Abstract. – Renal involvement is a common manifestation in course of systemic lupus erythematosus (SLE) and may occur at any time.

In SLE nephritis, the pattern of glomerular injury is primarily related to the formation of the immune deposits in situ, due major to antidual-stranded DNA (anti-dsDNA) antibodies and anti-C1q. Immune complexes deposits can induce the inflammatory response by activation of adhesion molecules on endothelium, resulting in the recruitment of pro inflammatory leukocytes. Activated and damaged glomerular cells, infiltrating macrophages, B and T cells produced cytokines that play a pivotal role as inflammatory mediators to extend renal injury.

In serum of SLE patients, the concentrations of IL-6, IL-17, IL-12, INF-γ, IL-18, IL-10 and TNF-α are higher than healthy people and this increase correlate with disease activity. It is well established possible correlation between urinary cytokines levels (IL-6, IL-10, INF-γ and TGF-β) and disease activity. In fact, Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) correlate with cytokines over-expression, in particular IL-17, IL-10, TNF-α and the axis INF-γ/IL-12.

Recent studies are promising about proteinuria reduction and improving renal function through cytokine blockade therapy.

Key Words:
SLE, Lupus nephritis, Cytokines, Disease activity index, Renal biopsy.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune, multisystemic disorder, characterized by a broad spectrum of clinical and immunological features with variable course. SLE has a 12:1 female-to-male ratio during the ages of 15 to 45 years, but the female-to-male ratio fall to 2:1 when disease develops in either children or the elderly. African Americans, Asian Americans, and Hispanics have three to four times higher frequency of lupus than white non-Hispanics and often have more severe disease. Since the 1950s, the estimated 5-year survival of SLE patients rose from <50% to >95%. Survival rates for lupus patients have improved greatly with the ability to treat disease-specific manifestations and infections and to lessen the impact of co-morbidity conditions. Cardiovascular disease, infections and renal failure remain a significant risk factor for mortality.

SLE pathogenesis involves different factors: UV radiation, stress, viral infection, hormonal imbalance, drugs (about 400 medications can cause this condition, the most common of which are procainamide, hydralazine, quinidine, and phenytin). The loose of immuno-tolerance lead to a chronic inflammatory condition in which are involved cellular mediators as antigen presenting cells (APC), T lymphocytes and B lymphocytes and molecular mediators (cytokines, chemokines, complement fractions, extracellular matrix proteases, small peptides, reactive oxygen species and others). The common final pathway is polarized on B cells hyperactivation and autoantibodies production.

Synthetic antimalarials, steroids, alone or in combination with immunosuppressant therapy, still are the cardinal treatment option for the disease. In the last decade, a better understanding of lupus pathogenesis has led to the development of biological agents, as B-cells targeted or anti-cytokine agents that should improve lupus management.
Recent evidence suggests that anti-C1q antibodies are strongly associated with the development of proliferative LN18. Immune complexes deposits can promote the inflammatory response by activation of adhesion molecules on endothelium, resulting in the recruitment of pro-inflammatory leukocytes and development of autoimmune injury. Moreover, activated and damaged glomerular cells, infiltrating macrophages, B and T cells produced cytokines that play a pivotal role as inflammatory mediators to extend renal injury.

**Interleukin-6**

Interleukin-6 (IL-6) is a glycoprotein with a molecular mass of 26 kDa and its structure consists of 184 amino acids (aa). IL-6 signals through a specific receptor (IL-6R) and two signal transducers (gp130 subunits) expressed on the surface of most cells. When IL-6 binds its receptor, gp130 subunits trigger the JAK-STAT pathway, activating gene transcription and the mitogen-activated protein kinase cascade, which is involved in cell survival and stress responses. IL-6 signalling can be inhibited by antibodies directed against IL-6R, such as tocilizumab, preventing IL-6 signal transduction to inflammatory. In human SLE, IL-6 acts as a critical factor not only in B cell immunopathology and hyperactivity by producing Ig, but also facilitating the production of auto antibodies by T cells and decreasing activity of CD8+ suppressor T cells19. Genetic differences may have a pivotal role in IL-6 levels in SLE patients. In fact, both in Caucasian and African-American populations, a 3′ minisatellite of IL-6 gene had different allele frequencies in SLE patients respect to healthy controls. In patients with minisatellite alleles, IL-6 levels were higher, increasing the possibility that the 3′ minisatellite alleles may have biological effects20. Urinary IL-6 is produced both by renal parenchyma21 and by urinary tract22; urinary levels of IL-6 are significantly higher in patients with active LN23, especially in course of class IV24. Peterson et al25, in a study of 56 SLE patients, measuring serum and urine IL-6, observed that SLE disease activity did not correlate with serum IL-6 levels, whereas urine IL-6 levels correlated with overall disease activity and with the presence of active urinary sediment, indicating that urine IL-6 may be a marker of active nephritis. On the other hand, recent data26,27, have demonstrated that serum IL-6 levels is significantly elevated in active SLE patients correlating...
### Table I. Classification of lupus nephritis (International Society of Nephrology/Renal Pathology Society, 2003).

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
<th>LM, IF, EM Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Minimal mesangial lupus nephritis</td>
<td>Normal glomeruli, mesangial immune deposits by IF</td>
</tr>
<tr>
<td>II</td>
<td>Mesangial proliferative lupus nephritis</td>
<td>Purely mesangial hypercellularity of any degree or mesangial matrix expansion by LM, mesangial immune deposits by IF or EM, but not by LM</td>
</tr>
<tr>
<td>III</td>
<td>Focal lupus nephritis</td>
<td>Active or inactive focal, segmental or global endo or extracapillary glomerulonephritis involving &lt;50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations</td>
</tr>
<tr>
<td>Class III (A)</td>
<td>Active lesions: focal proliferative lupus nephritis</td>
<td></td>
</tr>
<tr>
<td>Class III (A/C)</td>
<td>Active and chronic lesions: focal proliferative and sclerosing lupus nephritis</td>
<td></td>
</tr>
<tr>
<td>Class III (C)</td>
<td>Chronic inactive lesions with glomerular scars: focal sclerosing lupus nephritis</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Diffuse lupus nephritis</td>
<td>Active or inactive diffuse, segmental or global endo- or extracapillary glomerulonephritis involving &gt;50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class is divided into diffuse segmental (IV-S) lupus nephritis when 50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G) lupus nephritis when 50% of the involved glomeruli have global lesions. Segmental is defined as a glomerular lesion that involves less than half of the glomerular tuft. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation</td>
</tr>
<tr>
<td>Class IV-S (A)</td>
<td>Active lesions: diffuse segmental proliferative lupus nephritis</td>
<td></td>
</tr>
<tr>
<td>Class IV-G (A)</td>
<td>Active lesions: diffuse global proliferative lupus nephritis</td>
<td></td>
</tr>
<tr>
<td>Class IV-S (A/C)</td>
<td>Active and chronic lesions: diffuse segmental proliferative and sclerosing lupus nephritis</td>
<td></td>
</tr>
<tr>
<td>Class IV-S (C)</td>
<td>Chronic inactive lesions with scars: diffuse segmental sclerosing lupus nephritis</td>
<td></td>
</tr>
<tr>
<td>Class IV-G (C)</td>
<td>Chronic inactive lesions with scars: diffuse global sclerosing lupus nephritis</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>Membranous lupus nephritis</td>
<td>Global or segmental subepithelial immune deposits or their morphologic sequelae by LM and by IM or EM, with or without mesangial alterations</td>
</tr>
<tr>
<td>Class V</td>
<td>Lupus nephritis may occur in combination with class III or IV in which both will be diagnosed</td>
<td></td>
</tr>
<tr>
<td>Class V</td>
<td>Lupus nephritis show advanced sclerosis</td>
<td></td>
</tr>
<tr>
<td>VI</td>
<td>Advanced sclerosis lupus nephritis</td>
<td>90% of glomeruli globally sclerosed without residual activity</td>
</tr>
</tbody>
</table>

Indicate and grade (mild, moderate, severe) tubular atrophy, interstitial inflammation and fibrosis, severity of arteriosclerosis or other vascular lesions. LM: Light microscopy; IF: Immunofluorescence; EM: Electron microscopy. 

1. Indicate the proportion of glomeruli with active and with sclerotic lesions. 
2. Indicate the proportion of glomeruli with fibrinoid necrosis and/or cellular crescents.

with SLEDAI score, erythrocyte sedimentation rate and C-reactive protein (CRP). IL-6 and its soluble receptor (sIL-6R) levels are higher in LN patients with active disease. IL-6 is also detected in atrophic tubules, and the distribution correlates with tubular atrophy. Herrera-Esparza et al., in a small series of renal biopsies with III or IV classes LN, demonstrated that more than half (52%) showed IL-6 deposition along the glomeruli and tubules. 

**Interleukin-17**

Interleukin-17 (IL-17) is a type I transmembrane glycoprotein with a molecular mass of 32 kDa, structured in a signal peptide of 23 aa followed by a chain region characteristic of the IL-17 family. To elicit its functions, IL-17 needs to bind to a cell surface receptor called IL-17R.

Th17 cells, a subset of CD4+ helper T cells, secrete mainly IL-17, to mediate inflammation, by stimulating production of inflammatory cyto-
Transforming growth factor-β

Transforming growth factor-β (TGF-β) family includes three members, TGF-β1 (390 aa), TGF-β2 and TGF-β3 (each of which had 412 aa) that becomes activated form of TGF-β molecule after proteolytic cleavage. Via receptors, TGF-β ligands signal and activate intracellular effectors, regulating transcription and defining the biological effect of TGF-β family members. TGF-β is a cytokine involved both in normal renal function and in the development of glomerulosclerosis. This fibrogenic cytokine is produced by natural killer cells (NK), lymphocytes, monocytes/macrophages and renal mesangial cells. TGF-β has stimulatory effect on T cells and down-regulatory effect on antibody production.

In human SLE several studies demonstrated the nephrotoxic effects of TGF-β at the various cells of kidney: there is a strong relationship between expression of TGF-β and the podocytes depletion and apoptosis.

TGF-β also increases epithelial to mesenchymal cells transdifferentiation, induces peritubular capillary loss and causes glomerular endothelial cells apoptosis. Instead, the cytoprotective effects are mediated by hepatocyte growth factor (HGF). Therefore, studies found that the balance between TGF-β and HGF seems to be an important prognostic factor in LN.

In patients with LN, Lu et al demonstrated that plasma TGF-β levels are decreased compared to controls and to SLE patients without nephritis. It is recognized that plasma TGF-β levels have a role in the pathogenesis of LN. In fact, the reduction of TGF-β levels contributes to block the regulatory T cells production and this might be one of the mechanisms that leads to B cell hyperactivity and overproduction of autoantibodies.

Despite to decreased plasma TGF-β levels, its urinary levels are increased showing a positive correlation with the development and progression of LN. Urinary TGF-β correlates with index of acute glomerular inflammation (mesangial proliferation and macrophage infiltration). Thus, a significant relationship is observed between urinary TGF-β levels and symptomatic nephritis, while increased latent renal TGF-β may be responsible for the chronic nature and progression of renal damage.

Instead, elevated renal production of TGF-β in patients with LN had no significant correlation with SLEDAI score and with the degree of proteinuria.

Interleukin-10

Interleukin-10 (IL-10) is a small homodimeric cytokine that interacts with its heterodimeric receptor complex to modulate the biological activities of immune cells. Major cellular sources of IL-10 are T cells subpopulation, B cells, B CD5+ in particular, monocytes-macrophages. Moreover, several non-hematopoietic cells producing IL-10 have been reported, as keratinocytes and IL-10 strongly inhibits the activation of monocytes, macrophages and dendritic cells (DC).

IL-10 antagonizes activation of granulocytes, NK cells, keratinocytes and endothelial cells and this complex inhibitory activity results in a reduced production of pro-inflammatory mediators, including cytokines and chemokines, adhesion and accessory molecules, and leads to reduce T cell stimulation. Furthermore, IL-10 has been identified as the principal cytokine secreted by a subtype of CD4+ T regulatory cells. On the other side, a number of studies in mice and humans clearly demonstrated that IL-10 is a potent cofactor for the proliferation of human B cells activated by anti-IgM, SAC or CD40 cross-linking. Generally, IL-10 exerts an anti-apoptotic effect on B cells, is involved in B-cell isotype switching, and plays a role in autoimmune diseases with underlying B-cell dysregulation.

In SLE patients, increased levels of IL-10 correlate with disease activity index and anti-dsDNA overexpression in Peripheral Blood Mononuclear Cells (PBMC). However, Zhao et al, in a study with fifty seven patients with SLE, founded no significant difference regarding serum IL-17 level between patients with nephritis and those without nephritis.

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DNA antibodies levels. IL-10 gene polymorphisms have been shown to associate with SLE incidence in Scottish, Mexican, American, and Italian populations suggesting that high levels of this cytokine may be one of several predisposing factors for SLE incidence and severity40. In some study, is reported an association between IL-10 promoter polymorphisms and renal involvement41. Uhm et al42, in a study of cytokine balance in kidney tissue from SLE patients, reported that IL-10 expression on cells surface is reduced in class IV nephritis respect to class V. Similarly, Akahoshi et al43, showed a strong predominance of cytokine Th1 in course of IV LN. Chun et al27 demostrated that serum IL-10 level was significantly elevated in active SLE patients and positively correlated with SLEDAI and anti-dsDNA antibodies. However, there was no significant differences in the levels of cytokines between SLE patients with nephritis and those without nephritis.

Regarding the therapy on the urinary gene expression profile in patients with active LN, Chan et al44 found a significant reduction of urinary mRNA expression of IL-10 and other cytokines with successful immunosuppressive therapy.

**Interleukin-12**

Interleukin-12 (IL-12) is a complex heterodimeric cytokine encoded by two separate genes produced by monocytes, macrophages, DC and B cells45. IL-12 production is stimulated in a T-independent manner by Toll-like receptor signalling, or in a T-dependent manner through the engagement of CD40 on antigen-presenting cells and CD40L on T cells. The major inhibitors of IL-12 production are IL-10, IL-11, IL-13 and type I IFNs46. IL-12 is considered the main stimulator of IFN-production and of the development of Th1 mediated autoimmune response. Recent studies suggest that the Th17 differentiation is tightly controlled by IL-12 family with inhibitory effect47. The role of this cytokine in human SLE is unclear, although has reported increased IL-12 serum levels in SLE patients48. Min et al49 reported a reduction of IL-12 serum levels in patients with LN and the resultant shift towards the type 2 cytokine phenotype may be facilitate the LN development. In a more recent study, Tucci et al50 demonstrated that overexpression of IL-12 serum levels correlate to renal damage. Moreover, these Authors showed that IL-12 was present within glomerular mononuclear cells in classes IV and V LN. The glomerular accumulation of IL-12 was strongly associated with its urinary levels; in conclusion IL-12 measurement may thus be predictive of the development of LN.

**IFN-γ**

Interferon-γ (IFN-γ) is a critical cytokine for inflammatory and autoimmune diseases, because of its immunostimulatory and immunomodulatory effects produced predominantly by NK and by CD4 and CD8 T cells. There is evidence for the role of IFN-γ in the activation of the cellular immune response in SLE patients. In LN is observed a predominance of Th1 phenotype with high IFN-γ levels that correlate with the severity of renal disease51. Increased serum levels of IL-12 and INF-γ in LN are related to diffuse proliferative glomerulonephritis and membranous nephropathy (IV and V classes), whereas normal IL-12 and INF-γ levels are observed in II and III classes50.

The expression of INF-γ in urinary sediment is elevated in the active LN. Level of INF-γ correlate with SLEDAI score, whereas did not correlate with serum creatinine and proteinuria.

Since the main source of INF-γ are the lymphocytes, is recognized that increased urinary levels of INF-γ in SLE patients with active nephritis reflect the predominance of Th1 response in intrarenal inflammation52.

**Interleukin-18**

Interleukin-18 (IL-18) is cleaved by an endoprotease, generating a biologically active 18-kD molecule. IL-18, a member of IL-1 super-family, is produced by macrophages and two subsets (myeloid and plasmocytoid) of DC may stimulate its release. Although myeloid DC induce IL-18 production, only plasmocytoid DC express IL-18R. IL-18 is observed in the LN glomeruli and increased serum levels are related to the severity of renal injury. The IL-18-positive cells are demonstrated in the mesangial matrix, infiltrating mononuclear cells and in lower percentage in tubular epithelial cells.

The higher levels of IL-18 positive cells in glomeruli are detected in IV and V classes, whereas a low presence is observed in class III.

Circulating DC are decreased in SLE and particularly there is a positive correlation between the reduced number of plasmocytoid DC and the severity of renal disease; the peripheral decreased levels of plasmocytoid DC correlates with its renal accumulation53.
Tumor Necrosis Factor-α

Tumor necrosis factor-α (TNF-α) is a 212-aa type II transmembrane protein arranged in stable homotrimers and it exerts both physiologic and pathogenic effects. TNF-α signals through two specific receptors (TNF-R1 and TNF-R2) by different transduction pathways: promoting induction of apoptosis signaling (FADD, TRADD and TRAF) and cell survival and differentiation pathways (NF-κB and c-Jun kinase).

TNF-α initiates cell death process by a TRADD mediated activation of pro-caspase 8 and 10, a class of aspartate-specific cysteine proteases. Procaspase 8 and 10 promote a molecular mechanism that lead to cell death either directly (without mitochondrial amplification, involving caspase 3, 6, 7), or indirectly via the release of apoptogenic factors from mitochondria (caspase 8)54.

As a consequence of multiplicity of its biological function, TNF is involved in a great number of pathological condition, including inflammatory kidney disease. In fact NF-kappaB plays a role in the up-regulation of TNF-α in LN class IV55. Via transmitting abnormal cell proliferating and pro-inflammatory signals, TNF-α plays a role as strong mediator of inflammation, and serum levels of TNF-α are higher in patients with active disease correlating with SLEDAI score56. TNF-α was found in cytoplasm of glomerular epithelial cells57, mainly by infiltrating macrophages, but also endothelial cells, glomerular visceral epithelium and mesangial cells. TNF-α was also found in the tubular epithelium and in the interstitium58.

Malide et al59 demonstrated the presence of TNF-α in SLE renal biopsy, but not in healthy renal samples. TNF-α was observed in all WHO LN classes60 and its high expression correlated with high histological disease activity60.

Renal expression of TNF-α and signalling adapter proteins (TRADD, RIP and TRAF-2) up-regulated in patients with class III and IV LN, with staining in crescents, proximal and distal tubules and interstitial mononuclear cells. Moreover, the expression levels of TNF-α, TRADD, RIP, TRAF-2 correlated with active index of renal pathology61.

In SLE patients with class IV and V LN, different studies demonstrated that TNF-α blocker therapy with infliximab leads to good renal outcome62,63 and proteinuria reduction65.

Interleukin-1

Interleukin-1 (IL-1) superfamily includes IL-1α and IL-1β, produced as precursor and then processed by cleavage to active pro-inflammatory cytokines.

In LN patients, the presence of IL-1α was showed by detecting IL-1α mRNA in monocytes-macrophages infiltrating the glomeruli and interstitium and occasionally in glomerular mesangial and epithelial cells58.

Other cytokines (IFN-α, IL-4, IL-13, IL 8)

Interferon-α (IFN-α) has multiple effects on immune cells including the differentiation of B cells, DC maturation and activation of T cells.

Some studies documented the role of IFN-α in the onset of LN66 and in the progression of disease67 via plasmacytoid DC68 in different mice models. Recently, an IFN-α antibody (MEDI-545) has been developed because of its possible role in LN treatment69.

IL-4 is a cytokine produced by Th2 lymphocytes and it activates B and T lymphocytes, macrophages, fibroblasts and glomerular cells70, by binding to receptors on their cell surface.

IL-4 leads to production of antibodies by B cells activation, Th2 lymphocytes development71 and fibroblasts proliferation72. Also macrophages and DC can cause renal damage through the production of IL-12 that, in these cells, is induced just by IL-473.

Furthermore, this cytokine promotes the production of extracellular matrix by mesangial cells70.

The importance of IL-4 in LN has been analyzed in renal biopsies from patients in various stages of disease; it has been found that LN class IV patients showed high levels of IL-4, but also in LN III and V classes. In the glomeruli, the expression of IL-4 levels strongly correlated with haematuria, BUN, creatinine and chronicity index score, but not with SLEDAI and activity index scores. In the interstitium, IL-4 levels weakly correlate with haematuria, CH50, activity index, chronicity index and anti-dsDNA antibodies31.

IL-13, produced by Th2 lymphocytes, plays a role in regulating the activity of monocytes, macrophages and B lymphocytes74; it also promotes collagen type I production72.

Serum level of IL-13 and IL-13 mRNA expression in renal tissue of active LN patients are significantly higher than healthy controls. In
these patients, IL-13 mRNA levels in the tubulo-interstitial area correlate with serum creatinine, glomerular and tubulointerstitial activity index, and serum C3. IL-13 role in active LN patients needs further studies.

IL-8, is a pro-inflammatory cytokine involved in glomerular damage in LN and found in mesangial cells, podocytes, tubular epithelial cells and renal fibroblasts. In humans, glomerular expression of IL-8 correlated with different type of GN, including LN.

IL-8, released in glomeruli during the inflammatory process, may be involved in the cross-talk between resident and infiltrating cells, and in the regulation of cell-matrix interactions, preventing the subversion of glomerular structure.

**Conclusions**

In LN, some studies suggested the possible correlation between urinary cytokines levels (IL-6, IL-10, INF-γ and TGF-β) and disease activity, but currently, clinical course of LN by urinary biomarkers needs further studies with larger number of patients.

Activity indexes, such as SLEDAI, are correlated with cytokines overexpression, in particular IL-17, IL-10, TNF-α and the axis INF-γ/IL-12.

In SLE patients serum, the concentration of IL-6, IL-17, IL-12, INF-γ, IL-18, IL-10 and TNF-α are higher than healthy people and this increase correlate with disease activity. On the contrary, TGF-β levels are decreased in LN compared to controls and to SLE patients without nephritis.

The crucial role of renal biopsy is clearly established by the relationship between the histological features and the clinical course of LN.

In Table II we summarized the expression of the major cytokines studied in the different classes of LN observed in renal biopsies.

Which is the possible role of inhibition cytokines in LN therapy is actually hard to establish. Recent studies are promising about proteinuria reduction and renal outcome (TNF-α blockers, infliximab) and about renal flares via anti-dsDNA reduction (anti-IL-6R antibody, tocilizumab and INF-α, MEDI-545), considering only small number of patients.

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Cytokines expression in SLE nephritis


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