



### The Clinicopathological Study of Lupus Nephritis

#### Lupus Nefritinin Klinikopatolojik Çalışması

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#### ABSTRACT

**Purpose:** Lupus nephritis is one of the most serious manifestations of Systemic lupus erythematosus and it is a major cause of morbidity and mortality. The aim of this study is to compare males and females in lupus nephritis presentations.

**Material and Methods:** A cross-sectional study performed on forty five patients with biopsy proven Lupus Nephritis including 32 females and 13 males. All patients assessed by questionnaire form and investigated for hematological, biochemical, immunological, serological, urinalysis, and 24hrs urinary protein excretion.

**Results:** The current study shows female predominance 32(71.1%) compared with 13(28.9%) male. Class IV 15(33.3%) nephritis was the most common type followed by class III 9(20.9%).The male patients develop nephritis early in the course of Systemic lupus erythematosus than females, and they were more commonly had hypertension and edema, and the hematological, cardiovascular, pulmonary, and central nervous system were the most common extra renal manifestation in males while mucocutaneous manifestations were the commonest in females, and further more males had more proliferative type of Lupus nephritis than females.

**Conclusion:** Males had more severe type of lupus nephritis than females.

**Anahtar Kelimeler:** Systemic lupus erythematosus, Lupus nephritis, sex.

#### ÖZET

**Amaç:**Lupus nefriti sistemik lupuseritematozusun en ciddi belirtilerinden biridir ve morbidite ve mortalitenin esas sebebidir. Bu çalışmanın amacı lupus nefriti olgularında erkek ve kadınlar arasında karşılaştırma yapmaktır.

**Materyal ve Metod:**Biyopsi ile Lupus nefriti olduğu kanıtlanmış 45 hasta (32 kadın, 13 erkek) üzerinde kesitsel çalışma uygulandı. Tüm hastalara anket yapıldı. Hastalara biyokimyasal, immünolojik, serolojik, hematolojik tetkikler ve idrar tahlili yapıldı. 24 saatlik idrarda protein atılımına bakıldı.

**Bulgular:**Yapılan çalışmaya göre kadınların (32, %71.1) erkeklere (13, %28.9) nazaran daha baskın olduğu görülmüştür. En yaygın tip olarak 4. sınıf nefriti (15, %33.3) sonrasında ise 3. sınıf nefriti (9, %20.9) görülmüştür.Sistemik lupuseritematozusu erkek hastalar, kadınlardan daha erken bir dönemde nefriti geliştirmişlerdir.Erkeklerde daha yaygın hipertansiyon ve ödem vardı.Kadınlarda böbrek dışında en yaygın belirti mukokutanöziken erkeklerdehematolojik, kardiyovasküler, solunum ve merkezi sinir sistemi manifestasyonu görülür.Kadınlara nazaran erkeklerde daha fazla proliferatif tipte lupus nefriti gözlenmiştir.

**Sonuç:**Erkeklerde kadınlara nazaran daha ciddi tipte lupus nefriti görülmüştür.

**Anahtar Kelimeler:**Sistemik lupuseritematozus,Lupus nefriti, cinsiyet.

## INTRODUCTION

Systemic lupus erythematosus (SLE) is an inflammatory chronic disease with multisystem involvement, with different clinical and immunological manifestations, characterized by the presence of antinuclear antibodies<sup>1,2</sup>. The pathogenesis and etiology remain unclear which involves genetic, immune, environmental and hormonal factors; it has an immune-mediated pathogenesis through immune complex formation and deposition as well as immune and inflammatory cell participation in widespread tissue damage<sup>3,4</sup>.

As a distinct minority, males with SLE have been studied for years, although many studies showed that male lupus had its own distinguishing features in respect to etiology, clinical manifestations, therapy and outcomes, the results were controversial because of several factors such as genetic and environmental aspects, ethnic origins, and duration of follow-up and selected ascertainment of clinical features<sup>5</sup>.

The male patients develop similar typical clinical manifestations of lupus as in females, although male SLE may have some distinguishing frequencies of organ involvement notably hematological<sup>6,7</sup>, neurological involvement<sup>7,8</sup> or nephritis<sup>6,9</sup>.

The renal damage is common in SLE and most of the patients develop nephritis early in the course of their disease, the vast majority of patients who develop nephritis are younger than 55 years and children rather than elderly patients, the male sex more affected<sup>10,11</sup> their nephritis might be more severe<sup>7,12-20</sup>, and carries unfavorable prognostic factors.

## MATERIALS and METHODS

A cross sectional, descriptive study performed on 45 patients with systemic lupus erythematosus (SLE) who attended the Rheumatology Department in Slemani City from April 2012 to

April 2013, all patients had been diagnosed according to the American College of Rheumatology (ACR) classification criteria of 1997 revision of SLE, and had a kidney biopsy proven lupus nephritis.

The patients selected on the bases of clinical and laboratory evidence of renal disease which was defined as varying combinations of the following:

1. Active sediments in general urine examination (hematuria, granular casts and dipstick proteins).
2. Urinary protein excretion >0.5 g/24 hours.
3. Edema requiring diuretic therapy.
4. Diastolic blood pressure >90 mm Hg.
5. Serum creatinine more than (1.5 mg/dl) without compelling alternative causes (such as sepsis, hypovolemia, or medication).

The renal biopsies were done for all patients and classified according to international society of nephrology / renal pathology society (ISN/RPS 2003).

The patient with clinical and laboratory evidence of renal involvement who hasn't agreed to do renal biopsy or their results of biopsies were not consistent with any classes of lupus nephritis excluded from the study.

## STATISTICAL ANALYSIS

Different statistical analyses were carried out using statistical package for social science (SPSS) version 16.0 windows. Both Chi square and T test used to determine the level of significance (P-value).

## RESULTS

Out of the 45 lupus nephritis patients enrolled in the study, 32 (71.1%) patients were female and 13 (28.9%) were male, with a male to female ratio of 1:2.4.

The mean age of female patients when SLE diagnosed was 27.6±11.5 and for nephritis diagnosis was 30.1 ±11.6, ranging from (9.5-67 yr)

and (10–67) respectively, and for males for both SLE and nephritis diagnosis were  $26\pm 9.8$  and  $27.5\pm 10.2$ , ranging from (11–50 yr) and (12–52 yr) respectively.

There were no significance difference in the mean age at both SLE and nephritis diagnosis

between males and females with  $P = 0.5$  and  $P = 0.7$  respectively. The time interval between the two onsets was shorter in males  $1.6\pm 1.2$  vs  $2.4\pm 2.8$  with  $P = 0.003$ .

**Table 1. Demographic data:**

Variables	Female (n=32)	Male (n=13)	P-value
Age at SLE diagnosis	$27.6\pm 11.5$ (9.5-67)	$26\pm 9.8$ (11-50)	0.5
Age at nephritis diagnosis	$30.1\pm 11.6$ (10-67)	$27.5\pm 10.2$ (12-52)	0.7
Time interval between two onset	$2.4\pm 2.8$	$1.6\pm 1.2$	0.003

The commonest renal nephritis was class IV 15(33.3%), 5(38.5%) cases of were males and 10(31.3%) were females, followed by class III 9(20.0%), 4(30.8%) of them were males and 5(15.6%) females, class II 8(17.8 % ) all were females, class V+III 4(8.9%) and 2(15.4%) of them males and 2(6.3%) females. Both class V and class I had the same frequency which was

3(6.7%), in class V there were 2(6.3%) females and 1(7.7%) male, but in class I all of the three patients (9.4%) were females, class V+IV-S 2(4.4%) in which male and female equally distributed which were 1(7.7%) and 1(3.1%) for male and females respectively, class V+II found in 1(2.2%) of patients which was female (3.1%) as shown in table(2).

**Table2. Prevalence of classes of LN.**

Class	(N %)	Males (n %)	Females (n %)
Class I	3(6.7)	0(0)	3(9.4)
Class II	8(17.8)	0(0)	8(25)
Class III	9(20)	4(30.8)	5(15.6)
Class IV	15(33.3)	5(38.5)	10(31.3)
Class IV-S	10(22.2)	3(23.1)	7(21.9)
Class IV-G	5(11.11)	2(15.4)	3(9.4)
Class V	3(6.7)	1(7.7)	2(6.3)
Class VI	0(0)	0(0)	0(0)
Class ( V + II )	1(2.2)	0(0)	1(3.1)
Class ( V + III )	4(8.9)	2(15.4)	2(6.3)
Class ( V+ IV-S )	2(4.4)	1(7.7)	1(3.1)
Total	45(100)	13(100)	32(100)

Activity and chronicity of lupus nephritis were defined according to histopathological results, the

highest figure accounted was class IV-S nephritis of active-chronic nephritis for females and males(Table 3).

**Table3.Activity and chronicity in proliferative LN among males and females.**

Classes	Activity and chronicity	Total (n %)	Males (n %)	Females (n%)
Class III and Class V+III (n=13)	III (A)	5(38)	2(15)	3(23)
	III (A/C)	5(38)	2(15)	3(23)
	III (C)	3(23)	2(15)	1(8)
Class IV-S and Class V+IV-S (n=12)	IV-S (A)	-	-	-
	IV-S (A/C)	11(92)	3(25)	8(67)
	IV-S (C)	1(8.3)	1(8.3)	-
Class IV-G (n=5)	IV-G (A)	1(20)	-	1(20)
	IV-G (A/C)	4(80)	2(40)	2(40)
	IV-G (C)	-	-	-
Total		30(100)	12(40)	18(60)

The most common clinical presentation to indicate renal nephritis used to be a newly onset hypertension which was found in 32(71.1%) cases, 10(76.9%) males and the 22 (68.8%) females, followed by edema in 10(22.2%) of cases, 6(46.2%) males and 4(12.5%) females, and oliguria in 6(13.33%) of cases, 4(12.5%) of them were females and the other 2(15.4%) were males as shown in table (4).

**Table (4): Common renal clinical presentation in both genders.**

Symptom and sign (n %)	Total (n=45)	Females (n=32)	Males (n=13)	P-value
Hypertension	32(71.1%)	22(68.8%)	10(76.92%)	0.1
Edema	10(22.2%)	4(12.5%)	6(46.2%)	0.02
Oliguria	6(13.33%)	4(12.5%)	2(15.4%)	0.5

For categorical data P- value calculated by Chi-Square test or Fischer exact test.

The main extra-renal clinical manifestations were musculoskeletal accounted in 37(82.2%), mucocutaneous in 35(77.8%), hematological in 30(66.67%), pulmonary in 15(33.3%), CNS in 8(17.78%), cardiovascular in 7(15.56%), GIT in 2(4.44%).

The following manifestations were more common in males than females; hematological

10(76.9%) vs 20(62.5%), cardiovascular 6(46.2%) vs 1(3.1%), pulmonary 5(38.5%) vs 10(31.3%), CNS 3(23.1%) vs 5(15.6%) while some other features were more accounted in females, the figures of females to male for, musculoskeletal manifestations were 28(87.5%) vs 9(69.2%), mucocutaneous, 27(84.4%) vs 8(61.5%) and GIT 2(6.3%) vs 0(0%) as shown in table(5).

**Table(5) Prevalence of extra-renal clinical manifestation among patients with LN.**

Extra-renal manifestation(n %)	Total (n=45)	Females(n=32)	Males(n=13)
Musculoskeletal	37(82.2)	28(87.5)	9(69.2)
Mucocutaneous	35(77.8)	27(84.4)	8(61.5)
Hematological	30(66.7)	20(62.5)	10(76.9)
pulmonary system	15(33.3)	10(31.3)	5(38.5)
CNS	8(17.78)	5(15.6)	3(23.1)
CVS	7(15.56)	1(3.1)	6(46.2)
GIT	2(4.44)	2(6.3)	0(0)

**Table (6) Comparison between male and female in presentation of LN:**

Variables	Total	Female(n=32)	Male (n=13)	P-value
24 hrs urine protein(gm)	2.7±0.96	2.1±0.9	2.3±1.1	0.3
Nephrotic range proteinuria(g/day)	13(28.9)	8(25%)	5(38.5%)	0.2
Bl.urea (mg/dl)	47.7±32.9	41.5±22.6	63±48	0.000
S.Creatinine (mg/dl)	1.3±1	1.1±0.5	1.8±1.6	0.4
S.Albumine (g/dl)	3.1±0.8	3.2±0.9	3±0.6	0.1
S.cholesterol (mg/dl)	257±108.7	257±122.4	260±67	0.03
S.triglycerid (mg/dl)	224.8±91.5	221.3±100	233.4±69	0.2
ESR (mm/hr)	55.8±25.4	53.3±25.5	62±25.1	1
+ve ANA	30(66.7)	23(71.9%)	7(53.8%)	0.1
+ve Anti-dsDNA	36( 80)	23(71.9%)	13(100%)	0.01
+ve Anti-Sm	13(28.9)	10(31.3%)	3(23.1%)	0.3
low C3	31(68.9)	19(59.4%)	12(92.3%)	0.01
low C4	33(73.3)	21(65.6%)	12(92.3%)	0.03

NB: for continuous data values are represented as mean and standard deviations. For continuous data *P* - value calculated by T- test. For categorical data *P* - value calculated by Chi- Square or Fischer exact test.

## DISCUSSION

SLE is a complex autoimmune disease that can involve multiple organs and kidneys are the most common visceral organs affected<sup>21,22</sup>. Nephropathy occurs in about half or more of the patients with SLE and it is a presenting feature in 30% - 50% of patients<sup>23,24</sup>. Progression of the nephropathy to chronic renal insufficiency or end stage renal disease occurs in 45% and 12% respectively<sup>23</sup>, and it is well known that renal

disease is a major cause of death and is responsible for about half of the SLE related mortality<sup>25,26</sup>..

In the current study revealed the female preponderance for SLE by a ratio of 2.4:1 which was close to the result found by Zahra Mirfeiziet al<sup>27</sup> lower to the figure of Khader N. Mustafa et al<sup>28</sup>. Luo Ping Lu Shan et al<sup>29</sup> this difference might be explained on the bases of ethnicity, race and/or could be age related, although SLE is female

predominance but LN(lupus nephritis) female predominance is less prominent<sup>30</sup>.

There was no significant difference in the mean age between males and females for the onset diagnosis for the disease (SLE) and nephritis, but the mean time for the development of LN in course of SLE was shorter for males than females, the result differs from the study of Luo Ping Lu Shan et al<sup>29</sup> which claimed males were younger than females .

Regarding the frequency of grading classification of LN class IV found to be predominant 15(33.3%) followed by class III 9(20.0%), a similar results reported by Huong DLT et al in (France)<sup>31</sup>, Derksen RH et al in (Netherlands)<sup>32</sup>, Seedat YK et al in (South Africa)<sup>33</sup>, Shayakul C et al in (Thailand)<sup>34</sup> and Chu SJ et al in (Taiwan)<sup>35</sup>, non of male patients had classes I or II LN this was similar to the results of Wang Caili et al (36) but the classes III, IV, V and combination were more common in males than females which is similar to the results of LaenaOngaJyooth et al<sup>37</sup>, Y-F Wang et al (38) and Wang Caili et al<sup>36</sup>.

Among the features indicate the onset of nephritis are edema, oliguria and new onset hypertension(39-41), 22.2% of cases had edema which is close to the study of Niang A et al<sup>39</sup> and oliguria in 13.33% of cases which was close to the result of VarunDhir et al<sup>40</sup> and lower than that of Preetha A. et al<sup>41</sup> this might be explained by the fact that clinical symptoms and signs suggestive of renal disease have been found to have very low sensitivity to predict renal disease in SLE as patients are largely asymptomatic<sup>41</sup> and found that edema to be more common in males than females similar result found by LaenaOngaJyooth, et al<sup>37</sup>,and the new onset of hypertension was found in 71.1% of cases which was close to that of Carlos F et al<sup>42</sup> and differ from the result found by Niang A et al (39) and that of VarunDhir et al<sup>40</sup> and lower as compared to studies of Preetha A et al<sup>41</sup>,and hypertension was marginally higher in

males than females, similar result found by Soni S. S. et al<sup>43</sup>.

The musculoskeletal manifestations was the most common extra renal manifestation in this study followed by mucocutaneous and hematological , the conclusion is similar to the results found by Ana karla et al<sup>44</sup>, but differ from the results found by Niang A et al<sup>39</sup> in which the most common extra renal manifestations were hematological followed by mucocutaneous and musculoskeletal, these variations may be due to different sample sizes, different patient's ages, variable disease durations, unreported recent or mild cases, and seasonal, regional or racial variations<sup>33</sup>. The male patients had more hematological, cardiovascular, pulmonary and CNS manifestation than females, similar results concluded by some authors in which they detected higher frequency of the following features in male patients: hematological involvement<sup>45-49</sup>, serositis<sup>24-26</sup>, neurological involvement<sup>24</sup>, but the females had higher frequency of mucocutaneous manifestation which is similar the result of Khader N. Mustafa et al<sup>28</sup>.

The mean 24 hrs urinary protein excretion was 2.7±0.96 g, which is close to the results of Hitoshi Y. et al<sup>50</sup>, the nephrotic range proteinuria found in 28.9% of our cases which differs from the result reported by Jim LC Yong et al<sup>51</sup>, this could be explained by the fact that variable result may occur over a short period of time, probably due to changes in physical activity or collection errors<sup>11</sup>, although the difference in the 24 hrs urinary protein excretion between males and females doesn't reach a significant level still the nephrotic range proteinuria was more common in males than females, this statement is similar to the figures stated by Soni S. S et al<sup>43</sup>.

The mean serum creatinine was 1.3 mg/dl, the figure is close to the results of Ana Karla et al<sup>44</sup>, while the mean blood urea was 47.7 mg/dl, which differs from the result of Simin et al<sup>52</sup>, but The mean blood urea was higher in males than females, a similar result is reported by Soni S.

S. et al<sup>43</sup>. The mean serum creatinine was also marginally higher in males than females, which is similar result found by Soni S. S. et al<sup>43</sup>

The mean serum albumin found to be low in in both males and females in current study (3.1 g/dl) a similar figures also reported by Wang Guobao et al<sup>53</sup>, LaenaOngaJyooth et al<sup>37</sup> and De Carvalho JF et al<sup>54</sup>.

The mean serum cholesterol was  $257 \pm 108.7$ , this is close to the result found by LaenaOngaJyooth et al<sup>37</sup> and the mean S. triglyceride was  $224.8 \pm 91.5$ , which differs from the result of LaenaOngaJyooth et al<sup>37</sup>, but the male patients had slightly higher mean of S. cholesterol than females which differs from the result of LaenaOngaJyooth et al<sup>37</sup> who found it to be higher in females, also the higher mean of S. triglyceride here is reported in male patients than females, this was in agreement with the result of LaenaOngaJyooth et al<sup>37</sup>.

The immunological profile shows that ANA (anti-nuclear antibodies) to be positive in 66.7% of cases which is lower than the figures reported by Zahra Mirfeizi et al<sup>27</sup> and Habib Emre et al<sup>(55)</sup>, this could be explained on the base for the of ANA technical inaccuracy<sup>56-58</sup> because of using rat liver substrate instead of human epithelial (Hep-2) substrate has decreased the sensitivity of ANA<sup>56</sup> and the labs. in Slemani still using this old technique.

The positive Anti-dsDNA found in 80% of patients, a similar result found by Uthman IW et al in (Lebanon)<sup>(59)</sup> and it also closely related to the result of G Moroni et al<sup>60</sup> but differ from the result of Zahra Mirfeizi et al<sup>27</sup> and Al-Attia HM et al in (UAE)<sup>61</sup>. The male patients had a higher rate of Anti-dsDNA positivity than females, this is similar to the result reported by D. A. Isenberg et al<sup>(62)</sup> and also consistent with conclusions of studies<sup>46,63,64</sup>.

The percentage of positive Anti-Sm was 28.9%, it was higher than that found by DrakoulogkonaOurania et al<sup>65</sup> and P Alba et al<sup>66</sup>. The females had a higher rate of Anti-Sm positivity than males, similar result is found by D. A. Isenberg

et al<sup>62</sup>, who found that a part from anti-dsDNA other immunological profiles were more frequently positive in females, also it was in agreement with the report of Garcia et al<sup>45</sup>.

The low complement levels were 68.9% for C3 and 73.3% for C4, these were close to the results of Varun Dhiret al<sup>40</sup>, and differ from that found by G Moroni et al<sup>60</sup>. The frequency of low complements levels were more in males than females, this was comparable to the result of both M.E. Soto et al<sup>46</sup> and ParvizKhajehdehi et al<sup>67</sup>, but differed from the results found by De Carvalho JF et al<sup>54</sup>, who claimed that the frequency of low complements levels both C3 and C4 were comparable between males and females.

## CONCLUSION

We concluded that males develop LN earlier in the course of SLE, and were more frequently had proliferative types of LN. In the renal clinical presentation the new onset hypertension and edema more frequent in males, and the hematological, cardiovascular, pulmonary, and CNS were the most common extra renal manifestation in males while mucocutaneous manifestations were commonest in females.

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