Evidence for better response to somatostatin analogue treatment in acromegalic patients treated with metformin

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Background

- Surgery: 60% cure
- Medical therapy (somatostatin analogs): 40-50% cure, 40% resistance
- SA+DA
- GHR antagonist
- repeat surgery/radiotherapy

Comorbidities:
- Cardiomyopathy
- Hypertension
- Coronary artery disease
- Hypopituitarism
- Diabetes mellitus

Cohort presentation

<table>
<thead>
<tr>
<th>Therapy modalities</th>
<th>Total</th>
<th>Primary therapy</th>
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<tbody>
<tr>
<td>TSS</td>
<td>49</td>
<td>23</td>
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<tr>
<td>SSA</td>
<td>36</td>
<td>20</td>
</tr>
<tr>
<td>N=49</td>
<td>N=25</td>
<td>N=14</td>
</tr>
<tr>
<td>N=35</td>
<td>N=11</td>
<td>N=14</td>
</tr>
<tr>
<td>N=49</td>
<td>N=11</td>
<td>N=14</td>
</tr>
</tbody>
</table>

Response to treatment with SSA

- 2DM
  - N=12
- Hypopituitarism
  - N=18

Metformin treatment correlates with improved response to SSA treatment

No correlation between age, gender, disease duration, other treatment modalities and change of IGF-1 after SSA treatment:
- Age p=0.183
- Gender p=0.397
- Disease duration p=0.686
- Hydrocortisone p=0.173
- Testosterone p=0.085
- L-thyroxine p=0.721

No correlation between IGF-1 lowering response to SSA and substitution treatment with hydrocortisone, testosterone, thyroxin (variance inflation factor <3)

Metformin reduces GH synthesis in vitro

In vitro experiments in GH3 cells

<table>
<thead>
<tr>
<th>Metformin (nM)</th>
<th>GH (ng/ml)</th>
<th>CT</th>
<th>Met 500µM</th>
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<tbody>
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<tr>
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Human acromegalic tumors in vitro (n=7)

<table>
<thead>
<tr>
<th>Metformin (nM)</th>
<th>GH (ng/ml)</th>
<th>CT</th>
<th>Met 500µM +Oct 1nM</th>
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<tbody>
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<tr>
<td>100</td>
<td>120</td>
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</table>

Summary

- The aim of this study was to analyze the impact of the concomitant antidiabetic treatment with metformin and hormone replacement on the response to SSA
- Data showed no correlation between SSA (p=0.71) and transsphenoidal surgery (p=0.541) on the incidence of pituitary insufficiency
- Regression analysis showed no correlation between IGF-1 lowering response to SSA and substitution treatment with hydrocortisone, testosterone, l-thyroxin (VIF <3)
- No correlation between age, gender, disease duration, other treatment modalities and change of IGF-1 after SSA treatment
- Linear regression analysis showed correlation between metformin therapy and change of IGF-1 levels after SSA treatment (p=0.031; R-square change: 0.135; R-square: 0.321)
- In vitro investigation showed that metformin enhances GH-suppressive effect of octreotide
- These preliminary observations indicate that hormone replacement does not affect SSA response, but metformin treatment improves SSA response in terms of IGF-1 reduction