Urinary and Renal Research 2024, 5(1), 2762.
https://doi.org/10.54517/urr.v5i1.2762

Article

Albuminuria in patients with Systemic Lupus Erythematous

María Elena Corrales Vázquez[1,*], Silvia María Pozo Abreu[1], Elena Caridad Megret Vidal[1], José Pedro Martínez Larrarte[2]

[1] University of Medical Sciences of Havana, 10 de Octubre Clinical Surgical Teaching Hospital, Havana 10600, Cuba
[2] Miguel Enriquez Faculty of Medical Sciences, University of Medical Sciences of Havana, Havana 10500, Cuba
*** Corresponding author:** María Elena Corrales Vázquez, mariaecvazquez@infomed.sld.cu

CITATION

Corrales Vázquez ME, Pozo Abreu SM, Megret Vidal EC, Martínez Larrarte JP. Albuminuria in patients with Systemic Lupus Erythematous. Urinary and Renal Research. 2024; 5(1): 2762. https://doi.org/10.54517/urr.v5i1.2762

ARTICLE INFO

Received: 4 June 2024
Accepted: 20 June 2024
Available online: 14 August 2024

Abstract: Renal involvement is one of the main causes of morbidity and mortality in patients with Systemic Lupus Erythematous. Lupus Nephropathy should be detected early. Albuminuria may be the only finding in the early stage of kidney disease. An observational, descriptive and retrospective study was carried out to determine the presence of Albuminuria (> 30 mg/24 h) in 60 patients with SLE who were admitted to the Rheumatology Service of the "10 de Octubre" Surgical Clinical Hospital, between October 2013 and September 2014. Albuminuria was observed to increase with increasingly pronounced drops in Glomerular Filtration (predicted according to the equation used in the MDRD Study). A significant statistical association was also obtained between albuminuria and disease evolution time: the longer the disease evolution time, the greater the albuminuria observed. Albuminuria is frequent in patients with SLE, its values being directly proportional to the time of evolution of the disease. This did not occur with the Glomerular Filtration, which remained relatively constant for any time of disease evolution.

Keywords: Systemic Lupus Erythematous; Lupus Nephropathy; glomerular filtration; microalbuminuria

1. Introduction

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease, of unknown etiology, characterized by various immunological alterations, among which the loss of self-tolerance, polyclonal activation of B lymphocytes and the production of multiple non-organ-specific autoantibodies stand out. Clinical manifestations include a wide and diverse range in practically all organs and systems of the economy [1] which are due to the presence of immune complexes and autoimmune cellular destruction [2].

This disease has a universal distribution, its prevalence is higher in women than in men, both in white and black populations. The ratio between women and men is 3:1 in the pre-puberty and postmenopausal stage, and 9–12:1 during the reproductive age. These differences in the age-sex ratio have been related to hormonal changes that occur during puberty, reproductive life, and menopause [3].

In the community study carried out in Cuba on the prevalence of rheumatic diseases and associated disability (COPCORD), it was found that, in the case of SLE, this was 60 cases per 100,000 inhabitants [4,5], with a predominance of white and female ethnic group.

There are various problems related to patients with lupus and include the involvement of various organs and systems, including the kidney [6].

Renal involvement continues to be an important cause of morbidity and

mortality, 50% of patients have an abnormal urinalysis with or without elevated creatinine levels at the time of diagnosis, renal abnormalities occur rapidly after diagnosis of 6–36 months and nephropathy develops in more than 75% of patients [7,8].

Chronic renal failure occurs in approximately 30% of cases with nephropathy. The presence of albuminuria (microalbuminuria) could be the only finding in the initial stage of kidney disease since the decrease in Glomerular Filtration (GFR) estimated or determined from Serum Creatinine (SCr) is a later indicator [9].

Albuminuria has great clinical significance as it constitutes an early sign of loss of kidney function, a highly sensitive indicator in an inflammatory process and a predictor of patients at risk of ending up with end-stage renal failure [9].

Taking into account the importance of early diagnosis of Lupus Nephropathy (LN) to impose timely treatment and thereby improve the patient's quality of life, the motivation to carry out this research arose, with the purpose of evaluating the presence of albuminuria as an indicator of Chronic Kidney Disease (CKD) in lupus patients, especially in the early stages.

2. Methodology

A descriptive and retrospective observational study was carried out to evaluate the presence of albuminuria as an indicator of CKD in patients with SLE. The universe consisted of patients with SLE who were admitted to the Rheumatology Service of the 10 de Octubre Clinical-Surgical Hospital, known as the National Reference Center for Rheumatic Diseases (CNRER), in the period between October 2013 and September 2014.

The sample consisted of 60 lupus patients over 19 years of age. Those with associated arterial hypertension and diabetes mellitus were excluded, as well as patients with incomplete medical records.

For each patient included in the study, the sex (male/female), skin color (white/black/mixed race), age (stratified into 5 age groups) and the duration of the disease (months) were related elapsed since the diagnosis of SLE). The duration of the disease was divided as follows: up to 12 months, between 13 and 60 months, and more than 60 months.

The GFR value was divided as follows: decreased value: less than or equal to 60 mL/min and preserved value: greater than 60 mL/min. The current value of serum creatinine (μmol/L) was divided into expected values: less than or equal to 113.4 μmol/L, and increased values: greater than 113.4 μmol/L. The results of 24h Albuminuria were stratified as follows: Less than 30 mg/24h: normoalbuminuria; between 30–300 mg/24h: microalbuminuria and more than 300 mg/24h: macroalbuminuria.

2.1. Procedures

All data were obtained based on the review of medical records archived in the statistics department of the CNRER. All collected data were entered into the data collection model.

The expected behavior of the albumin/creatinine ratio (ACI) and 24 h

Albuminuria was obtained from other similar studies in populations different from the one studied in this work.

The results obtained from 24 h Albuminuria were stratified according to the time of evolution of the disease and the presence of a glomerular filtration rate ≤ 60 mL/min and > 60 mL/min.

Data processing was carried out using an Excel electronic spreadsheet for Office Windows, and the statistical program SPSS version 15 (SPSS Inc. New York).

The data were reduced according to the type of the variable to statistics of location (mean), dispersion (standard deviation) and aggregation (frequencies and percentages). To know the intensity of the association between the study variables, the Chi square test of independence was applied. We worked with a confidence level of 95%.

The results were presented in the form of tables and graphs to facilitate their understanding and analysis. The data represented statistically allowed us to discuss them and establish comparison with those provided by other authors.

2.2. Ethical considerations

This study was approved for its conduct by the head of the CNRER, as well as by the Scientific Council and the Ethics Committee of the institution.

3. Results

During the period covered by the study, 60 patients with SLE who were admitted to the CNRER of the Hospital Clínico Quirúrgico de 10 de Octubre who met the established inclusion and exclusion criteria were selected.

Table 1 shows their distribution according to age, sex, skin color and duration of SLE. According to the results obtained, and coinciding with what was stated by other authors [4,5,13–15], we observed that SLE is more frequent in women (57 patients for 95%), with white skin (45 patients for 75%), in the middle stages of life (patients in the fourth decade of life predominated with 21 cases for 35%). The average age was 39.7 ± 12.03 years (mean ± SD), the age around which most of the studies focus because it has been recognized, for many years, that SLE is a disease that it begins more frequently at this stage of life.

Taking into account the time of evolution of the disease, it was found that the majority of the patients studied had been diagnosed with SLE for more than 60 months (29 cases for 48%). They were followed (in descending order) by those who were between 13 and 60 months (18 cases for 30%), and those who were less than 12 months (13 cases for 22%).

Table 1. Distribution of patients according to age, sex, skin color and duration of SLE.

Variable	Classification scale	No.	%
Age (years)	Between 18 y 29	15	25
	Between 30 y 39	10	16.7
	Between 40 y 49	21	35
	Between 50 y 59	12	20
	De 60 and over	2	3.3
Sex	Male	3	5
	Female	57	95
Skin color	White	45	75
	Black	7	12
	Mixed race	8	13
Evolution time of SLE (months)	Up to 12 (less than 1 year)	13	22
	Entre 13 y 60 (between 1 and 5 years)	18	30
	More than 60 (more than 5 years)	29	48

Source: Clinical records.

The SCr results were stratified according to the established cut-off point, into normal and elevated. **Table 2** shows a predominance of normal values (52 patients for 87%). The average SCr value was 89.47 ± 25.62 µmol/L (mean ± SD).

Table 2. Distribution of patients according to serum creatinine results.

Serum Creatinine (µmol/L)	No.	%
Normal	52	87
High	8	13
Total	60	100

Source: Clinical records.

Table 3 reflects the behavior of the FG results, which were divided into preserved and altered, according to the established cut-off point. A predominance of preserved GFR values is observed, with 45 patients for 75%. The average value was 74.34 ± 24.15 mL/minute^{-1} (mean ± SD).

Table 3. Distribution of patients according to the results of glomerular filtration.

Glomerular Filtration	No.	%
Preserved	45	75
Altered	15	25
Total	60	100

Source: Clinical records.

In **Table 4**, the results of 24 h Albuminuria are categorized according to the established cut-off points. A predominance of values obtained in the microalbuminuria range is observed (24 patients for 40%), followed (in decreasing

order) by those found in the normoalbuminuria range (20 patients for 33%), and finally, those classified in the range of macroalbuminuria (16 patients for 27%). The average value was 253.94 ± 341.18 mg/24 h (mean ± SD).

Table 4. Distribution of patients according to the results of 24h albuminuria.

24-hours albuminuria	No.	%
Normoalbuminuria	20	33
Microalbuminuria	24	40
Macroalbuminuria	16	27
Total	60	100

Source: Clinical records.

Figure 1 shows the behavior of the 24 h Albuminuria results with respect to the GFR values obtained. It is observed that the number of patients with preserved GFR decreases as the Albuminuria values increase. Only 20 patients (33%) presented normoalbuminuria with preserved GFR; 24 (40%) presented microalbuminuria, of which 17 (28%) had preserved GFR, and 7 (12%) had altered GFR; 16 patients (27%) had macroalbuminuria, 8 (13.5%) with preserved GFR and 8 (13.5%) with altered GFR.

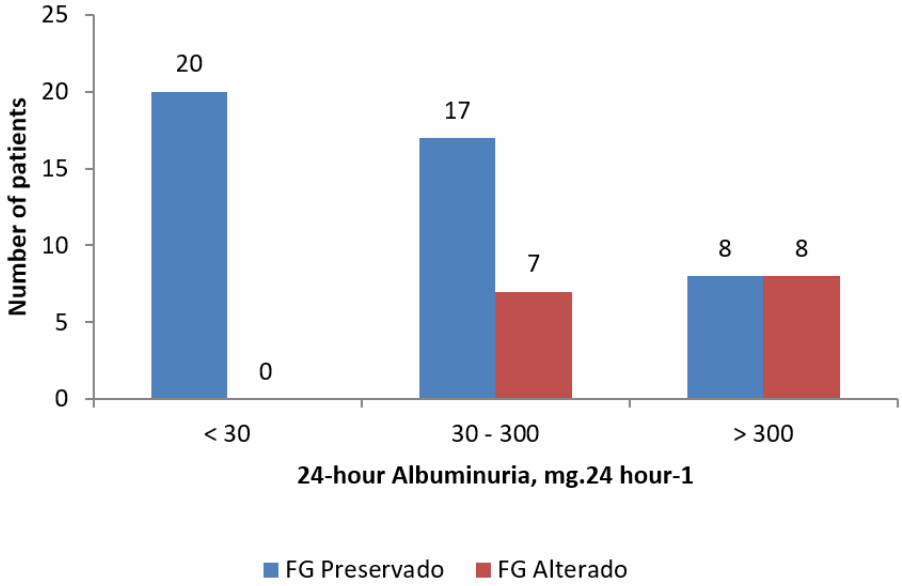

Figure 1. Association between the results of 24 h albuminuria and glomerular filtration.

Source: Clinical records; chi square test $p < 0.05$; statistical significance with 95% confidence.

Figure 2 presents a relevant statistical association between 24h Albuminuria, GFR and Time of disease evolution. The significant increase in Albuminuria values is notable as the duration of SLE increases. On the other hand, this is not the case with GFR, which remains relatively constant over time, that is, its modification is insignificant compared to the variation in Albuminuria.

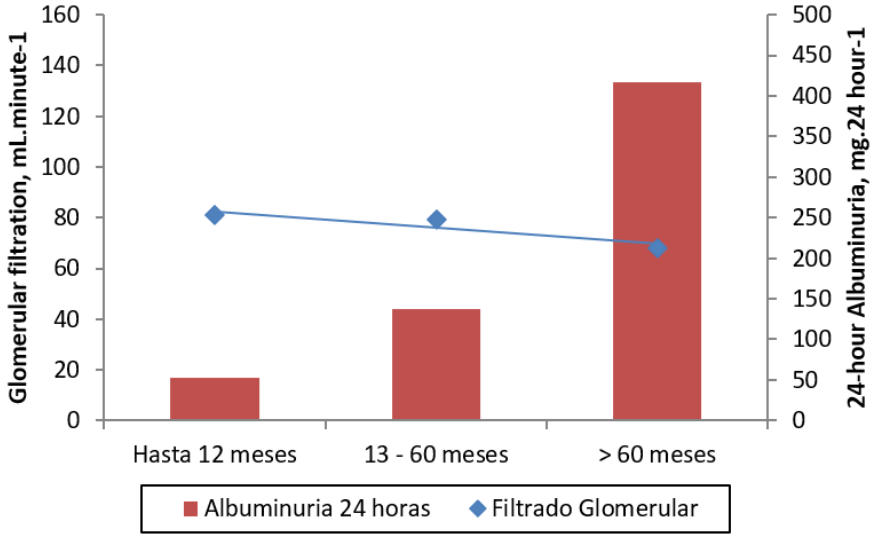

Figure 2. Behavior of the results of 24h albuminuria and glomerular filtration obtained according to the time of evolution of the disease.
Source: Clinical records.

4. Discussion

SLE is more common in women by 78%–96%, mainly in the third and fourth decades. Of every 10 to 12 cases of lupus, 9 are women, declining in frequency towards the ends of life. In other words, the female/male ratio is much lower in the pre-pubertal stage and after menopause. Concrete evidence shows the role played by female sex hormones in these patients, such that this difference could be explained by the relative immunostimulatory effect of estrogens and the immunosuppressive action of androgens. Women, during their reproductive years, are ten times more susceptible to developing lupus than men [1–3].

There are studies that show that the incidence of SLE is linked, not only to certain age groups, but also to some ethnic groups [4,5].

As the numbers indicate, in our study there was a predominance of lupus patients from the white ethnic group compared to non-whites. These percentages vary between the populations studied depending on the predominant ethnic composition in the different regions. So the evaluation of this aspect in the LES has been carried out taking into account the classifications proposed by the different researchers based on the anthropomorphic characteristics of the region in question. The epidemiology of lupus, and within it, skin color, has been assessed mainly in North America and some European countries, but there is very little information in Latin America [4,5].

The epidemiology of lupus, like other diseases, is far from being exact and static knowledge. On the contrary, it is subject to multiple influences that will make it vary between different populations and even within the same population at different times. Understanding and accepting this fact will allow us to better understand the disease. This, in turn, will give various results whose final product will be a new modification of the epidemiology of the disease [1].

Existing estimators reflect only an approximation of reality. The reality of the site and the population studied may be similar to that of a small number of patients,

but different from the vast majority. In each place, in each population, we will only know our reality when the figures are derived from our site and our population and their validity will be as long as we are able to update it [1].

It is striking that 87% of the patients had normal SCr levels, despite the predominance of those with more than 60 months of evolution of a disease that invariably affects the kidney. This confirms what other authors have stated that SCr, despite being the most widely used kidney function test for diagnostic purposes, may suffer from several drawbacks for its use as a GFR marker [17,18].

First, endogenous secretion of creatinine by proximal tubular cells plays an important role in the elimination of this analyte when GFR decreases. Therefore, the SCr concentration may be within the normal range, even with a GFR around 60 mL/min^{-1}, 1.73 m^{-2}, thus indicating the existence of what has been called the "blind" range of creatinine in chronic kidney disease. Second, endogenous creatinine production is primarily determined by skeletal muscle mass and the ingestion of red meat in the diet, and this probably explains the variability of serum creatinine levels observed in different population groups according to age, sex, skin color, ethnicity, and nationality. Daily creatinine production varies considerably intra- and inter-individual. The high inter-individual variability of SCr can make it difficult to reliably measure renal function from a simple SCr determination, without other additional patient data [9,17].

SCr has a low diagnostic sensitivity in cases of kidney failure or moderate kidney dysfunction, especially in children, malnourished patients, the elderly, and patients suffering from serious chronic diseases, with the consequent underdiagnosis of kidney damage [17].

In addition to these problems related to creatinine metabolism, creatinine measurement still suffers from technological limitations. The reaction continues to be the most widely used analytical method of all those developed, but its drawback is that it is affected by interferences caused by chromogens not related to creatinine, such as acetic acid, acetone, pyruvate, glucose, ascorbic acid, and bilirubin (among others) [17]. The appearance of enzymatic methods for measuring creatinine makes it possible to appreciably reduce the negative influence of interferences, but does not completely eliminate them, in addition to the cost of acquisition and exploitation [18].

When describing the behavior of the GFR, we observed a greater positivity in the results (25%) compared to those of SCr (13%), despite the fact that this marker was the one used to determine the GFR. This shows that the relationship between SCr concentration and GFR is not linear, which translates into low diagnostic sensitivity in the early detection of CKD and, in fact, decreases in GFR of at least 50% are required for SCr rises above the reference range [19,20].

It should be kept in mind that a normal result does not exclude the possibility of kidney disease; This may exist without having yet affected the filtration function enough for said impairment to be detected. On the other hand, a decreased result is a sure indicator of CKD, regardless of its etiology. On the other hand, a normal or very slightly elevated level of creatinine in the blood does not exclude the possibility of finding decreased filtration, since, as previously stated, this analyte begins to rise in the blood when renal function failure has reached some degree of progression

[19,20].

Regarding the behavior of 24 h Albuminuria, the positivity was 67% (40 patients), higher than that obtained in the results of SCr and GFR, which gives greater sensitivity in the diagnosis of kidney damage. incipient. It also reaffirms what has been stated in the literature that renal involvement in SLE occurs in 60% to 75% of patients [7,8].

LN usually develops insidiously during the first years of the disease, and in its beginning it is usually asymptomatic, so if it is not detected early, the risk of progression to kidney failure is high.

Until a few years ago, nephropathy could only be detected when it was already very advanced and was clinically manifested by the existence of proteinuria (> 500 mg/day), which was detected using a test strip (Albustix®) [21].

Currently, however, we can detect the early phase of nephropathy, which is manifested by the excretion of urinary albumin, since we have techniques that allow it to be located even if it is in small quantities [21].

Microalbuminuria is the earliest clinical finding of CKD and is a predictive variable of the appearance of macroalbuminuria or proteinuria (advanced phase of nephropathy) and the development of renal failure. Once macroalbuminuria appears, the drop in GFR accelerates at a rate of about 11 mL/min/year, although it can be as pronounced as 20 mL/min/year. In a patient with normal kidney function, this means the need for renal replacement therapy in less than 7–8 years [22].

The advantages obtained by screening for microalbuminuria in these patients are beyond doubt, because it allows the early phase of nephropathy to be detected, and there is an adequate treatment for it. It has been shown that the administration of angiotensin-converting enzyme (ACE) inhibitors, in this phase, reduces mortality and the entry of patients into renal replacement treatment (dialysis or transplant) [23,24].

ACE inhibitors reduce proteinuria and can delay the progression to kidney failure because they produce dilation of the efferent artery, reduce glomerular hyperfiltration and hypertrophy, reduce or suppress microalbuminuria, and delay the appearance of glomerulosclerosis [23].

LN presents in most patients as CKD, typically with remissions and exacerbations. Laboratory tests in SLE kidney disease have a fundamental role in: a) initial diagnosis of SLE; b) the initial evaluation of kidney disease, and c) the monitoring of eventual remissions, relapses and therapeutic response. However, normal urinalysis and renal function results may be found in the presence of significant subclinical kidney disease [1].

CKD is a very unknown disease in its initial phases and about which we only know data mainly from its very advanced stages in which the restoration of kidney function through dialysis and transplant is necessary [25].

CKD is one of the main causes of death in the industrialized world. And not only for those patients who reach the need to be treated with dialysis or transplant whose evolution in many cases is even worse than advanced cancer, but also because those who do not reach dialysis and who present proteinuria or an asymptomatic decrease in GFR They have a high prevalence of complications [25].

CKD is classified into 5 stages. The first two, with GFR greater than 60

mL/min^{-1}, are defined as kidney damage for at least 3 months with structural or functional abnormalities of the kidney with or without a decrease in GFR and manifested by pathological alterations or markers of kidney damage (alterations in the composition of blood or urine or alterations in renal images). These two initial stages are very important because they can present with normal creatinine despite the danger of kidney failure. Kidney damage in these phases can be certified by the presence of albuminuria defined as ACI greater than 30 mg/g in two or three urine samples. In the most advanced stages of loss of renal function with reduced GFR: stage 3 (GFR 59–30 mL/minute^{-1}), 4 (GFR 29–15 mL/minute^{-1}) and 5 (GFR < 15 mL/minute^{-1}) −1 or dialysis), GFR can be estimated by a simple formula that includes a calibrated SCr, sex and skin color (MDRD-4), and weight (Cockroft-Gault). In many cases there is what is called "occult kidney disease"; That is, normal plasma creatinine values but with a reduced glomerular filtration rate below 60 mL/min, something common in women over 65 years of age [26,27].

5. Conclusions

In the lupus patients studied, preserved SCr and GFR values predominated. The pathological results of 24 h Albuminuria prevailed, especially those located in the microalbuminuria range. Albuminuria values increased with increasingly pronounced drops in GFR. A significant statistical association was obtained between Albuminuria and Time of evolution of the disease: the longer the time of evolution of SLE, the greater the Albuminuria observed.

According to the results obtained, the diagnostic value of Albuminuria in LN is demonstrated, especially in its initial stages, in which the GFR numbers have not yet decreased, constituting a good indicator of severity and progression of kidney disease.

Author contributions: Conceptualization, MECV; methodology, MECV, SMPA and JPML; software, MECV and SMPA; validation, MECV, SMPA and JPML; formal analysis, MECV; investigation, MECV and ECMV; resources, MECV and ECMV; writing—original draft preparation, MECV; writing—review and editing, MECV; visualization, MECV, SMPA and JPML; supervision, MECV; project administration, MECV; funding acquisition, MECV. All authors have read and agreed to the published version of the manuscript.

Conflict of interest: The authors declare no conflict of interest.

References

1. Rivera F, Romera AM, Villabón P, et al. Systemic lupus erythematosus. Lupus nephropathy. Available online: https://www.nefrologiaaldia.org/es-articulo-lupus-eritematoso-sistemico-nefropatia-lupica—263 (accessed on 13 January 2024).
2. Navarrete CL, Ibáñez C. Role of Apoptosis in the Pathophysiology of Systemic Lupus Erythematosus. Rev Chilena Reumatol. 2008; 24(1): 30–38.
3. Hernández Y, Brizuelas L, Hernández C. Late-onset lupus. Case presentation. Rev. Cub Reumatol. 2012; 14(19): 3–12.
4. Reyes Llerena Gil A. Community prevalence of rheumatic diseases and associated disability [PhD thesis]. MINSAP; 2004.
5. Benitez VN. An autoimmune disease that is difficult to manage: Case Analysis. Available online:

https://repositorio.usfq.edu.ec/bitstream/23000/8687/1/144504.pdf (accessed on 13 January 2023).
6. Mussano E, Onetti L, Cadile I, et al. Systemic lupus erythematosus: sociodemographic data and its clinical-analytical correlation in a university hospital. Available online: https://www.scielo.org.ar/scielo.php?pid=S2362-36752019000400002&script=sci_arttext (accessed on 13 January 2024).
7. Guibert Toledano M, Reyes Llerena G, Hernández Martínez A, Torres Carballeira R. Measurement of Lupus activity in patients with Systemic Lupus Erythematosus. Cuban Rev. of Reumatol. 2000; II(1): 4–11.
8. Perl A, Fernandez D, Telarico T, et al. Endogenous retroviral pathogenesis in lupus. Current Opinion in Rheumatology. 2010; 22(5): 483–492. doi: 10.1097/bor.0b013e32833c6297
9. Carvajal C. Proteinuria and microalbuminuria. Rev Med leg Costa Rica. 2017; 34(1).
10. López SM, López JA, Montenegro LP, et al. Laboratory analysis for early diagnosis of chronic kidney failure. Rev Mex Urol. 2019; 78(1).
11. Gainza de los Ríos FJ. Acute Kidney Failure. Available online: https://www.nefrologiaaldia.org/317 (accessed on 4 April 2024).
12. Treviño BA, Baca ER, Meza CC, et al. Comparative glomerular filtration measurement by cystatin C and conventional methods based on creatinine clearance. Rev Hosp Jua Mex. 2010; 77(1): 22–7.
13. JC lasted. Systemic lupus erythematosus. In Clinical Rheumatology. Spain: Elsevier; 2010. pp. 163–78.
14. González D, Mejía S, Cruz M. Systemic lupus erythematosus: general approach to the disease. Rev Med Sinergia. 2021; 6(1): 1–17.
15. Rojas JE, Praga M. Lupus Nephropathy. Systemic lupus erythematosus. Available online: https://www.nefrologiaaldia.org/589 (accessed on 9 April 2024).
16. Levey AS, Greene T, Kusek J, et al. A simplified equation to predict glomerular filtration rate from serum creatinine (abstract). J Am Soc Nephrol. 2000; 11: A0828.
17. Huidobro EJP, Tagle R, Guzmán AM. Creatinine and its use for the estimation of glomerular filtration rate. Revista médica de Chile. 2018; 146(3): 344–350. doi: 10.4067/s0034-98872018000300344
18. Munguía C, Paniagua JR. Biomarkers in chronic kidney disease. Rev Med Ins Mex Seg Soc. 2017; 55(2).
19. Shahjahan YR, Amin MM, Khan M, et al. Correlation of Beta 2 microglobulin with Serum Creatinine and Creatinine Clearance in patients with different levels of renal function. J Med Sci. 2011; 9(2): 178–82.
20. Rivera F, Anaya S, Romera AM. Clinical Syndromes in Nephrology. Available online: https://www.nefrologiaaldia.org/es-articulo-sindromes-clinicos-nefrologia-258 (accessed on 11 April 2024).
21. Castellanos Y, Fong JA, Vázquez JM, Oliva J. Markers of kidney damage in patients with risk factors for chronic kidney disease. MEDISAN. 2018; 22(2): 142–8.
22. Hemmelgarn BR. Relation Between Kidney Function, Proteinuria, and Adverse Outcomes. JAMA. 2010; 303(5): 423. doi: 10.1001/jama.2010.39
23. Herrera Y, Menéndez ML, Serra MA. Microalbuminuria as a marker of kidney damage in patients with arterial hypertension. Rev habancienc méd. 2019; 18(2).
24. Hinojosa GI, Paramio A. Microalbuminuria in the early diagnosis of kidney damage in diabetic patients. Rev Finlay. 2021; 11(2).
25. Farías F, Páez N, Acosta E, et al. Correlation between protein/creatinine ratio and 24-hour proteinuria in patients with kidney disease. Acta Bioquím Clín Latinoam. 2015; 49(2): 215–20.
26. García R, Bover J, Segura J, et al. Information and consensus document for the detection and management of chronic kidney disease. Rev nefrol. 2022; 42(3): 223–362.
27. Montañés R, Bover J, Oliver A, et al. Assessment of the new CKD-EPI equation for estimating glomerular filtration rate. Available online: https://scielo.isciii.es/scielo.php?script=sci_arttext&pid=S0211-69952010000200007 (accessed on 12 April 2024).