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ORIGINAL ARTICLES

Correlation Between Systemic Lupus Erythematosus and Renal Damage

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Abstract

Introduction: Two of the most frequent Lupus nephritis (LN) diseases are multiple glomerulonephritis and renal fibrosis. Recent studies have verified that 10-30% of patients with SLE after several years (3-6 years) develop LN and end-stage chronic renal disease (ESRD) when there is a need for chronic intermittent hemodialysis (HD) treatment. [1, 2, 3]

The paper aimed to assess renal damage due to LN using the results obtained from the examined parameters in patients with chronic kidney disease (CKD) in the third stage (a and b).

Materials and Methods: This prospective cohort research (cross-section ") study included 100 patients with CKD (55 were men with an average age of 57.00±8.50 years old with chronic renal disease, 20 with diabetes mellitus (DM) and nephropathy diabetics, 15 were arterial hypertension (AHT), 11 were with chronic glomerulonephritis (CGN), 3 with Adult polycystic kidney disease (APCKD) and six patients were with undefined renal disease, while 45 were female with an average age of 55.80 ±10.50 years old), with primary kidney disease: 16-with diabetes mellitus and diabetic nephropathy,11 with HTA…

Statistical analysis of the examined material: The obtained results from the studied patients with CKD and the control group were statistically processed with arithmetic mean value, standard deviation X ± SD, with Student, "t" test, Mann-Whitney and Wilcoxon test. The results were processed with the appropriate state-of-the-art statistical program, SPSS V26.

Results Tables and graphs 4 and 8 present the results obtained at the beginning of the study (for all patients with LN and CKD: women and men) and after 12 months of treatment.

Conclusion: The results obtained suggest that LES affects the appearance of renal damage; therefore, early detection and treatment of the initial stages of LN influence the reduction of its activity.

Keywords: Lupus Nephritis, LES, Clinical manifestations, Renal damage.

Introduction

Systemic Lupus Erythematosus (SLE) is a chronic inflammatory disease of the connective tissue. It is multisystemic in nature and has an unknown etiology. SLE mainly affects women during their reproductive years and is characterized by damage to the joints, kidneys, and serous membranes, as well as antinuclear antibodies (ANA).

Renal damage is the leading cause of morbidity and hospitalization for a patient with SLE.

Renal damage appears within the first two years but also after five years of the disease.

According to the classification made according to histopathological findings by the International Society of Nephrology (ISN)/Renal Pathology Society (RPS), Kidney International, and Journal of the American Society of

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Nephrology public-shed in February 2004, LN manifests with VI classes [4-7].

Global or segmental glomerular cicatrices that manifest as a chronic consequence of endocapillary glomerular proliferation, with the appearance of crescents, immunoglobulin deposits, and in the laboratory examination of urine for 24 hours, hematuria and proteinuria>150-3000 mg/24 hours appear, which symptoms should be counted as manifestations of LN [8].

The classification of lupus nephritis is based on kidney biopsy. Over time, LN can worsen and lead to end-stage chronic renal failure when treatment with chronic hemodialysis is imposed. Renal failure (acute or chronic) and sepsis are the two leading causes of death in patients with SLE.

LN affects 30-60% of adults and up to 70% of children. It is characterized by the deposition of immune complexes in the glomeruli, which is accompanied by inflammation and progresses until renal fibrosis appears [9, 10].

The symptoms of LN tend to develop about five years after the first appearance of symptoms. They are manifested by edema in the lower part of the body or around the eyes, fever without any known cause, hematuria, hypertension, nocturnal, oliguria, proteinuria, muscle pain, redness of the skin on the face (i.e., the form of "butterflies"), inappetence, etc. [11-15].

Chronic renal damage as a consequence of LN includes modifications of chromatin structure, DNA demethylation that regulates C3 production, histone acetylation that governs the production of profibrotic Platelet-derived growth factor (PDGF) genes, infiltration and activation of immune cells, extracellular matrix fibrosis, endothelial cell activation, fibrinolysis, mitochondrial dysfunction, and tubular damage [16].

Assessing renal function in patients with SLE is vital because early detection and treatment of renal involvement can significantly improve the outcome and course of renal disease [17].

Patients with SLE have poor clearance mechanisms for cellular debris and nuclear debris from apoptotic cells that induce plasmacytoid dendritic cells to produce interferon-α, which is a powerful promoter of the immune system and auto-immunity.

Autoreactive B lymphocytes, which are generally inactive during SLE, become active due to the malfunctioning of standard mechanisms homeostatic, resulting in a departure from tolerance.

This leads to the production of autoantibodies. Other autoantibodies, including anti-ds DNA antibodies, develop through epitope spreading.

These autoantibodies develop over time, typically months to years before the onset of clinical SLE.

Table 1 presents the classification of LES according to the International Society of Nephrology (ISN) / Renal Pathology Society and the Renal Pathology Society (RPS), 2003/2004.

Class I	Minimal mesangial LN
Class II	Mesangial proliferative LN
Class III	Focal LN (<50% of glomeruli)
Class III (A)	active lesions
Class III (A/C)	active and chronic lesions
Class III C	chronic lesions
Class IV	Diffuse LN (≥50% of glomeruli).
Class IV-S) or global (IV-G) LN	Diffuse segmental (IV-S) or international (IV-G) LN
Class IV (A)	active lesions
Class IV (A/C)	active and chronic lesions
Class IV C	active and chronic lesions
Class V	Membranous LN
Class VI	Advanced sclerosing LN ≥90%, Globally without residual activity

Table 1. Classification of LES according to the International Society of Nephrology (ISN) / Renal Pathology Society and the Renal Pathology Society (RPS), 2003/2004.

The paper aimed to assess renal damage due to LN using the results obtained from the examined parameters in patients with CKD in the third stage (a and b).

Materials and Methods:

This prospective cohort research (cross-section ") study included 100 patients with SKR (55 were men with an average age of 57.00±8.50 years old with CKD, Twenty with diabetes mellitus (DM) and nephropathy diabetics, fifteen with AHT, eleven were with chronic GMN, three with APKD, and six patients with undefined renal disease, while forty-five were female with an average age of 55.80 ±10.50 years old), with primary kidney disease: sixteen with DM and diabetic nephron-pathy, eleven with AHT, 10-with chronic GMN; six with APCKD and four with undefined renal disease. All patients (men + women) were in the third-degree a and b according to the degree of glomerular filtration within the limits of values 30-59 mL/min/1.73 m2, table number 3) with the onset of the disease 5-6 years ago. All patients were monitored in the period April-2022-April-2023.

Of the total number of patients (100) with CKD,16 of them manifested symptoms of LN (eleven women; five men), and all fulfilled the clinical and laboratory criteria for LN according to the International Society of Nephrology (ISN)/ Renal Pathology Society (RPS), 2003/2004.

Table 2 presents the patients with CKD according to gender and average age.

Total number of patients with CKD-100	Females-45 (45%)	Males-55 (55%)
Mean age ± SD	55.80±10.50 years	57.00±8.50 years

Table 2. Presentation of patients with CKD according to gender and average age

Table 3 presents the patients with CKD in the third stage, with GFR of 30-59 mL/min/1.73 m2 according to MDRD, gender, and underlying disease.

Patients' data	Gender	DM	AHT	Chr GMN	APCKD	Undefined
Males	**55**	**20**	**15**	**11**	**3**	**6**
Female	**45**	**15**	**11**	**10**	**5**	**4**
Total	**100**	**35**	**26**	**21**	**8**	**10**

Table 3: Presentation of patients with CKD in the third stage, GFR of 30-59 mL/min/1.73 m2 according to MDRD, according to gender, underlying disease

Table 4 presents patients with LN according to classes according to the International Society of Nephrology (ISN) / Renal Pathology Society and the Renal Pathology Society (RPS) 2003/2004 (16 females-11, and males-5).

Total number (M+F) with CRD and LN= 16	Males 5	Females 11
Class I-Minimal mesangial LN	**3**	**8**
Class II-mesangial proliferative LN	**1**	**2**
Class III-Focal LN (<50% of glomerulus)	**1**	**1**

Table 4: Presentation of patients with LN according to classes according to the International Society of Nephrology (ISN) /Renal Pathology Society and the Renal Pathology Society (RPS) 2003/2004,

Statistical analysis of the examined material: The obtained results from the studied patients with CKD and the control group were statistically processed with arithmetic mean value, standard deviation X ± SD, with Student's t, "t" test, Mann-Whitney and Wilcoxon test. The results were processed with the appropriate state-of-the-art statistical program, SPSS V26.

Results

Obtained at the beginning of the study (for all patients with LN and ESRD: women and men) and after 12 months of treatment are presented in Tables 5, 6, 7, and 8.

Table 5 presents results obtained from the examined parameters of patients with LN at the beginning of the study.

Examined parameters	RV	Females with LN=11	Males with LN=5
SE - mm/30 min	4-10	110±10.50 ↑↑	116±20.00↑↑
Hb - mmol/l	7.76-10.6	5.40±0.60 ↓	6.20±0.90 ↓
RBC - 10^{12}/L	4.2-5.5	3.10±0.40 ↓	3.50±0.80 ↓
Htc	0,37-0,40	0.25±0.30↓	0.36±0.20 ↓
Plt - 10^{9}/L	140-340	90,40±6.50 ↓	95.60±3.80 ↓
WBC - 10^{9}/L	4-9	15,00±2.00 ↑	17.00±1.00 ↑
Neutrophils %	0.58-0.66	0.40±0.30 ↓	0.45±0.36 ↓
CRP- mg/l	0-50	42.00±8.60 ↑	60±0.40 ↓
Glycemia - mmol/l,	3.5-5.5	5.30±1.00	5.20±0,80
Serum Iron - µmol/l	7.3-28	6.00±1.00 ↓	6.50±1.50 ↓
C3	80-128	C3<43 ↓	C3<44 ↓
C4	12-42	C4<13 ↓	C4<15↓
ANA	≤1:60	>190 (positive)	>186 (positive)

Table 5. Results obtained from the examined parameters of patients with LN at the beginning of the study

Table 6 presents results obtained from the examined parameters of nitrogen degradation products in patients with LN at the beginning of the study.

Examined parameters	RV	Females with LN=11	Males with LN=5
Urea - mmol/l	2.0-8.3	16,50±10,80 ↑	16.50±10.80 ↑
Creatinine - µmol/l	F=53-88; M=71-115	170.50±18.00 ↑	180.60±15.60 ↑
Uric Acid - µmol/l	F=155-357; M=208-428	380.00±10.60 ↑	430±8,50µmol/l ↑
Proteinuria - g/24 h	<150mg/24/ 15 g/mmol	>3,6 g/24 h ↑	>3,9 g/24 h ↑
BUN	2.4-6.4 mmol/L	>9,4 ↑	>11,5 ↑
GFR	90-120 mL/min/ 1.73 m^2	50 mL/min/1.73 m^2↓	47 mL/min/1.73 m^2↓

Table 6. The results obtained from the examined parameters of nitrogen degradation products in patients with LN at the beginning of the study

The table of results obtained at the beginning of the study shows a disorder of all the examined parameters of the patients (F+M) with LES and LN during diagnosis and manifestations of the disease.

Table 7 presents results obtained after 12 months of LN treatment

Examined parameters	RV	Females with LN=11	Males with LN=5
SE - mm/30 min	4-10	40.00±5.00	48.00±2.00
Hb - mmol/l	7.76-10.6	6.70±1.50	7.20±1.30
RBC - 10^{12}/L	4.2-5.5	4.10±0.80	4.80±1.00
Htc	0,37-0,40	0.35±040	0.42±0.60
Plt - 10^9/L	140-340	126.00±14.00	175±14.00
WBC - 10^9/L	4-9	12.00±1.30	13.60±1.00
Neutrophils %	0.58-0.66	0.54±0.80	0.60±0.30
CRP - mg/l	0-50	10.00±1.50	14.00±6.00
Glycemia - mmol/l,	3.5-5.5	5.80±1.00	5.20±0,80
Serum Iron - µmol/l	7.3-28	9.60±4.90	12.00±14.50
C3	80-128	92.00	94.00
C4	12-42	28	30
ANA	≤1:60	>170	>176

Table 7. Results obtained after 12 months of LN treatment

Table 8 presents results received from the examined parameters of nitrogen degradation products in patients with LN after 12 months of treatment

Examined parameters	RV	Females with LN=11	Males with LN=5
Urea - mmol/l	2.0-8.3	20.40±6.50	25.30±3.00
Creatinine - µmol/l	F=53-88; M=71-115	250.00±23.00	270.00±204.00
Uric Acid - µmol/l	F=155-357; M=208-428	340±9.50	410±6.00µmol/l
Proteinuria - g/24 h	<150mg/24/ 15 g/mmol	>3,0 g/24 h	>3,2 g/24 h,
BUN	2.4-6.4 mmol/L	7.6	8.2
GFR	90-120 mL/min/ 1.73 m^2	44 mL/min/1.73 m^2	40 mL/min/1.73 m^2

Table 8 The results obtained from the examined parameters of nitrogen degradation products in patients with LN after 12 months of treatment

After 12 months of treatment by the accepted recommendations and the clinical overview, improvements are observed based on the laboratory parameters examined in the patient with LN (Table 6). After treatment within 12 months with nonsteroidal anti-inflammatory drugs, low doses of Aspirin (80-160 mg/day, antimalarials-hydroxychloroquine (Plaquenil, Chloroquine, Quinacrine) or 200 mg 1-2×/day, Prednisone in quantities of 40-60 mg 1×day (the dose was according to the clinical picture).

Azathioprine 1-2.5 mg/kg 1×/day or cyclophosphamide -4 mg/kg 1×/day was used for immunosuppression, capsules Ketosteril S.2x1, tab. CaCO3 a 1.0 S.3x1, Rocaltrol tablets 0.5 microgram S. two days a week The levels of C3 and C4 were significantly low, which indicates kidney damage such as the consequences of LES were manifested with lower values, which shows that the progression of the renal disease has slowed down, which demonstrates that the therapy has shown appropriate effects. High blood pressure was treated with ACE inhibitors: perindopril, fosinopril, ramipril, enalapril, trandolapril, lisinopril, benazepril, and zofenopril, each at a dose of 2x20 mg (individually with ACE inhibitor and diuretic).

Discussion

One of the most common manifestations caused by SLE is kidney damage. Out of 10 elderly SLE patients, five of them, after a few years, develop kidney damage. Lupus nephritis (LN) is a type of kidney disease caused by SLE. Lupus is an autoimmune disease with a disorder in the body's immune system that attacks the body's cells and organs. Kidney disease caused by lupus can worsen over time and lead to chronic kidney disease. 30-40% of patients with SLE manifest symptoms of nephritic syndrome, while 10% of them manifest symptoms of glomerulonephritis. With untreated SLE, initially have a slight proteinuria (<1g/day) accompanied by hematuria. Patients with membranous glomerulonephritis have proteinuria at the level of nephrotic syndrome. Still, without urinary sediment, the concentration of C3 is average, while anti-DNA, even when positive, appears in low titers.

The opposite happens with patients with proliferative nephritis who have increased proteinuria, hypertension, and improved urinary sediment; C3 is decreased, and anti-DNA is positive in high titers. The most suitable method to detect and monitor disease activity in lupus nephritis is proteinuria hematuria (microscopic and rarely macroscopic), which indicates glomerular damage of an inflammatory nature. Granular elements and fragmented erythrocytes in urine are signs of nephritic syndrome. Renal biopsy rarely affects the diagnosis of SLE, but it is the best way to document kidney damage from SLE. In the clinical picture, SLE is manifested by arterial hypertension, hyperuricemia, hyperleptinemia, low glomerular filtration rate, and the decreased titer of C3, C4, and anti-DNA (ds) positive. During the evaluation of LN, monitoring the review of the titer of complement C3 and C4 and anti-DNA (ds), which appears positive, is essential. The progress of lupus nephritis is different in its different forms.

Significant changes in predictive parameters of the course of the disease cause the course of the disease to be different in people of other races. In general, individuals of the black race have the worst performance compared to those of the white race. An evaluation of the factors that lead to the development of CKD from LES in the initial phase (including inflammation, fibrosis of renal tissues, renal hypoxia, activation of internal kidney cells, oxidative stress...) and with quality treatment, they can affect the slowing down of the progress of the disease [16]. In most cases, LN is manifested by the deposition of immunoglobulin G (IgG) and complement in the glomeruli [17-22]. Renal damage during LN is manifested by causing mesangial hyperproliferation, matrix production, cytokine, chemokine release, and renal fibrosis through GBM damage [23].

In diseased tissues, activated glomerular endothelial cells and damaged podocytes release endothelin, accelerating MBG damage and causing mitochondrial stress and podocyte loss, leading to glomerulosclerosis. At the same time, nephrons lose compensatory mechanisms, increasing intraglomerular pressure and glomerular stress in the remaining nephrons [24-31].

The cellular components that most contribute to interstitial damage are tubular cells, lymphocytes, pericytes, fibroblasts, macrophages, endothelial cells, inflammatory lymphocytes, and infiltrating dendritic cells.

In the pathogenesis of LN, autoimmunity and immunological mechanisms that affect the production of nephrogenic autoantibodies directed against nuclear elements against nucleosome DNA, autoantibodies of specific isotypes (Ig1 and Ig3), which are deposited in glomeruli [32-35].

Therapy for managing LN should be initiated in the early stages and according to the disease classification based on the pathogenetic mechanisms. The long-term result depends on the degree of treatment response, where the resolution of proteinuria is the best indicator of a favorable prognosis. Hypertension should be managed with angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin II receptor blockers(ARBs), diuretics, nonsteroidal anti-inflammatory, and antirheumatic drugs, while dyslipidemia with statins or fibrates, changes in diet(salt restriction, reduced protein consumption, not exposing to the sun are the most common treatments for LN. Chloroquine, corticosteroid, and immunosuppressive therapy are essential in treating LN because they prevent the immune system from attacking the blood vessels in the kidneys. During the last four decades, the changes in treating LN and general medical care have greatly improved renal involvement and overall survival [36-40]. Contemporary studies have verified that T cells are the fundamental parameter in the pathogenesis of SLE through their ability to communicate with and provide exceptional assistance to B cells in inducing autoantibody production.

Several phenotypic changes that increase the propensity to activate lupus-associated inflammation have recently been identified in lupus T cells [41, 42]

Conclusion

From the obtained results, we can conclude that LES affects the appearance of renal damage. Therefore, early detection and treatment in the initial stages of LN influence the reduction of its activity in patients with CKD. Consequently, we prefer that timely treatment properly (with nonsteroidal anti-inflammatory antirheumatic, corticosteroid therapy, antimalarial, immunosuppressive therapy, ACE inhibitors or Angiotensin Receptor Blockers (ARBs and antilipemic in patients with pre-uremia should be the main goals and objectives of nephrologists, rheumatologists and dermatovenerologists to prevent progression of the disease towards end-stage chronic renal failure.

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Abbreviations;
Lupus Nephritis - LN; Systemic Lupus Erythematosus – SLE; Antibodies Antinuclear – ANA; Lupus Erythematosus Systemic – LES; End Stage Chronic Renal Disease – ESRD; Haemodialysis - HD; Glomerular Filtration Rate - GFR; Chronic Kidney Disease - CKD; Diabetes Mellitus - DM; Arterial Hypertension - AHT; Chronic Glomerulonephritis (CGN); Adult Polycystic Kidney Disease - APCKD; International Society of Nephrology - ISN; Renal Pathology Society - RPS; chronic glomerulonephritis - chr GMN; Sediment – SE; Haemoglobin – Hb; Red Blood Cells – RBC; Haematocrit - Htc; Platelets - Plt; White Blood Cells - WBC; C-Reactive Protein – CRP; Reference values – RV; Complement Fraction 3 - C3*; Complement Fraction 4* – C4*; Blood Urea Nitrogen – BUN; National Kidney Foundation – NKF; Immunoglobulin G - IgG; Angiotensin II Receptor Blockers - ARB; Angiotensin-Converting Enzyme – ACE; Glomerular Basement Membrane – GBM;*

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