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Clinicopathological Significance of Urinary N-acetyl-beta-D Glucosaminidase (NAG) in Nephrotic Syndrome

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Abstract

Background

We previously experienced two patients, who were diagnosed with nephrotic syndrome (NS), who did not exhibit a large enough quantity of urine protein to cause NS and reported the utility of scintigraphy (3). We here in recommend urinary N-acetyl-beta-D glucosaminidase (NAG) as a potential marker for the diagnosis of these NS.

Patients and Methods

The correlations between the concentrations of serum creatinine (SCr), total protein (TP), albumin (Alb), total cholesterol (TC), both the urinary protein/creatinine ratio (UP/C) and urinary NAG/creatinine ratio (NAG/C) were evaluated in a total of 44 adult patients with NS.

Results

The NAG/C reveal a moderate correlation with the SCr (R = 0.46) and Alb concentrations (R = -0.42) and the UP/C (R = -0.49), whereas the correlation between the UP/C and the Alb concentration was weak (R=-0.28).The TC concentration showed a relatively strong negative correlation with the Alb concentration (R= -0.55) and a positive correlation with the UP/C (R = 0.38); however, no correlation was observed between the TC and NAG concentrations (R = 0.12).

Discussion

The increased urinary excretion of NAG in glomerular diseases was shown to be due to an increased release by the damaged renal tubular cells; however, increased filtration across the damaged glomerular capillary wall was not observed.

In this study, the NAG/C tended to correlate with the Alb concentration more strongly than with the UP/C. These results suggested that NAG maybe a better and earlier marker of hypoalbuminemia, possibly due to a large amount of protein leakage through the glomerulus than the amount of protein in the urine.

Introduction

It has been shown that a small amount of albumin leaks through the glomerulus even in healthy individuals [1], while nearly 100% of the albumin concentration in the primitive urine is reabsorbed at the proximal tubule epithelium (PTE). Therefore, the amount of urine protein excretion that is commonly measured may not necessarily reflect the amount of albumin leakage from the glomerulus. We previously experienced two patients diagnosed with nephrotic syndrome (NS) who did not exhibit a large enough quantity of urine protein to cause NS [2] and reported the utility of technetium-99m human serum albumin diethylenetriaminepentaacetic acid (^{99m}Tc-HSAD) scintigraphy in the diagnosis of these cases [3].

However, such testing is hard to routinely implement due to radiation exposure. Therefore, we evaluated the use of urinary N-acetyl-beta-D glucosaminidase (NAG) as a potential marker for the diagnosis of NS.

Patients and Methods (Table1)

A total of 44 adult patients with NS who had presented for the first time to our hospital during the period of January 2012 to December 2014 and received a NAG measurement before medication were enrolled in this study. We evaluated the correlations between the serum creatinine (SCr), total protein (TP), albumin (Alb) and total cholesterol (TC) concentrations and the urinary protein/creatinine ratio (UP/C) and the urinary NAG/creatinine ratio (NAG/C).The urinary NAG activity was measured by the enzyme method using 6-Methyl-2-pyridyl-N-acetyl-1-thio-beta-D-glucopyranoside.

Table 1 Clinical Characteristics

Gender (M:F)	20:24
Age (year)	60.8 ± 21.5
BUN (mg/dL)	18.1 ± 16.8
Cr (mg/dL)	0.99 ± 0.68
TP (g/dL)	5.3 ± 0.8
ALB (g/dL)	2.0 ± 0.7
TC (mg/dL)	314 ± 105
U-NAG (IU/L)	41.8 ± 44.5
NAG/C (IU/g Cr)	30.3 ± 18.6
UP/UC (g/g Cr)	10.1 ± 7.6

Results (Table 2)

The NAG/C reveal a moderate correlation with the SCr (R = 0.46) and Alb concentrations (R = -0.42) and the UP/C (R = -0.49), whereas the correlation between the UP/C and Alb concentration was weak (R= -0.28). The TC concentration showed a relatively strong negative correlation with the Alb concentration(R = -0.55) and a positive correlation with the UP/C (R = 0.38); however, no correlation was observed between the TC and the NAG/C (R = 0.12).

Table 2 Correlation Coefficients of Each Laboratory Value

	SCr	TP	ALB	TC	NAG/C	UP/C
SCr	1.00					
TP	-0.11	1.00				
ALB	-0.03	0.73	1.00			
TC	-0.01	-0.40	-0.55	1.00		
NAG/C	0.46	-0.25	-0.42	0.12	1.00	
UP/C	0.08	-0.19	-0.28	0.38	0.49	1.00

Discussion

NAG is a lysosomal enzyme of 130 kDa molecular mass, normally excreted in low amounts in the urine as a consequence of the normal exocytosis process. It is distributed along the entire nephron, with the highest activity observed in the proximal tubules [4]. Therefore, it is one of the reliable markers of tubular damage as an enzyme released due to tubulointerstitial damage. However, it has also been demonstrated in various glomerular diseases that the filtrated proteins across the damaged glomerular capillary wall maybe toxic to the tubular epithelium and, in turn, could affect urinary NAG excretion [4,5].

Interestingly, a previously analysis of NAG isoenzymes showed that the increased urinary excretion of this enzyme in glomerular diseases is due to an increased release by damaged renal tubular cells and not to increased filtration across the damaged glomerular capillary wall [6]. Although an examination of NAG in NS has been previously investigated [4], the origin of NAG as a proportion of the large amount of protein secreted into urine has not been previously determined; however, we speculated that it originated from renal tubule cells as described above. We previously reported [2] that there may be patients with NS who do not exhibit a large enough quantity of urine protein to cause disease, because the catabolic reaction that occurs when serum albumin is reabsorbed via the PTE following glomerular filtration is thought to be an important causative factor of hypoalbuminemia in patients with NS. Moreover, we previously demonstrated the use of ^{99m}Tc-HSAD scintigraphy for diagnosing NS [3]. However, it is difficult to universally implement these radiographic examinations. Hence, we believed that NAG could be a better and earlier marker of the large amount of protein leakage from the glomerulus than the amount of protein in the urine.

Although this study only included a small number of patients, we should pay attention to the following findings. First, the NAG/C correlated with the UP/C and Alb; specifically, it tended to correlate with Alb more strongly than with the UP/C. Furthermore, the NAG/C did not correlate with TC, whereas the UP/C tended to correlate with TC more strongly than with Alb. These results suggest that NAG may be a better and earlier marker of hypoalbuminemia that may be caused by a large amount of protein leakage from the glomerulus than the amount of protein in the urine.

However, it has been demonstrated that NAG levels vary with the type of NS and its clinical condition [4]. It was difficult to carry out this examination because of the uneven number of cases (Table 3), and therefore additionally studies should be conducted with a larger cohort size with analyses adjusted for these various confounders.

Table 3 Primary Diseases and NAG/C

Primary Diseases	(N)	NAG/C (IU/g•Cr)
MC	(13)	24.3 ± 17.8
MGN	(7)	26.7 ± 16.5
FSGS	(3)	30.9 ± 13.6
IgAN	(3)	30.6 ± 22.7
MPGN	(1)	17.3 ± 0.0
DMN	(3)	38.0 ± 16.8
AN	(3)	34.8 ± 16.5
UN	(11)	37.5 ± 17.2

MC: Minimal Chang, MGN: Membranous Glomerulonephritis, FSGS: Focal Segmental Glomerulosclerosis, IgAN: IgA Nephropathy, MPGN: Membrano Proliferative Glomerulonephritis, DMN: Diabetic Nephropathy, AN: Amyloid Nephropathy, UN: Unknown

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