Serum pentosidine levels in systemic lupus erythematosus

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ABSTRACT

Background: Chronic inflammatory diseases lead to glycation of protein, lipids and nuclear acids. One product generated in this context is pentosidine.

Aim: To study pentosidine levels in Systemic Lupus Erythematosus (SLE) and its possible association with disease activity and cumulative damage.

Methods: Pentosidine serum levels were measured in the serum by ELISA commercial kits in 79 patients with SLE. Disease activity index and cumulative damage were studied by SELENA-SLEDAI (Safety of Estrogen in Lupus National Assessment Systemic Lupus Erythematosus Disease Activity Index) and cumulative damage by SLICC/ACR DI (Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for Systemic Lupus Erythematosus) respectively and simultaneously with determination of pentosidine levels. Epidemiological and clinical and serological profile were collected from the charts.

Results: In the 79 studied patients, the SLEDAI ranged from 0 to 12 (median of 0) and the SLICC/ACR-DI from 0 to 4 (median of 0). Serum pentosidine levels did not correlate with SLEDAI neither with SLICC. Patients with discoid skin lesions and photosensitivity had lower levels than those without them, with \( p = 0.04 \) in both.

Conclusion: In SLE, serum pentosidine levels did not reflect activity and cumulative damage. Patients with skin manifestations had lower levels of this biomarker.

1. Introduction

Inflammation causes oxidative stress and favors protein, lipid and nuclear acids glycation creating products collectively denominated as AGEs (Advanced Glycation Products) \[1,2\].

Glycation is a non-enzymatic protein modification that occurs in situations of hyper and normal glycaemia being accelerated in the first situation \[3\].

AGEs are source of neoepitopes because they cause protein structural changes that might be recognized by immune system as non self, leading to autoantibodies formation \[4,5\]. Furthermore, they may bind to specific receptors (RAGEs) found in endothelial cells, monocytes, hepatocytes, etc. And further increase the oxidative stress by producing cytokines and growth factors responsible for angiogenic and thrombogenic responses in endothelial cells \[4\].

One of the members of the AGE family is pentosidine that results from the reaction of pentoses with free amino groups such as...
arginine and lysine [6]. Pentosidine serum and synovial levels have been studied in rheumatoid arthritis (RA) with conflicting results [6, 7]. Senolt et al. [6] found that pentosidine levels were higher in RA patients than in healthy controls but could not find any correlation with clinical disease activity, markers of immune response, or cartilage breakdown. Myiata et al. [3] and Chen et al. [7] found association of this biomarker with RA disease activity.

In the present study we analyzed serum pentosidine in a group of patients with systemic lupus (SLE) and its relationship with disease activity and cumulative damage.

2. Methods

This is a cross sectional study approved by the local Committee of Ethics in Research. All participants signed consent. We included 79 patients that fulfilled at least 4 of the Classification Criteria for SLE from SLICC (Systemic Lupus International Collaborating Clinics) [8]. Patients with associated chronic inflammatory diseases, diabetes, renal failure and who were pregnant were excluded. Information collected from the charts contained epidemiological data (gender, age, ethnic background, disease duration, body mass index and tobacco exposure), cumulative clinical data according to the definition of SLICC classification criteria [8] and autoantibodies profile. Five ml of venous blood was obtained from peripheral vein, aliquoted and stored to –80 °C until pentosidine was measured. At the time of blood collection, ESR (erythrocyte sedimentation rate, C reactive protein (CRP), disease activity by SELENA-SLEDAI (Safety of Estrogen in Lupus National Assessment Systemic Lupus Erythematosus Disease Activity Index) [9] and cumulative damage by SLICC/ACR DI (Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index) [10] were also measured.

Serum pentosidine levels were measured by commercial ELISA kits (XpressBio, Frederick, USA).

For statistical analysis we used the test of Shapiro Wilk to access data distribution. Comparison of serum pentosidine levels according to clinical and serological profile was done by Mann Whitney test. To compare pentosidine levels according to the age groups we used the Kruskall Wallis test. The correlation studies were done by Spearman test, with help of the software Graph Pad Prism version 6.01. The adopted significance was of 5% with Bonferroni correction for multiple comparisons.

| Table 1 |
| Description of epidemiological, clinical and serological characteristics of the studied sample (79 systemic lupus erythematous patients). |

| Female sex (n) | 73/79 | 92.4% |
|----------------|-------|-------|
| Median age (years) | 42 | IQR = 29-51 |
| Median Disease duration (months) | 24 | IQR = 12-62 |
| Auto declared ethnic background (n) | | |
| Caucasians - | 50 | 63.2% |
| Afro descendants- | 29 | 36.7% |
| Disoid lesions (n) | 7/79 | 8.8% |
| Malar rash (n) | 38/79 | 48.1% |
| Photosensitivity (n) | 55/79 | 69.6% |
| Oral ulcers (n) | 31/79 | 39.2% |
| Arthritis (n) | 62/79 | 78.4% |
| Convulsions (n) | 7/79 | 8.8% |
| Psychosis (n) | 7/79 | 8.8% |
| Serositis (n) | 21/79 | 26.5% |
| Hemolysis (n) | 8/79 | 10.1% |
| Leukopenia (n) | 25/79 | 31.6% |
| Lymphopenia (n) | 15/79 | 18.9% |
| Thrombocytopenia (n) | 19/79 | 24.0% |
| Glomerulonephritis (n) | 36/79 | 45.5% |
| Anti-Ro(n) | 33/79 | 41.7% |
| Anti-La (n) | 20/79 | 25.3% |
| Anti-dsDNA (n) | 30/77 | 38.9% |
| Anti -Sm (n) | 20/77 | 25.9% |
| Anti-RNP (n) | 19/77 | 24.6% |
| Direct Coombs (n) | 5/77 | 6.4% |
| Antiphospholipid Antibody syndrome (n) | 5/75 | 6.6% |
| Median SLEDAI | 0 | IQR = 0–3.5 |
| SLICC ACR DI | 0 | IQR = 0-1 |
| Median erythrocyte sedimentation rate (mm) | 22 | IQR = 11.5–40 |
| Median C reactive protein (mg/dL) | 5.0 | IQR = 3.0-11.5 |

All clinical data was considered cumulatively; n = number; IQR = interquartile range; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index; SLICC/ACR DI (Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index).
3. Results

3.1. A- Description of studied sample

Table 1 shows the main characteristics of the studied sample. The serum levels of pentosidine in this sample are in Fig. 1.

3.2. B- study of pentosidine levels according to epidemiological, clinical and serological variables

Table 2 shows that there is no evidence that age, gender and ethnic background impact serum pentosidine levels although lower levels of serum pentosidine were seen in older individuals had.

Table 3 shows the comparison of pentosidine levels according to clinical data.

The comparison of pentosidine levels according to serological profile is on Table 4 that shows that no differences were found.

Levels of pentosidine did not correlate with patients’ ESR (rho = −0.12; 95% CI = −0.35 to +0.12) and CRP levels (rho = −0.17; 95% CI = −0.41 to +0.09), proteinuria (rho = −0.02; 95% IC = −0.24 to +0.20), C3 levels (rho = −0.10; 95%IC = −0.33 to 0.13). Correlation studies of pentosidine level with SLEDAI are shown in Fig. 2. We also did not observe change in pentosidine levels if the patient had active nephritis at time of blood collection or not (p = 0.16).

### Table 2
Serum pentosidine levels according to epidemiological variables.

| Variable                     | Median pentosidine values ng/mL (IQR) | P     |
|------------------------------|--------------------------------------|-------|
| Age (years)                  |                                      |       |
| 19-30                        | 2459 (184.6-3000)                    | 0.40  |
| 31-40                        | 2008 (403.2-2609)                    |       |
| 41-50                        | 1925 (662.4-2664)                    |       |
| >51                          | 1016 (133.6-2363)                    |       |
| Gender                       |                                      |       |
| Female                       | 1892 (377.3-2590.0)                  | 0.87  |
| Male                         | 1411 (31.0-2932.0)                   |       |
| Ethnic Background (auto declared) |                                      |       |
| Caucasians                   | 1865 (182.8-2829.0)                  | 0.50  |
| Afro descendants             | 1892 (368.2-2337.0)                  |       |
| Body mass index              |                                      |       |
| >25 Kg/m²                    | 1865 (31.0-2617.0)                   | 0.63  |
| 25-29.9 kg/m²                | 2088 (804.2-2734.0)                  |       |
| ≤20 kg/m²                    | 1271 (547.8-2660)                    |       |

IQR = interquartile range.
Correlation study of pentosidine levels with SLICC showed \( \rho = 0.02; p = 0.85 \).

4. Discussion

Glycation products are classically linked to poorly controlled diabetes mellitus but they do occur in situations of normoglycemia where they reflect the redox balance [4]. It is believed that they favor the occurrence of macro and microangiopathy in diabetes [4]. So,
it is reasonable to hypothesize that they are elevated in inflammation and may favor cumulative damage in chronic inflammatory diseases. However, our results showed that, in lupus, pentosidine levels do not follow disease activity neither reflect cumulative damage. In RA [3,7] and psoriasis [4] some authors have found association of this biomarker with the degree of inflammation. To understand our results, it is interesting to remember that lupus is a disease with cyclic activity [12] and that the AGF formation is a slow process involving long lived proteins [13]. So, a single measurement evaluates only a momentary value not reflecting the whole process. Also, our studied sample had a low median SLEDAI and this may have precluded a correct interpretation. This was a limitation of the present study; further analysis in patients with higher disease activity are desirable to clarify this point.

Lupus is a disease where inflammation biomarkers are difficult to interpret. C reactive protein, one of the most commonly used inflammatory indicators is usually low in active lupus and one of the given explanations is that patients with this disease can develop autoantibodies against it [14]. A similar process could have happened with pentosidine. Antibodies against glycated IgG have being found in RF-positive RA [5]. Future studies looking further into the presence of pentosidine autoantibodies and into the possible association of immunoglobulin-levels and pentosidine levels would be interesting.

An interesting observation was the finding that patients with skin symptoms (discoid lesions and photosensitivity) had lower levels of serum pentosidine than those without them. In psoriasis, a disease that, contrary to lupus, ameliorates with ultraviolet exposure [15], patients with skin lesions had higher levels of this biomarker [4,16]. Studies by Mizutari et al. [17] showed that AGEs accumulated in sun exposed skin. In this context it would be interesting to study the pentosidine concentration in local skin lesions.

Concluding, we found that pentosidine levels did not correlate with disease activity or cumulative damage in lupus. Further studies are needed to understand the role of this biomarker in skin manifestations of SLE.

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Declaration of competing interest

None.

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