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

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Patients with chronic kidney disease

- High mortality rate mainly due to cardiovascular complications
- They differ from the general population
- Classical risk factors as well as non-traditional/uremia-related ones are involved

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

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 – cTnl, BNP
- inflammatory markers – CRP, retinol

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

Study design: Prospective observational cohort 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>109±13.2</td>
<td>141±10.1</td>
<td>&lt;0.001</td>
</tr>
<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</td>
<td>44±4.2</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 (x10³/L)</td>
<td>6.9±2.95</td>
<td>6.4±1.70</td>
<td>0.1</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.4±5.2</td>
<td>25.5±4.2</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 to due other reason

Laboratory methods

- PAPP-A – TRACE (KRYPTOR, Brahms)
- PI GF, IGFBP-4, MMP-2 and MMP-9 – ELISA (RD Systems)
- IGF-1 – IRMA
- BNP and cTnl – 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

Results: PAPP-A

- 27.6±15.5 μIU/mL in HD vs. 9.4±2.5 μIU/mL 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 μIU/mL (upper quartile), p=0.03

Other markers and mortality

all increased in HD except for MMP-9

- PI GF – 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
- cTnl – 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 cardiovascular mortality (Kalousová et al. Am J Kidney Dis 2010)

Conclusion

This study demonstrates PAPP-A as an independent predictor of overall mortality and mortality due to infection in hemodialysis patients. Our results suggest superior relationship of PAPP-A to infection-inflammation than to cardiovascular risk in HD patients.

Acknowledgement

- physicians and nurses from co-operating dialysis centres
- Dr. Křížková, Dr. H. Benáková and Dr. Dr. Němeček (Prague)
- Dr. Květa, Dr. H. Benáková and Dr. Dr. Němeček (Ostrava)
- laboratory staff
  - Dr. Soukupová and Mrs. Hudcová
- patients and controls

Significant Independent Mortality Predictors for Overall, Cardiovascular and due to Infection Mortality

<table>
<thead>
<tr>
<th>Overall mortality</th>
<th>Cardiovascular mortality</th>
<th>Mortality due to infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAPP-A</td>
<td>1.237 (1.060-1.444)</td>
<td>1.416 (1.115-1.798)</td>
</tr>
<tr>
<td>cTnl</td>
<td>1.417 (1.200-1.658)</td>
<td>2.000 (1.200-3.300)</td>
</tr>
<tr>
<td>Albumin</td>
<td>0.725 (0.589-0.875)</td>
<td>0.905 (0.647-1.274)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.790 (0.607-0.978)</td>
<td>1.072 (0.875-1.306)</td>
</tr>
<tr>
<td>Retinol</td>
<td>0.775 (0.682-0.860)</td>
<td>0.871 (0.692-1.092)</td>
</tr>
<tr>
<td>Paraoxonase</td>
<td>0.621 (0.368-1.058)</td>
<td>0.983 (0.588-1.682)</td>
</tr>
<tr>
<td>Age</td>
<td>1.035 (1.031-1.049)</td>
<td>1.000 (1.000-1.000)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.025 (0.909-1.048)</td>
<td>2.966 (2.500-3.540)</td>
</tr>
<tr>
<td>CVD</td>
<td>1.039 (0.909-1.048)</td>
<td>1.000 (1.000-1.000)</td>
</tr>
<tr>
<td>Transplantation</td>
<td>1.031 (0.980-1.082)</td>
<td>1.000 (1.000-1.000)</td>
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The study was supported by grant GA MŠk N 1043-4/2008 and by the research project MSM 0021602087.