Role of Fetuin-A in Systemic Sclerosis-associated Calcinosis

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To the Editor:

Calcinosis, a soft-tissue calcification occurring in the setting of normal serum calcium and phosphate levels, has been observed in connective tissue diseases, including systemic sclerosis (SSc)\(^1\), more frequently in the limited form (lcSSc) and in patients who are anticientromere antibody (ACA)-positive\(^1\). Calcinosis may be exceedingly painful and cause major clinical problems, including ulceration, infection, and joint contractures\(^1\). Hypovascularity, hypoxia, and tissue damage seem to favor its development, with genetic factors also playing a role. No treatment exists so far, and even surgical removal is unsatisfactory, since recurrences are common\(^1\).

Fetuin-A (α-2-Heremans-Schmid glycoprotein, AHSG) is a major inhibitor of systemic calcification, and low serum levels have been associated with vascular and soft-tissue calcifications\(^2\). Any situation that lowers serum fetuin-A, including inflammatory conditions, could increase the risk of calcification, because fetuin-A is a negative acute-phase protein. AHSG gene variations seem to influence fetuin-A serum concentration\(^3\).

Forty-one consecutive Italian patients with SSc (40 women, age 63 ± 13 years, 16 diffuse SSc (dcSSc), 25 lcSSc) were studied. Standard hand, shoulder, pelvis, knee, and foot radiographs were reviewed by a radiologist blinded to the clinical data. All patients were screened for ACA (indirect immunofluorescence, Hep-2 cells) and topoisomerase I (ELISA); all had plasma levels of glucose, calcium, phosphorus, and C-reactive protein within normal limits; none had renal disease or cancer. Evaluation included disease duration, skin thickness, digital ulcers, visceral (lung, heart, gastrointestinal tract) and microvascular involvements, and treatment (immunosuppressants, calcium-channel blockers, prostanoids, endothelin receptor antagonists, proton pump inhibitors). Nailfold capillaroscopic analysis (videocapillaroscopy 200, DS Medica, Milan, Italy) was performed following the Sulli, \textit{et al} indications\(^4\) using a semiquantitative scale from 0 to 3 (0, no changes; 1, 33% capillary alterations/reduction per linear mm; 2, 33%-66%; 3, >66%), and adding the scores to globally assess the microangiopathy\(^5\).

Genotype analysis for the most common polymorphisms on the AHSG gene (T256S) was performed as described\(^3\). Due to technical problems, fetuin-A was measured (ELISA, Epitope Diagnostics Inc., San Diego, CA, USA) in only 23 randomly selected patients (13 lcSSc, 10 dcSSc, 15 calcinosis), and capillaroscopic analysis was done in 11 of these 23.

Patients gave written informed consent. Approval was obtained by our Ethics Committee (ASL Milano 2, Italy; protocol number 2076).

Calcinosis was found in 48.8% of patients (13 lcSSc, 7 dcSSc) and the hand was the most frequent site (65% of patients, 7 lcSSc, 6 dcSSc).

Fetuin-A levels were significantly lower in patients with calcinosis (0.66 ± 0.25 vs 0.94 ± 0.26 g/l; \(p = 0.019\)), in patients with lcSSc, independently of calcinosis (0.67 ± 0.29 g/l in lcSSc vs 0.88 ± 0.23 g/l in dcSSc; \(p = 0.065\)), and tended to be lower in ACA-positive patients (0.71 ± 0.08 vs 0.82 ± 0.09 g/l). No differences were found with respect to anti-topoisomerase I autoantibodies. A significant relationship was found between fetuin-A, capillaroscopic abnormalities (Figure 1) and digital ulcers (0.68 ± 0.27 g/l in patients with ulcers vs 0.91 ± 0.26 g/l, patients with no ulcers; \(p = 0.07\)). No relationships were found between fetuin-A, SSc duration, visceral involvement, skin thickness, or drugs (data not shown), nor between AHSG 256 C/G polymorphism, calcinosis (Table 1), and fetuin-A levels (data not shown).

To our knowledge, this is the first study to address the role of fetuin-A in SSc calcinosis. The high frequency of calcinosis we found is in agreement with the majority of reported data\(^1\).

The lower fetuin-A levels found in calcinosis would suggest its role as a calcification inhibitor also in SSc, and the lower levels found in patients with lcSSc are in accord with lcSSc as the type of SSc more frequently associated with calcinosis.

Few contrasting data exist concerning the relationship between fetuin-A levels and AHSG polymorphisms\(^5,6\), probably because of small sample sizes examined and different populations. In this respect, our study is in accord with the only other Italian report, which showed no association between AHSG polymorphisms and circulating fetuin-A\(^7\).

Our capillaroscopic data seem to indicate a role for fetuin-A in SSc microvascular damage, and are consistent with previous observations linking calcinosis to SSc vascular complications, and with the recent observation of a more prominent vascular disease in patients with lcSSc\(^8\). The observations that fetuin-A can contribute to endothelial dysfunction, has antifibrotic characteristics, and participates in tissue remodeling, coupled with the finding of an independent association between fetuin-A levels and endothelin-1 (ET-1)\(^9\), further support its role in SSc microangiopathy, since endothelial dysfunction, fibrosis, and ET-1 are involved in SSc pathogenesis\(^10\).

Any association of fetuin-A with vascular disorders is under intense investigation, because of the potential for using fetuin-A as a treatment for calcifications. It worth noting that increasing fetuin-A with the phosphate binder sevelamer improved flow-mediated dilatation in chronic kidney diseases\(^10\).

Our data suggest a potential role for fetuin-A in microvascular involvement of SSc.

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\(\text{AHSG: α-2-Heremans-Schmid glycoprotein; NS: not significant.}\)

\(\text{Table 1. AHSG 256C/G gene polymorphism distribution in 41 patients with systemic sclerosis.}\)

<table>
<thead>
<tr>
<th>AHSG 256 C/G</th>
<th>Calcinosis +, No. (%)</th>
<th>Calcinosis –, No. (%)</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC</td>
<td>1 (5)</td>
<td>3 (14)</td>
<td>NS</td>
</tr>
<tr>
<td>GC</td>
<td>5 (25)</td>
<td>5 (24)</td>
<td>NS</td>
</tr>
<tr>
<td>GG</td>
<td>14 (70)</td>
<td>13 (62)</td>
<td>NS</td>
</tr>
<tr>
<td>G allele frequency</td>
<td>0.82</td>
<td>0.74</td>
<td>NS</td>
</tr>
</tbody>
</table>

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\(\text{Figure 1. Relationship between fetuin-A serum levels and global capillaroscopic score in 11 patients with SSc. Global score was obtained from the sum of the scores of loss of capillaries, disorganization of the vascular array, giant capillaries, irregularly enlarged capillaries, capillary ramifications, and hemorrhages (r = 0.72, p = 0.01).}\)

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\(\text{Figure 2. Relationships between AHSG 256 C/G polymorphism and fetuin-A serum levels in patients with systemic sclerosis.}\)
REFERENCES


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