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Clinical Application of Measuring Serum Fructosamine as an Index of Glycemic Control in Diabetic Patients

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Abstract Measurement of serum fructosamine is a new method for the quantification of glycated serum proteins. We examined the clinical application of measuring serum fructosamine as an index of glycemic control in diabetic patients. Serum fructosamine had good correlation with mean fasting plasma glucose obtained 0-3 weeks before the fructosamine measurement and had best correlation with that obtained 1 week before the measurement ($r=0.531$, $p<0.001$). Correlations with mean fasting plasma glucose obtained 4 week before the measurement ($r=0.407$, $p<0.1$) or hemoglobin A_1 at the nearly same sampling time ($r=0.306$, $p<0.2$) were not significant. The patients tested were divided into 4 groups according to diabetic control evaluated from mean fasting plasma glucose obtained 1 week before the fructosamine measurement ; an excellent group (<120 mg/dl) ; a good group (121-140 mg/dl) ; a fair group (141-160 mg/dl) ; a poor group (>161 mg/dl). Mean value of serum fructosamine in an excellent group was significantly higher than that in healthy controls ($p<0.05$), and increased according to worsening of glycemic control, and that in a poor group was significantly higher than that of an excellent group ($p<0.001$). These results suggest that measurement of serum fructosamine is useful as a medium term (0-3 weeks) index of glycemic control in diabetic patients, especially who have had a rapid fluctuation in glycemic control for a couple of weeks.

Key Words : Serum fructosamine, Hemoglobin A_1, Glycemic control, Diabetic patients

Introduction

Glycation of proteins can occur as a non-enzymatic posttranslational modification directly dependent upon prevailing glucose concentration[1]. This reaction is not influenced by sudden changes in blood glucose, since it is slow reaction which progresses within weeks[2]. Therefore, measurment of glycation of proteins is expected to be useful as an index of glycemic control in diabetic patients[3]. Measurement of hemoglobin A_1 (glycated hemoglobin) has been recognized as a method of assessing long term (1-2 month) glycemic control, because hemoglobin A_1 has a long half-life (60-90 days)[4]. Since glycation of serum proteins can also occur, it is supposed that it may reflect the integrated glycemia over 0-2 weeks by means of their half-life span (2-20 days)[5].

Recently, Johnson et al reported a novel approach for measurement of glycated proteins, based on the ability of glucose bound to protein with ketoamine linkage (generically

termed fructosamine) to reduce nitro blue tetrazolium in alkaline conditions[6].

In this study, we examined the clinical usefulness of measurement of serum fructosamine as an index of glycemic control in diabetic patients.

Subjects and methods

We studied 11 healthy controls and 12 diabetic patients (5 males, 7 females, 41-73 years old) admitted to our ward.

Protocol. Blood specimens were obtained at fasting in the morning and the sera were stored at −20℃. In diabetic patients, serum fructosamine measurement was done once a week. Fasting plasma glucose was measured at least twice a week and their mean value of the week was calculated. Hemoglobin A_1 was medsured once a month.

Assay. Fructosamine was measured by the methods of Johnson et al[6] : 20 μl of serum was added to 200 μl of 1 M bicarbonate buffer (pH 10. 35) containing 0.25 M nitro blue tetrazolium, and incubated at 37℃. Absorbance at 530 nm was measured at 10 and 15 min of the reaction, and compared with that of secondary standards originally standardized against 1-deoxy-1-morpholinofructose. Plasma glucose was measured by glucose oxidase method and hemoglobin A_1 was measured by ion exchange chromatography[4].

Date are given as means ± SE. The results were evaluated statistically using Student's t -test.

Results

Correlation between serum fructosamine and mean fasting plasma glucose obtained 0 -4 weeks before the fructosamine measurement (Table 1). Serum fructosamine levels had good correlation with mean fasting plasma glucose obtained 0-3 week before the measurement, and had best correlation with that obtained 1 week before the measurement ($r=0.531$, $p<0.001$), while were not correlated with that obtained 4 weeks before the measurement ($r=0.407$, $p<0.1$).

The patients tested were divided into 4 groups according to diabetic control evaluated from mean fasting plasma glucose obtained 1 week before the fructosamine measurement ; an excellent group (<120 mg/dl) ; a good group (121-140 mg/dl) ; a fair group (141-160 mg/dl) ; a poor group (>161 mg/dl) (Fig. 1). Mean value of serum fructosamine in an excellent group was significantly higher than that in healthy controls (2.82±0.04 mmol/l). Mean value of serum fructosamine increased according to worsening of glycemic control, and that in a poor group was significantly higher than that in excellent group ($p<0.001$).

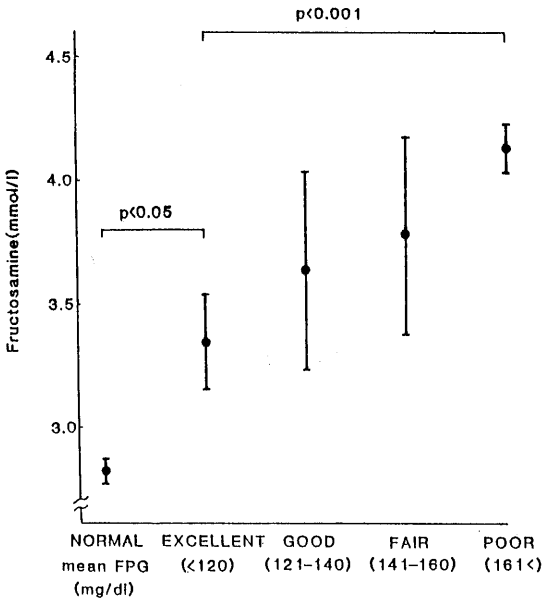

Fig. 1. Diabetic contral and serum fructosamine. The patients tested were divided into 4 groups according to diabetic control evaluted from mean fasting plasma glucose (mean FPG) obtained 1 week before the fructosamine measurement. The values represented means ± SE.

Correlation between serum fructosamine and hemoglobin A_1 at nearly same sampling time was not significant ($r=0.306$, $p>0.2$) (Fig. 2).

Fig. 3 shows clinical courses of fasting plasma glucose, hemoglobin A_1 and serum fructosamine in three diabetic patients. Serum fructosamine changed in response to changes in fasting plasma glucose (Cases 1 and 2 in Fig. 3). As shown in case 2, changes of glycemic control occurred within 1 or 2 weeks could be detected by serum

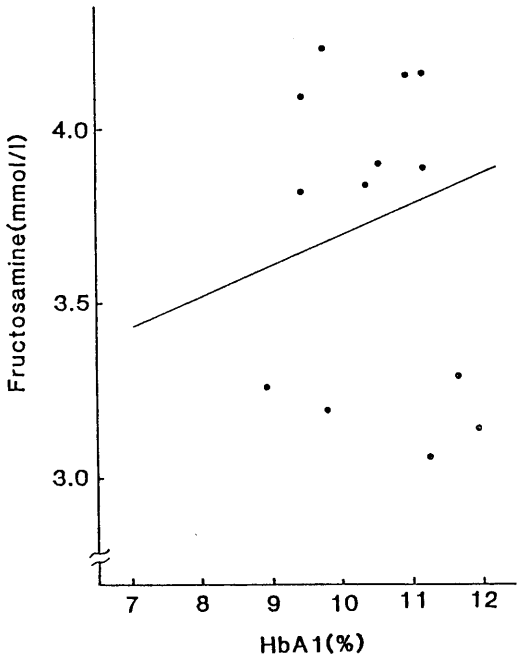

Fig. 2. Correlation between serum fructosamine and hemoglobin A_1 at nearly same sampling time (n=14, r=0.306,p>0.2).

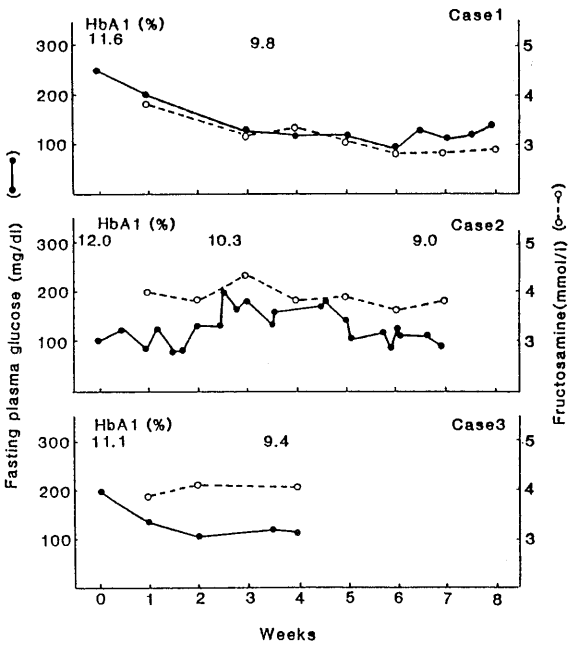

Fig. 3. Clinical courses of fasting plasma glucose (●——●), serum fructosamine (○- - -○) and hemoglobin A_1 in three diabetic patients.

fructosamine but not by hemoglobin A_1. Case 3 showed that serum fructosamine did not improved in spite of improvement of fasting plasma glucose and hemoglobin A_1 (Case 3 in Fig. 3).

Discussion

Present results showed that serum fructosamine reflected the integrated glycemia over 0-3 weeks (Table 1), and its measurement was useful for an index of glycemic control in diabetic patients (Fig. 2) (normal, <3.0 mmol/l ; excellent or good < 3.5 mmol/l ; fair, 3.5-4.0 mmol/l ; poor, >4.0 mmol/l).

It was reported that there was a good correlation between serum fructosamine and hemoglobin A_1.[7,8] Our present study, however, demonstrated no correlation. Since most patients showed poor glycemic control at admission and improved within 4 weeks after admission, such rapid changes of glycemic control could not be detected by hemoglobin A_1 (Case 2 in Fig. 3). Therefore, measurement of serum fructosamine appears to be a suitable index for medium term glycemic control (0-3 weeks), especially in patients whose glycemic control is changed by alteration of therapy (Case 1 and 2 in Fig. 3) or other factors which affect glycemic control.

Hemoglobin A_1 level is influenced by various factors (hemolytic anemia, presence of hemoglobin F, etc.)[3]. In such cases, measurement of serum fructosamine appears to be more useful. Serum fructosamine may be influenced by changes of protein turnover

Table 1. Correlation between mean fasting plasma glucose obtained 0-4 weeks before the fructosamine measurement and serum fructosamine.

	n	r	p
0 week	48	0.518	<0.001
1 week	40	0.531	<0.001
2 week	35	0.501	<0.01
3 week	25	0.444	<0.05
4 week	22	0.407	<0.1

(hypoalbuminemia, nephrotic syndrome, pregnancy, steroid diabetes, hypo- and hyperthyroidism etc.)[9]. It should be kept in mind that serum fructosamine is not the only alternative (Case 3 in Fig. 3) for assessment of glycemic control and it requires to take other indexes (body weight, glycosuria, proteinuria, ketonuria, blood glucose, Hemoglobin A_1, lipid, etc.) into consideration.

References

1) Bunn, H. F., Gabbay, K.H. and Gallop, P. M. : The glycosylation of hemoglobin : relevance to diabetes mellitus. *Science,* **200** : 21-27, 1978.

2) Bunn, F. H., Haney, D. N., Kamin, S., Gabbay, K. H. and Gallop, P. M. : The biosynthesis of human hemoglobin A_{1c} : slow glycosylation of hemoglobin in vivo. *J. Clin. Invest.,* **57** : 1652-1659, 1976.

3) Mayer, T. K. and Freedman, Z. R. : Protein glycation in diabetes mellitus : a review of laboratory measurements and of their clinical utility. *Clin. Chim. Acta,* **127** : 147-184, 1983.

4) Bunn, H. F. : Evaluation of glycosylated hemoglobin in diabetic patients. *Diabetes,* **30** : 613-617, 1981.

5) Kennedy, A. L. and Merimee, T. J. : Glycosylated serum protein and hemoglobin A_1 levels to measure control of glycemia. *Ann. Intern. Med.,* **95** : 56-58, 1981.

6) Johnson, R. N. Metcalf, P. A. and Baker, J. R. : Fructosamine : a new approach to the estimation of serum glycosylation. An index of diabetic control. *Clin. Chim. Acta,* **127** : 87-95, 1982.

7) Baker, J. R., Metcalf, P. A., Holdaway, I. M. and Johnson, R. N. : Serum fructosamine concentration as measure of blood glucose control in type I (insulin dependent) diabetes mellitus. *Br. Med. J.* [*Clin. Res.*] , **290** : 352-355, 1985.

8) Hindle, E. J., Rostron, G. M., Clark, S. A. and Gatt, J. A. : Serum fructosamine and glycated haemoglobin measurements in diabetic control. *Arch. Dis. Child.,* **61** : 113-117, 1986.

9) Sekikawa, A., Tominaga, M., Sasaki, H., Watanabe, H. and Miyazawa, K. : Usefulness of measurement of fructosamine. (in Japanese) *Diabetes J.,* **16** : 61-66, 1988.