

Original Paper

Serum Beta 2-Microglobulin/ Cystatin C Index: A Useful Biomarker in Lupus Nephritis?

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Key Words

Beta 2-microglobulin · Cystatin C · Systemic lupus erythematosus · Disease activity · Relapse · Biomarker

Abstract

Background: Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease with frequent flares. Our aim was to evaluate the beta 2-microglobulin/cystatin C (β 2M/CysC) index versus other markers as a predictor factor for assessment of SLE reactivation. **Methods:** We prospectively analyzed 42 patients with lupus nephritis. Disease activity was classified using SLEDAI-2K and BILAG. Routine renal function and laboratory markers of SLE activity were performed, as well as serum β 2M (S β 2M)/serum CysC (SCysC) and S β 2M/serum creatinine (SCreat) indexes determinations. **Results:** The 42 enrolled patients had a mean age of 37.7 ± 13.1 years, 88% were female and 67% Caucasians; mean estimated glomerular filtration rate was 61.9 ± 20.0 ml/min/1.73 m². There was a strong correlation between SCreat versus SCysC ($r = 0.887$), SCreat versus S β 2M ($r = 0.865$), and SCysC versus S β 2M ($r = 0.880$). Multivariate analysis showed that the S β 2M/SCreat index is a prognostic factor predicting active lupus nephritis. **Conclusion:** As SCysC is a good marker of renal function, it would be expected that the S β 2M/SCysC index could be a better indicator of renal activity than S β 2M/SCreat, but in the present study it did not add relevant clinical information in the assessment of renal activity in SLE.

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Introduction

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease with frequent flares, often requiring hospitalization and immunosuppressive therapy [1–5]. Several immunologic markers are used in laboratory monitoring of disease activity in SLE patients, and some of them are components of disease activity indexes such as SLE Disease Activity Index (SLEDAI), Systemic Lupus Activity Measure (SLAM) and British Isles Lupus Assessment Group (BILAG) [6–9]. Considering the morbidity associated with SLE and particularly with lupus nephritis, it is important to identify sensitive and specific biomarkers of disease activity which could aid in the detection and assessment of flares and degree of disease activity [10, 11].

Beta 2-microglobulin (β2M) is a low-molecular-weight protein (11 kDa) mainly released by activated lymphocytes. Daily synthesis of β2M ranges from 50 to 200 mg with an estimated half-life of approximately 2 h [12–14]. High levels of serum β2M (Sβ2M) were described in rheumatoid arthritis, Sjögren's syndrome and SLE. β2M is catabolized by the kidneys, and there is a linear inverse correlation between levels of Sβ2M and glomerular filtration rate (GFR); its elimination is constant in normal people when its production is also constant [15]. Approximately 99.5% of β2M is freely filtered by glomeruli and reabsorbed in renal proximal tubules. In the presence of renal dysfunction, β2M serum levels are increased when compared to those of patients with normal renal function [12–16].

Some studies have previously failed to show a role for Sβ2M as a biomarker in SLE activity due mainly to its limited use in patients with renal involvement characterized by a reduction of the GFR [12–19].

On the other hand, routinely used endogenous markers, such as serum urea and creatinine (SCreat), have several limitations [20, 21]. The lack of an ideal index of renal function requires a search for new substances [22]. Serum cystatin C (SCysC) has been proposed as a promising marker of GFR and it is seen as equivalent or even superior to SCreat [17–23]. In addition SCysC has been recently recognized as a marker of inflammation and cardiovascular mortality [20–26].

In order to reduce possible misinterpretation in the assessment of Sβ2M in SLE patients with disease activity and renal dysfunction, we have proposed to correct Sβ2M levels through an index where a marker of kidney function (such as SCysC or SCreat) is the denominator. We hypothesize that the Sβ2M/SCysC index could be a more accurate biomarker of SLE activity in cases of reduced GFR than Sβ2M.

Patients and Methods

Study Population

Forty-two patients with SLE whose diagnosis was established by the presence of at least four criteria of ARA [1–4] were prospectively enrolled. These patients were followed in the Glomerulopathy Section (Nephrology Division) of the Federal University of São Paulo. All of them had renal involvement during the course of SLE. Those patients with a previous renal biopsy were classified according to WHO lupus nephritis classification [26].

The study was approved by the Ethics Committee and the patients were included in the study after giving their informed consent. At some time during the course of SLE, all of them have used corticosteroids, and during this study the doses were defined according to clinical status and the presence of lupus activity evidence, which was evaluated by the application of SLEDAI-2K criteria [1–3].

In the evaluation of all patients, SCysC, S β 2M, urine retinol-binding protein (urRBP), clinical history, physical examination and routine laboratory exams were performed, as well as the determination of the laboratory items necessary to calculate SLEDAI-2K and BILAG indexes.

The exclusion criteria corresponded to concurrent lymphoproliferative or autoimmune diseases (as rheumatoid arthritis, ankylosing spondylitis and Crohn disease), chronic infectious diseases (such as AIDS), active infections (such as tuberculosis and viral hepatitis), chronic kidney disease stage 5, renal transplantation, malignances and concurrent non-lupus-related glomerulopathies.

Many therapies were used to control SLE and lupus nephritis manifestations, including corticosteroids, azathioprine, cyclosporine, cyclophosphamide and antimalarials. Statins, angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor antagonists (ARA II) were also frequently administered. In addition, no patient used nonsteroidal anti-inflammatory drugs (NSAID) during the period of follow-up, in order to reduce nephrotoxicity risk.

SCreat levels were used as reference to establish whether SCysC levels could be attributed only to renal function variation.

Criteria of SLE Activity

SLE activity was determined using SLEDAI-2K and BILAG criteria. By the SLEDAI-2K, activity manifestations until ten days before medical appointment had a score equal or higher than six [7, 8]. BILAG A and B corresponded to the presence of disease activity, and BILAG C, D and E to the absence [9] until four weeks before medical visit.

Methods

S β 2M was determined with a one-step immunoenzymometric assay developed in house. RBP levels were measured in urine samples as described by Pereira et al. [27]. Serum CysC was determined with an in-house developed assay using an automated microsphere-based flow cytometric methodology (Luminex, Austin, Tex., USA) [29]. The results were expressed in mg/l, using as reference a standard curve with calibrators from the Cystatin C PET Kit by Dako. The values obtained were comparable to those of the commercial assay kit N Latex Cystatin C by Dade Behring ($r^2 = 0.884$) and Cystatin C PET Kit by Dako ($r^2 = 0.814$). In a population of patients and normal individuals ($n = 156$) we studied measurements of GFR obtained by the iothexol clearance and CysC, and we obtained a good correlation coefficient between them ($r^2 = 0.821$). There was no difference between means in males and females (t test, $p = 0.844$). The range of CysC was 0.40–0.91 mg/l, and the reference interval of normality (mean \pm 2 SD) was 0.38–0.86 mg/l, similar to that observed in other studies [28, 29].

Serum creatinine was determined by an automated method based on the alkaline picrate reaction, in a Hitachi 912 (Roche) chemistry analyzer and the results were expressed as mg/dl. Estimated GFR (eGFR) was determined by the 4-variable MDRD formula [30].

Statistical Analysis

Continuous variables were presented as mean \pm SD. For comparison among sample means, Student's t test, ANOVA or Kruskal-Wallis tests (followed by Tukey multiple comparison test) were performed. The significance level was set at $p \leq 0.05$. The correlation of SLEDAI-2K and BILAG with anti-dsDNA, C3, C4, S β 2M/SCysC, S β 2M/SCreat and urRBP were evaluated by Pearson/Spearman correlation test. The strength of the correlation was defined as per Cohen et al.: strong: $r > 0.5$, moderate: $r \geq 0.3$ and $r < 0.5$, weak: $r \geq 0.1$ and $r < 0.3$, or absent $r < 0.1$. The sensitivity/specificity indexes and receiver operating characteristic (ROC) curve analysis were used to discriminate the best value for a positive test to

Table 1. The sensitivity/specificity indexes and ROC curve analysis for S β 2M/SCreat and S β 2M/SCysC

		Sensitivity	Specificity	TPV	FPV
S β 2M/SCreat*	SLEDAI-2K	52.2%	68.4%	66.7%	54.2%
S β 2M/SCysC**	SLEDAI-2K	52.2%	57.9%	60.0%	50.0%

* The value for the area under the ROC curve for S β 2M/SCreat = 0.27. ** The value for the area under the ROC curve for S β 2M/SCysC = 2.85. TPV = True positive value; FPV = false positive value.

Table 2. Demographic, laboratory, clinical and histological characteristics of lupus nephritis patients

Characteristics (n = 42)		Range
Age, years	37.2 \pm 13.1*	18–78
Gender (male/female)	5/37	
Race (Caucasian/mulatto/Afro-descendant)	28/8/6	
Hypertension	26	
Diabetes mellitus	3	
Tobacco use	1	
Renal biopsy (class III/IV/V/VI)	3/18/11/1	
Serum creatinine, mg/dl	1.20 \pm 0.62*	0.70–4.30
Serum cystatin C, mg/l	1.26 \pm 0.78*	0.45–4.86
eGFR (MDRD), ml/min/1.73 m ²	61.9 \pm 20.0*	11.4–101.0

* Mean \pm SD.

determine lupus nephritis activity (using SLEDAI-2K score and S β 2M/SCysC, S β 2M/SCreat) (see table 1). Multiple linear regression analysis was used to evaluate the association between SLEDAI-2K score and S β 2M/SCysC index after adjusting for age and sex. We used Stata statistical software (SPSS) 12.0 for all statistical analyses (Stata Corporation, Tex., USA).

Results

Demographic Analyses of the Enrolled Population

The mean age of the patients was 37.1 \pm 13.1 years (18–78); 37 (88%) of them were females, 67% Caucasians, 19% mulattos and 14% Afro-descendants. Mean duration of SLE diagnosis was 9.0 \pm 6.5 years (0.1–26.0). Mean GFR measured by the MDRD formula was 61.9 \pm 20.0 ml/min. All patients had used corticosteroids before inclusion in this study as well as during the follow-up according to their global clinical situation and presence or not of SLE activity. Seventy-seven percent of the patients had a renal biopsy, and 54.5% were categorized as class IV (table 2).

Patients who presented with a higher SLEDAI-2K score received a significantly higher dose of corticosteroid or at least there was a tendency to this behavior when considered all groups of doses (data not shown).

Mean S β 2M levels in lupus nephritis was 2.60 \pm 1.50 mg/l. Mean SCreat was 1.20 \pm 0.60 mg/dl and SCysC was 1.26 \pm 0.78 mg/l. Mean S β 2M/SCreat and S β 2M/SCysC were

0.23 \pm 0.07 and 2.02 \pm 0.59, respectively. Mean urRBP level was 0.54 \pm 0.62 mg/l. Correlation coefficients were: SCysC versus SCreat, $r = 0.900$, 1/SCreat versus eGFR (MDRD), $r = 0.949$, 1/SCysC versus eGFR (MDRD), $r = 0.716$. Correlation between the studied indexes (S β 2M/SCreat vs. S β 2M/SCysC) was moderate ($r = 0.571$).

Correlation between Disease Activity and Serum Levels of β 2M and β 2M/CysC

S β 2M showed a stronger correlation with SLEDAI-2K ($r = 0.660$, $p = 0.000$) than S β 2M/SCysC ($r = 0.180$, $p = 0.140$). Using as reference the SLEDAI-2K, the S β 2M/SCreat index was only able to distinguish presence versus absence of activity ($r = 0.589$, $p = 0.00$). dsDNA and C4 showed a weak correlation with SLEDAI-2K ($r = 0.133$, $p = 0.580$), while urRBP showed a moderate correlation ($r = 0.489$, $p = 0.009$). Correlation coefficients of S β 2M/SCreat and S β 2M/SCysC were both weak considering renal criteria of BILAG, as well as C3 and C4 levels, tests classically utilized in the monitoring of SLE activity.

In a multivariate analysis, using multiple linear regression model, predictive factors for SLE activity (using SLEDAI-2K score) were: S β 2M (OR = 1.6, 95% CI: 0.26–2.94, $p < 0.21$), S β 2M/SCreat (OR = 4.0, 95% CI: 1.88–6.21, $p = 0.001$), urRBP (OR = 1.4, 95% CI: 0.39–3.00, $p < 0.50$). S β 2M/SCysC, C4, C3 and dsDNA ($p = 0.119$) did not have statistical association with these activity criteria (SLEDAI-2K score). The odds ratios (initial multiple linear regression model) for those were: S β 2M/SCysC (OR = 0.431, 95% CI: –2.066 to 2.938, $p = 0.725$), C4 (OR = 0.056, 95% CI: –0.102 to 0.215, $p = 0.471$), C3 (OR = 0.009, 95% CI: –0.056 to 0.074, $p = 0.776$) and dsDNA (OR = –2.285, 95% CI: –5.202 to 0.633, $p = 0.119$).

Discussion

SLE is characterized by a large range of possible clinical and serological manifestations and a relapsing-remitting course [1–7]. Distinguishing disease activity from chronic damage and other comorbid diseases could alter its management [8–11]. On the other hand, there is no gold standard for measuring disease activity in SLE [31]. The use of a suitable activity index is desirable even in routine clinical practice as a way for guiding therapeutic decisions as objectively as possible [11].

We proposed the evaluation of S β 2M/SCysC as a possible predictor of SLE activity in lupus nephritis since previous studies had shown increased S β 2M in patients with active SLE [11–18]. It is of note that such previous findings could be influenced by GFR, so we included a GFR level adjustment, using the ratios S β 2M/SCysC and S β 2M/SCreat. Nevertheless, our results showed a weak correlation between SLE activity (using SLEDAI-2K criteria) and such indexes.

Interestingly S β 2M showed a stronger correlation with SLEDAI-2K, as well as with the S β 2M/SCreat index than with S β 2M/SCysC, and the correlation between both serum indexes was moderate. In a multiple linear regression model using as reference the SLEDAI-2K, the S β 2M/SCreat index was able to distinguish presence versus absence of activity as well as S β 2M and urRBP.

This weak correlation between S β 2M/SCysC and SLEDAI-2K could be explained by limitations of this activity criteria score as an outcome measure. For example, it is weighted only by perceived importance of an organ system rather than by the graded severity of manifestations within that organ system. In addition it evaluates the presence or absence of symptoms but not their improvement or worsening within a 10-day window [7, 8]. When we analyzed isolated S β 2M levels, we found high levels of S β 2M in this study population that indicated the GFR influence in its levels; so it was not a good index of activity in lupus nephritis. However, the good correlation observed between S β 2M levels and SLEDAI-2K index could

be due to the fact that S β 2M is a good marker of SLE activity [12–14], and SLEDAI-2K evaluates global SLE activity and not only renal activity. On the other hand, we showed a moderate correlation between S β 2M/SCreat and S β 2M/SCysC. This finding is probably related to a better performance of the SCysC test, being able to detect renal dysfunction earlier than SCreat.

SCysC values showed a tendency to be elevated in our population, a pattern that is probably related to a GFR decline in this group of patients. We expected that S β 2M/SCysC index could be a marker of SLE activity independently of the intensity of GFR impairment, since SCysC is considered as a potential candidate to replace SCreat in renal function evaluation, among other reasons for being less affected by muscle mass [32]. However, recent reports have shown substantial variability in the relationship between GFR and CysC among populations, suggesting that there may be differences in generation, tubular reabsorption, extra-renal elimination or interference of the use of steroid [20, 33, 34]. In fact, there are discrepancies among reports on the association between steroid use and SCysC concentration [35–40], which was not confirmed by us in a previous study too [41].

RBP is a tubular renal dysfunction marker that has been evaluated in patients with active lupus nephritis [42, 43]. In concordance with Sesso et al. [43], we have also shown that urRBP is a predictive marker of SLE activity.

It is of note that our study design has some limitations, such as the small sample and the lack of a gold standard method to evaluate GFR. Minimizing the latter, before the present study, we have evaluated SCysC performance versus a widely accepted GFR test, the plasma iothexol clearance. In such pilot study we observed a good correlation between SCysC and iothexol clearance in the evaluation of healthy voluntary individuals and patients with chronic kidney disease.

In a multivariate analysis, S β 2M, S β 2M/SCreat and urRBP were predictive factors for SLE activity (using SLEDAI-2K score); S β 2M/SCysC and C4 have statistical association with those activity criteria, but not with dsDNA.

As many authors claim that SCysC is a better marker of renal function than SCreat, it would be expected that a serum S β 2M/SCysC index could be a better indicator of renal activity than S β 2M/SCreat, but in the present study it did not add relevant clinical information in the assessment of renal activity in SLE. Considering that SCysC has a higher sensitivity and lower specificity to detected loss of renal function when compared with SCreat, it is possible that S β 2M/SCreat is a better marker for assessment of SLE activity in the lower ranges of GFR.

Further randomized studies are necessary to evaluate the S β 2M/SCysC index in lupus nephritis, to avoid misinterpretation of this marker and define its usefulness in the evaluation of SLE patients.

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