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Relationship between neutrophil gelatinase-associated lipocalin levels and disease parameters including clinicopathological parameters and various cytokine levels in systemic lupus erythematosus

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ABSTRACT. Urine neutrophil gelatinase-associated lipocalin (NGAL) is a marker of acute kidney injury and indicates tubular damage. Lupus nephritis-associated renal injury is characterized by damage to the glomeruli and tubular portions of the kidneys. Therefore, NGAL concentrations are expected to vary according to the severity of systemic lupus erythematosus (SLE). In this study, samples from (NZB × NZW) F1 mice at an advanced stage of SLE were used to determine whether serum and urine NGAL concentrations or the urine NGAL:creatinine (uNGAL/C) ratio can be used to reflect diet, disease state, and treatment efficacy. Additionally, the relationship between the levels of NGAL and various cytokines in the serum in SLE was evaluated. Mice were divided into the following four groups (n=15): CN, chow diet and no treatment (saline; intraperitonially injected [*i.p.*]; 200 µL/day); CP, chow diet and methylprednisolone (*i.p.*; 5 mg/kg/day); HN, high-fat diet and no treatment (saline [*i.p.*]; 200 µL/day); and HP, high-fat diet and methylprednisolone treatment (*i.p.*; 5 mg/kg/day) every day from 6 to 42 weeks of age. The serum and urine NGAL levels and uNGAL/C values were significantly lower in the CP group than those in the CN group. Further, serum NGAL concentration demonstrated a strong positive correlation with urine NGAL levels, uNGAL/C, urine protein concentrations, urine protein:creatinine ratio, and the expression of several cytokines associated with SLE pathogenesis (interleukin [IL]-6, tumor necrosis factor [TNF]-α, and interferon-induced protein [IP]-10). These results suggest that NGAL has a strong positive correlation with the clinicopathological parameters and several key cytokines in SLE.

KEYWORDS: cytokine, lupus nephritis, neutrophil gelatinase-associated lipocalin, (NZB×NZW) F1 mice, systemic lupus erythematosus

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Neutrophil gelatinase-associated lipocalin (NGAL) synthesis is induced in the macrophages, glial cells, and epithelial cells during inflammation and plays a role in various cellular processes, including the innate immune response, differentiation, tumorigenesis, and cell survival. NGAL is activated in various non-bacterial inflammatory pathologies, such as psoriasis and ulcerative colitis, and in the adipose tissue of individuals with obesity [28].

Urinary NGAL is a marker of acute kidney injury and a known indicator of tubular injury. However, the detection of acute kidney injury (AKI) is challenging if conventional markers of kidney function are within the reference range. For example, ten min of ischemia does not alter blood urea nitrogen (BUN) or kidney histology; however, it increases plasma and urine NGAL levels [17].

NGAL level closely reflects renal impairment, and an increased urine NGAL level is also a good predictor of disease progression in patients with chronic kidney disease (CKD) [4]. In addition, elevated NGAL levels have been reported in patients with diabetic nephropathy, immunoglobulin A nephropathy, and tubulointerstitial nephritis [5, 9].

Systemic lupus erythematosus (SLE) is an autoimmune disease which often involves multiple organs. SLE was first reported in humans in the 13th century and has also been reported in dogs, cats, and mice [11]. In this disease, antinuclear antibodies, including anti-dsDNA antibodies, are generated, and antigen–antibody immune complexes are produced and deposited in small blood vessels

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[11]. Thus, SLE can cause inflammation and damage to various organs, including the basement membranes of the skin and kidneys [25].

A recent study showed that patients with SLE had significantly higher serum NGAL levels than those in healthy individuals. Furthermore, serum NGAL levels in patients with SLE with lupus nephritis were significantly higher than those in patients with SLE without lupus nephritis [23].

The exact etiology of SLE is unknown; however, complex interactions among genetic factors, inappropriate immune regulation, and other factors, such as hormonal and environmental variables and epigenetic regulatory defects, have been considered as causes [8]. Human and murine lupus are characterized by the deregulation of autoreactive T helper cells, B and dendritic cell activation, and cytokine production [34]. The defective function of regulatory T cells and ineffective clearance of immune complexes contribute to the loss of tolerance and tissue damage in lupus [34].

In (NZB ×NZW) F1 female mice, the lupus-like phenotypes include elevated serum antinuclear autoantibodies (including anti-dsDNA antibodies), lymphadenopathy, splenomegaly, and immune complex-mediated glomerulonephritis. These phenotypes are very similar to the pathology observed in human lupus. The (NZB × NZW) F1 female mice show increased proteinuria and anti-dsDNA titer from 5 weeks of age. Immunocomplex glomerulonephritis develops at 4–5 months of age; if no treatment is given, the mortality rate due to renal failure reaches 93% by the age of 10 months [37].

Previous studies have suggested a strong link between obesity and autoimmune diseases; a recent cohort study showed a significantly increased risk (85%) of SLE in women who were obese compared to that in women with a normal body mass index (BMI) [33]. In our previous study, methylprednisolone treatment significantly increased survival in a chow-diet group, but not in a high-fat diet (HFD) group [8]. HFD also increased the incidence of severe proteinuria and glucose intolerance in an SLE model [8]. Furthermore, NGAL synthesis is activated in the adipose tissue of individuals with obesity [28].

Glomerular and tubular damage occurs during autoimmune renal injury in lupus nephritis; therefore, serum and urine NGAL concentrations are expected to differ depending on SLE disease severity [23]. Autoimmune-related renal injuries associated with lupus nephritis affect the glomeruli and the tubules, resulting in changes in NGAL concentration, which may then be used as a marker of disease severity in SLE. Further, as a HFD has been found to have a negative effect on methylprednisolone treatment, one would expect that a HFD group would have higher NGAL concentrations than those in a chow-diet group.

Although several reports have suggested that NGAL can be used as a marker for SLE, there have been no studies on the association of NGAL with SLE disease parameters, including clinicopathological data or cytokine levels.

The purpose of this study was to determine whether the serum NGAL and urine NGAL:creatinine (uNGAL/C) values can be used to reflect diet, disease state, and treatment efficacy using samples from (NZB × NZW) F1 mice in the advanced stages of SLE. In addition, the author evaluated the relationship between NGAL concentration and the expression of various cytokines during SLE.

MATERIALS AND METHODS

Study design

Blood, urine, and kidney extract samples were collected from 36 SLE mice (NZB/W F1 mice [groups are defined below], CN: n=6, CP: n=14, HN: n=6, HP: n=10) at 43 weeks of age to evaluate the impact of diet, treatment, and disease states on various biomarkers including serum NGAL, urine NGAL, uNGAL/C, urine protein, urine protein:creatinine, blood urea nitrogen (BUN), and total cholesterol and the expression of various cytokines. Data obtained from these evaluations were also used in the correlation analysis.

Experimental animals & groups

Sixty female NZB/W F1 mice aged 4 weeks were purchased from Jackson Laboratory (Bar Harbor, ME, USA) and housed in a specific pathogen free room. These animals were then categorized into the following four treatment groups (n=15): CN, chow diet and no treatment (saline, 200 µL/day); CP, chow diet and methylprednisolone (5 mg/kg/day); HN, high-fat diet and no-treatment (saline, 200 µL/day); and HP, high-fat diet and methylprednisolone (5 mg/kg/day) via daily intraperitoneal injection from 6 to 42 weeks of age [8].

The mice were housed in an animal care facility at CHA University in the CHA biocomplex in a temperature-controlled environment under a 12-hr light/dark cycle with access to food and water *ad libitum*. This study was reviewed and approved by the Institutional Animal Care and Use Committee of CHA University (CE2018068). All procedures were performed in compliance with the Animal Welfare Act Regulations and Guide for the Care and Use of Laboratory Animals [8].

Determination of anti-dsDNA antibodies, BUN, and total cholesterol

Blood samples were collected from the mice under isoflurane anesthesia at autopsy (43 weeks of age). Anti-dsDNA antibodies, BUN, and total cholesterol levels were determined using a mouse anti-dsDNA enzyme-linked immunosorbent assay (ELISA) kit (Shibayagi Co., Ltd., Ishihara, Shibukawa, Japan), a urea nitrogen colorimetric detection kit (EIABUN; Invitrogen, Carlsbad, CA, USA), and a total cholesterol colorimetric assay kit (MBS2540484, Mybiosource, San Diego, CA, USA), as described in our previous study [8].

Determination of urine protein and urine creatinine

Fresh urine samples were collected via abdominal massage. Urine protein at 42 weeks of age was measured using the Coomassie Brilliant Blue method, as described in our previous study [10]. Urine creatinine at 42 weeks of ages was measured using a Creatinine Assay (KGE005; R&D Systems) with urine diluted in deionized water (1:20 dilution).

Determination of serum and urine NGAL

Serum and urine NGAL levels were measured using mouse Lipocalin-2/NGAL immunoassay kits (MLCN20; R&D Systems). Each sample was measured at a dilution factor corresponding to an absorbance within the standard range.

Determination of serum cytokine levels

Serum cytokine levels were determined as described in our previous study [8]. Serum samples were assayed using Milliplex® MAP Kits (Millipore Bedford, MA, USA) for interferon-γ (IFN-γ), interleukin-1β (IL-1β), IL-2, IL-4, IL-6, IL-10, IL-12 (p70), IL-15, IL-17a, IL-27, tumor necrosis factor α (TNF-α), chemokine (C-C motif) ligand 2 (CCL2 (MCP-1)), and IFN-inducible protein 10 (IP-10 (CXCL10)).

Determination of serum levels of adipokines

Serum adipokine levels were determined as described previously [8]. Serum samples from all mice were assayed using a multiplex adipokine kit for insulin, leptin, resistin, and plasminogen activator inhibitor-1 (PAI-1) (MADCYMAG-71K, Millipore). Serum samples were also assayed for adiponectin using a Mouse Adiponectin/Acrp30 Immunoassay (R&D Systems).

Determination of cytokine levels in kidney extracts

Cytokine levels in the kidney extracts were determined as described in our previous study [8]. Total protein concentrations of the kidney extracts were adjusted to 2 mg/mL and used for the analysis of IFN-γ, IL-1β, IL-4, IL-6, IL-10, IP-10, MCP-1, CCL4, and TNF-α with a Milliplex® MAP Kit (Millipore).

Statistical analysis

Data are expressed as mean ± standard error of the mean (SEM). Normal distribution was assessed using the Shapiro–Wilk test. Most of the data failed the normality test; therefore, we reverted to non-parametric tests for most of our analyses. Serum NGAL and uNGAL/C values in each group were compared using the Kruskal–Wallis and Dunn's tests. Spearman's rank correlations were used to evaluate the relationships between biomarkers, and correlations were defined as weak positive (0.1–0.3), moderate positive (0.3–0.7), strong positive (0.7–1.0), weak negative (−0.1– −0.3), moderate negative (−0.3– −0.7), or strong negative (−0.7– −1.0). P values <0.05 were considered significant. All statistical analyses were performed using SPSS version 26.0 software (IBM, Armonk, NY, USA).

RESULTS

Serum NGAL levels in a murine model of SLE

Serum NGAL levels were evaluated at 42 weeks of age and differed significantly between the various treatment groups (Kruskal-Wallis, P=0.002). The median values in the CN, CP, HN, and HP groups were 5,127.20, 352.25, 1,507.65, and 1,244.10 pg/mL, respectively. Serum NGAL levels at 42 weeks of age were significantly lower in the CP group than those in the CN group (Dunn's test, P<0.001); however, these values were not significantly different between the HP and HN groups (Fig. 1A). Serum NGAL levels were significantly lower in the CP group than those in the HP group (Dunn's test, P=0.013) (Fig. 1A).

Urine NGAL in a murine model of SLE

Urine NGAL levels collected at 42 weeks of age were significantly different between the groups (Kruskal-Wallis, P=0.028). The median values of the CN, CP, HN, and HP groups were 5.60, 0.35, 3.35, and 1.95 ng/mL, respectively. Urine NGAL levels were significantly lower in the CP group than those in the CN group (Dunn's test, P=0.011); however, these differences were not maintained in the HP and HN groups. Urine NGAL levels were not significantly different between the CN and HN groups or between the CP and HP groups (Fig. 1B).

uNGAL/C in a murine model of SLE

The uNGAL/C values collected at 42 weeks of age were significantly different between the treatment groups (Kruskal-Wallis, P=0.038). The median values of the CN, CP, HN, and HP groups were 30.35, 0.7, 7.15, and 4.4 ng/mg, respectively. The uNGAL/C values were significantly lower in the CP group than those in the CN group (Dunn's test, P=0.021); however, these differences were not observed in the HP and HN groups. The uNGAL/C values were not significantly different between the CN and HN groups or between the CP and HP groups (Fig. 1C).

Relationship between the evaluated parameters in a murine model of SLE

Study data were also used to evaluate the relationship between NGAL levels and the expression of several cytokines associated with SLE pathogenesis. Serum NGAL levels showed a strong positive correlation with urine NGAL levels, uNGAL/C ratios, urine protein concentration, urine protein/creatinine ratios (Table 1), and the concentrations of IL-6, TNF-α, and IP-10 in the serum (Table 2).

Urine NGAL levels showed a strong positive correlation with serum NGAL levels, uNGAL/C ratios, urine protein concentrations, urine protein/creatinine ratios, BUN, and total cholesterol levels (Table 1).

The uNGAL/C ratios showed strong positive correlations with serum and urine NGAL levels, urine protein:creatinine ratios, BUN, and total cholesterol levels (Table 1).

Serum NGAL, urine NGAL, and uNGAL/C ratios showed a moderate positive correlation with IL-6, MCP-1, and MIP1b expression

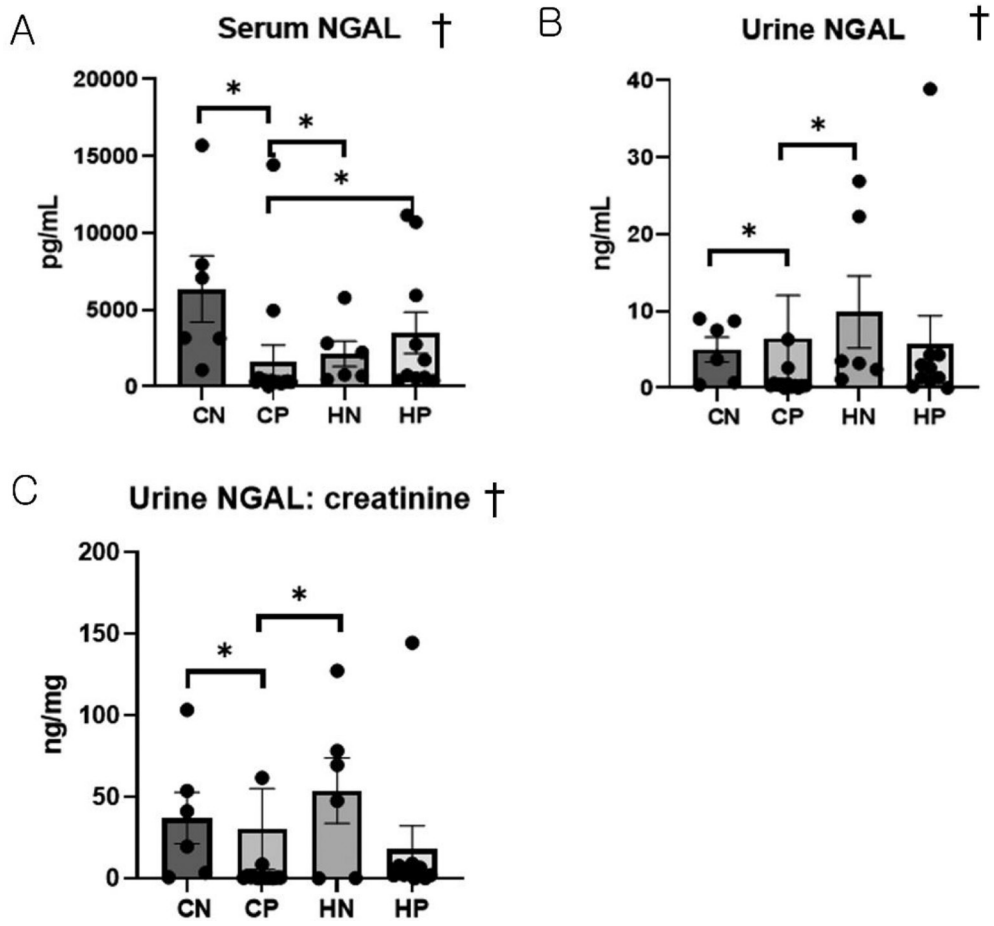

Fig. 1. Serum and urine neutrophil gelatinase-associated lipocalin (NGAL) levels and urine NGAL: creatinine ratio in a murine model of systemic lupus erythematosus. Data are expressed as mean ± SEM. Data obtained from each group were compared using the Kruskal–Wallis test (†) followed by Dunn's tests (*). †, *indicates significant differences (P<0.05).

Table 1. Relationship between neutrophil gelatinase-associated lipocalin (NGAL) and clinicopathological parameters in a murine model of systemic lupus erythematosus

(n=36)	Serum NGAL		Urine NGAL		Urine NGAL: creatinine	
Parameter	rho	P value	rho	P value	rho	P value
Serum NGAL	1.000	-	0.704**	<0.001	0.731**	<0.001
Urine NGAL	0.704**	<0.001	1.000	-	0.974**	<0.001
Urine creatinine	−0.583**	<0.001	−0.576**	<0.001	−0.721**	<0.001
uNGAL:creatinine	0.731**	<0.001	0.974**	<0.001	1.000	-
BUN	0.686**	<0.001	0.710**	<0.001	0.755**	<0.001
Total cholesterol	0.573**	<0.001	0.772**	<0.001	0.719**	<0.001
Anti-dsDNA abs	−0.150	0.382	−0.254	0.136	−0.250	0.142
Urine protein	0.728**	<0.001	0.750**	<0.001	0.699**	<0.001
UPC	0.815**	<0.001	0.835**	<0.001	0.827**	<0.001

Spearman's rank correlation tests were used to evaluate these relationships and correlations were defined as weak positive (0.1–0.3), moderate positive (0.3–0.7), strong positive (0.7–1.0), weak negative (−0.1– −0.3), moderate negative (−0.3– −0.7), or strong negative (−0.7– −1.0). P value: (two-tailed), *: P<0.05, **: P<0.01. NGAL: neutrophil gelatinase-associated lipocalin, uNGAL: creatinine: urine NGAL: creatinine, BUN: blood urea nitrogen, anti-dsDNA abs: anti-double-stranded deoxyribonucleic acid antibodies, UPC: urine protein: creatinine.

levels in the kidney and a moderate negative correlation with IL-10 and TNF-α expression in the kidney (Table 3).

Serum NGAL, urine NGAL, and uNGAL/C ratios showed a moderate positive correlation with serum levels of insulin, PAI-1, and resistin. Serum resistin levels had the highest degree of correlation with these parameters (Table 4).

Table 2. Relationship between NGAL and various serum cytokines in a murine model of systemic lupus erythematosus

(*n*=36)	Serum NGAL		Urine NGAL		Urine NGAL: creatinine	
Parameter	rho	*P* value	rho	*P* value	rho	*P* value
Serum IL-6	0.722**	<0.001	0.453**	0.006	0.458**	0.006
Serum MCP-1	0.583**	<0.001	0.280	0.098	0.339*	0.043
Serum TNF-α	0.727**	<0.001	0.500**	0.002	0.565**	<0.001
Serum IFN-γ	−0.106	0.540	−0.103	0.548	−0.118	0.494
Serum IL-1β	0.217	0.204	0.146	0.394	0.158	0.358
Serum IL-2	−0.028	0.872	−0.079	0.645	−0.064	0.712
Serum IL-4	0.095	0.581	0.069	0.690	0.088	0.608
Serum IL-10	0.480**	0.003	0.319	0.058	0.327	0.052
Serum IL-12p40	0.142	0.409	0.247	0.147	0.243	0.153
Serum IL-27	0.146	0.394	0.059	0.733	0.086	0.620
Serum IL-15	0.367*	0.028	0.405*	0.014	0.480**	0.003
Serum IL-17A	0.073	0.672	−0.040	0.818	−0.026	0.882
Serum IP-10	0.705**	<0.001	0.547**	0.001	0.595**	<0.001

Spearman's rank correlation tests were used to evaluate these relationships and correlations were defined as weak positive (0.1−0.3), moderate positive (0.3−0.7), strong positive (0.7−1.0), weak negative (−0.1− −0.3), moderate negative (−0.3− −0.7), or strong negative (−0.7− −1.0). *P* value: (two-tailed), *: *P*<0.05, **: *P*<0.01. NGAL: neutrophil gelatinase-associated lipocalin, uNGAL: creatinine: urine NGAL: creatinine, IL: interleukin, MCP-1: monocyte chemoattractant protein 1, TNF-α: tumor necrosis factor-alpha.

Table 3. Relationship between NGAL and various cytokine levels of kidney in a murine model of systemic lupus erythematosus

(*n*=36)	Serum NGAL		Urine NGAL		Urine NGAL: creatinine	
Parameter	rho	*P* value	rho	*P* value	rho	*P* value
Kidney IL-6	0.317	0.059	0.355*	0.034	0.422*	0.010
Kidney IL-10	−0.492**	0.002	−0.522	0.001	−0.559**	<0.001
Kidney MCP-1	0.599**	<0.001	0.481**	<0.001	0.556**	<0.001
Kidney MIP1β	0.380**	0.022	0.299	0.077	0.384*	0.021
Kidney TNF-α	−0.473**	0.004	−0.651**	<0.001	−0.660**	<0.001

Spearman's rank correlation tests were used to evaluate these relationships and correlations were defined as weak positive (0.1−0.3), moderate positive (0.3−0.7), strong positive (0.7−1.0), weak negative (−0.1− −0.3), moderate negative (−0.3− −0.7), or strong negative (−0.7− −1.0). *P* value: (two-tailed), *: *P*<0.05, **: *P*<0.01. NGAL: neutrophil gelatinase-associated lipocalin, uNGAL: creatinine: urine NGAL: creatinine, IL: interleukin, MCP-1: monocyte chemoattractant protein 1, MIP1β: macrophage inflammatory protein-1 beta, TNF-α: tumor necrosis factor-alpha.

Table 4. Relationship between neutrophil gelatinase-associated lipocalin and various serum adipokines in a murine model of systemic lupus erythematosus

(*n*=36)	Serum NGAL		Urine NGAL		Urine NGAL: creatinine	
Parameter	rho	*P* value	rho	*P* value	rho	*P* value
Serum insulin	0.428**	0.009	0.382*	0.022	0.413*	0.012
Serum leptin	−0.209	0.221	−0.175	0.307	−0.262	0.122
Serum PAI-1	0.400*	0.016	0.338*	0.044	0.330*	0.049
Serum resistin	0.645**	<0.001	0.637**	<0.001	0.674**	<0.001

Spearman's rank correlation tests were used to evaluate these relationships and correlations were defined as weak positive (0.1−0.3), moderate positive (0.3−0.7), strong positive (0.7−1.0), weak negative (−0.1− −0.3), moderate negative (−0.3− −0.7), or strong negative (−0.7− −1.0). *P* value: (two-tailed), *: *P*<0.05, **: *P*<0.01. NGAL: neutrophil gelatinase-associated lipocalin, uNGAL: creatinine: urine NGAL: creatinine, PAI-1: Plasminogen activator inhibitor-1.

DISCUSSION

NGAL is a small 25-kDa protein released from renal tubular cells after various injuries. NGAL is an emerging marker for the early diagnosis of AKI and can be a good predictor of CKD progression beyond glomerular filtration rate estimation [4].

The prevalence of CKD is increasing, and it has become a severe public health concern in recent years. The three most common causes of CKD are diabetes mellitus, hypertension, and glomerulonephritis; however, additional causes include polycystic kidney disease [12].

Several previous studies have suggested that NGAL can also be used as a biomarker that reflects renal damage in patients with SLE. However, the cytokines or disease parameters that are strongly correlated with NGAL in SLE have not been fully elucidated.

In human patients, interpreting the correlation results may be difficult because of the influence of various environmental factors or the coexistence of these correlations with other diseases. However, genetic or environmental factors can be controlled in the disease animal model. Therefore, the influence of other factors can be excluded in the interpretation of correlation results between NGAL and other disease parameters such as clinicopathological parameters and various cytokines. A study of the potential strong correlations of disease parameters and cytokines with NGAL provides an understanding of and strong support for the suggestion that NGAL can be used as a clinical biomarker for SLE.

Glomerular and tubular damage occur during an autoimmune renal injury. As hypothesized, the levels of serum and urine NGAL and the uNGAL/C ratio should change with SLE disease severity. Serum and urine NGAL concentrations and the uNGAL/C ratio at 43 weeks of age in the methylprednisolone-treated group were significantly lower than those in the saline-treated control group on the chow diet.

Based on these findings, serum and urine NGAL levels, and the uNGAL/C ratio, which are widely used to investigate tubular damage in AKI, were also used to monitor lupus nephritis. These indices reflect the therapeutic and protective effects of the tubules. Among these parameters, serum NGAL levels had the highest correlation with serum levels of IL-6, TNF-α, and IP-10.

The chow diet group showed significant differences between the saline-treated and methylprednisolone-treated groups in serum and urine NGAL concentrations and uNGAL/C ratio at 43 weeks of age. Treatment with methylprednisolone significantly lowered the serum IL-6 and TNF-α levels in the chow diet group; however, methylprednisolone did not significantly lower these levels in the HFD group. In contrast, treatment with methylprednisolone significantly lowered serum IP-10 and resistin levels, regardless of diet [8].

IL-6 has various effects on the biological activities of target cells and plays a key role in the modulation of various inflammatory states. Patients with autoimmune diseases may show increased IL-6 serum levels [15]. In a human study, IL-6 serum levels were significantly higher in patients with SLE than those in healthy controls, and IL-6 has been found to have an important role in the development of murine lupus nephritis [7].

Immune complexes induce the production of TNF-α from monocytes [36], and TNF-α itself exhibits pro-inflammatory activity and causes vascular injury and organ damage [3]. Increased TNF-α levels have been observed in patients with SLE and correlated with disease activity [32].

IFN-α is an important cytokine in SLE [22, 26], and the role of its response protein, IP-10, has also been studied. Previous studies on patients with SLE revealed that SLE disease activity is highly correlated with serum levels of IP-10 [19, 24, 27]. In addition, one previous study suggested that IP-10 is a useful marker of disease activity in SLE [26]. IP-10 is a ligand of CXCR3 that recruits activated T lymphocytes, macrophages, dendritic cells, NK cells, and activated T lymphocytes to the sites of inflammation [6, 10, 13, 20].

In obese white adipose tissue, the number of M1 macrophages, which secrete TNF-α and IL-6, is increased, resulting in local and systemic low-grade inflammation and insulin resistance [18].

CCL2 (MCP-1), CCL4 (MIP-1b), IL-6, IL-10, and TNF-α are expressed in the kidneys of patients with SLE and in animal models of lupus nephritis [1, 29, 38]. In the present study, serum and urine NGAL levels and the uNGAL/C ratio showed moderate correlations with the kidney levels of these cytokines.

A previous study showed that resistin and NGAL were associated with illness severity and clinical outcomes in sepsis; resistin and NGAL were significantly correlated with the Sequential Organ Failure Assessment (SOFA) score (moderately positive, Spearman's rho=0.41, $P<0.001$ and Spearman's rho=0.51, $P<0.001$, respectively). In addition, resistin and NGAL levels correlated with IL-6 and IL-10, soluble endothelial adhesion molecules (VCAM-1 and ICAM-1), and organ failure. Sepsis is a life-threatening organ dysfunction involving pro- and anti-inflammatory components of the host innate immune system and is caused by a dysregulated host response to infection [30].

Resistin, an adipokine with possible pathogenic roles in diabetes and obesity, is also involved in the pathogenesis of SLE. In a previous study, resistin concentration was positively correlated with the glomerular filtration rate, high-sensitivity C-reactive protein levels, erythrocyte sedimentation rate, and disease duration in patients with SLE [2]. In the current study, NGAL levels significantly correlated with resistin levels and disease severity in a murine model of SLE. Resistin was first identified in adipocytes of mice and is associated with the pathogenesis of diabetes [31]. It is produced by neutrophils and macrophages [16], and its ability to activate endothelial cells is thought to play a role in the pathogenesis of atherosclerosis [35]. Thus, high concentrations of NGAL and resistin may contribute to increased atherosclerotic risk in patients with SLE. Multiple mechanisms may be involved, resulting from the complex interplay between traditional cardiac risk factors and SLE-driven inflammation [21]. SLE involves the interplay of multiple inflammatory mediators, including leukocytes, cytokines, chemokines, adhesion molecules, complements, and antibodies, resulting in the formation of atherosclerotic plaques [14].

In summary, serum and urine NGAL levels and the uNGAL/C ratio were significantly decreased following methylprednisolone treatment; however, a high-fat diet offset these therapeutic effects. In addition, serum NGAL levels showed a strong positive correlation with the expression of several cytokines associated with SLE pathogenesis. These results suggest that NGAL levels strongly correlate with the clinicopathological parameters and several key cytokines in SLE.

These data improve our understanding of the relationship between NGAL levels and various disease parameters in SLE, which could have clinical implications.

CONFLICT OF INTEREST. The author declares no competing interests.

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