Clinical and subclinical pancreatitis in a cohort of patients diagnosed with systemic lupus erythematosus

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Abstract

Objectives
To evaluate amylase and lipase levels in a cohort of patients diagnosed with SLE, identify patients with subclinical and clinical pancreatitis and investigate factors associated.

Methods
Demographic, clinical and laboratory data were collected, including recent clinical symptoms possibly related to pancreatitis, use of medication, disease activity (SLEDAI-2K), and serum amylase and lipase levels. Patients with pancreatic enzyme levels ≥1.5 times in excess of the upper limit of normal and/or patients with clinical suspicion of pancreatitis were submitted to abdominal CT or US.

Results
The study included 136 SLE patients aged 33.9±11.2 years. Three patients (2.2%) were diagnosed with clinical pancreatitis and 7 (5.1%) with subclinical pancreatitis. Multiple causal factors were associated with increased enzymes levels such as activity of the disease, drug toxicity, hypertriglyceridemia and chronic kidney failure. Patients with clinical and subclinical pancreatitis (n=10) when compared with pancreatitis-free patients had more SLE active, levels were lower for haemoglobin, platelets and albumin, and higher for triglycerides and AST. Thrombocytopenia, high blood sedimentation rate and hypertriglyceridemia were the only variables associated with pancreatitis in the logistic regression model.

Conclusions
The prevalence of clinical and subclinical pancreatitis in SLE patients was low and associated with multiple potential factors. The association of thrombocytopenia and pancreatitis in SLE patients requires further studies.

Key words
systemic lupus erythematosus, clinical pancreatitis, subclinical pancreatitis
Introduction
Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that can affect any organ of the body. Although the joints, skin, kidneys, lungs, heart, vessels and nervous system are the most frequently affected parts, SLE may involve the gastrointestinal tract in up to 22% of patients (1) and — though much more rarely — the pancreas (2-4). The etiology of clinical pancreatitis is usually mechanical (biliary lithiasis) or toxic/metabolic (alcohol, drugs, infection, hypertriglyceridemia). In SLE, in addition to these potential etiologies, pancreatitis has been associated with autoimmune, vascular and thrombotic mechanisms (5-13) and with toxicity induced by drugs (azathioprine, cyclosporin, corticosteroids) (14-17). The prognosis of SLE-related pancreatitis is poor, with a mortality rate of 5–27% (2-3, 18-19).

The diagnosis of pancreatitis is based primarily on the presence of highly increased serum levels of amylase and lipase, but because these enzymes may be affected in a number of other conditions unrelated to pancreatitis, the American College of Gastroenterology (ACG) (20) requires the presence of at least two of the following criteria to confirm diagnosis: 1) characteristic abdominal pain, 2) amylase and/or lipase levels in excess of three times the upper limit of normal and 3) image findings by ultrasound (US), abdominal computed tomography (CT) or magnetic resonance (MRI).

While most studies reporting pancreatic enzyme levels in SLE have been based on patients with clinical symptoms, it is believed that pancreatitis in SLE patients is most often subclinical and therefore asymptomatic. However, to our knowledge, no study has so far systematically investigated subclinical pancreatitis in SLE patients. The objective of this study was to evaluate amylase and lipase levels in a cohort of patients diagnosed with SLE, identify patients with subclinical and clinical pancreatitis and investigate factors associated with increased enzyme levels.

Methods
Consecutive patients diagnosed with SLE according to the criteria of the American College of Rheumatology attending Walter Cantidio University Hospital (HUWC, UFC Medical School, Brazil) between March 2006 and April 2008 were invited to enroll. Following study entry, demographic and clinical data (duration of disease, history of alcoholism, presence of pancreatitis-related disorders such as cholecystopathy, hyperparathyroidism and dyslipidemia) and laboratory findings (blood work-up, blood sedimentation rate, albumin, serum calcium levels, glycemia, total cholesterol and fractions, triglycerides, alkaline phosphatase, creatinine phosphokinase, aspartate transaminase (AST), alanine transaminase (ALT), urea, creatinine, urine analysis, serum amylase and lipase levels) were obtained from all patients. At the same time, patients were systematically evaluated for recent clinical symptoms possibly related to pancreatitis (abdominal pain, nausea, vomiting, abdominal distension, fever) and use of medication during the preceding 30 days. SLE activity was measured with the SLE disease activity index (SLEDAI-2K). Patients with pancreatic enzyme levels ≥1.5 times in excess of the upper limit of normal and/or patients with clinical suspicion of pancreatitis were submitted to abdominal CT or US. Although the findings were evaluated by different radiologists, pancreatitis was diagnosed with the same well established technical and diagnostic criteria (US: increased size and decreased echodensity as well as possible fluid collections (21); CT: diffuse or segmental enlargement of the pancreas, irregularity of the pancreatic contour with obliteration of the peripancreatic fat planes, heterogeneous appearance and areas of decreased density within the pancreas, and variable ill-defined fluid collections (22)). Patients diagnosed with pancreatitis received qualified medical treatment at the rheumatology service and the outcome was registered (cure of pancreatitis, death or complications). Following ACG guidelines (20), patients were diagnosed with clinical pancreatitis when presenting at least
showed the demographic and clinical characteristics of patients with and without pancreatitis. Four patients (2.9%) had lipase levels ≥3 times in excess of the upper limit of normal, respectively. Results

The study included 136 SLE patients aged 33.9±11.2 years, the vast majority of whom were women (94.8%). The average duration of disease following diagnosis was 81.1±67.5 months. The most frequent manifestations were musculoskeletal (85.7%), cutaneous (75.6%) and renal (53.6%). APS (phospholipid antibody syndrome) was observed in 12.5% of the patients. The average SLEDAI was 6.7±8.0. The average levels of haemoglobin and hematocrits were 11.6±2.1 g/dL and 34.8±6.4%, respectively. The average levels of leukocytes and platelets were 7.130±3.947 cells/mm³ and 242,000±90,180 cells/mm³, respectively. The average level of creatinine was 1.18±1.56 mg/dL and the blood sedimentation rate during the first hour was 45.6±30.1 mm. Based on ACG diagnostic criteria of pancreatitis, only 3 patients (2.2%) were diagnosed with clinical pancreatitis and 7 (5.1%) were diagnosed with subclinical pancreatitis (lipase and/or amylase >2× in excess of the upper limit of normal). Table I shows the demographic and clinical characteristics of patients with and without pancreatitis.

Fifteen (11%) and fourteen patients (10.3%) presented serum lipase and amylase levels ≥1.5 times in excess of the upper limit of normal, respectively. Four patients (2.9%) had lipase levels ≥3× in excess of the upper limit of normal (Table II).

### Table I. Demographic and clinical characteristics of patients diagnosed with systemic lupus erythematosus with and without clinical and subclinical pancreatitis.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>SLE patients with clinical and subclinical pancreatitis (n=10)</th>
<th>SLE patients without pancreatitis (n=126)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average ± SD</td>
<td>30.3 ± 10.3</td>
<td>34.3 ± 11.3</td>
<td>NS</td>
</tr>
<tr>
<td>Median (range)</td>
<td>27.5 (22-40)</td>
<td>33 (26-41)</td>
<td>NS</td>
</tr>
<tr>
<td>Female (%)</td>
<td>100</td>
<td>94.4</td>
<td>NS</td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>20</td>
<td>37.3</td>
<td>NS</td>
</tr>
<tr>
<td>Time since diagnosis (months)</td>
<td>51.2 ± 45.9</td>
<td>84.2 ± 68.5</td>
<td>NS</td>
</tr>
<tr>
<td>Median (range)</td>
<td>42 (7-96)</td>
<td>72 (36-108)</td>
<td></td>
</tr>
<tr>
<td>Clinical manifestations present at any time during the course of SLE (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joints</td>
<td>90</td>
<td>83.3</td>
<td>NS</td>
</tr>
<tr>
<td>Skin</td>
<td>80</td>
<td>73.8</td>
<td>NS</td>
</tr>
<tr>
<td>Serosis</td>
<td>10</td>
<td>26.2</td>
<td>NS</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>50</td>
<td>11.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>30</td>
<td>15.0</td>
<td>NS</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>0</td>
<td>10.3</td>
<td>NS</td>
</tr>
<tr>
<td>Nephritis</td>
<td>60</td>
<td>52.4</td>
<td>NS</td>
</tr>
<tr>
<td>Phospholipid antibody syndrome</td>
<td>10</td>
<td>12.7</td>
<td>NS</td>
</tr>
<tr>
<td>Comorbidities (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholecystopathy</td>
<td>20</td>
<td>4.7</td>
<td>0.04</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>10</td>
<td>7.1</td>
<td>NS</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>0</td>
<td>4.7</td>
<td>NS</td>
</tr>
<tr>
<td>Systemic arterial hypertension</td>
<td>40</td>
<td>35.7</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0</td>
<td>3.2</td>
<td>NS</td>
</tr>
<tr>
<td>Recently used drugs (% patients/cumulative average dose ± SD over preceding 30 days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral prednisone (mg)</td>
<td>90/439.5 ± 403</td>
<td>88.1/435.3 ± 530.1</td>
<td>NS</td>
</tr>
<tr>
<td>Oral azathioprine (mg)</td>
<td>20/2650 ± 494.9</td>
<td>20.6/4234.6 ± 5866</td>
<td>NS</td>
</tr>
<tr>
<td>IV pulse cyclophosphamide (mg)</td>
<td>0</td>
<td>6.3/837.5 ± 245.1</td>
<td>NS</td>
</tr>
<tr>
<td>Oral methotrexate (mg)</td>
<td>0</td>
<td>5.5/571 ± 37.2</td>
<td>NS</td>
</tr>
<tr>
<td>Ingestion of alcohol (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>60</td>
<td>53.2</td>
<td>NS</td>
</tr>
<tr>
<td>Presently</td>
<td>10</td>
<td>8.7</td>
<td>NS</td>
</tr>
<tr>
<td>Previously</td>
<td>30</td>
<td>38.1</td>
<td>NS</td>
</tr>
<tr>
<td>SLEDAI-2K</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average ± SD</td>
<td>11.1 ± 8</td>
<td>6.3 ± 7.9</td>
<td>0.05</td>
</tr>
<tr>
<td>Median (range)</td>
<td>12 (5-17)</td>
<td>3 (0-11)</td>
<td></td>
</tr>
</tbody>
</table>

### Table II. Increased amylase and lipase levels in a sample of 136 patients diagnosed with systemic lupus erythematosus.

<table>
<thead>
<tr>
<th>Increased amylase* (n / %)</th>
<th>Increased lipase** (n / %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1.5 times in excess of the upper limit of normal</td>
<td>14 / 10.3</td>
</tr>
<tr>
<td>&gt;2.0 times in excess of the upper limit of normal</td>
<td>5 / 3.7</td>
</tr>
<tr>
<td>&gt;3.0 times in excess of the upper limit of normal</td>
<td>0</td>
</tr>
</tbody>
</table>

* reference value: 28-100 U/L; ** reference value: 13-60 U/L.
One of the 3 patients diagnosed with clinical pancreatitis presented clinical abdominal symptoms, enzyme levels and images compatible with pancreatitis (Table III), a SLEDAI score of 18, high levels of triglycerides (554mg/dL) and serum levels of amylase and lipase 2.5x and 10x in excess of the upper limit of normal, respectively. Pancreatitis resolved after treatment of SLE with corticosteroids concurrently with treatment for hypertriglyceridemia. Another patient with clinical pancreatitis presented no clinical abdominal complaints. Diagnosis was based on increased lipase levels (>3x in excess of the upper limit of normal) and compatible US findings. At the time of evaluation, the disease activity score was 14 and the patient was receiving high dosages of corticosteroids, antibiotics and antifungals. Amylase and lipase levels eventually normalised. One patient was hospitalised with a suspicion of SLE (skin and joint manifestations, vasculitis, thrombocytopenia and antiphospholipid antibody syndrome) and complaints of nausea, vomiting and abdominal pain and distension. The diagnosis of SLE and pancreatitis was confirmed, with the latter attributed to the former. The condition eventually resolved with the administration of corticosteroids and chloroquine.

For the 7 patients (all female) with subclinical pancreatitis, the duration of SLE following diagnosis ranged from 1 month to 8 years. The most frequently observed lupus-related manifestations were nephritis (n=7), skin and joint problems (n=6), thrombocytopenia (n=5), APS (n=2) and lupus anticoagulant positivity (n=1). Most of the patients (n=5) reported no abdominal clinical symptoms and none had com-

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Table III. Characteristics of SLE patients with clinical and subclinical pancreatitis.

<table>
<thead>
<tr>
<th>Age</th>
<th>Duration</th>
<th>Manifestations of SLE</th>
<th>SLEDAI score</th>
<th>Abdominal symptoms resolved?</th>
<th>Probable causes of increased enzyme levels</th>
<th>Image analysis</th>
<th>Serum levels of amylase (A) and lipase (L)*</th>
<th>Times in excess of the upper limit of normal</th>
<th>Manifestation of pancreatitis</th>
<th>Outcome of pancreatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>38</td>
<td>11 y</td>
<td>Skin, joints, nephritis</td>
<td>18</td>
<td>yes</td>
<td>Hypertriglyceridemia (554mg/dL); disease activity?</td>
<td>US: suggestive of pancreatitis; CT: thickening of the pancreas</td>
<td>A=280 L=597</td>
<td>&gt;2.5 &gt;10</td>
<td>Clinical</td>
<td>Resolution</td>
</tr>
<tr>
<td>25</td>
<td>2 y</td>
<td>Skin, joints, thrombocytopenia, seizure, psychosis</td>
<td>14</td>
<td>no</td>
<td>Disease activity? Drugs? (vancomycin, fluconazole)</td>
<td>US: suggestive of pancreatitis</td>
<td>A=201 L=223</td>
<td>&gt;2 &gt;3</td>
<td>Clinical</td>
<td>Resolution</td>
</tr>
<tr>
<td>44</td>
<td>2 w</td>
<td>Skin, joints, vasculitis, thrombocytopenia, antiphospholipid antibody positivity</td>
<td>16</td>
<td>yes</td>
<td>Disease activity</td>
<td>US: suggestive of pancreatitis</td>
<td>A=196 L=220</td>
<td>&gt;2 &gt;3</td>
<td>Clinical</td>
<td>Resolution</td>
</tr>
<tr>
<td>25</td>
<td>8 y</td>
<td>Skin, joints, nephritis, thrombocytopenia</td>
<td>0</td>
<td>no</td>
<td>Drugs? (Azathioprine + Chloroquine)</td>
<td>US and CT: normal</td>
<td>A=51 L=270</td>
<td>Normal &gt;4.5</td>
<td>Subclinical</td>
<td>Resolution</td>
</tr>
<tr>
<td>40</td>
<td>3 y</td>
<td>Skin, joints, nephritis, thrombocytopenia</td>
<td>11</td>
<td>no</td>
<td>Mild chronic kidney failure (Cr=1.3mg/dL), mild hypertriglyceridemia (308mg/dL))</td>
<td>US: normal</td>
<td>L=95</td>
<td>A=280 &gt;1.5</td>
<td>Subclinical</td>
<td>Resolution</td>
</tr>
<tr>
<td>44</td>
<td>8 y</td>
<td>Skin, joints, thrombocytopenia, nephritis</td>
<td>5</td>
<td>no</td>
<td>Mild hypertriglyceridemia (252mg/dL), mild chronic kidney failure (Cr=1.77mg/dL), azathioprine use</td>
<td>Us: normal</td>
<td>L=158</td>
<td>A=163 &gt;2.5</td>
<td>Subclinical</td>
<td>Resolution</td>
</tr>
<tr>
<td>19</td>
<td>1 m</td>
<td>Skin, joints, vasculitis, nephritis, APS</td>
<td>25</td>
<td>yes</td>
<td>Disease activity</td>
<td>TC: normal</td>
<td>A=169 L=164</td>
<td>&gt;1.5 &gt;2</td>
<td>Subclinical</td>
<td>Resolution</td>
</tr>
<tr>
<td>19</td>
<td>6 m</td>
<td>Skin, serositis, nephritis</td>
<td>17</td>
<td>yes</td>
<td>Disease activity, moderate hypertriglyceridemia (499mg/dL)</td>
<td>US: normal</td>
<td>A=109 L=143</td>
<td>Normal &gt;2</td>
<td>Subclinical</td>
<td>Resolution</td>
</tr>
<tr>
<td>30</td>
<td>6 y</td>
<td>Thrombocytopenia, nephritis, CNS involvement, APS</td>
<td>13</td>
<td>no</td>
<td>Terminal chronic kidney failure (Cr=4.5mg/dL)</td>
<td>US: normal</td>
<td>A=205 L=111</td>
<td>&gt;2 &gt;1.5</td>
<td>Subclinical Death from septic shock</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>4 y</td>
<td>Skin, joints, thrombocytopenia, nephritis, lupus ant.coag. positivity</td>
<td>0</td>
<td>no</td>
<td>Terminal chronic kidney failure (Cr=8.6mg/dL)</td>
<td>US: normal</td>
<td>A=225 L=147</td>
<td>&gt;2 &gt;2</td>
<td>Subclinical Did not repeat tests</td>
<td></td>
</tr>
</tbody>
</table>

APS: Phospholipid antibody syndrome; US: ultrasound; CT: computed tomography; * serum amylase reference value: 28-100 U/L; serum lipase reference value: 13-60 U/L; Cr: creatinine.
In lupus patients, apart from increased levels of lipase and amylase, other laboratory tests such as alanine transaminase, triglycerides, blood sedimentation, serum calcium, glycemia, and platelets were also abnormal. The SLEDAI score (average ± SD) was 11.1 ± 0.001. The Clinical manifestations (% were as follows:

- Thrombocytopenia 0.003
- High blood sedimentation rate 0.02
- Hypertriglyceridemia 0.004

The incidence of clinical pancreatitis observed at rheumatology services in the U.S., Europe, China and Mexico varies from 0.7 to 4% (1-2, 4, 24-25). In spite of differences in the ethnic composition of the respective study populations, the incidence found in the present study lies within the expected range. Determining the etiology of pancreatic damage in lupus patients can be very challenging but is important when planning individual therapy. In the general population, pancreatitis is related to biliary lithiasis and alcohol consumption with a frequency of 60–80% (26). In lupus patients, apart from the most well-known pathogenic factors, pancreatitis may be associated with the activity of the disease itself or with toxicity from drug therapy, or it may result from a combination of multiple factors. In one of the 3 patients diagnosed with clinical pancreatitis, the disorder was found to be an early manifestation of SLE activity. This form of manifestation has been described in the literature for 17 cases so far (27), making the current case number 18. The patient was treated with corticosteroids and chloroquine followed by complete resolution of clinical symptoms of SLE and pancreatitis.

In a cohort of 1,811 SLE patients from Johns Hopkins University (4), 71 experienced one or more episodes of clinical pancreatitis. The etiology of pancreatitis was found to be related to SLE in 63 patients (3.5% of the cohort), while it was attributed to other causes in 7 patients (alcoholism n=2; post-traumatic shock n=1; sepsis n=1, cholelithiasis n=1; Despakote-induced toxicity n=1; pancreatic anatomic abnormality n=1). In contrast, in a cohort of 895 SLE patients from Mexico (2) with a prevalence of clinical pancreatitis of 3.5%, sixty percent of the episodes were attributed to mechanical causes (especially cholelithiasis) or toxic/metabolic causes (especially terminal chronic kidney failure, hypertriglyceridemia and alcohol). Thus, to distinguish between lupus-induced pancreatitis and idiopathic pancreatitis, mechanical and toxic/metabolic causes

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### Table IV. Characteristics of subjects displaying levels of amylase and/or lipase >2x in excess of the upper limit of normal in a sample of 136 patients diagnosed with systemic lupus erythematosus.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>SLE patients with clinical or subclinical pancreatitis (n=10)</th>
<th>SLE patients without pancreatitis (n=126)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (average ± SD)</td>
<td>30.3 ± 10.3</td>
<td>34.3 ± 11.3</td>
<td>NS</td>
</tr>
<tr>
<td>Time of diagnosis in months (average ± SD)</td>
<td>51.2 ± 45.9</td>
<td>83.9 ± 68.8</td>
<td>NS</td>
</tr>
<tr>
<td>SLEDAI score (average ± SD)</td>
<td>11.1 ± 0.003</td>
<td>6.3 ± 8.0</td>
<td>0.04</td>
</tr>
<tr>
<td>Clinical manifestations (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>30.0</td>
<td>11.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Laboratory tests (average ± SD)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>9.8 ± 2.8</td>
<td>11.8 ± 2.0</td>
<td>0.02</td>
</tr>
<tr>
<td>Platelets (cells/mm³)</td>
<td>153,000 ± 45,900</td>
<td>250,000 ± 84,565</td>
<td>0.0002</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.2 ± 0.7</td>
<td>3.7 ± 0.8</td>
<td>0.018</td>
</tr>
<tr>
<td>Glycemia (mg/dL)</td>
<td>90.11 ± 20.0</td>
<td>90.6 ± 31.0</td>
<td>NS</td>
</tr>
<tr>
<td>Serum calcium (mg/dL)</td>
<td>8.0 ± 1.5</td>
<td>8.6 ± 1.6</td>
<td>NS</td>
</tr>
<tr>
<td>Blood sedimentation (mm/h)</td>
<td>68.2 ± 46.4</td>
<td>43.7 ± 27.8</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>2.0 ± 2.6</td>
<td>1.1 ± 1.4</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>297.8 ± 149.4</td>
<td>158.9 ± 102.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Aspartate transaminase (U/L)</td>
<td>53.7 ± 0.01</td>
<td>24.2 ± 13.6</td>
<td>0.008</td>
</tr>
<tr>
<td>Alanine transaminase (U/L)</td>
<td>32.7 ± 37.0</td>
<td>24.2 ± 19.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Normal values: Haemoglobin (11.5–16.4g/dL); platelets (130,000–400,000/mm³); albumin (4.3–5.1g/dL); glycemia (70–99mg/dL); serum calcium (8.6–10.4mg/dL); blood sedimentation rate (1-18mm); creatinine (0.4–1.0mg/dL); triglycerides (up to 199mg/dL); aspartate transaminase (5–32 U/L); alanine transaminase (6 –31 U/L). NS: non-significant p-value.

### Table V. Variables associated with clinical and subclinical pancreatitis in 136 patients with systemic lupus erythematosus.

<table>
<thead>
<tr>
<th>Variable</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>0.003</td>
</tr>
<tr>
<td>High blood sedimentation rate</td>
<td>0.02</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Diabetic criteria, approximately 2.2% had clinical pancreatitis and 5.1% had subclinical pancreatitis.
must first be ruled out. Even then, the
pathogenic mechanisms responsible for pancreatic injury remain unexplained,
although vascular mechanisms have
been pointed out as the most likely, in-
cluding vasculitis and arterial occlusion
associated with APS (5–9, 11).

SLE activity has been associated with
the appearance of clinical pancreatitis
in a number of reports (2, 19). In a re-
view of 77 subjects with SLE and clini-
cal pancreatitis, disease activity was
associated with a frequency of 84% (19).
SLE activity was significantly greater
among lupus patients with idiopathic
pancreatitis than in lupus patients with
pancreatitis associated with mechanical
toxic/metabolic causes (2). In our study,
all 3 patients with clinical pan-
creatitis displayed high SLEDAI-2K
scores. However, clinical pancreatitis
in SLE patients may present in vari-
ous forms: it may be associated with a
flare of the disease, it may occur during
remission or at the beginning of SLE,
and it may unexpectedly affect patients
with long-standing disease (26).

Some drugs used in the treatment of
SLE (corticosteroids, azathioprine)
have been implicated in the etiology
of clinical pancreatitis, but causality
has never been clearly established (14-
17). In a study by Saab et al. involving
a series of 8 patients with inactive lu-
pus, clinical and laboratory parameters
of acute pancreatitis improved with
increased administration of corticoids
(16). Other studies have confirmed the
therapeutic effect of corticosteroids on
lupus-related pancreatitis (2, 3, 19, 26,
27). Several authors suggest treating
pancreatitis with corticosteroids only
after ruling out toxic/metabolic and
mechanical factors, and recommend
discontinuing any drug suspected of in-
ducing pancreatitis.

Lipase levels were higher than amylase
levels in all 3 cases of clinical pancrea-
titis. Thus, in these patients the labora-
tory criterion for clinical pancreatitis
(amylase and/or lipase levels >3x in
excess of the upper limit of normal)
was met for lipase only. The proportion
of clinical pancreatitis patients with
hyperlipasemia alone is reported to be
up to 32% (28–32). Nevertheless, some
authors believe hyperlipasemia in the
presence of normal amylase levels is
more likely related to non-pancreatic
sources of lipase (kidney failure, ma-
lignant neoplasia, acute cholecystitis,
esophagitis and hypertriglyceridemia)
(33).

Although serum levels of amylase are
conventionally considered the gold
standard for diagnosing pancreatitis
due to their high sensitivity, as a marker
lipase displays both high sensitivity and
high specificity as it is mainly released
by the acinar cells of the pancreas. In
contrast, amylase may come not only
from the pancreas, but from the sali-
ary glands and, to a smaller extent,
the Fallopian tubes, lungs and liver.

Several non-pancreas-related condi-
tions are also associated with hyper-
amylasemia, including kidney failure,
macroamylasemia, parotitis, perforated
esophagus, pregnancy and endoscopic
retrograde cholangiopancreatography,
but amylase levels 3x in excess of the
upper limit of normal are highly spe-
cific for pancreatitis.

Although about 57% of lupus patients
affected with clinical pancreatitis are
reported to develop severe complica-
tions with 45% mortality (19), no com-
plications or deaths were observed in
our patients. It is possible that the sys-
tematic investigation carried out for
this study helped diagnose and treat
patients earlier, thereby affecting the
outcome positively. Likewise, the mor-
tality rate of the Hopkins Lupus Cohort
(3%) was considerably lower than av-
dage due to close monitoring and early
diagnosis and treatment (4).

Based on ACG criteria, the incidence
of subclinical pancreatitis (5.1%) in our
sample was considerably lower than the
incidence reported by most authors.
Eberhard et al. measured serum immu-
noreactive cationic trypsinogen levels
sequentially in 20 children with SLE
(high levels reflect pancreatic injury)
and found a 35% increase at the time
of diagnosis, which normalised dur-
ing treatment for lupus (34). In a study
from 1988 evaluating amylase levels
in 25 SLE patients and 15 controls, 5
patients (20%) had hyperamylasemia
without symptoms (controls displayed
normal levels) (35). Several authors re-
fer to a ~30% incidence of hyperamy-
lasemia in asymptomatic SLE-related
pancreatitis, to our knowledge no other
studies systematically evaluating amy-
lase and lipase levels in asymptomatic
SLE patients have been published. The
observed incidence of 5.1% might at
first sight appear underestimated, but
the figure is based on blood samples
collected from all consented SLE in-
and outpatients, regardless of demo-
graphic and clinical aspects. The low
or moderate SLEDAI scores (average:
6.7) and low rates of alcohol consump-
tion, cholecystopathy and dyslipidemia
among our patients may have contrib-
uted to reduce the incidence.

None of our patients with subclini-
cal pancreatitis displayed pancreatic
changes on US or CT and most had no
clinical abdominal complaints. Two
were diagnosed with APS and one was
lupus anticoagulant-positive, but none
had thrombotic manifestations at the
time of diagnosis of pancreatitis. Of the
7 patients with subclinical pancreatitis,
only one (with active SLE) presented
no other factors potentially associated
with increased pancreatic enzyme lev-
els. Interestingly, 4 of the 7 patients
experienced chronic kidney failure, in-
cluding 2 patients receiving haemodi-
alysis. Amylase and lipase levels may
be moderately increased in patients
with chronic kidney failure due to re-
duced renal excretion of enzymes.

Clinical and subclinical pancreatitis
were associated with the same condi-
tions: disease activity, mild to moderate
hypertriglyceridemia, terminal chronic
kidney failure, use of azathioprine and
use of mycophenolate mofetil. Overall,
much more than one factor was associated
with the observed increase enzyme lev-
els. The latter returned to normal in al-
most all cases.

Interestingly, thrombocytopenia was
an unusually common manifestation of
SLE in patients with both clinical and
subclinical pancreatitis. In fact, throm-
bocytopenia, high blood sedimentation
rate and hypertriglyceridemia were the
only variables to remain independently
associated with clinical and/or subclini-
cal pancreatitis in the logistic regres-
sion model. A high blood sedimentation
rate may reflect either pancreatitis-
related SLE activity or inflammatory
injury from pancreatitis. Hypertriglyceridermia is known to be associated with pancreatic injury, especially at high levels. SLE patients may present several conditions associated with increased levels of triglycerides, including obesity, diabetes mellitus, hypothyroidism, alcoholism and corticotherapy. Levels of triglycerides above 1000mg/dL may cause pancreatitis, while levels above 2000mg/dL practically indicate a causal relation (36). Since none of our patients with hypertriglyceridermia displayed levels above 600mg/dL, the etiology of pancreatitis must in this case be attributed to a combination of factors. The finding of thrombocytopenia and pancreatitis in SLE patients gives rise to a range of speculations. It may reflect severe disease and a greater potential for complications caused by the disease itself or by the toxicity of the drugs employed in the treatment, or it may be secondary to APS-related or non-APS-related vascular thrombotic manifestations. The association of thrombocytopenia and pancreatitis in SLE patients requires further studies.

References