

—Short Communications—

Effect of Control of Blood Glucose on Urinary Excretion of N-acetyl- β -D-glucosaminidase in Elderly Type 2 Diabetes Mellitus

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Diabetic nephropathy is the major cause of death in diabetes mellitus. Once diabetic nephropathy is well established, attempts to modify the relentless progression of the disease have been essentially unsuccessful. Thus, indicators are needed to identify the early structural and functional changes of diabetic nephropathy which may be reversed by strict blood glucose control. A growing body of evidence reveals that a persistent elevation of urinary albumin excretion (microalbuminuria) in diabetic patients without clinical proteinuria predicts future development of overt diabetic nephropathy¹.

N-acetyl- β -D-glucosaminidase (NAG) is a widely distributed lysosomal enzyme, located predominantly in the renal proximal tubules and is normally not filtered at the glomerulus². NAG has been shown to be increased in the urine of patients with various renal diseases³ including diabetic nephropathy⁴. Some studies in diabetic patients have also shown that the elevation of urinary NAG is an early predictor of the development of diabetic nephropathy⁵⁻⁸. In addition, ratios of urinary NAG to urinary creatinine (NAG index) for random specimens provides a useful, convenient measurement of daily NAG excretion and avoids many of the problems of 24-hour collections⁴. However, some cross-sectional studies have demonstrated that urinary NAG activity may reflect metabolic control for patients with diabetes mellitus.

The aim of the present study was to examine whether any correlation exists between the concentrations of urinary NAG and control of long-term blood glucose in elderly type 2 diabetes mellitus.

The present study included 31 type 2 diabetic patients without retinopathy and 29 with retinopathy, aged from 60 to 88 years (mean age; 71.7 ± 5.9 , 70.3 ± 7.4 years, respectively). Twenty-three of these patients had a decrease in mean HbA_{1c} of more than 2% and 37 patients had an increase of more than 2% during the 5 year follow-up period. Urinary NAG and HbA_{1c} were measured from random samples collected on three or more separate occasions over six months. The mean NAG index and HbA_{1c} were calculated every six months throughout the study.

Urinary NAG activity was measured spectrophotometrically with sodio m-cresolsulfonphthleiny N-acetyl- β -D-glucosaminide as substrate (NAG test Shionogi)⁹. HbA_{1c} was measured by the HPLC method. Statistical analysis was carried out using the paired t test. Data in the text and figures were expressed as mean \pm SD.

Fig. 1 shows the change in mean NAG index in the patients who had a decrease in mean HbA_{1c} of more than 2% during the follow-up period. The mean HbA_{1c} decreased from 11.1 ± 1.4 to $7.4 \pm 0.7\%$ in patients without retinopathy and from 10.4 ± 1.0 to $7.3 \pm 1.0\%$ in those with retinopathy (both $p < 0.001$). A signifi-

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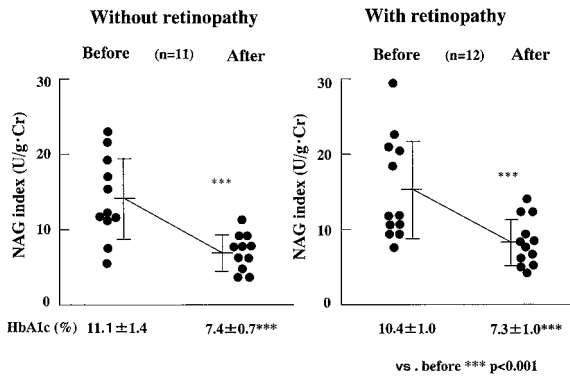


Fig. 1 The change in mean NAG index in the patients who had a decrease in mean HbA_{1c} of more than 2% during the follow-up period.

cant decrease in NAG index was found in both patients without retinopathy and in those with retinopathy (14.1 ± 5.6 vs. 7.1 ± 2.4 U/g · Cr; $p < 0.001$, 15.5 ± 6.8 vs. 8.6 ± 3.2 U/g · Cr; $p < 0.001$, respectively).

Fig. 2 shows the change in mean NAG index in the patients who had an increase in mean HbA_{1c} of more than 2% during the follow-up period. The mean HbA_{1c} increased from 7.2 ± 0.7 to $10.4 \pm 1.2\%$ in patients without retinopathy and from 7.9 ± 1.1 to $10.5 \pm 1.1\%$ in those with retinopathy (both $p < 0.001$). A significant increase of NAG index was found in both patients without retinopathy and in those with retinopathy (6.4 ± 2.9 vs. 14.2 ± 4.4 U/g · Cr; $p < 0.001$, 8.7 ± 4.3 vs. 14.7 ± 7.6 U/g · Cr; $p < 0.001$, respectively).

Ellis et al⁴ demonstrated a significantly positive correlation between random measurements of HbA_{1c} and urinary NAG activity in 40 children with type 1 diabetes mellitus. Schmidt et al¹⁰ also confirmed these findings in children with type 1 diabetes mellitus. These studies showed that urinary NAG activity may vary with concomitant changes in blood glucose. However, studies mainly involved type 1 diabetic patients and were cross-sectional studies. There has been relatively little work on the temporal changes in this activity in relation to long-term control of blood glucose in type 2 diabetes mellitus. In the present study, we demonstrate in elderly type 2 diabetes mellitus that urinary NAG concentration reflects long-term blood glucose control in longitudinal data. Whiting et al¹¹ have also reported that treatment of newly diagnosed diabetic patients resulted in decreased excretion of NAG in urine. Recently, in UKPDS¹², the excretion of urinary albumin and NAG decreased in response to 3

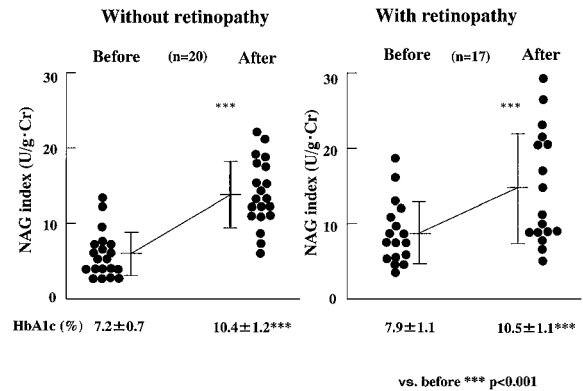


Fig. 2 The change in mean NAG index in the patients who had an increase in mean HbA_{1c} of more than 2% during the follow-up period.

months diet treatment which lowered the fasting plasma glucose. The relationship with the degree of glycaemia was stronger for urinary NAG than for urinary albumin, as only urine NAG reduction correlated with the degree of fall in the glucose levels.

In addition, it was demonstrated that urinary NAG increased 12 hours after the appearance of hyperglycemia in streptozotocin-induced diabetic rats¹³, and decreased 25 hours after the normalization of the blood glucose level by an artificial pancreas in type 1 diabetes mellitus¹⁴. Watanabe et al¹⁵ also reported that urinary NAG was strongly affected by the blood glucose control over the 1 to 7 days before the collection of urine, but did not correlate with the glycaemic level at the time of urine collection or stable HbA_{1c}. These studies suggest that urinary NAG may be changeable even with the short-term alterations in blood glucose.

Characteristic structural changes are found in the kidneys of diabetics, both in the glomerular basement membrane and in the tubular cells¹⁶. Increased excretion of albumin is generally assumed to result from changes in the glomerular basement membrane, whereas increased excretion of urinary NAG supposedly indicates tubular dysfunction. In the diabetic state, the proximal renal tubules are exposed to high urinary glucose and might secrete more NAG into the urine associated with the urinary glucose concentration and the amount of glucose metabolized or reabsorbed by the cell. The relationship between the increased NAG and the development of clinical nephropathy in the future should be clarified by long-term observations.

In conclusion, not only quantitative levels but also qualitative increases or decreases may be necessary for defining the clinical significance of urinary NAG index in diabetic patients.

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(Received, December 13, 1999)
(Accepted, December 28, 1999)
