Therapeutic Evaluation of the Effect of Biotin on Hyperglycemia in Patients with Non-Insulin Dependent Diabetes Mellitus

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(Received January 28, 1993)

Summary The therapeutic efficacy of biotin was evaluated in 43 patients with non-insulin dependent diabetes mellitus. The serum biotin concentration in the patients was significantly lower than that in the 64 healthy control subjects and inversely correlated with the fasting blood glucose level. The oral administration of biotin, 9 mg daily, corrected the hyperglycemia in the patients with no change in their serum insulin level. The serum levels of pyruvate and lactate decreased to their normal ranges after the administration. These observations suggest that the biotin administration ameliorates abnormal glucose metabolism in diabetic patients, presumably by enhancing the activity of the biotin-dependent enzyme, pyruvate carboxylase, with a subsequent promotion of glucose utilization for the entry into the tricarboxylic acid cycle. The administration also enhanced the response to glibenclamide in patients who had been resistant to the agent, suggesting a significant increase in the potency of the endogenous insulin action. The result demonstrates that biotin administration is effective for the treatment of the patients. Neither a relapse of clinical symptoms nor an occurrence of undesirable side effects has been observed.

Key Words: biotin depletion, diabetes mellitus, pyruvate, fatty acids, insulin resistance

It has been demonstrated that oral glucose tolerance and insulin response to

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an oral glucose load in mice with non-insulin dependent diabetes (diabetic kk mice) were improved by treatment with 2 to 4 mg of biotin per kg diet for 10 weeks [1]. In clinical studies, we reported that the serum biotin level in psoriasis vulgaris and pustulosis palmaris et plantaris (PPP) patients is significantly less than that in normal subjects [2]. Uehara et al. [3] reported that of the 41 patients with PPP, 68% showed an abnormal glucose tolerance test result. Furthermore, we also observed that there was a high incidence of osteosclerosis and absorption of bone of the clavicule especially in the PPP patient [2]. The administration of biotin can improve a variety of clinical symptoms as well as associated metabolite abnormalities such as hyperglycemia, which interested us in the possible efficacy of biotin in the management of diabetes mellitus. Hyperglycemia is one of the common complications in the patients because of a diminished ability to utilize glucose by entry into the tricarboxylic acid cycle. We have recently shown that in biotin-deficient rats, induced by the feeding of a diet containing raw egg white, the oral glucose tolerance and the plasma insulin level in response to an oral glucose load were lower than in rats with sufficient biotin [4]. Coggeshall et al. demonstrated that a pharmacologic dose of biotin lowered the concentration of fasting blood glucose in insulin-dependent diabetic subjects during insulin withdrawal [5].

Despite these emerging reports, the metabolic mechanism of these effects remains unclear. In addition, the use of biotin has found no place in the routine management of diabetic patients. Thus, the present study was aimed to establish whether a relationship exists between the serum biotin concentration and the blood glucose level, whether biotin depletion is one of the factors contributing to hyperglycemia in non-insulin dependent diabetic patients, and whether the administration of biotin is useful in the maintenance therapy for the patients.

SUBJECTS AND METHODS

Patients. Forty-three out-patients with non-insulin dependent diabetes mellitus (NIDDM), 25 males and 18 females, were recruited for the present study. The mean age of the patients as 46 years (range, 35 to 56 years). The mean disease duration was 4.6 years (range, 2 to 6 years). At the beginning of the study, all patients had been treated with a dietary regimen alone or with a sulfonylurea agent, glibenclamide, with minimal or no benefit to their clinical features. The patients had fasting blood glucose levels greater than 9.5 mmol/liter and showed a diabetic pattern in response to a 75 g-load glucose tolerance test. The patients were normotensive and chemically euthyroid, and had no clinical evidences of hepatic, renal, gastrointestinal, endocrine, and immune diseases. The patients were instructed to maintain their ordinary diet during the study and not to take any medication at least 4 weeks prior to the study, unless otherwise indicated. The purpose of this study was fully explained to all patients and consent was obtained from each patient. As a control, 64 healthy subjects, matched for sex and age,
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volunteered for the determinations of the serum biotin concentration and fasting blood glucose level.

Experimental. The study started usually with an oral administration of biotin, 9 mg daily in three divided doses. The patients on long-term maintenance administration were given a kind of anti-microbial drug, Miya-BM® (a product from Clostridium butylicum, Miyarisan Pharmaceutical Co., Tokyo), at a daily dose of 3 g divided into 3 portions in addition to the biotin, in order to prevent the proliferation of the usual intestinal microflora that might digest or degrade the administered biotin. Clinical and laboratory findings were usually checked every 2 weeks. Undesirable side effects were assessed by a questionnaire completed by each patient and from clinical and laboratory findings at each visit. Venous blood was drawn for determinations of blood glucose level, serum biotin concentration, and serum levels of insulin, pyruvate, and lactate in the morning after an overnight fast. The blood glucose level was determined by a standard glucose oxidase method (Glucose C-test Wako, Wako Pure Chemical, Osaka). The serum insulin IRI [6] was determined with a Shionogi Insulin RIA kit (Shionogi and Co. Ltd., Osaka) that employs the double-antibody method of radioimmunoassay. The serum levels of pyruvate and lactate were determined by high-performance liquid chromatography as described previously [7]. The serum biotin concentration was determined microbiologically by a procedure similar to that described earlier [7]. The test organism was Lactobacillus plantarum (ATCC 8014).

Statistic analysis. The results are expressed as mean ±SEM. Statistical analysis was performed with the two-tailed Student’s t-test for paired and unpaired data, with \( p < 0.05 \) accepted as the level of significance.

RESULTS

Serum biotin and blood glucose

The serum biotin concentration in the 43 patients with NIDDM was significantly lower than in the 64 control subjects (56.7 ± 4.8 vs. 96.8 ± 3.1 nmol/liter, \( p < 0.01 \)). The fasting blood glucose and the serum insulin levels were determined in the 43 patients and in 25 of the control subjects. There was an inverse correlation between the serum biotin concentration and the fasting blood glucose level (r = −0.74, data not shown). No correlation could be observed between the serum biotin concentration and the serum insulin level (r = −0.11, data not shown).

Trial administration of biotin

A trial administration study was done in 28 patients. Among them, 18 patients were randomly selected and given biotin, 9 mg daily. The remaining 10 patients were given a placebo (maize starch). The biotin and the placebo were identical in appearance. The fasting blood glucose levels were determined before administration, after 1 month of administration of biotin, and 1 month after cessation of the administration. In patients who were given biotin, the glucose level decreased from
12.9±2.6 mmol/liter to 7.1±1.2 mmol/liter (p<0.05) after the 1-month administration (Fig. 1). After the cessation, the level returned to the initial value. The serum levels of pyruvate and lactate in the patients decreased significantly from 107.4±19.1 μmol/liter to 63.8±5.7 μmol/liter and from 2.32±0.47 mmol/liter to 1.25±0.13 mmol/liter, respectively, after the administration (p<0.05). After the cessation of treatment, the levels returned nearly to the initial values. The serum insulin level was not altered by biotin administration (data not shown). In comparison, the patients who had received placebos showed no changes in the levels of blood glucose and serum pyruvate and lactate during the trial study.

**Long-term administration of biotin**

The long-term administration of biotin was tested in 20 patients (Fig. 2). The patients were given a combination of biotin and the antimicrobial drug. Among them, 5 patients were followed up for more than 4 years. The fasting blood glucose level decreased to normal level within 2 months and remained within the normal range thereafter. The serum insulin level was almost unchanged. The body weight of the patients was not affected by the administration. A single administration of the antimicrobial drug slightly increased the serum biotin concentration, but not significantly. The drug itself did not affect the blood glucose level and the serum insulin profile (data not shown). Clinical aggravation and undesirable side effects were not observed.

**Effect of biotin addition on sulfonylurea treatment**

To determine whether biotin administration modifies the potential prevalence

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**Fig. 1.** Effect of the oral administration of biotin or a placebo on the fasting blood glucose level in diabetic patients before (Before treat.), after 1 month of administration (On treat.), and 1 month after cessation of the administration (Post treat.). Shaded and open columns represent the mean values of the blood glucose levels in patients administered biotin (n=18, 9 mg daily) and the placebo (n=10), respectively. The standard errors are represented by vertical bars, and significant differences are indicated by *p<0.05 with respect to the corresponding “Before treat.” value and *(p<0.05 with respect to the corresponding “On treat.” value.

of insulin resistance in diabetic patients, we administered biotin, 9 mg daily, to 5 patients who had been treated with glibenclamide, over 10 mg daily, for more than 1 year with minimal or no benefit. As exemplified in Fig. 3, a reduction in the fasting blood glucose level was evident after the addition. In this patient, the glibenclamide could be reduced to a half of the initial dose after the addition. Similarly, in other patients, the blood glucose was maintained within the normal range even with a smaller dose of the agent. The serum insulin level was not affected by the addition of the biotin.

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DISCUSSION

The present study demonstrated that biotin administration improved hyperglycemia in patients with NIDDM. After cessation of the administration, however, the fasting blood glucose returned to its initial level. The study also demonstrated a low serum biotin concentration in the patients and an inverse correlation between the serum biotin concentration and fasting blood glucose level in the patients. These findings thus suggest therapeutic efficacy of biotin for the treatment of NIDDM patients.

Biotin is essential for the function of pyruvate carboxylase, the enzyme that plays a key role in the conversion of pyruvate to oxaloacetate [8-11]. Therefore we presume that the biotin depletion observed in diabetic patient may interfere with pyruvate catabolism as a consequence of reduced activity of the enzyme, resulting in an accumulation of pyruvate and subsequent hyperglycemia. Experimentally it has been shown that there is an impairment in glucose catabolism in biotin-deficient rats [4, 12-15] and that administration of a biotin supplement counteracts the defect in the oral glucose tolerance and in the insulin response to the oral glucose load in diabetic kk mice [1]. In the present patients, biotin administration decreased the serum levels of pyruvate and lactate. The rates of glucose oxidation and disposal and the activities of the enzymes involved in glucose catabolism were not determined in the present study. However, the data obtained, namely, the changes in glucose level and serum levels of pyruvate and lactate after biotin administration, may reflect the enhanced rate of glucose utilization. It has been demonstrated that biotin enhanced guanylate cyclase activity, thus increasing the cGMP level and thereby stimulating the synthesis of glucose kinase at the level of translation in rat liver [16]. Furthermore, Li Hsieh and Mistry [17] pointed out that the activity of glucokinase was low in diabetic, fasting and/or biotin-deficient rats and that the de novo synthesis of the enzyme was induced by the insulin and biotin in the intact rats. Thus, a similar argument as made in the rat experiments [1, 12-15] could also be made to account for the improved glucose catabolism in the present patients during biotin administration.

In the patients, low serum biotin was closely associated with hyperglycemia. This abnormality could be improved by biotin administration without any dietary manipulation or loss of body weight, indicating that the increase in serum biotin may directly drive the reaction towards glucose utilization in the patients. If biotin administration were to increase the serum insulin level, the resultant hyperinsulinemia would induce a state of tissue insulin resistance by down-regulating both receptor and postreceptor events involved in insulin action [18-22]. Biotin administration, however, did not affect the serum insulin level in this study. Therefore, it seems unlikely that biotin directly stimulates the insulin release with a resultant decrease in the blood glucose level. On the other hand, we demonstrated that the plasma insulin level remarkably declined so that insulin synthesis or
the excretion system of the rats may be impaired at an early stage during the course of development of biotin deficiency in osteogenic disorder Shionogi rats [4]. Furthermore, the plasma insulin secreted in response to the glucose load in the deficient rats was approximately one-third the concentration of that in the control rats. This indicates that biotin deficiency may induce a defect in insulin secretion and that the biotin effect in the patients with hyperglycemia may be different than that in the case of the biotin-deficient rats with a low serum glucose level.

In a clinical trial among patients who had been poorly responsive to glibenclamide treatment, biotin addition enhanced the response to the agent and could minimize the requirement of the agent with a metabolic benefit. The mechanism of this beneficial effect of biotin of glibenclamide treatment is unclear. However, the clinical improvement seen with biotin addition suggests the possibility that the addition of the vitamin may favorably modify the potency of insulin action or insulin resistance in the patients by altering the fatty acid composition of the cell membranes that affect the functions of receptors and the activities of enzymes responsible for glucose transport and intracellular glucose catabolism, because biotin promotes the synthesis of fatty acids [10, 11] that are an important component of cell membrane lipids. More detailed studies are necessary to explain more fully the present observation.

The reason for the low serum biotin in the patients in this study is not clear. Since biotin is mainly produced by intestinal microflora, absorbed from the intestine into the circulation and utilized [10, 11, 23–25], its depletion may be attributed to the insufficient synthesis of the vitamin, increased digestion or degradation of the vitamin by an abnormal level of microflora, impaired absorption of the vitamin from the intestine, increased renal loss of the vitamin, or any combination of these possibilities.

REFERENCES

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