*Research Article*

# Role of T- regulatory cells and FOXP3 in lupus nephritis

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## Abstract
**Introduction:** Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by a progressive breakdown of tolerance to self-antigens and the presence of concomitant hyperactive immune responses (Giang and La Cava, 2016). **Aim of the work:** The aim of this study is to assess the level of CD4, CD25 and FOXP3 T-regulatory cells in lupus nephritis patients in regard to disease activity. **Subjects and Methods:** The present study was conducted out on 100 subjects from the attendants of the outpatient clinics of internal medicine department, Minia university hospital, during the period from April 2016 to June 2017, 70 patients were diagnosed as lupus nephritis according to the presence of proteinuria (>500mg/24h) and/or hematuria and/or urinary casts, according to the recent recommendations from European League Against Rheumatism and 30 apparently healthy subjects as control matched for age and sex (Bertsias GK et al., 2012). **Results: This study was carried out on 100 subjects classified into two groups: Group 1:** Included 70 patients diagnosed as lupus nephritis 15 males and 55 females, their ages range from (22-40) years. **Group 2:** Included 30 apparently healthy subjects, 7 males and 23 females their ages from (20-40) years. **Discussion:** Lupus nephritis (LN) is mainly used to define the immune complex-mediated glomerulonephritis (GN) and it is the most important complication of systemic lupus erythematosus (SLE), which is responsible for SLE related mortality and morbidity. LN occurs in up to 50% of patients with SLE. In LN, the deposition of immune complexes plays a leading role in the initiation of the disease (Shakweer et al., 2016). **Conclusion:** Tregs % was found significantly lower in active lupus nephritis especially stage (III and IV) and correlates with all parameters of disease activity.
**Limitations:** Limitations to be considered in the present study including the small number of patients, which does not allow for definite conclusions, and the lack of functional assays for more precise Tregs characterization. Furthermore, it would be helpful to assess the urinary levels of Foxp3 mRNA, in parallel to serum levels, in order to clarify their importance in LN activity and response to treatment.
**Keywords:** AC9:Adenylyl cyclase 9, APCs: Antigen-presenting cells, IgM: Immunoglobulin M

## Introduction
Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by a progressive breakdown of tolerance to self-antigens and the presence of concomitant hyperactive immune responses (Giang and La Cava, 2016).

Lupus nephritis (LN) is the most important complication of systemic lupus erythematosus (SLE), which is responsible for SLE-related mortality and morbidity. LN occurs in up to 50% of patients with SLE. In LN, the deposition of immune complexes plays a leading role in the initiation of the disease, (Shakweer et al., 2016).

T- regulatory cells play a key role in maintaining immune tolerance and homeo-stasis through diverse mechanisms which involve interactions with components of both the innate and adaptive immune systems. As in many autoimmune diseases, Tregs have been proposed to play a relevant role in the pathogenesis of lupus nephritis (Giang and La Cava, 2016).

Forkhead box P3 (Foxp3) protein is a transcription factor of the forkhead family,

which is required for the development and function of most thymus-derived, naturally occurring Treg cells. This molecule also plays a crucial role in the regulation of immune responses mediated by peripheral, T- cells, preventing autoimmunity and permitting the maintenance of Treg cells. Foxp3 is the most specific marker of Treg cells currently available (Shakweer et al., 2016).

## Aim of the work

The aim of this study is to assess the level of CD4, CD25 and FOXP3 T-regulatory cells in lupus nephritis patients in regard to disease activity.

## Subjects and Methods

The present study was conducted out on 100 subjects from the attendants of the outpatient clinics of internal medicine department, Minia university hospital, during the period from April 2016 to June 2017, 70 patients were diagnosed as lupus nephritis according to the presence of proteinuria (>500mg/24h) and/or hematuria and/or urinary casts, according to the recent recommendations from European League Against Rheumatism and 30 apparently healthy subjects as control matched for age and sex (Bertsias GK et al.,2012).

**The studied population was classified into 2 groups:**

**Group I:**

This group included 70 patients with LN their age ranged from 22 to 40 years old and 55 females and 15 males.

Renal biopsy had been performed and glomerulonephritis was classified according to World Health Organization(WHO) (Markowitz and D, Agati, 2009), and all patients were classified as having GN WHO III (44 patients) and IV (26 patients).

**Group II:**

This group included 30 apparently healthy persons, their ages ranged from 20 - 40 years old, and 23 females and 7 males.

**Exclusion criteria:**

Other autoimmune diseases as (rheumatoid arthritis and diabetes mellitus).

**Hypertension.**

**End stage renal disease (ESRD).**

**Chronic infections.**

**Malignancies.**

## Results

This study was carried out on 100 subjects classified into two groups:

**Group 1:**

Included 70 patients diagnosed as lupus nephritis 15 males and 55 females, their ages range from (22-40) years.

**Group 2:**

Included 30 apparently healthy subjects, 7 males and 23 females their ages from (20-40) years.

**Table (1): Comparison between studied groups regarding age and sex.**

| Variable | LN group (N =70) | Control group (N =30) | P-value |
|---|---|---|---|
| **Age (years)** | | | |
| Range | 22-40 | 20-40 | 0.9 |
| Mean ± SD | 34.2±5.1 | 34.3±5.3 | NS |
| **Sex No. (%)** | | | |
| Male | 15 (21.4%) | 7 (23.3%) | 0.1 |
| Female | 55 (78.6%) | 23 (76.7%) | NS |

**NS: no significant difference between groups**

There were no statistically significant difference in age and sex in group 1 when compared with group2.

## Discussion

Lupus nephritis (LN) is mainly used to define the immune complex-mediated glomerulonephritis (GN) and it is the most important complication of systemic lupus erythematosus (SLE), which is responsible

for SLE related mortality and morbidity. LN occurs in up to 50% of patients with SLE. In LN, the deposition of immune complexes plays a leading role in the initiation of the disease (Shakweer et al., 2016).

In LN there is IC glomerular deposits generate release of proinflammatory cytokines and cell adhesion molecules (CAMs) causing inflammation. This leads to monocytes and polymorphonuclear cells chemotaxis. Subsequent release of proteases generates endothelial injury and mesangial proliferation. Presence of ICs promotes adaptive immune response and causes dendritic cells (DCs) to release type I interferon (IFN). This induces maturation and activation of infiltrating T cells, and amplification of T helper 2 (Th2), T helper 1 (Th1) and T helper 17 (Th17) lymphocytes. Each of them, amplify B cells and activates macrophages to release more proinflammatory molecules, generating effector cells that cannot be modulated promoting kidney epithelial proliferation and fibrosis (Martinez-Martinez et al., 2014).

Tregs can be divided according to their phenotype and function. The broad categories include tTregs (derived from the thymus), pTregs (induced in the periphery), and iTregs (or in vitro-induced Tregs). (Shevach and Thornton, 2014)

It has been challenging to find a phenotypic marker that can be unique to Tregs, two main Treg markers are important : the IL-2 receptor-α (CD25) and FOXP3 (Pinheiro et al., 2011).

## Conclusion

Tregs % was found significantly lower in active lupus nephritis especially stage (III and IV) and correlates with all parameters of disease activity.

**Limitations:**

Limitations to be considered in the present study including the small number of patients, which does not allow for definite conclusions, and the lack of functional assays for more precise Tregs characterization. Furthermore, it would be helpful to assess the urinary levels of Foxp3 mRNA, in parallel to serum levels, in order to clarify their importance in LN activity and response to treatment.

## References

1. Abbas AK, Benoist C, Bluestone JA, Campbell DJ, Ghosh S, Hori S and Roncarolo MG. (2013): Regulatory T cells: Recommendations to simplify the nomenclature. Nature immunology, 14(4), 307-8.
2. Abujam B, Cheekatla S and Aggarwal A. (2013): Urinary CXCL-10/IP-10 and MCP-1 as markers to assess activity of lupus nephritis. Lupus, 22(6), 614-23.
3. Afeltra A, Gigante A, Margiotta DPE, Taffon C, Cianci R, Barbano B and Fanelli FR. (2015): The involvement of T regulatory lymphocytes in a cohort of lupus nephritis patients: A pilot study. Internal and emergency medicine, 10(6), 677-83.
4. Agmon-Levin N, Damoiseaux J, Kallenberg C, Sack U, Witte T, Herold M and Plaza-Lopez A. (2013): International recommendations for the assessment of autoantibodies to cellular antigens referred to as anti-nuclear antibodies. Annals of the rheumatic diseases,203-63.
5. Al-Hefny A, El-Bakry SA, Mobasher SA, Abaza N, and Nada OH. (2013): Renal biopsy findings in lupus patient with insignificant proteinuria: Relation to disease activity and clinical manifestations. Life Sci J, 10, 1872-79.
6. Almahariq M, Mei FC, Wang H, Cao AT, Yao S, Soong L and Cheng X. (2015): Exchange protein directly activated by camp modulates regulatory T-cell-mediated immune-suppression. Biochemical Journal, 465(2), 295-303.