Research Article
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Clinical utility of beta 2 microglobulin in kidney damage due to systemic lupus erythematosus

Summary

Introduction: Kidney damage in systemic lupus erythematosus is one of the most serious and frequent complications of the disease. Tubulo-interstitial involvement constitutes the main determinant of kidney disease progression, regardless of the nephropathy involved. The clinical and analytical parameters used in routine clinical practice predict glomerular injury, but not tubular injury. Beta 2 microglobulin may be a useful marker to diagnose renal tubular injury in lupus patients.

Objective: To determine the clinical usefulness of B2M in the diagnosis of renal tubular damage due to systemic lupus erythematosus.

Methodological design: An observational, descriptive and cross-sectional study was carried out at the National Reference Center for Rheumatic Diseases, at the "10 de Octubre" Clinical Surgical Teaching Hospital, in the period between June/2023 and December/2023. The sample was made up of 30 lupus patients who met the established criteria.

Results: The average age was 45 years with a predominance of the female sex (93.3%) and white skin color (53.3%). The Beta 2 microglobulin values obtained were adjusted to those of urinary creatinine, calculating the Beta 2 microglobulin/Creatinine Index, which was elevated in 26.7% of the patients. 50% had a decreased Glomerular Filtration Rate, either due to Creatinine and/or Cystatin C. No statistical association was obtained between tubular damage and decreased renal function.

Conclusions: Beta 2 microglobulin is a useful marker to detect tubular damage in lupus patients.

Keywords: systemic lupus erythematosus, Beta 2 microglobulin, lupus nephropathy, renal tubular damage

Volume 16 Issue 3 - 2024

María Elena Corrales Vázquez,[1] Silvia María Pozo Abreu,[1] José Pedro Martínez Larrarte[2]
[1]University of Medical Sciences of Havana. 10 de Octubre Surgical Clinical Teaching Hospital. Havana. Cuba
[2]University of Medical Sciences of Havana. Miguel Enriquez Faculty of Medical Sciences, Havana, Cuba

Correspondence: María Elena Corrales Vázquez, University of Medical Sciences of Havana. 10 de Octubre Surgical Clinical Teaching Hospital, Havana, Cuba,
Email mariaecvazque@infomed.sld.cu

Received: May 30, 2024 | **Published:** July 01, 2024

Introduction

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease characterized by multiple organ involvement due to altered immune responses with production of antibodies against cellular antigens. It is not only a disease, it is a syndrome; this is because the disease has a wide variety of expression patterns and no organ, apparatus or system can be considered free of it.[1] There are several factors such as genetic, hormonal and environmental factors involved in the onset and development of this disease and contribute to the differences in its incidence and clinical expression.[2] They favor the dysregulation of the innate and adaptive immune system, T cells, B cells, plasmacytes are activated and proliferate, there is production of inflammatory cytokines and complement is activated. The end result is the loss of immune tolerance, the development of pathogenic autoantibodies and systemic and local inflammation.[3]

Immune complexes, local complement activation, leukocyte recruitment and intrarenal cytokine signaling at the renal level promote glomerular and tubulointerstitial injury.[4] The genetic basis of SLE shows a heritability of 43.9% and a relative risk in first-degree relatives of 5.9%. Most cases are of polygenic origin, although early onset cases may be monogenic or familial, with genes involved in DNA elimination and the complement pathway.[3,4]

It is proposed that various environmental factors such as smoking, industrial products, pesticides, ultraviolet light, infections, hormonal drugs and recently, intestinal dysbiosis, may contribute to the loss of immune tolerance and the development of autoimmunity.[3,4] It is estimated that more than 5 million people in the world suffer from this disease and there are more than 100,000 new cases diagnosed each year. Statistics vary according to geographical areas. In North America, Asia and northern Europe it affects 40 out of every 100,000 inhabitants, with a higher incidence in the Hispanic and African-American population; in Spain its prevalence is 9 per 100,000 inhabitants. About 90% of cases are women.[5–7]

In South America, an incidence rate of 1 to 25 cases per 100,000 inhabitants has been estimated, with prevalence rates varying between 20-70 cases per 100,000 inhabitants, with higher prevalence and severity in Afro-Caribbean populations.[8] Research on morbidity and mortality in Cuba has shown that this disease is more frequent in women and ranges from more benign to more severe forms. It has been described that, due to complications, up to 10% of patients have died. New cases of lupus are reported every year, with diverse manifestations during its evolution; to them are associated the effects of the treatments used to control them.[5,6] Studies have estimated that between 10% and 15% of patients diagnosed with SLE will die early due to complications of the disease itself.[7,8]

In patients with SLE, survival in Western nations has improved from around 50% at 5 years in the middle of the last century to 80-90% at 10 years at the end of the century. Some of this improvement is attributed in part to earlier and milder stages of diagnosis and improvements in the treatment of kidney disease and infections.[9] Predictors of mortality vary among the different cohorts studied, but in general mortality is associated with renal disease, accumulation of irreversible damage, hypertension and glucocorticoid use. [9]

In SLE, renal involvement grouped under the term lupus nephropathy (LN) appears clinically or analytically in a considerable number of patients, between 25% and 75%, depending on the population studied (age, sex, skin color and geographic region), diagnostic criteria and the search for renal impairment.[10]

Usually when renal biopsy is performed on patients with SLE, about 90% have some lesion.[10] According to data from the Spanish Registry of Glomerular Diseases, LN is the third renal disease biopsied in adults, with a prevalence of 10% of all renal biopsies, and the first among systemic glomerular diseases.[11]

LN is considered the most important predictor of mortality in patients with SLE.[5] It is present in half of the patients and tends to occur early in the course of the disease, usually within 36 months of diagnosis.[9,12] Approximately 5-20% of patients with LN progress to chronic renal failure.[10]

All renal structures may be involved, but commonly it is the glomerulus. However, the renal arteries, interstitium and renal tubules may also be involved,[13] by direct effect of the disease or secondary to treatment. In the kidney, immune complexes are deposited in the subendothelial and mesangial part of the organ, followed by the basement membrane and subepithelium, producing an influx of inflammatory cells by activating the complement cascade. All this is due to mesangial, interstitial and podocyte cells acquiring properties to present antigens and secrete proinflammatory factors upon exposure to interferon α (IFN-α).[12]

The clinical expression of renal involvement due to SLE is nonspecific and may be due to other etiologies. These patients frequently receive anti-inflammatory and immunosuppressive drugs, so damage secondary to nephrotoxicity or infections is not easy to rule out.[13,14] Renal injury is evidenced directly by histologic changes in the kidney biopsy or indirectly by the presence of proteinuria, albuminuria, or changes in the urinary sediment and through imaging techniques.[15] Indirect signs of renal injury evidence glomerular, but not tubular, damage.

LN has a wide form of presentation; the most frequent are the presence of proteinuria (95%, up to 40-50% in the nephrotic range), microscopic hematuria (80%), renal dysfunction (30-50%), arterial hypertension (30-50%), hematic casts in urine (10-30%) and rapidly progressive glomerulonephritis (<15%).[16,17]

Renal biopsy allows the diagnosis and classification of NL, and should be assessed by expert neuropathologists.[18]

Although the histological classification of NL is "glomerulocentric", tubulointerstitial and vascular lesions are of key importance in the prognosis of NL.[3,19] More recent studies have suggested that this classification can be improved by adding studies with molecular markers, in order to identify therapeutic targets and design more individualized treatments.[10]

Renal biopsy gives certainty and allows the characterization of renal damage, but the clinical and laboratory tests are the ones that guide the diagnosis and establish the guidelines for the indication of biopsy. The different way in which the glomerulus and tubule treat proteins is mainly linked to the dimensions of the molecule (molecular weight). Protein groups of molecular weight within a certain range are treated similarly.[20]

Proteinuria is one of the signs that characterizes glomerular damage and is one of the criteria for biopsy. The proteins that normally filter through the glomerular filtration barrier because of their low molecular weight, less than 50 kDa approximately, are called urinary microproteins. They are serum proteins that ultrafiltrate through the glomerulus and are reabsorbed and catabolized, practically in their totality, in the proximal tubule. [20,21]

In the presence of proximal tubule dysfunction, urinary microproteins are eliminated early in the urine. Their excretion profile is modified according to the various diseases that compromise tubular function, as in diabetes mellitus, pregnancy and cadmium intoxication. Detection of some of them allows characterization of the type of proteinuria, so that Alpha 1 Microglobulin, 30 kDa, Retinol Binding Protein, 20 kDa, and B2M, 12 kDa, are useful as markers of tubular damage.[20,21]

In clinical practice, so far the presence of medium molecular weight proteins such as albumin, transferrin and immunoglobulin G have been observed in urine when the damage originates in the glomerulus, and urinary microproteins when the damage originates in the tubulointerstitium. In the case of glomerulopathies, when the lesion progresses, the tubulointerstitium is subsequently involved, showing mixed proteinuria (glomerulo-tubular).[21] It is very important to detect tubular proteinuria since it may precede glycosuria, aminoaciduria or phosphaturia and is often the first and only sign of tubular dysfunction.[21]

Tubular damage can also be seen in nephropathies with glomerular proteinuria, and this is due to the adverse effect of protein overload and to an eventual biological activity that they can exert in their microenvironment. Proteinuria is an independent risk factor for the progression of chronic glomerular disease and is associated with the extension of damage to the tubulointerstitium.[22,23]

In patients with LN, it has been found that in the cells of the proximal tubular epithelium there is an increase in the number of receptors capable of binding to immunocomplexes formed by nuclear debris, antinuclear antibodies (ANA) and anti-DNA. Experimental inhibition of these receptors was linked to a significant improvement of tubulointerstitial involvement in non-human models of NL.[24]

An accumulation of protein in tubular cells leads to increased expression of a variety of inflammatory and fibrogenic cytokines, resulting in the development of interstitial inflammation, proliferation of fibroblasts, increased production of extracellular matrix, and formation of interstitial fibrosis. Therefore, it is important to detect tubular proteinuria because it can indicate an early sign of tubular damage or the progression of glomerular damage.[23,24]

Renal function is evidenced by measuring the glomerular filtration rate (GFR), which is reduced before the onset of renal failure symptoms.[25] The GFR corresponds to the volume of plasma from which a substance is filtered by the kidney per unit of time. It is calculated by creatinine clearance (measuring its concentration in blood and 24-hour urine), which has several problems since, on the one hand, it is inconvenient to collect and, on the other, it can overestimate GFR due to tubular secretion of creatinine.[26] To improve this situation, different formulas have been developed (MDRD-4 or MDRD-IDMS, CKD-EPI), adjusted to the individual body surface area, which allow an approximation or estimation of GFR.[25,26]

Serum creatinine is the endogenous marker most commonly used to determine GFR, but it has the disadvantage that it is not capable of detecting small decreases in glomerular filtration rate, and can even be maintained at normal concentrations when renal function is impaired.[25,26] In addition, its analysis is exposed to interferences with other endogenous substances (bilirubins, triglycerides, glucose, ketones, uric acid) and some drugs.[25,26]

For these reasons, it became necessary to search for a new method, more sensitive and specific and just as easy and economical to perform, that could replace serum creatinine as a routine value for the early detection of renal dysfunction in its initial stages. In this line, research focused on new endogenous markers, among which Cystatin C (CsC) was proposed.[25,27] There have been several investigations demonstrating higher sensitivity of CsC with respect to creatinine, in different population groups.[27]

One of the possible advantages that CsC appears to have over creatinine is the greater sensitivity for detecting mild reductions in GFR. Therefore, it would be a more accurate marker for detecting mild renal failure.[27] In recent years, progress has been made in detecting markers of renal damage that allow: 1) early diagnosis of renal damage in order to be able to act in advance; 2) to establish differential diagnosis between different diseases; and 3) to establish prognostic stratification. These markers include molecules such as CsC and B2M that are produced in other cells of the organism and are filtered, or others that are released by the renal tissue into the urine or blood.[28]

In 1968 Berggard and Bearn isolated from the urine of patients with Wilson's disease, characterized by proximal tubular damage, B2M, which is a low molecular weight polypeptide (approximately 12 kDa) of about 100 amino acids and contains no associated carbohydrates in its molecule. It is synthesized in all nucleated cells in the body and is part of the light chain of the major histocompatibility complex (HLA-1). B2M is important for cell recognition processes; it is filtered in the kidney and reabsorbed in the proximal convoluted tubule.[29,30]

The renal metabolism of B2M is common to that of other low molecular weight proteins. Injection of I-labeled $B2M^{125}$ into the rat demonstrates that reabsorption takes place at the level of proximal tubular cells by a process of brush border micropinocytosis, followed by the formation of endocytosis vacuoles, where it is degraded by lysosomal enzymes.[30]

The normal kidney excretes up to 150 mg/24h of urinary protein, and is capable of reabsorbing approximately 99.9% of the filtered B2M, which means that a maximum of 370 µg/24h is excreted in the urine. In patients with abnormal renal function renal excretion is doubled compared to the normal population.[30,31]

Normal glomerular filtration rate and decreased proximal tubular function are associated with decreased tubular reabsorption and increased urinary excretion of B2M; this is a useful criterion for differentiating proximal tubulopathies from glomerular kidney diseases.[31,32] Proximal renal tubular dysfunction due to increased urinary excretion of β2M has been demonstrated in pathologies such as pre-eclampsia, urinary tract infections, in rheumatoid arthritis, and in patients under chemotherapeutic treatment.[33]

The increase in plasma levels of B2M is verified in two situations: one, because it decreases glomerular filtration rate, which makes it very useful to detect tubular dysfunctions, and therefore it can be used to monitor this function, for example in obstetric patients or in infants with sepsis, and two, because of the increase in synthesis, as occurs in diseases in which the immune system is involved such as SLE, rheumatoid arthritis, multiple myeloma, B-cell lymphoma, and in some viral and neoplastic infections.[32,33]As a validation of the urinary proteome classification model, Papale et al. performed an evaluation of urinary proteomic profiles generated by mass spectrometry, with the purpose of isolating a set of biomarkers that could reliably identify renal damage, and found two proteins: ubiquitin and B2M were among the best predictors of the classification model.[34]

It is a fact that early diagnosis and treatment of kidney damage in SLE is vital to control the disease and to avoid its progression to expensive replacement therapy in the terminal phase of the disease, and the extreme increase in the risk of cardiovascular events, with the consequent economic costs, largely derived from complex hospital admissions, premature mortality and reduced quality of life. At present there is a growing need for new reliable and easily detectable substances that can serve as indicators of renal injury, so that they can be incorporated into the programs used for the early diagnosis of the disease. Thus, the study of Beta 2 Microglobulin (B2M) is proposed as a useful, sensitive and reliable marker for the diagnosis of renal tubular dysfunction in our environment, based on international bibliography.

At the Hospital Docente Clínico Quirúrgico "10 de Octubre", where the Centro Nacional de Referencia de Enfermedades Reumáticas (CNRER) is located, there are rheumatologists with vast experience in the comprehensive care of lupus patients. The established diagnostic protocols do not include markers that allow evidence of renal tubular damage in patients with SLE. For this reason, our research aimed to determine the clinical usefulness of B2M as a marker of renal tubular damage in patients with SLE, with the objective of providing a tool that allows the physician to provide more comprehensive care for these patients.

Methodological design

Place of study

Centro Nacional de Referencia de Enfermedades Reumáticas, Hospital Clínico-Quirúrgico "10 de Octubre", Havana, Cuba.

Study design: observational, descriptive and cross-sectional.

Thirty lupus patients older than 19 years who were admitted or attended for outpatient consultation at the CNRER between June 2023 and December of the same year were selected for the study, after reading and signing the informed consent form.

Those with urinary tract infection, hematuria or any other condition affecting the sensitivity, specificity and accuracy of the analytical methods used to determine the substances of interest for the study, pregnant women, bedridden patients and those with associated diabetes mellitus were excluded.

The sex (male/female), skin color (white/black/mixed race) and age (in years of age) of each patient included in the study were related.

The GFR value, both by CsC and creatinine, was divided as follows: decreased value:

less than 60ml/min and normal value: greater than or equal to 60ml/min. The urinary

B2M value (mg/L) was divided, for women, into normal values: less than or equal to

0.183mg/L, and elevated values: greater than 0.183 mg/L; for men, the cut-off point was

0.300 mg/L. The results of the B2M/creatinine index (BCI) were stratified in the same way for both sexes: normal: less than or equal to 0.029 mg/mmol and elevated: greater than 0.029 mg/mmol.

Methods and techniques

Primary data were collected on the basis of review of medical records. The results of serum creatinine and CsC, B2M and urine

creatinine tests for each patient were obtained after collection and processing of the biological samples in the clinical laboratory of the hospital where the investigation was carried out. To calculate IBC, quantitative determination of B2M (immunoturbidimetric method) and creatinine (kinetic Jaffé method) was performed in plain urine samples. The plain urine sample was collected in the first hour of the morning in a sterile bottle with a lid provided to each patient. It was then taken to the laboratory for processing.

From the IBC results, the presence or absence of renal tubular damage was determined in each case. Renal function was estimated by calculating GFR from serum creatinine (MDRD equation (acronym for *Modified Diet Renal Disease Study*)) and CsC (Grubbs-Adult Equation), taking into account demographic variables: age, sex and skin color. The results were corrected according to the body surface area of each subject.

GFR was calculated using the Nefrocalc system for Windows. This is a computer system for the calculation of renal function tests developed and implemented in our country since 2008. This database manager has implicit formulas, mentioned above, through which body surface area and GFR were found. Each patient underwent a fasting blood sample for the quantification of creatinine (kinetic Jaffé method) and CsC (immunoturbidimetric method), in compliance with the established biosafety measures.

The analytical methods were performed on the Roche Cobas 311 autoanalyzer, perfectly calibrated and certified. In all cases, the instructions of the manufacturer of the reagents used in the analytical determinations were followed. The creatinine reagent is of national origin (Centro de Inmunoensayos). The B2M and CsC reagents came from abroad (Roche Diagnostics, Indianapolis, United States).

The results obtained from the IBC and glomerular filtration rate were correlated by creatinine and CsC. The expected behavior of B2M and GFR was obtained from other similar studies in populations different from the one studied in this work.

The results were discussed using the comparative method in relation to the literature reviewed and the statistical data obtained. The results were presented in tables and graphs for better analysis and understanding.

Statistical processing

It was performed with the PSPP statistical package and jamovi. A descriptive study of all variables was performed: categorical variables were summarized by absolute frequencies and percentage. Through inferential statistics, Fisher's exact test was used to identify possible relationships between GFR Creatinine and GFR Cystatin C, between IBC with GFR Creatinine and with GFR Cystatin C, since these are two qualitative variables where no cell had expected values lower than 5. A significance level of 5% was used for all hypothesis tests.

Ethical aspects

The research protocol was approved by the Ethics Committee and the Scientific Council of the institution before starting the research. The head of the CNRER, at the Hospital Docente Clínico Quirúrgico ¨10 de Octubre¨ was informed about the objectives of the research and its benefits. In addition, informed consent was requested from each patient, after an explanation of the study to be performed. The information concerning the patients will be treated according to the principles of confidentiality that govern scientific research.

Results

The average age was 45 years, with a minimum of 21 years and a maximum of 74 years (Standard deviation= 12.4 years and 95% CI: 40.3-49.6). As for sex, 93.3% (28) of the patients studied were women and only 6.7% (2) were men, as can be seen in Table 1.

The skin color with the highest percentage was white, with 53.3% (16), followed by black and mestizo, both with 23.3% (7), as can be seen in Table 2.

Table 3 shows that 40.0% (12) of the total number of patients in the study had elevated urine B2M. Table 4 shows that 26.7% (8) of the total number of patients under study had an increased IBC. Table 5 shows that 16.7% (5) of the total number of patients had decreased GFR, both by creatinine and by CsC. Another 16.7 % (5) presented decreased GFR by creatinine, being normal by CsC. The opposite was observed in another 5 cases, which had decreased GFR by CsC and normal by creatinine. Generalizing, it was observed that 50% (15) of the patients had decreased GFR.

There was insufficient evidence, from a statistical point of view (Fisher's exact test: 0.2308), to affirm that there is an association between GFR Creatinine and GFR Cystatin C, i.e., they are independent.

Table 6 shows that of the total number of patients, 8 (26.7%) had an elevated IBC; only 10% (3 of them) had a decreased creatinine GFR. There was insufficient statistical evidence (Fisher's exact test: 0.5480) of association between IBC and creatinine GFR at 5% level of significance.

Table 1 Distribution of patients according to sex

Source: Medical Records

Sex	No.	%
Female	28	93,3
Male	2	6,7
Total	30	100,0

Table 2 Distribution of patients according to skin color

Source: Medical Records

Skin color	No.	%
Blanca	16	53,4
Black	7	23,3
Mestiza	7	23,3
Total	30	100,0

Table 3 Patients according to sex and B2M in urine.

B2M in urine						
Sex	**Elevated**		**Normal**		**Total**	
	No.	**%**	**No.**	**%**	**No.**	**%**
Female	11	36,7	17	56,7	28	93,3
Male	1	3,3	1	3,3	2	6,7
Total	12	40,0	18	60,0	30	100,0

Table 4 Patients according to sex and IBC

IBC						
Sex	**Elevated**		**Normal**		**Total**	
	No.	**%**	**No.**	**%**	**No.**	**%**
Female	7	23,3	21	70,0	28	93,3
Male	1	3,3	1	3,3	2	6,7
Total	8	26,7	22	73,3	30	100,0

Citation: Vázquez MEC, Abreu SMP, Larrarte JPM. Clinical utility of beta 2 microglobulin in kidney damage due to systemic lupus erythematosus. *MOJ Orthop Rheumatol.* 2024;16(3):97–104. DOI: 10.15406/mojor.2024.16.00670

Table 5 Patients according to GFR Creatinine and GFR Cystatin C

TFG Cystatin C							
		Decreased		Normal		Total	
		No.	%	No.	%	No.	%
GFR	Decreased	5	16,7	5	16,7	10	33,3
Creatinine	Normal	5	16,7	15	50,0	20	66,7
Total		10	33,3	20	66,7	30	100,0
		Fisher's exact test: 0.2308					

Table 6 Patients according to IBC and creatinine GFR

		FG creatinine					
		Decreased		Normal		Total	
		No.	%	No.	%	No.	%
IBC	Elevated	3	10,0	5	16,7	8	26,7
	Normal	7	23,3	15	50,0	22	73,3
	Total	10	33,3	20	66,7	30	100,0
		Fisher's exact test: 0.5480					

Table 7 Patients according to IBC and GFR cystatin

		FG CsC					
		Decreased		Normal		Total	
		No.	%	No.	%	No.	%
IBC	Elevated	5	16,7	3	10,0	8	26,7
	Normal	5	16,7	17	56,7	22	73,3
Total		10	33,3	20	66,7	30	100,0
	Fisher's exact test: 0.1423						

Graph 2 shows that of the total number of patients (8 for 26.7%) who were found to have elevated IBC, 16.7% (5) of them had a decreased GFR per CsC. We did not reach sufficient statistical evidence (Fisher's exact test: 0.1423) of association between IBC and GFR CsC, with a 5 % significance level.

Of the 8 patients with tubular damage, according to the IBC, 3 of them coincided with a decreased GFR, both by creatinine and by CsC; another 2, presented only decreased GFR by CsC and 3, had no GFR affectation.

Discussion

Considering the distribution of demographic variables, we observed, as in other studies, that SLE is more frequent in white-skinned women and in the middle age of life, that is, in the reproductive stage.[1–4,35] For every 10 adults diagnosed with SLE, 9 are women, although men, adolescents and children are not exempt. The age of incidence ranges from approximately 15 to 44 years of age.[8]

In a study conducted by Bermudez, in 2016, it was reported that the average age of disease diagnosis was 30 years, similar finding reported by the GLADEL group, through the cohort study conducted by Velarde et al, who observed that SLE was diagnosed between 21-30 years of age with female sex predominating.[36]

The reason why lupus occurs predominantly in women is difficult to explain. It is possible that genes related to sex and hormones, mainly estrogens, play an important role in the etiopathogenesis. It has been shown that women who have had early menarche or have received estrogen therapy are at increased risk for SLE.[8] However, lupus in men, although less frequent, has been associated with greater renal, neurological, serositis and hematological damage.[8,37]

SLE, more than a disease with defined clinical features, should be considered as a true autoimmune syndrome with a highly pleomorphic clinical picture, in which different types of autoantigens are involved, which largely determine not only the clinical picture but also the degree of renal involvement.[10,38] Its prognosis is classically closely related to clinical, serological and histopathological criteria of multiorgan involvement with almost constant renal involvement.[16,38]

Renal damage can be mixed and heterogeneous, coinciding acute and chronic evolutive lesions with different glomerular, tubulointerstitial and/or vascular repercussions. Although glomerular damage is the most frequent, it is important to determine the existence of tubulointerstitial lesions.[16,38,39] Exclusively tubulointerstitial cases of LN are very rare. However, the interstitial inflammatory component is relatively frequent in NL and it is almost always associated with diffuse proliferative glomerular disease with abundant deposits of immunocomplexes.[19,38,39]

In the present study 40% of the patients studied had elevated urine B2M levels, which was reduced to 26.7% when calculating the IBC. This ratio has the advantage of eradicating false high or low values, dependent on concentrated or dilute urine in the physiological state, by affecting the numerator and denominator equally.[40] Adjustment of urinary β2-microglobulin β2 by creatininuria concentration decreases the dispersion of the values obtained by adjusting the results analyzed in urine to individual renal function.[30,40] Based on the above, we can define that elevated IBC levels demonstrate renal tubular damage, and according to the results obtained, it can be suggested that tubular injury in SLE occurs with a certain frequency.

In 2010, a study was performed in which the results obtained from B2M in urine of patients diagnosed with type 2 diabetes were characterized, showing that patients with normal proteinuria presented elevated levels of B2M in urine, which indicated that there is no direct correspondence between these two markers. This result is coherent because if there were a strict correlation it would indicate that high B2M values would evaluate damage not only at the tubular level, but also at the glomerular level as occurs with proteinuria. These results showed the usefulness of this protein as a diagnostic marker of renal damage at the proximal tubular level.[41]

Portman et al. in 1986 conducted a study using B2M to investigate possible renal tubular damage in children with various biopsy-diagnosed renal problems. It was demonstrated that the determination of B2M in urine is a reliable method to identify tubular damage in renal diseases and also provides a useful guide to help determine the prognosis in patients with this type of lesions.[42]

In 2008, Hofstra et al. performed a comparative study between urinary N-acetyl-beta-glucosaminidase (NAG) and B2M as prognostic markers in idiopathic membranous nephropathy, concluding that B2M is more precise and accurate to assess progression and remission of cases with this disease, in addition to being more specific than NAG as a marker of tubulo-interstitial damage.[43]

In another study conducted in a non-diabetic Japanese population in 2008, it was shown that the combination of macroalbuminuria and increased urine B2M are predictors of progressive deterioration of renal function as they evidence damage in both the glomerular and tubular compartments, respectively.[44]

Research conducted in HIV-infected patients to evaluate the renal toxicity of antiretroviral therapy, especially in the case of tenofovir, has shown that B2M is a sensitive marker of tubular dysfunction and that the increase in its values in urine precedes the deterioration of tubular phosphate reabsorption. In addition, it is useful for assessing the reversibility of damage upon discontinuation of treatment.[45] An investigation conducted, in 2014, to evaluate the correlation between elevated urinary B2M concentration with proximal tubular damage evidenced by KIM-1 (Kidney Injury Molecule- 1) expression in renal biopsies, demonstrated a significant correlation between the two (out of 35 positive biopsies, 30 patients had elevated urinary B2M), concluding that urinary B2M determination is a sensitive method to diagnose proximal tubular damage.[46]

Tubulointerstitial involvement in SLE can occur independently of glomerular injury and is usually related to renal prognosis. Tubulointerstitial involvement has been associated with impaired tubular function, metabolic acidosis, hypokalemia, urinary concentration disturbances and progression to chronic kidney disease (CKD).[23,38]

The incidence of interstitial nephritis in SLE increases from 14% in class II NL to 50% in class IV NL. The infiltrates contain lymphocytes, plasma cells, neutrophils and macrophages with tubular injury, which is characterized by atrophy and regeneration.[47]

Tubulointerstitial lesions can be secondary to sclerosis and glomerular ischemia, but in 50 % there is presence of extraglomerular deposits of immunoglobulins, which is suggestive of a tubular lesion by immune complexes. Similar histologic findings are observed in drug-induced interstitial nephritis or acute tubular necrosis, which is important to take into account when making a therapeutic decision.[47] Regarding the behavior of GFR, in a general sense, it is evident that 50% of the cases are carriers of CKD secondary to SLE.

It is considered that CKD has no expectation of cure, has a rapid and progressive evolution, triggers various reactions for patients and affects their quality of life.[48] Currently, early GFR reduction has become the gold standard for the detection of early CKD. The Uruguayan Society recommends that the diagnosis of this disease should be based on the decrease in GFR and the presence of albuminuria.[48]

GFR is considered to be the general index that best reflects renal function, both in health and in disease; in the absence of renal disease, this rate decreases in the normal range with age (particularly after 70 years of age). Such age-related loss of renal function may be accelerated by morbid conditions, such as atherosclerosis, arterial hypertension, diabetes mellitus, SLE, among others.[49,50]

The MDRD equation estimates renal function and classifies CKD into 5 stages. When the calculated GFR decreases below 60 ml/min/1.73 m^2 , the estimate is less accurate in the range of normal filtrate and in patients with decreased body mass such as children, elderly or amputees.[51]

A study in 86 patients with lupus nephropathy found that MDRD at the time of biopsy predicted long-term renal outcome more effectively than serum creatinine.[51]

No differences were obtained between creatinine GFR and CsC GFR values, despite the fact that the latter has been shown to estimate renal function more accurately than creatinine. CsC has been validated to detect early alterations of renal function, finding its usefulness in conditions accompanied by muscle loss such as senile patients, with liver disease, malnourished, hyperthyroid, etc.[27,52]

According to the results, there was no statistical association between IBC and GFR, either by CsC or creatinine. This demonstrates what is stated in the literature,[23,24,25] that tubular damage may or may not coexist with glomerular injury.

However, a more end-to-end behavior was observed between elevated IBC values with decreased GFR by CsC. Serum creatinine levels reflect the filtration capacity of the kidney; elevated values are evidence of late renal dysfunction, when 50% of renal function has already deteriorated. On the other hand, CsC and B2M, both serum and urine, detect renal damage earlier.[53]

Facio and collaborators, in 2016, demonstrated that the increase in the concentration of low molecular weight proteins in urine, with GFR per creatinine, less than 45 ml/min would be indicating an extension of chronic vascular and glomerular injury, with different degrees of chronic tubulo-interstitial damage, overloading the remaining glomeruli.[20]

They further conceptualized that urinary microproteins in CKD are sensitive to tubular dysfunction, hypoperfusion and loss of renal mass, but are not sensitive to increased vascular permeability or increased glomerular capillary hydrostatic pressure.[20]

GFR estimated through CsC has consistently provided a stronger association with outcomes compared to equations based on estimating GFR measured through serum creatinine.[54] An elevated IBC with a decreased GFR indicates deeper renal damage because both the glomerular and tubular compartments are affected.

There are few reports in the literature evaluating the clinical implication of urinary leakage of low molecular weight proteins such as B2M. The existing data are encouraging for the possibility that this urinary marker may serve as a prognostic indicator, and perhaps also for the assessment of therapeutic response for both tubulointerstitial damage and risk of renal failure. [41]

Conclusions

The IBC was defined as the one that reports the real value of B2M, by adjusting its values to the concentration of creatinine in urine. It was determined that B2M is a useful marker to detect tubular damage in lupus patients. It was also confirmed that renal complication in SLE is frequent due to the decrease in renal function found in patients. There was no association between tubular damage, diagnosed by elevated IBC levels, with the decrease in GFR, either by creatinine or by CsC, which shows that tubular damage may or may not coexist with glomerular damage.

Author contributions

María Elena Corrales Vázquez: participated in the conception of the investigation, information search, information processing, elaboration of results and final revision of the manuscript.

Silvia María Pozo Abreu: participated in the conception of the investigation, search for information, elaboration of results and writing of the manuscript.

José Pedro Martínez Larrarte: participated in the conception of the investigation, information search and writing of the manuscript.

Acknowledgments

None.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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