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CLINICAL STUDY OF VITAMIN INFLUENCE IN DIABETES MELLITUS

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Abstract

Vitamin deficiency is a result of an inadequate diet. Education on the importance of trace nutrients in diabetic patients with poor blood sugar control is examined. Those who prepare meals must consider the loss of vitamins in the process of cooking. Our study also suggested that marginal vitamin deficiency plays an indirect but important role in the development of diabetic complications. Vitamin C as altering total cholesterol and vitamin E as altering triglyceride could modify diabetic retinopathy. Pharmacologically, niacin might be responsible for the decrease in lipoprotein (a) and vitamin C would inhibit the influence of rapid blood glucose control on diabetic retinopathy.

Key words: diabetes mellitus, cholesterol, lipoprotein (a), triglyceride, vitamin

INTRODUCTION

Increased demand for vitamins and difficulty in their use is anticipated in diabetes. In addition, doctors, nutritionists and patients alike have little concern about vitamins in dietary guidance [1]. It was therefore considered that subclinical vitamin deficiencies may be found in many diabetics. First, we investigated subclinical vitamin deficiencies in diabetics and examined the relationship between these deficiencies and diabetic neurosis and diabetic vasculopathy.

Recently, it is reported that lipoprotein (a) ("Lp(a)") is a substance which has been drawing attention as a risk factor for arteriosclerosis. Rath & Pauling [2] hypothesized that Lp(a) is a metabolite of vitamin C and rather prevents arteriosclerosis from the fact that Lp(a) is detected in the blood of such animals as primates and guinea pigs which lack the ability to synthesize vitamin C, whereas it is scarcely found or found only in minimal amounts in animals with the ability to synthesize vitamin C. Secondary, we examined the relationship between Lp(a) and vitamin C in diabetes.

Moreover, it is known that retinopathy develops and worsens through rapid correction of blood sugar levels and hypoglycemia. The mechanisms of this phenomenon have not yet been elucidated in

detail, but there is a theory that rapid control of blood sugar induces the secretion of catecholamine resulting in contraction of blood vessels, which increases capillary blood pressure in the retina and makes the capillary more likely to break. In addition, it has been said that increased blood coagulation caused by platelets and other factors may induce ischemia in the retina. On the other hand, although vitamin C is involved in the synthesis of catecholamine, a large quantity of vitamin C may suppress catecholamine [3]. Finally, we thus administered vitamin C to patients with poor blood sugar control, corrected their blood sugar levels using insulin for one month and observed the development and worsening of retinopathy.

MATERIALS AND METHODS

Diabetic patients excluding liver and (or) kidney disease were investigated in the analysis of relationship betweem diabetes and subclinical vitamin deficiency. Subclinical vitamin deficiencies were determined using levels in the blood. The borderlines for the levels of various vitamins were: plasma vitamin A (measured using HPLC), < 230 ng/ml; whole blood vitamin B1 (measured using thiochrome), < 50 ng/dl; whole blood vitamin B2 (measured using lumiflavin), < 50 ng/ml; whole blood vitamin B6 (measured using HPLC), < 3 ng/ml; whole blood niacin (measured using HPLC), < 3 m/l; plasma folic acid (measured using isotope) < 2.3 ng/ml; plasma vitamin B12 (measured using isotope) < 229 pg/ml; plasma vitamin C (measured using hydralazine), < 0.7 mg/dl; plasma vitamin E (measured using HPLC), < 0.58 mg/dl; and HDL-vitamin E, < 0.33 mg/dl. Statistical analyses were performed by t-test, chi-square test and Fisher exact test.

In the analysis of effect of vitamins on lipoprotein (a), patients with non-insulin-dependent diabetes were investigated. Fasting blood sugar and blood vitamin C and Lp(a) levels were measured using HPLC and EIA, respectively.

While in the analysis of preventive effect of vitamin C on exacerbated retinopathy, the subjects were 15 female inpatients aged from 24 to 80 inclusive (average: 60), whose fasting blood sugar (FBS) levels were 256 to 520 mg/dl, urinary ketone bodies were +/- to 2 (+), and HbA1c levels were 8.2% to 12.5% (10.4+/-1.9%) upon admission. Immediately after admission, insulin was used and FBS was measured every three to four days, and insulin doses were increased or decreased by 4 to 8 units depending on the results. Funduscopy showed that one subject had no retinopathy and all others had simple diabetic retinopathy, one of which had minor bleeding. Funduscopy was performed by an ophthalmologist on the first occasion and at week 4. In the meantime, subjects self-performed funduscopy once a week. After discharge, subjects were asked to see an ophthalmologist once a month. In addition, beta-TG, PF4 and tromboxane B2 (TXB2), molecular markers for platelet

aggregation, were measured one week after the start of insulin injections. 2000 mg of vitamin C was orally administered and the same molecular markers were measured four weeks later.

RESULTS AND DISCUSSION

Diabetes and Subclinical Vitamin Deficiency

Subclinical deficiencies in various vitamins were frequently found in diabetic patients. Vitamin B1 was deficient in 24% of healthy people compared to 54.4% in diabetics. Decreased vitamin C levels were found in the blood of the diabetics. It is considered that high vitamin E levels correlate with lipid levels in the blood. As diet is considered to be the most likely cause for subclinical vitamin deficiencies, we compared the calculated amounts and observed amounts of vitamins B1 and vitamin C in a 1200 kcal/day diet for three days. The results showed that the calculated amounts were 1.05+/-0.12 mg/day and 122+/-0.9 mg/day for vitamins B1 and vitamin C, respectively, whereas the observed amounts were 0.46+/-0.08 mg/day and 44.3+/-0.3 mg/day for vitamins B1 and vitamin C, respectively. Differences were found between the calculated and observed amounts.

The most likely cause for subclinical vitamin deficiencies is dietary factors. Although both vitamins B1 and vitamin C were sufficient in calculation, observed amounts were smaller by 46.8% and 36.4% for vitamins B1 and vitamin C, respectively. This results from loss through cooking and decreased vitamin C levels in vegetables caused by differences in fertilizers, cultivating techniques, distribution processes, etc. Patients may develop subclinical vitamin deficiencies while in hospital unless these factors are taken into account when preparing their diet. In particular, caution must be used for patients with geriatric diabetes as they excrete large amounts of water-soluble vitamins in the urine in the stage of polyuria.

Then complications were examined. The relationship between vitamins B1, vitamin B6 and vitamin B12 levels and diabetic neurosis was examined. The vitamin B1 level in the blood of the group of patients with neurosis was 45.3+/-15.8 ng/ml, showing a significant decrease compared to that for the group without neurosis, which was 54.9+/-13.0 ng/ml. In addition, 69% of the subjects in the neurosis group showed subclinical vitamin B1 deficiency, and TPP effects showed a similar tendency. However, there were no significant differences in vitamins B6 and vitamin B12 levels in the blood.

From these results, it was considered that vitamin B1 deficiency may be a modifier for diabetic neurosis. The examination of diabetic vasculopathy found that the group of patients with vasculopathy showed a tendency to have decreased vitamin C levels in the blood and high frequency of subclinical vitamin C deficiency. The examination of lipid metabolism found that plasma vitamin C levels of 0.7

mg/dl or lower were associated with a tendency to have decreased total cholesterol levels in the serum and that higher serum HDL-cholesterol levels were associated with higher plasma vitamin C levels. LDL-cholesterol levels and the ratio of LDL-cholesterol to HDL-cholesterol tended to decrease with decreased plasma vitamin C levels (Fig. 1). Serum total cholesterol levels of 220 mg/dl or higher were found in 62.2%, 55.0% and 36.4% of those whose plasma vitamin C levels were 0.4 mg/dl or lower, 0.4 to 0.7 mg/dl, and higher than 0.7 mg/dl, respectively. LDL-cholesterol levels of 150 mg/dl or higher were found in 50.0%, 35.3% and 19.2% for the respective three groups, showing lower levels in those with higher plasma vitamin C levels. The examination of lipid metabolism and HDL-vitamin E (HDL-E) showed that the group of subjects whose HDL-E levels were 0.3 mg/dl or lower had significantly lower serum triglyceride levels (Fig. 2). These results indicate that subclinical deficiency in vitamins C and vitamin E may promote diabetic angiopathy.

Lipoprotein (a) and Vitamins

The results showed that the correlation coefficient between Lp(a) and vitamin C was r= 0.128. If Rath's hypothesis is right, there should be a negative correlation. In addition, in order to examine the possibility that the administration of AsA may decrease Lp(a) levels in the blood, subjects whose Lp(a) levels were 20 mg/dl or higher were treated with 2000 mg of vitamin C, but no decrease in Lp(a) levels was found (Fig. 3). From these results, it is considered that Lp(a) may be a substitute for vitamin C. In addition, it is intriguing that the administration of 1,500 mg of a nicotinic acid derivative induced a significant decrease in Lp(a) levels.

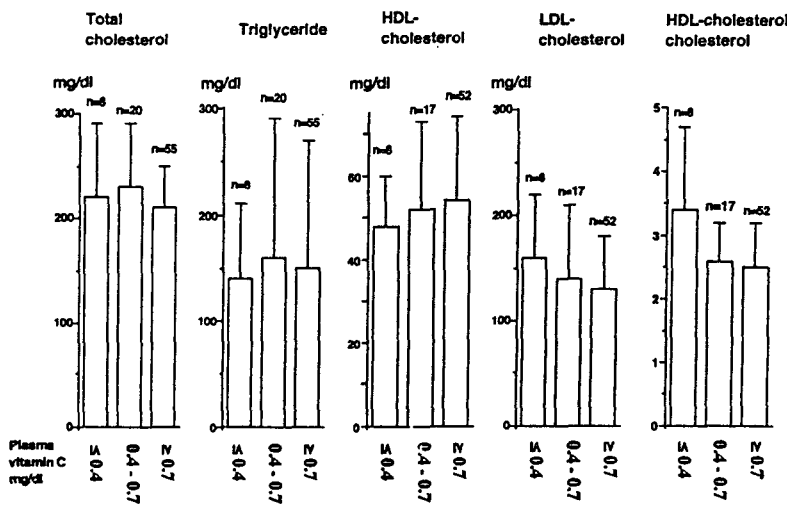

Fig. 1. Plasma vitamin C and serum lipid concentrations in diabetic patients.
LDL-cholesterol= total cholesterol – (HDL-cholesterol) – (triglyceride/5)

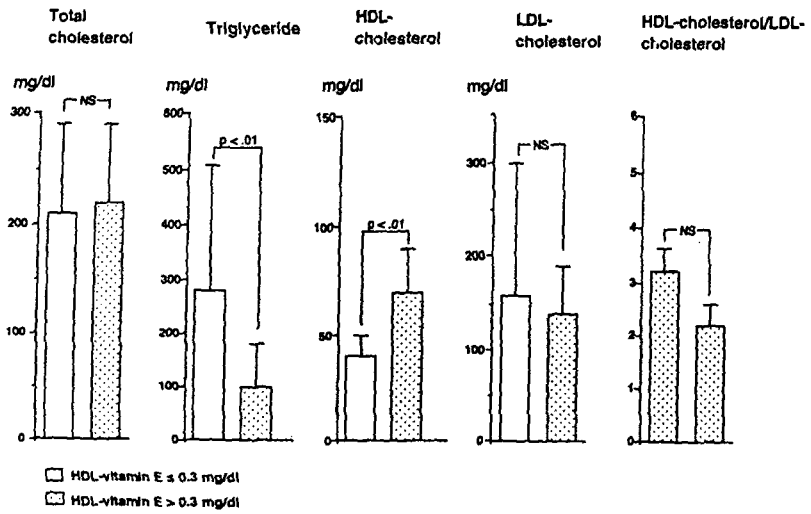

Fig. 2. HDL-vitamin E and serum lipid levels in diabetic patients.
LDL-cholesterol= total cholesterol – (HDL-cholesterol) – (triglyceride/5)

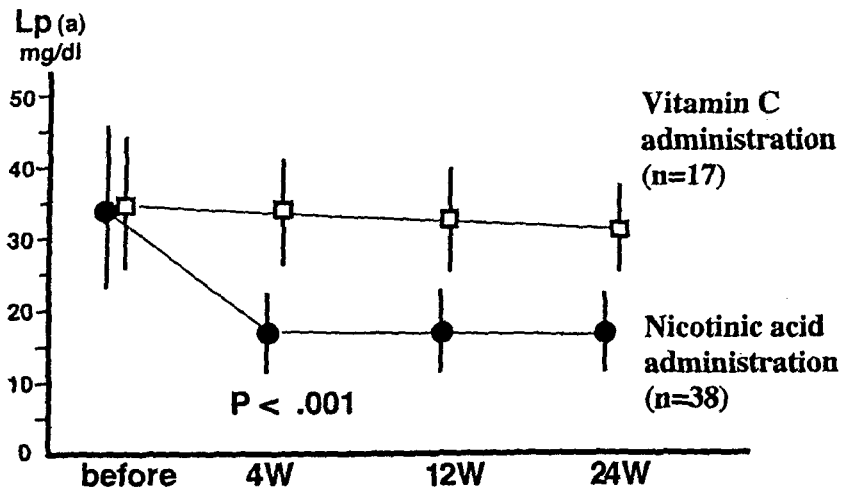

Fig. 3. Changes of Lp (a) with the administration of nicotinic acid and derivative of vitamin C.

Prevention of Exacerbated Retinopathy and Vitamin C

The blood sugar level upon admission was 371.6+/-103.3 mg/dl which decreased but not significantly to 292+/-67.6 mg/dl after one week of insulin treatment. Four weeks later the blood sugar was 122.8+/-4.1 mg/dl, showing a significant decrease compared to that measured upon admission (Fig. 4). Subsequently, the levels were found to be 113.2+/-6.4 mg/dl and 108.8+/-8.9 ml/dl at weeks 12 and 24, respectively. HbA1c was 10.4+/-1.9% upon admission which decreased significantly to 7.1+/-0.2% at

week 4. Subsequent levels were 6.2+/-0.5% and 5.8+/-0.1% at weeks 12 and 24, respectively. One week after the start of insulin treatment, beta-TG, PF4 and TXB2 measured 47.4+/-23.5 mg/dl, 7.2+/-3.5 ng/ml and 33.6+/-8.4 pg/ml, respectively, showing levels above relevant reference ranges except TXB2. This seems to show that decreased blood sugar levels induce increased platelet aggregation. Beta-TG, PF4 and TXB2 at week 4 after the administration of 2000 mg of vitamin C decreased significantly. In addition, no worsening of retinopathy was found by funduscopy at weeks 4, 12 and 24. The minor bleeding found in one subject disappeared by week 12.

From these results, it was suggested that vitamin C suppresses the enhancement of platelet aggregation through unknown mechanisms and prevents the worsening of retinopathy induced by the rapid control of blood sugar.

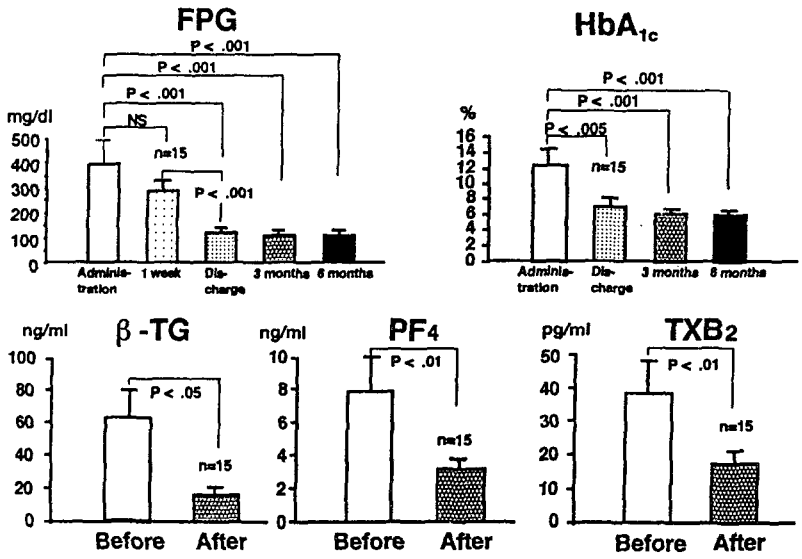

Fig. 4. Levels of platelet molecular markers, blood sugar, HbA1c before and after administration of 2000 mg vitamin C.

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