957 steps at baseline in protocols-1 and -2, respectively. After instruction they walked 10,980±2,558 and 11,285±2,456 steps a day at least 3 days weekly in protocols-1 and -2, respectively.

Change in BP (Table 1)

Systolic and diastolic BP were significantly lowered by temocapril alone, but not significantly by walking alone. The combination of both temocapril and walking lowered BP further in both protocols.

Plasma Concentrations of Glucose, Insulin and Lipids (Table 2)

Walking exercise and temocapril treatment each decreased the plasma insulin concentrations significantly, and the combination of temocapril and walking significantly decreased the fasting concentration of plasma glucose. Temocapril-treatment or walking alone significantly decreased the HOMA-R, and the combination of both treatments further lowered HOMA-R (Fig 1). Hemoglobin (Hb) A1c was slightly but significantly improved by the combination therapy in both protocols. Blood concentration of triglyceride was lower in walking and the combination of both treatments than in baseline. There were no significant differences in serum concentrations of total cholesterol or high density lipoprotein (HDL)-cholesterol in each treatment group.

Discussion

In the present study, temocapril, an ACEI, and an increase in walking distance improved HOMA-R in insulin-resistant hypertensive patients; however, the lipid profile was not improved. The most important finding is that the combination of exercise and ACEI greatly improved the impaired glucose metabolism.

Insulin sensitivity is usually measured by assessing the
Insulin Resistance Therapy of Walking and ACEI

HOMA-R14 is a useful method not only for diagnosing glucose sampling makes it both intensive labor and costly. HOMA-R18 however, it is still controversial whether or not low-intensity exercise, such as walking, improved the Insulin Resistance Therapy of Walking and ACEI patients with marked insulin deficiency.19,20 The patients in exercise itself cannot substitute for insulin in patients with inadequate secretion, only a minimal improvement of glucose tolerance has been observed in type 2 diabetic patients with marked insulin deficiency.19,20 The patients in the present study had high insulin concentrations but only slightly increased glucose concentrations, suggesting that their insulin secretion was not severely impaired and it is in such patients that exercise can most effectively improve insulin action and lower the fasting blood concentrations of insulin.

In the present study, the decrease in fasting blood glucose was minimal or none with walking or temocapril alone, although blood insulin was significantly decreased by either treatment alone or in combination of for 8–16 weeks, which would be the main explanation for the decrease in HOMA-R. In contrast to our study, Katsuki et al found that both fasting concentrations of insulin and glucose were lowered by a combination of diet and walking therapy; and the discrepancy in results might be related to the background of the patients as well as the combination therapy.

In our data suggest that insulin resistance, as indicated by HOMA-R, was improved more easily than the serum concentrations of total cholesterol and HDL-cholesterol. The serum concentration of triglycerides showed a slight increase in protocol-2, but not in protocol-1, which suggests that either drug or exercise more effectively improve insulin resistance than the serum lipid profile in insulin-resistant hypertensive patients.

The improving effect of ACEI was once attributed to an increased blood flow, leading to increased delivery of glucose and insulin to the peripheral tissues. In our previous studies we found the combination of temocapril and exercise training improved insulin resistance in a rat model of type 2 diabetes, but not by losartan, an angiotensin-receptor antagonist.23 In vitro and in vivo studies have found that the improving effect of ACEI on glucose utilization is blocked by a kinin antagonist, which suggests a contribution by kinins in increased insulin sensitivity. However, some studies reported that the contribution of BK was minimal or none in ACEI-induced insulin sensitivity, and the reason for the discrepancy is not known. However, these results indicate that improvement in insulin resistance is mediated by many pathways.

Exercise increases the uptake of the glucose but the signaling pathways related to increased glucose uptake differ between insulin- and exercise-mediated stimulation.29 The molecular basis for this phenomenon has not been completely elucidated but appears to be dependent on multiple factors, including muscle glycogen concentrations, humoral factors and autocrine/paracrine mechanisms. Exercise training augments the plasma concentration of kallikrein or skeletal muscle phospholipase A2 activity, which is a target of BK and leads to prostaglandin synthesis, and there is a positive correlation between these increased parameters and muscular glucose uptake. Increased kallikrein also occurs in skeletal muscle with high oxidative activity21 a finding that may be related to the observation of Stebbins et al that the contraction of the skeletal muscle enhanced the release of BK.22 Given these findings, it is possible that during exercise BK may be highly involved in increased glucose uptake from the circulation. We also consider that there are other mechanisms because improvement in insulin resistance by ACEI or exercise is mediated by a number of factors. However, the potentiated improvement of glucose metabolism induced by a combination of exercise training (increased BK release) and ACEI (decreased degradation of BK) is an effective, and reasonable treatment for hypertensive patients with insulin resistance.

References