Pregnancy-associated plasma protein-A (PAPP-A) as a mortality predictor of long-term hemodialysis patients

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PAPP-A
pregnancy-associated plasma protein A

- metalloproteinase, cleaves IGFBP-4 → IGF-1 increase
- screening of Down syndrome in the 1st trimester
- present in ruptured atherosclerotic plaques
- biomarker of acute coronary syndrome
- increased in HD patients, related to renal function
PAPP-A and survival of HD patients – a pilot study

40 patients, 20 months follow-up, 22 patients+
dead vs. living patients 26.8 (21.6-36.8) vs. 20 (14.9-26.6), p=0.034

Kalousová et al., Blood Purif 2004
Aim of the study

PAPP-A and related parameters
- other pregnancy protein – placental growth factor - PI GF
- matrix metalloproteinases – MMP-2 and MMP-9
- molecules linked to PAPP-A action – IGFBP-4 and IGF-1
- established cardiac markers – cTnI, BNP
- inflammatory markers – CRP; retinol

→ relationship of their serum levels
to prognosis of long term hemodialysis patients
in 5-years follow-up
Prospective observational study

261 long-term hemodialysis patients
  • follow-up for 5 years (11/2003-11/2008)
  • patients from 6 HD centres in the Czech Republic
  • 141 men and 120 women, mean age 64±13 years
  • clinical and laboratory characteristics collected at the beginning of the study

66 healthy controls
  • 25 men and 41 women, mean age 59±9 years
Clinical characteristics of hemodialysis patients

- duration of HD treatment – median 2 years
- diabetes mellitus - 33%
- dyslipidemia - 41%
- hypertension - 84%
- cardiovascular disease - 61%
- cerebrovascular disease - 24%
- peripheral vascular disease - 25%
Basic laboratory parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HD patients</th>
<th>Controls</th>
<th>p HD vs. controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/L)</td>
<td>106±13.2</td>
<td>141±10.1</td>
<td>&lt;0.001</td>
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<tr>
<td>Creatinine (µmol/L)</td>
<td>753±198</td>
<td>88±13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>37.8±3.8</td>
<td>44.4±2.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>10.0±16.5</td>
<td>3.3±2.4</td>
<td>0.002</td>
</tr>
<tr>
<td>Leukocytes (x10⁹/L)</td>
<td>6.92±1.95</td>
<td>6.41±1.70</td>
<td>0.1</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.4±4.52</td>
<td>25.5±3.42</td>
<td>0.9</td>
</tr>
</tbody>
</table>
Follow up of HD patients - 5 years

- + 146 patients (56%)
  - 71 – cardiovascular cause
  - 42 – infection
  - 14 – tumour
  - 15 – other cause

- 52 patients – transplantation, 8 of them +
- 2 patients censored due to other reason
Laboratory methods

- **PAPP-A** – TRACE (KRYPTOR, Brahms)
- **PlGF, IGFBP-4, MMP-2 and MMP-9** – ELISA (RD Systems)
- **IGF-1** – IRMA
- **BNP and cTnI** – CLIA
- **Retinol** – HPLC
- Basic nutritional and inflammatory parameters - standard methods, automated analyzers
Statistical analysis

- software SPSS v.16.0
- Survival analysis
  - Kaplan-Meier analysis
  - Cox regression – univariate and multivariate analysis (forward and backward methods)
- overall mortality, cardiovascular mortality, mortality due to infection
- transplantation taken as time dependent covariate
- BCH parameters treated as continuous variables
- HR (95%CI) expressed per SD, for age per year
PAPP-A

• 27.6±15.5 mIU/L in HD vs. 9.4±2.5 mIU/L in controls, p<0.001

• Significant independent predictor
  – for overall mortality
    HR/SD (95%CI) 1.237 (1.060-1.444), p=0.007
  – for mortality due to infection
    HR/SD (95%CI) 1.416 (1.115-1.798), p=0.004
  – not for cardiovascular mortality
Overall mortality
PAPP-A below and over 30.8 mIU/L (upper quartile), p=0.03
Other markers and mortality
all increased in HD except for MMP-9

• **PlGF** – n.s. (p=0.08-0.1)
• **MMP-2 and MMP-9** – n.s.
• **IGFBP-4** – n.s.
• **IGF-1** – significant in uni-variate analysis
• **cTnI** – significant in both uni-variate and multi-variate analysis for overall and cardiovascular mortality
• **BNP** - significant only in uni-variate analysis for overall and cardiovascular mortality
• **Retinol** - significant in both uni-variate and multi-variate analysis for overall and cardiovascular mortality

### Significant independent mortality predictors

<table>
<thead>
<tr>
<th>Overall</th>
<th>Cardiovascular</th>
<th>Due to infection</th>
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</thead>
<tbody>
<tr>
<td>PAPP-A</td>
<td>cTnI</td>
<td>PAPP-A</td>
</tr>
<tr>
<td>cTnI</td>
<td>Albumin</td>
<td>Creatinine</td>
</tr>
<tr>
<td>Albumin</td>
<td>Retinol</td>
<td>Diabetes mellitus</td>
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<td>Creatinine</td>
<td>Cardiovascular disease</td>
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<tr>
<td>Retinol</td>
<td></td>
<td>in the personal history</td>
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<tr>
<td>Age</td>
<td>Transplantation</td>
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  Dr. Nýdlová (Strakonice)
- laboratory staff
  Dr. Soukupová and Mrs. Hudcová
- patients and controls

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