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Pregnancy-associated plasma protein A associates with cardiovascular events in diabetic hemodialysis patients

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ABSTRACT

Objective: Pregnancy-associated plasma protein A (PAPP-A) has prognostic impact in pregnancy and acute coronary syndrome. Patients with chronic kidney disease have an excessive cardiovascular risk. In an effort to identify novel risk factors for cardiovascular disease, we investigated the relationship of PAPP-A with specific outcomes in diabetic patients undergoing dialysis.
Methods: PAPP-A was measured in 1098 diabetic hemodialysis patients, who participated in the German Diabetes and Dialysis Study and followed-up for a median of 4 years. By Cox regression analysis, we assessed the association of baseline levels of PAPP-A with all-cause mortality, combined cardiovascular events and the specific outcomes of sudden death, stroke, myocardial infarction and infectious mortality.
Results: Patients had a mean age of 66 ± 8 years (54% male) and median PAPP-A concentration of 17 mIU/L (IQR 13.4–20.9 mIU/L). Per standard deviation increase in PAPP-A the adjusted risk of sudden cardiac death increased by 23% (HR 1.23, 95%CI 1.12–1.36). Categorical analyses showed that the patients in the 4th PAPP-A quartile had an adjusted 2.6 fold increased risk of sudden death and 2.8 fold increased risk of stroke as compared to the patients in the 1st quartile. Similarly, the risk of combined cardiovascular events was significantly elevated by the factor 1.5 in patients of the 4th quartile. Additionally, PAPP-A levels were associated with infectious deaths and all-cause mortality.
Conclusions: PAPP-A is associated with sudden death, stroke and infectious complications in diabetic dialysis patients. PAPP-A may be useful for risk assessment and monitoring in populations at high risk of cardiovascular events.

Abbreviations: PAPP-A, pregnancy associated-plasma protein A; HR, hazard ratio; IGFBP, insulin like growth factor binding protein; IGF, insulin like growth factor; CKD, chronic kidney disease; CAD, coronary artery disease; CHF, congestive heart failure; MI, myocardial infarction; BMI, body mass index; TRACE, time resolved amplified cryptate emission; CVE, cardiovascular events; SCD, sudden cardiac death; CI, confidence interval; BP, blood pressure; PVD, peripheral vascular disease; LDL, low density lipoproteins; HDL, high density lipoproteins.

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1. Introduction

Mortality of dialysis patients is excessive; the registry in the United States (USRDS) reports an annual mortality of >20%. Cardiovascular disease largely contributes to the excess risk. Diabetic dialysis patients have a higher comorbidity and even poorer outcome as compared to non diabetic patients on dialysis [1], which is reflected by a five year survival of only 35% [2]. Therefore, identification of unknown risk factors is an important task in order to develop novel interventional strategies.

Pregnancy-associated plasma protein A (PAPP-A) is a zinc-binding metalloproteinase which cleaves insulin like growth factor binding proteins, mainly IGFBP-4 [3] thus increasing insulin like growth factor (IGFs) and so allowing their action. The protein was first described in plasma of pregnant women (1974) [4]. Its concentration markedly increases during pregnancy and is 100-fold elevated in the first trimester of pregnancy as compared to healthy non-pregnant women and men [5,6]. PAPP-A is also used routinely for screening of chromosomal anomalies in the first trimester of pregnancy [7]. Studies in previous years clearly demonstrate its significance also outside pregnancy, mainly in coronary artery disease [5] and chronic kidney disease [6,8–10]. Similarly to other proteins, which appear and increase in pregnancy, PAPP-A is required for normal growth and prenatal development [11], while its increased concentrations later in the life is connected with pathological states [5,6,12].

In 2001, the presence of PAPP-A was shown for the first time in eroded and ruptured atherosclerotic plaques as well as increased levels in patients with acute coronary syndrome [5]. It was further shown that PAPP-A is a predictor of cardiovascular events among patients presenting with cardiac chest pain [13].

Studies in patients with kidney diseases found a relationship of PAPP-A to renal function with highest levels in patients on dialysis [12]. The molecule demonstrated prognostic potential in long-term hemodialysis patients [8–10] and renal transplant recipients [14]. Its role in specific cardiac and vascular events is unknown and of major interest. Patients with CKD represent a high-risk population for cardiovascular events and the pattern and composition of adverse events is changing in advanced stages of CKD.

Hence, the aim of our study was to evaluate the relationship of PAPP-A with adverse clinical events, including sudden death, stroke, myocardial infarction and infectious deaths in a large cohort of patients with diabetes undergoing hemodialysis namely participants of the German Diabetes and Dialysis Study (4D study).

2. Material and methods

2.1. Study design and participants

The 4D study methodology has previously been reported in detail [15]. The 4D study was a prospective randomized controlled trial investigating atorvastatin in 1255 patients with type 2 diabetes mellitus, age 18–80 years, and on hemodialysis for less than 2 years. Between March 1998 and October 2002, patients were recruited in 178 dialysis centers in Germany. The study conformed with the principles outlined in the Declaration of Helsinki. It was approved by the medical ethical committee, and all patients gave their written informed consent before inclusion.

2.2. Data collection

Information on age, gender and smoking status was obtained through patient interviews. Comorbidities, including the presence of coronary artery disease (CAD) and congestive heart failure (CHF), as well as the duration of diabetes mellitus and dialysis treatment were reported by the patients' nephrologists. CAD was defined by a history of MI, coronary artery bypass grafting surgery, percutaneous coronary intervention, and the presence of CAD, as documented by angiography. CHF was defined according to the classification system of the New York Heart Association. Blood pressure was measured in sitting position. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared.

2.3. PAPP-A measurements

PAPP-A was measured in serum samples taken at baseline before randomization and stored at −80 °C. Blood was sampled before the start of dialysis sessions and administration of heparin or other medication.

PAPP-A was assessed immunochemically with TRACE (Time Resolved Amplified Cryptate Emission) technology based on non-radiating energy transfer. The commercial kit for PAPP-A determination (BRAHMS GmbH, Thermo Fisher Scientific) contains two different monoclonal antibodies – one is conjugated with europium cryptate and the other one with the fluorescent agent XL 665. The antigen (PAPP-A) present in serum samples is sandwiched between two conjugates. The fluorescent signal measured during the formation of the antigen–antibody complex by the KRYPTOR analyzer is proportional to the antigen concentration. The results are expressed in mIU/L. The intra-assay and inter-assay coefficients of variation were 9.6% and 8.8%, respectively [16].

2.4. Outcome assessment

The primary endpoint of the 4D study was defined as a composite of cardiac death, non-fatal myocardial infarction (MI) and stroke, whichever occurred first (combined cardiovascular events; CVE). Sudden cardiac death (SCD) was considered as: death verified by terminal rhythm disorders in an electrocardiogram; death observed by witnesses within 1 h after onset of cardiac symptoms; death confirmed by autopsy; unexpected death, presumably or possibly of cardiac origin and in the absence of a potassium level larger or equal to 7.5 mmol/L before start of the three most recent hemodialysis sessions. MI was diagnosed when at least two of three criteria were met: typical symptoms; elevated levels of cardiac enzymes; diagnostic changes in the electrocardiogram. Stroke was defined as a neurologic deficit lasting longer than 24 h. Computed tomographic or magnetic resonance imaging was available in all but 16 cases. The 4D study endpoints were centrally adjudicated by three members of the endpoint committee blinded to study treatment and according to pre-defined criteria.

For the present analysis, combined cardiovascular events (CVE), sudden death, MI, stroke, all-cause mortality and deaths due to infection were all chosen as separate outcome measures. The categorization of these events was based on the primary judgment of the endpoint committee during the 4D Study.

2.5. Statistical analysis

Continuous variables were expressed as mean with standard deviation or median with interquartile ranges, as appropriate. Categorical variables were expressed as percentages.

The study population was divided into quartiles according to the PAPP-A concentration at baseline: ≤13.4 mIU/L (quartile 1), 13.5–17.0 mIU/L (quartile 2), 17.1–20.9 mIU/L (quartile 3), >20.9 mIU/L (quartile 4).

The Cox proportional hazards regression model was used to estimate hazard ratios (HR) and corresponding 95% confidence intervals (CI) for the clinical outcomes of combined cardiovascular events (CVE), sudden death, MI, stroke, all-cause death and death