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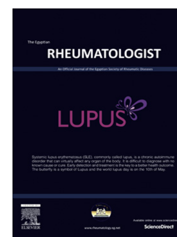

ORIGINAL ARTICLE

Urinary and serum neutrophil gelatinase-associated lipocalin as a biomarker in Egyptian systemic lupus erythematosus patients: Relation to lupus nephritis and disease activity

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KEYWORDS

Urinary neutrophil gelatinase-associated lipocalin;
Acute kidney injury;
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Lupus nephritis;
SLEDAI

Abstract *Background:* Neutrophil gelatinase-associated lipocalin (NGAL) is an excellent structural biomarker for the early diagnosis of acute kidney injury, prognosis, dialysis requirement and mortality in several common clinical scenarios.

Aim of the work: The aim of this work is to detect the levels of both urinary and serum NGAL in SLE patients with and without lupus nephritis (LN) and to correlate their levels with renal biopsy class and disease activity.

Patients and methods: The study included 35 SLE patients; 22 with LN and 13 without as well as 30 matched controls. The SLE Disease Activity Index (SLEDAI) was assessed and the renal biopsy class determined. Urinary and serum levels of NGAL were assessed by ELISA.

Results: The 35 patients had a median age of 30 years and disease duration of 4 years. They were 31 females and 4 males. The SLE patients had an elevated urinary NGAL (UNGAL) (median 19 ng/ml, IQR 8–87) as compared to controls (median 2 ng/ml, IQR 1–18.3) ($p < 0.006$). Levels of UNGAL were higher in patients with LN than those without ($p < 0.023$). In patients with LN, serum levels of NGAL were not significantly different from controls ($p = 0.6$). The UNGAL level significantly correlated with the renal score of SLEDAI ($r = 0.54$, $p = 0.001$) but serum NGAL level did not ($r = 0.25$, $p = 0.15$). UNGAL significantly correlated with grade III and IV

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of renal biopsy ($r = 0.67$, $p = 0.009$). The sensitivity of UNGAL levels for the diagnosis of LN was 85.7%, with a specificity of 80%.

Conclusion: Urinary NGAL is a sensitive marker of proliferative nephritis in SLE and disease activity.

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1. Introduction

SLE is a chronic inflammatory disease of unknown etiology which can affect the skin, joints, kidneys, lungs, nervous system, serous membranes and/or other organs of the body. Main features of the disease are immunologic abnormalities; the disease is characterized by the production of auto-antibodies. The course of SLE is variable and may be associated by periods of remissions and relapses [1] and could remarkably affect the quality of life in those patients [2]. Other factors have been implicated in the pathogenesis of SLE including cytokine imbalance [3] and gene polymorphisms [4].

One of the most severe manifestations of SLE is lupus nephritis (LN), which remains a serious cause of morbidity and mortality, either secondary to kidney disease or to immunosuppressive drug toxicity [5]. In studies on Egyptian SLE patients, LN was frequently reported and assessed in relation to many biomarkers for apoptosis [6], adipocytokines [7], cartilage degradation [8], oxidative stress [9] and nephritogenic autoantibodies [10]. Novel markers of renal involvement including urinary neutrophil gelatinase-associated lipocalin (UNGAL) have also been assessed in SLE patients [11].

Neutrophil gelatinase-associated lipocalin (NGAL) is a 25 kDa protein of the lipocalin superfamily. This protein is secreted by immune cells, hepatocytes and renal tubular cells in several pathological conditions. NGAL has recently generated great interest as an early marker of renal injury. However, like many other endogenous biomarkers it is produced by several cell types and it exists in several molecular forms. Different pathological conditions may be involved in the production of this molecule [12]. A prominent role of UNGAL was suggested as a potential biomarker of lupus nephritis that could serially forecast renal disease activity in SLE patients [13].

The aim of the present study was to assess the serum and urinary NGAL in Egyptian SLE patients with and without renal involvement and study their relation to other biochemical parameters, renal biopsy class and disease activity. Detecting its sensitivity, specificity and predictive values for LN in SLE patients was considered.

2. Patients and methods

The present study was carried out on 35 SLE patients; 31 females and 4 males with an age interquartile range (IQR) of 24–37 years (median 30 years). All patients fulfilled the systemic lupus international collaborating clinics (SLICC) classification criteria for SLE [14]. They were selected from the outpatient clinics of the Rheumatology and Rehabilitation and Internal Medicine Departments as well as the Nephrology Department of the Urology Center (Mansoura University Hospitals). Patients were grouped according to the presence or absence of active renal disease or a renal SLE Disease Activity Index (SLEDAI) score of $\geqslant 4$ and considered with or without LN respectively. Thirty healthy subjects were included as a control group. This study was approved by the Ethics Committee of Faculty of Medicine Mansoura University. Written informed consent was obtained from all participants.

Exclusion criteria: Patients suffering of any of the following were excluded: Breast tumors, inflammatory bowel diseases, polycystic kidneys, acute kidney injury (AKI), post-renal transplantation, chronic heart diseases as there is an increase in the level of NGAL in these conditions.

All patients were subjected to full history taking and clinical examination. Disease activity in the SLE patient was detected by the SLEDAI [15]. Renal activity was assessed using renal SLEDAI which includes four renal elements in total SLEDAI score namely proteinuria, hematuria, pyuria and urinary casts. Each item in the renal SLEDAI is scored 4 points; the renal SLEDAI score ranged from 0 to 16. Renal biopsy was performed to assess the grade of LN for patients with persistent hypertension, rising creatinine levels, persistent hematuria, proteinuria, casts. The world health organization (WHO) classification of LN [16] was used to define the histopathological lesions.

Assessment of serum and urinary NGAL by ELISA: Urine and serum samples were concomitantly taken from all patients immediately after diagnosis. Serum NGAL was measured using a serum separator tube (SST) and samples were allowed to clot for 30 min before centrifugation for 15 min at 1000*g*. Serum was removed and immediately assayed or aliquot and sample stored at $\leqslant -20$ °C. Repeated freeze–thaw cycles were avoided. For urinary NGAL aseptically collected morning urine sample (mid-stream) was collected voided directly into a sterile container. It was then centrifuged to remove particulate matter, immediately assayed or aliquot and stored at $\leqslant -20$ °C. Repeated freeze–thaw cycles were avoided. Human NGAL was measured using the quantitative sandwich enzyme immunoassay technique using Human Lipocalin-2/NGAL Immunoassay [Quantikine, R&D system, Minneapolis, USA]. A monoclonal antibody specific for Lipocalin-2 has been pre-coated onto a microplate. Standards and samples are pipetted into the wells and any Lipocalin-2 present in the samples bounded by the immobilized antibody. After washing away any unbound substances, an enzyme-linked monoclonal antibody specific for Lipocalin-2 is added to the wells. Following a wash to remove any unbound antibody-enzyme reagent, a substrate solution is added to the wells and color develops in proportion to the amount of Lipocalin-2 bound in the initial step. The color development is stopped and the intensity of the color is measured.

Statistical analysis: The clinical and laboratory data were tabulated, coded then analyzed using the computer program 'statistical package for social science' (SPSS) version 17.0.

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