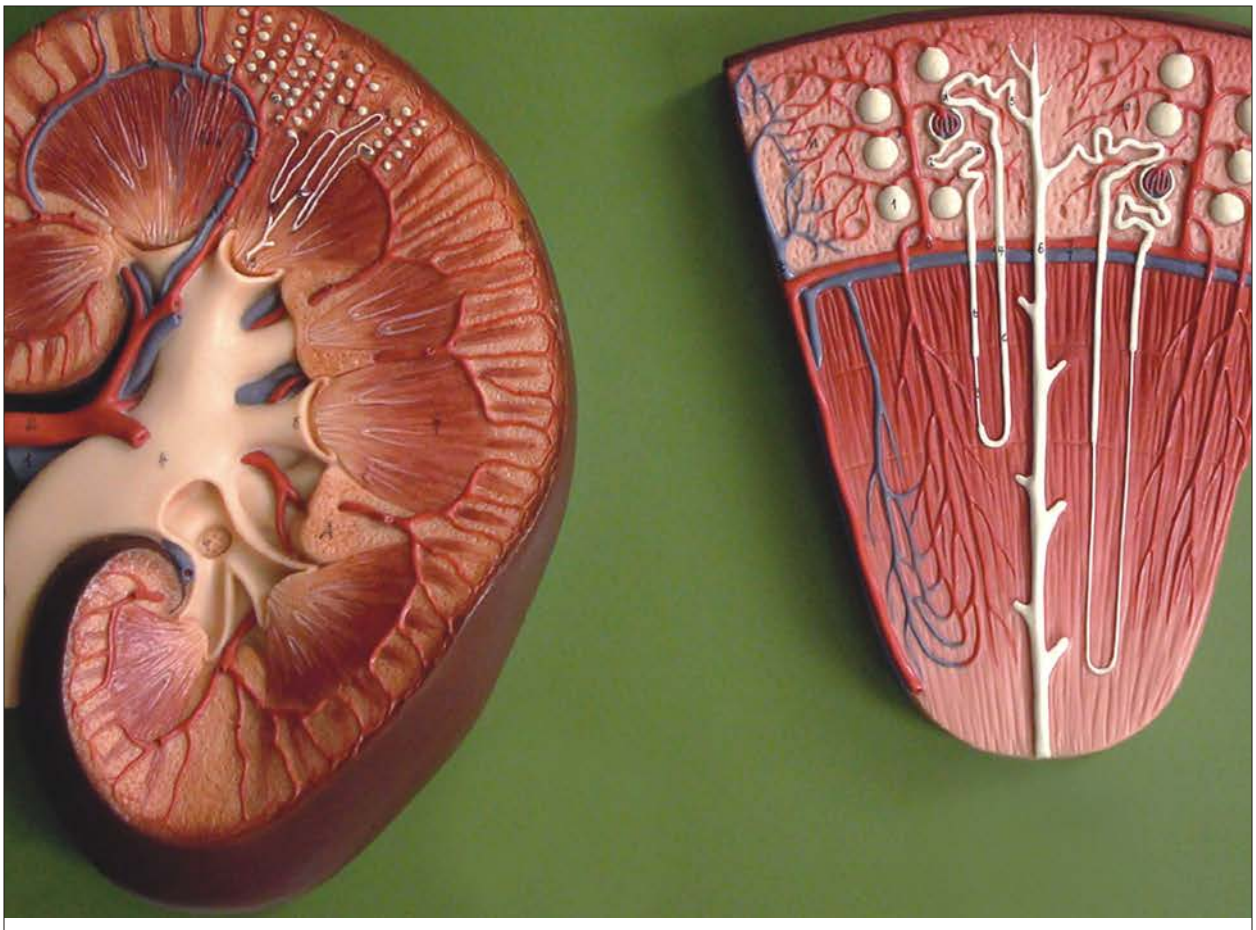

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Urinary N-Acetyl-Beta-D Glucosaminidase, a Marker of Tubular Dysfunction, in Patients with Systemic Lupus Erythematosus

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ABSTRACT

Kidney involvement in systemic lupus erythematosus (SLE) is life threatening complication. Urinary N-acetyl-beta-D glucosaminidase (uNAG) activity has emerged as potentially useful early marker of renal tubular injury. The uNAG excretion was investigated in 72 SLE patients to assess tubular dysfunction and determine its relationship with disease activity and pathological classes of lupus nephritis (LN). SLE patients were divided into two groups: 41 patients with LN and 31 patients without evidence of nephritis. Disease activity was assessed by SLEDAI. Renal disease activity was measured by the Systemic Lupus International Collaborating Clinics Renal Activity Score. uNAG levels were measured using colorimetric assay kit and compared to 25 healthy controls. Renal biopsies were performed for LN patients and glomerular lesions were classified according to WHO criteria. Severity of tubulointerstitial involvement was also assessed. The uNAG activity was significantly higher in LN patients than in lupus non nephritis patients and healthy controls (both $p<0.001$). Tubular dysfunction with elevated uNAG was present in 6 lupus non-nephritis patients with no evidence of glomerular disease. There was positive significant relation between uNAG and proteinuria ($p<0.005$) and renal activity score ($p<0.001$) in LN patients. Conversely, uNAG excretion was not significantly correlated with SLEDAI, WHO classes of nephritis and tubulointerstitial index. In conclusion, increased uNAG activity in lupus non-nephritis patients may predict the development of LN prior to the onset of proteinuria. Increased uNAG activity parallels the degree of renal disease activity in LN patients and is probably more sensitive indicator of tubulointerstitial disease.

Key words: N-acetyl-β-D-glucosaminidase, lupus nephritis, disease activity scores, proteinuria.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a systemic autoimmune disorder characterized by the activation of T and B lymphocytes, production of auto-antibodies and formation of immune complexes causing wide spectrum of tissue and organ damage (Manson and Rahman, 2006). Kidney involvement is a common occurrence and the most serious complication in patients with SLE that is often associated with poor outcome. However, early detection and appropriate immunosuppressive therapy of renal disease is likely to result in significant improvement in long- term survival and quality of life (Pitashny *et al*., 2007).

Tubulointerstitial involvement has been described in up to 70% of biopsies from lupus patients, usually in association with glomerular lesions (Jeruc *et al*., 2000). For some few patients, the

interstitial changes may be the major renal lesions (the so-called predominant tubulointerstitial LN) where acute tubulointerstitial nephritis is seen in the absence of glomerular disease and may debut as acute renal failure (Hodgin *et al.*, 2009). In about 50% of SLE patients with nephritis, mainly in those with the endothelial pattern of injury, immune aggregates are present in the tubular basement membrane (Cameron, 1999). Furthermore, active infiltration of tubules by mainly lymphocytes and monocytes, is frequently seen in active disease. In more chronic disease, the interstitium is expanded to a variable degree with fibrous tissue (Mori *et al.*, 2005). Most patients have a benign, steroid-responsive course, but in some cases a progressive decline in renal function is observed (Ponticelli *et al.*, 2005).

It has become apparent that the response of the renal tubules to proteinuria plays a central role in the progression of renal disease (D'Amico, 1999). Excessive reabsorption of abnormally filtered proteins by proximal tubular cells upregulates the cellular expression of several inflammatory and vasoactive genes. These proteins elaborated in tubular cells can then be released into the interstitium where they enhance the appearance of T-cells and macrophages, with up-regulation of transforming growth factor-beta, platelet derived growth factor and other chemokines. These lead in turn to fibroblast proliferation, myofibroblastic transformation and ensuing interstitial fibrosis (Zoja *et al.*, 1999).

Despite the fact that SLE may be associated with a variety of tubular defects which may provide an earlier indication of renal disease than glomerular defects and also have implications for immunosuppressive treatment, renal tubular function is not routinely assessed in lupus patients (Gluhovschi *et al.*, 2012). N-Acetyl-β-d-glucosaminidase (NAG) is a lysosomal brush border enzyme of proximal renal tubular cells that is normally excreted in low amounts in urine. It has been proposed as a valuable marker for renal tubular dysfunction because its relatively large molecular weight (>130 kD) precludes filtration by the glomerulus (Bosomworth *et al.*, 1999). The urinary excretion of NAG is increased in subjects exposed to substances that are toxic to renal tubular cells as lead, mercury and contrast media (Ren *et al.*, 2011), nephrotoxic drugs as aminoglycosides (Olsen *et al.*, 2004), antineoplastic drugs as methotrexate and cisplatin (Bardi *et al.*, 2004). It is also increased in various human glomerular diseases, including diabetic nephropathy (Gatua *et al.*, 2011). Moreover, it has been proposed that uNAG activity is probably an indicator of the increased lysosomal turnover that occurs when increased protein is presented to the tubular cells (Bazzi *et al.*, 2002). Increased uNAG activity in patients with glomerulonephritis and proteinuria has been suggested as indicating functional changes within the kidney, rather than renal tubular damage (Bosomworth *et al.*, 1999).

The aim of the present study was to investigate uNAG excretion in SLE patients with and without LN in order to assess tubular dysfunction in lupus patients and to find out the relationship between tubular function and glomerular function. The relationship of uNAG excretion with disease activity and pathological classes of LN was also assessed.

MATERIALS AND METHODS

This study was conducted on 72 SLE patients recruited from the Department of Nephrology at Mansoura Urology and Nephrology Center and Rheumatology and Rehabilitation Department, Mansoura University, Egypt. Diagnosis of SLE was established according to the American College of Rheumatology revised classification criteria for SLE (Hochberg, 1997).

The SLE patients were divided into two groups according to the presence of renal involvement. The first group consisted of 41 patients with LN clinically and biopsy proven. The second group

involved 31 patients who have never shown clinical or laboratory evidence of nephritis and were designated "lupus non-nephritis". These patients had a normal serum creatinine ($\leq$1.2 mg dL^{-1}), a protein/creatinine ratio <0.2 mg mg^{-1} , inactive urinary sediment and no casts. Exclusion criteria included patients with other chronic renal diseases, those with urinary tract infection and those with diagnosis of overlap syndrome. Patients with diabetes mellitus, uncontrolled hypertension, malignancy, cardiac surgery and patients receiving nephrotoxic drugs (as aminoglycosides, anticonvulsants, antineoplastic drugs) were also excluded. Twenty five apparently healthy subjects matched for age and sex served as control group. An informed consent was obtained from all participants at the start of the study.

All 41 patients with LN were treated with prednisolone±other immunosuppressives as pulse cyclophosphamide (CYC), hydroxychloroquine (OHCQ), azathioprine (AZA) and mycophenolate mofetil, while 29 (93.5%) patients with lupus non-nephritis received prednisolone ±OHCQ and/or AZA and 5 (16.12%) patients were receiving NSAIDs.

SLE patients were subjected to thorough history taking, general and local examination. Laboratory investigations included: full blood picture, ESR, CRP, serum creatinine, simple urine analysis and estimation of 24 h urinary protein, urinary protein/creatinine ratio (P/C ratio), ALT, AST, C3, C4, ANA and anti- dsDNA. Blood and urine samples were always collected on the same day. The urine samples were collected 2 days before renal biopsy was performed.

Disease activity was assessed using the SLE Disease Activity Index (SLEDAI) (Bombardier *et al*., 1992). Renal disease activity for patients with LN was measured by the Systemic Lupus International Collaborating Clinics (SLICC) Renal Activity Score (Petri *et al*., 2008). It was calculated as follows; proteinuria 0.5-1 g day^{-1} (3 points), proteinuria 1-3 g day^{-1} (5 points), proteinuria >3 g day^{-1} (11 points), urine RBC's >5/hpf (3 points), urine WBC's >5/hpf (1 point).

Assessment of the level of urinary N-acetyl-β-D-glucosaminidase (NAG): Twenty four hours urine samples were collected to eliminate fluctuations in the effect of urine volume on the enzyme concentration in the urine. Urine samples were collected without a preservative and kept at 4°C during the collection period (Wellwood *et al*., 1976).

The uNAG activity was analyzed using a colorimetric assay (FAR srl Via Fermi, 12-37026 Pescantina-VERONA-ITALY). The principle of that assay is that NAG catalyzes the hydrolysis of p-nitrophenyl N-acetyl-β-D-glucosaminide to p-nitrophenol and N-acetylglucosamine. The liberated p-nitrophenol is proportional to the enzymatic activity and is colorimetric defined in an alkaline medium which is expressed as IU L^{-1} (Gressner and Roebruck, 1982).

Renal biopsy: It was obtained from all patients with LN at the start of the study. Renal biopsy specimens were evaluated according to the World Health Organization (WHO) classification of LN (Weening *et al*., 2004). The tubulointerstitial involvement in LN was determined by tubulointerstitial index which was calculated by the method of O'Dell *et al*. (1985), allowing quantification of the degree of tubular and interstitial damage. The tubulointerstitial index equaled the sum of the scores achieved for the degree of mononuclear cell infiltrates, interstitial fibrosis and tubular atrophy (0-3 each item making a total tubulointerstitial index of 9). The renal biopsy specimens were blindly reviewed by two independent observers and tubulointerstitial indices reported were the mean scores obtained by the two observers.

Statistical analysis: Statistical analysis was performed using SPSS version 16.0 software. The description of the data was done in the form of mean±Standard Deviation (SD) for quantitative data and frequency and proportion for qualitative data. For quantitative data, "student t-test" was used to compare between two groups and "one way ANOVA" to compare between more than two groups. To test the association between variables, Pearson correlation co-efficiency test was used. P is significant if = 0.05 at confidence interval 95%.

RESULTS

Baseline characteristics and laboratory investigations of patients with LN and lupus non-nephritis patients are shown in Table 1. Forty-one patients with LN (32 females and 9 males, with mean age of 32.41±11.57 years) and 31 lupus non nephritis patients (28 females and 3 males, with mean age of 36.03±12.15 years) were recruited. As can be seen in this table, there was no significant difference in disease duration between patients with LN (4.67±3.86 years) and lupus non-nephritis patients (6.07±6.02 years) (p = 0.23). The mean SLEDAI scores of patients with LN and lupus non-nephritis patients were 24.63±12.92 and 23.0±9.88, respectively with no significant difference between them (p = 0.56). In addition, there was no significant difference in ESR, C3 and anti-dsDNA titre between the two groups (p = 0.64, p = 0.245 and p = 0.163, respectively). The mean 24 h urinary protein in patients with LN was 2.88± 1.76 g day^{-1}, while the mean serum creatinine 1.02±0.23 mg dL^{-1}. All patients with LN has an elevated P/C ratio (>0.2 mg mg^{-1}) with mean renal activity score of 8.75±4.95. Their histological diagnosis were WHO class II (n = 5), class III (n = 12), class IV (n = 17) and class V (n = 7) nephritis. The mean

Table 1: Baseline characteristics and laboratory investigations of lupus nephritis and lupus non-nephritis patients

Characteristics	Patients with lupus nephritis (N = 41)	Lupus non-nephritis patients (N = 31)
Sex (Female/Male)	32/9	28/3
Age (years)	32.41±11.57	36.03±12.15
Duration of the disease (years)	4. 67±3.86	6.07±6.02
Arthritis	13 (31.7%)	13 (41.9%)
Photosensitivity	13 (31.7%)	26 (83.9%)
Alopecia	19 (46.3%)	23 (74.2%)
Serositis	11 (26.8%)	13 (41.9%)
Oral ulcers	7 (17.1%)	13 (41.9%)
Malar rash	22 (53.7%)	31 (100.0%)
Seizures/Psychosis	8 (19.5%)	17 (54.8%)
Haematological disorders	13 (31.7%)	20 (64.5%)
Serum creatinine (mg dL^{-1})	1.02±0.23	0.81±0.13
24 h urinary protein (g day^{-1})	2.88±1.76	0.09±0.04
P/C ratio (mg mg^{-1})	1.73±0.88	0.11±0.06
ESR 1st h (mm h^{-1})	37.37±23.67	34.90±19.80
C3 (mg dL^{-1})	86.73.±36.07	97.39±29.74
Anti ds-DNA titre (IU mL^{-1})	79.42±67.53	59.28±48.40
SLEDAI score	24.63±12.92	23.00±9.88
Renal activity score	8.75±4.95	
WHO Class of LN		
II	5 (12.2%)	
III	12 (29.3%)	
IV	17 (41.5%)	
V	7 (17.1%)	
Tubulointerstitial index (/9)	1.93±1.02	

tubulointerstitial index was 1.93±1.02. Twenty five healthy subjects (20 females and 5 males) with mean age of 35.92±10.60 years served as controls. There were no statistical differences for gender or age between the study and control groups.

Patients with LN were found to have statistically significant higher activity of uNAG than lupus non-nephritis patients and healthy controls (6.54±4.64, 3.26±1.70, 2.93±1.28 IU L^{-1}, respectively, both p<0.001). Furthermore, lupus non-nephritis patients had higher uNAG than healthy controls; however, the difference was not statistically significant (p = 0.42) (Fig. 1). Abnormalities of tubular function were present in 6 patients in the lupus non-nephritis group who had elevated uNAG levels.

Comparison between the urinary level of NAG in female and male patients with SLE showed that male patients had statistically significant higher uNAG than female patients (8.83±7.43, 4.61±3.77 IU L^{-1}, respectively) (p = 0.004). On the other hand, uNAG excretion showed no significant correlations with patients' age, age at disease onset and duration of the disease (Table 2).

Furthermore, no significant correlation was found between uNAG and total SLEDAI score in patients with LN (r = 0.065, p = 0.685) and lupus non-nephritis patients (r = 0.075, p = 0.689). Moreover, no significant correlation was found between uNAG activity and serological markers of disease activity including anti ds-DNA, C3 and C4 and with ESR in patients with LN or in lupus non-nephritis patients. However, Positive significant correlation was demonstrated between uNAG activity and renal activity score in patients with LN (r = 0.645, p<0.001) (Table 3).

Positive significant correlation was found between uNAG and 24 h urinary protein and P/C ratio in patients with LN (r = 0.57, p = 0.005/ r = 0.53, p = 0.006, respectively), while no significant correlation was found between uNAG and serum creatinine in patients with LN (r = 0.054, p = 0.736) (Table 4).

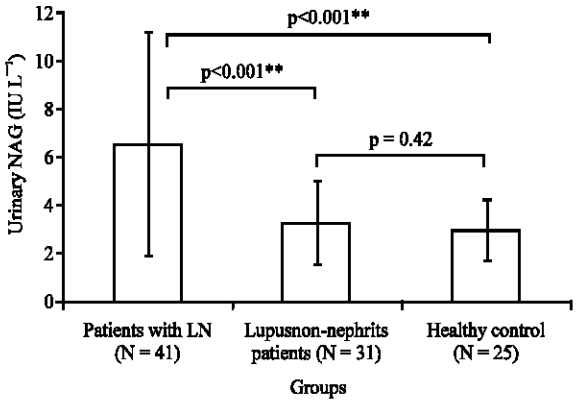

Fig. 1: Comparison between the urinary NAG levels in the 3 studied groups, p is significant if ≤0.05

Table 2: Correlation between urinary NAG excretion and SLE patient's demographic data

	Patient's age	Age at disease onset	Disease duration
uNAG in SLE patients (N = 72)			
r	-0.068	-0.226	-0.017
p-value	0.571	0.056	0.888

Table 3: Correlation between urinary NAG and SLEDAI scores, markers of disease activity and renal activity score in lupus patients groups

	SLEDAI score	ESR	Anti-dsDNA titer	C3	C4	Renal activity score
uNAG in LN patients						
r	0.065	0.124	0.146	-0.068	-0.211	0.645
p-value	0.685	0.439	0.360	0.672	0.185	<0.001
uNAG in lupus non-nephritis patients						
r	0.075	0.207	-0.142	0.246	0.196	-
p-value	0.689	0.264	0.440	0.181	0.290	-

p-value is significant if≤0.05 by Pearson correlation co-efficiency test

Table 4: Correlation between urinary NAG and laboratory tests for assessment of glomerular function

uNAG in LN patients (N = 41)	Serum creatinine	24 h urinary protein	P/C ratio
r	0.054	0.570	0.530
p-value	0.736	0.005	0.006

p-value is significant if≤0.05 by Pearson correlation co-efficiency test

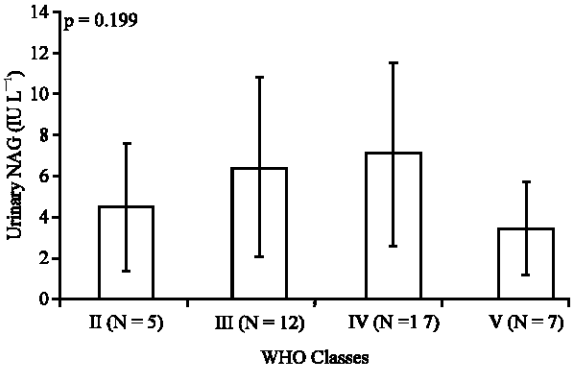

Fig. 2: Comparison between the urinary levels of NAG in different classes of lupus nephritis patients, p-value is insignificant (p = 0.199) by ANOVA test

By comparing uNAG activity in different classes of LN, it was found that class IV patients had higher uNAG activity (7.07±4.41 IU L^{-1})>class III (6.34±4.31 IU L^{-1})>class II (4.47±3.12 IU L^{-1})>class V (3.46±2.28 IU L^{-1}) but the difference was not statistically significant (p = 0.199) (Fig. 2). Furthermore, insignificant correlation was found between uNAG activity and tubulointerstitial index in the same patients (r = 0.264, p = 0.063).

DISCUSSION

The glomerular pathology in SLE has been considered the main determinant of outcome in LN, although evidence is emerging of the major role of tubulointerstitial disease in prognosis. Interestingly, multivariate Cox hazard analysis showed that the risk of doubling creatinine or end stage renal disease increases in proportion to increasing tubulointerstitial lesions (Yu *et al*., 2010). Whilst a variety of tubular defects have been described in SLE, tubular function in lupus patients is not assessed in routine practice (Gluhovschi *et al*., 2012). In addition, there are patients with SLE in whom LN is not suspected due to the absence of haematuria, proteinuria, hypertension and renal dysfunction but who may have tubular involvement. These patients have not warranted percutaneous renal biopsies (Marks *et al*., 2005).

Urinary enzymes appear capable of offering a more sensitive and rapid means in detecting nephron toxicity and even minor changes in tubular epithelial cell function in various pathological conditions (D'Amico and Bazzi, 2003). NAG is active glycosidase enzyme present mainly in the lysosomes of renal proximal tubules. It has been proposed as a valuable marker for renal tubular dysfunction. uNAG activity remains elevated during the course of active renal disease. On the basis of these attributes, earlier reports proposed that uNAG might serve as an early detection and prognostic marker (Liangos *et al.*, 2007).

uNAG activity is probably an indicator of the increased lysosomal turnover that occurs when increased protein is presented to the tubular cells (Bazzi *et al.*, 2002). An abnormally increased entry of proteins in the urinary space, subsequent to an alteration of glomerular barrier, overwhelms the protein-reabsorptive capacity of proximal tubular cells and leads to their damage. This toxic effect of protein upon the epithelial tubular cells can be demonstrated in different glomerular diseases (Erdener *et al.*, 2005). Patients with LN may exhibit additional factors that contribute to tubular dysfunction other than proteinuria, such as pathogenic antitubular basement membrane antibodies and extraglomerular deposits of immune complexes which are thought to mediate the development of various degrees of damage within the tubulointerstitium (Masuda *et al.*, 2008; Gluhovschi *et al.*, 2012). Moreover, the tubulopathy may be secondary to iatrogenic factors resulting from the use of NSAIDs such as ibuprofen or diclofenac sodium or acrolein, a urinary metabolite of CYC (Mohrmann *et al.*, 1994; Cook *et al.*, 1997).

In this study, it has been revealed that patients with LN had significantly higher levels of uNAG than that of lupus non-nephritis patients and healthy controls. This finding is concordant with the results reported by Marks *et al.* (2005), Erdener *et al.* (2005) and Abbas *et al.* (2010) who found that uNAG activity in patients with LN were significantly higher than in healthy controls. Furthermore, Gluhovschi *et al.* (2012) reported that uNAG values in patients with LN before treatment were significantly higher than in controls, indicating the presence of renal tubular dysfunction.

Moreover, our lupus non-nephritis patients had higher mean level of uNAG than that of healthy controls; however, the difference was not statistically significant. Elevated uNAG levels were observed in 6 patients among the lupus non-nephritis group, two of them were on NSAIDs. This finding couldn't be explained whether it is related to the use of NSAIDs as it may influence renal tubular function (Cook *et al.*, 1997), or due to high disease activity which may cause tubulopathy (Tsai *et al.*, 2000) or it is just an indication that these patients may develop an overt nephropathy later on. Whatever the cause, this evidence of tubular dysfunction in the absence of manifest glomerular disease necessitates follow-up. It may also need further investigations, including renal biopsy and perhaps further treatment with increased immunosuppression because they may be susceptible to develop nephritis later on. This result is in agreement with that of Delektorskaya *et al.* (1990) who demonstrated an increase in the activity of uNAG in the group of SLE patients who did not have clinical and laboratory signs of LN. Furthermore, Marks *et al.* (2005) reported the presence of abnormalities of tubular function in 2 patients in the lupus non-nephritis group who had elevated uNAG levels and concluded that tubular markers define renal disease earlier than proteinuria.

In this study, no significant correlation was demonstrated between uNAG activity and age of patients, age at disease onset or disease duration. To find the influence of gender on the severity of tubular dysfunction in patients with SLE, we have compared the urinary level of NAG between female and male patients. We found that male patients had statistically significant higher

uNAG than female patients. It is known that sex (male) is one of the important univariate risk factors for renal outcome in LN (Yu *et al.*, 2010). In a recent study, it was reported that male patients had a more severe LN compared to women diagnosed with this renal abnormality (De Carvalho *et al.*, 2010).

A positive significant correlation was demonstrated in our study between uNAG activity and renal activity score in patients with LN. On the other hand, there was no significant correlation between uNAG and total SLEDAI score in patients with or without LN. This verified the result of Erdener *et al.* (2005) in patients with LN. Moreover, our data revealed no significant correlation between uNAG activity and markers of disease activity as ESR, anti ds-DNA, C3 and C4 in either LN or lupus non-nephritis patients, the same as observed by Abbas *et al.* (2010) in their patients with LN. The lack of such correlation is expected as uNAG activity reflect the activity of nephritis within the kidney mainly the tubulointerstitium and not the total activity of the disease.

We have found a positive significant correlation between uNAG and 24 h urinary protein and P/C ratio in patients with LN. On the other hand, no significant correlation was found between uNAG and serum creatinine in those patients. This can be explained by the fact that rising serum creatinine concentrations are insensitive marker to detect subclinical renal damage as they are generally not detectable until more than 50% of glomerular function is compromised . Moreover, serum creatinine is widely used to assess the level of glomerular dysfunction, which is often preceded by tubular dysfunction (Gatua *et al.*, 2011). Our results coincide with that of Erdener *et al.* (2005) who observed a strong positive correlation between proteinuria and uNAG activity in patients with LN. In addition, Kuzniar *et al.* (2004) in their study on 91 patients with morphologically different primary and secondary glomerulopathies observed that uNAG excretion was significantly correlated with proteinuria, while no significant relationship between serum creatinine and excretion of NAG was found in the whole examined group, similar to that demonstrated by Abbas *et al.* (2010) in patients with LN.

Furthermore, Masuda *et al.* (2008) described a case of LN with nephrotic range proteinuria and elevated uNAG activity. They clearly demonstrated that the urinary excretion of NAG decreased along with an improvement of proteinuria during the treatment. This observation suggests the prompt recovery of the tubulointerstitial damage probably induced by the high urinary protein. Therefore, the monitoring of uNAG seems to be useful for evaluating the effect of treatment of LN as well as the disease activity within the interstitium. In another study by Gluhovschi *et al.* (2012), uNAG showed a significant reduction between 7 and 30 days of therapy and this reduction in urinary NAG set in later than the decline in proteinuria. They concluded that the reduction in uNAG may be a more subtle indicator than proteinuria that active lupus nephritis begins to recede.

By comparing uNAG activity in different classes of LN, it was found that class IV patients had the highest uNAG activity followed by class III then class II and the least uNAG activity was for class V but the difference was not statistically significant, in concordant with results of Erdener *et al.* (2005) and Abbas *et al.* (2010). Also, no significant correlation was found in our work between uNAG activity and tubulointerstitial index in the same patients suggesting that tubular function studies are probably a more sensitive indicator of tubulointerstitial disease. This result is in agreement with a previous prospective study that has shown no correlation between the different tubular function studies and tubulointerstitial abnormalities in the renal biopsy (Ter Borg *et al.*, 1991). Furthermore, no significant correlation between uNAG and the extent of the tubulointerstitial damage was observed in both patients with focal segmental

glomerulosclerosis (FSGS) and idiopathic membranous nephropathy in the study by Bazzi *et al*. (2002), verifying that in proteinuric glomerular diseases the increased excretion of NAG can occur even in the absence of morphological evidence of tubular cell damage, probably reflecting increased lysosomal activity of these cells due to the increased uptake of filtered proteins. Therefore, it is an indicator of the functional status of the renal tubules as well as tubular damage.

CONCLUSION

Increased uNAG activity in absence of proteinuria or deteriorating renal function in SLE patients may predict the development of LN later on. Moreover, measurement of its activity in patients with LN provides more information than a simple measurement of 24 h proteinuria as increased NAG activity reflects the activity of LN. Therefore, Determination of uNAG activity as a marker of tubular dysfunction may be a useful supplement to the routine biochemical analysis performed on the urine in cases of SLE because its use in detecting early renal tubular injury could prompt management changes that decrease morbidity and mortality in affected patients.

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