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Research Article

Urine albumin is a superior predictor of preeclampsia compared to urine plasminogen in type I diabetes patients

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Abstract

Pregnant women with type I diabetes mellitus (T1DM) are at increased risk of developing preeclampsia (PE). Plasminogen is aberrantly filtrated from plasma into tubular fluid in PE patients and activated to plasmin. Plasmin activates the epithelial sodium channel in the collecting ducts potentially causing impaired sodium excretion, suppression of the renin-angiotensin-aldosterone system, and hypertension in PE. The objective of the study was to test whether urinary total plasmin(ogen)/creatinine ratio and plasma concentration of aldosterone were better predictors of PE in pregnant women with T1DM compared with urine albumin and haemoglobin A_{1C}. The design was a longitudinal observational study of 88 pregnant T1DM patients at 2 Danish centers. Spot urine- and blood samples were collected at gestational weeks 12, 20, 28, 32, and 36. U-plasmin(ogen)/creatinine ratio increased during pregnancy. In gestational week 36, the ratio was significantly increased in the T1DM patients developing PE ($P < .05$). P-aldosterone was significantly increased in gestational week 20 in the group developing PE ($P < .05$). Creatinine Ratio and Association With Development of /creatinine ratio was significantly increased and predicted PE at all tested gestational ages. Creatinine Ratio and Association With Development of /creatinine ratio had a stronger association with the development of PE compared to u-total plasmin(ogen)/creatinine ratio and p-aldosterone. The positive association between u-total plasmin(ogen) and development of PE late in pregnancy is compatible with involvement in PE pathophysiology. The significance of albumin in urine emphasizes the importance of preventing renal complications when planning pregnancy in patients with type I diabetes. J Am Soc Hypertens 2017;■(■):1–11.

Keywords: Aldosterone; diabetes; pregnancy; proteinuria.

Introduction

Preeclampsia (PE) is one of the most frequent complications in pregnancy (2%–8%) occurring after gestational week 20. It is characterized by de novo hypertension and proteinuria. Pregnant women with pregestational type I diabetes mellitus (T1DM) are in a high risk group with a 2- to 7-fold increased risk of developing PE.[1,2]

Reliable predictors of PE are missing, both in healthy and diabetic pregnancies. Numerous biomarkers and clinical risk factors have been investigated, and most recent data focus on

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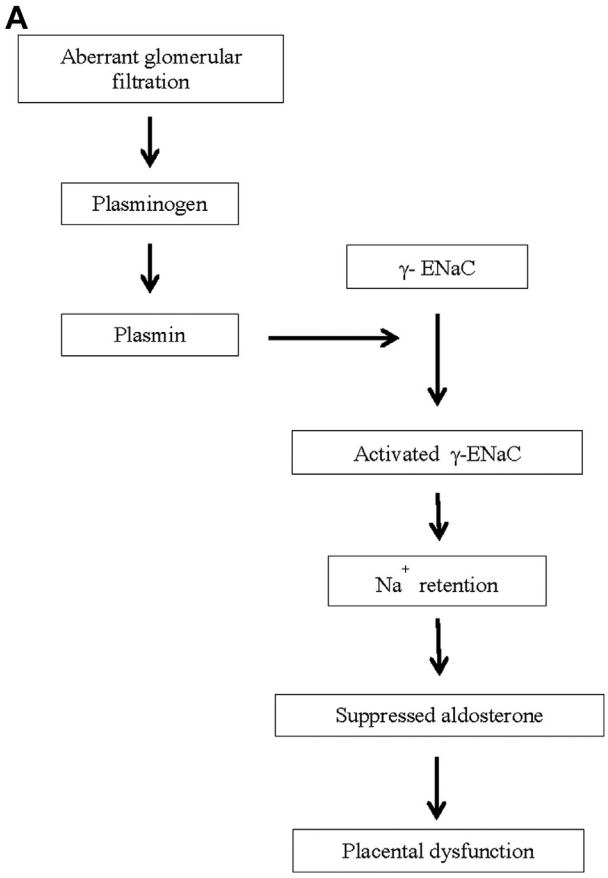

Figure 1. (A) Proposed scheme of the hypothesized pathophysiological mechanism involved in preeclampsia. Activation of ENaC by plasmin in PE patients with glomerular filtration barrier injury and proteinuria. Plasminogen in tubular fluid is activated to plasmin likely by urokinase-type plasminogen activator. Plasmin activates ENaC through proteolytic cleavage of the γ-subunit, which causes channel activation and impaired Na^+ excretion. The renin-angiotensin aldosterone system is subsequently suppressed, and lower circulating plasma levels of aldosterone in PE may potentially further aggravate placental dysfunction.

the ratio between the soluble splice variant of the vascular endothelial growth factor receptor, the fms-like tyrosine kinase receptor-1 (sFlt-1), and placental growth factor (the sFlt-1/PlGF ratio).[3] Established predictors that associate with the development of PE in women with T1DM are duration of diabetes[4]; increased level of haemoglobin A_{1C} (HbA_{1C})[5,6] increased plasma level of sFlt-1[7] and albuminuria.[8–10] Pregestational microalbuminuria predicts PE in women with T1DM.[4] A 2016 review concluded that the strongest predictors of PE early in T1DM-pregnancies are HbA_{1C} and increased levels of urinary (u-) albumin/protein.[11]

The present study hypothesized that aberrant filtration of the zymogen plasminogen to preurine may be more strongly associated with and better predict the development of PE compared with established markers. This hypothesis is based on a putative mechanistic model coupling tubular proteolytic activation of the epithelial sodium channel (ENaC) and subsequent impaired renal sodium excretion causing suppressed aldosterone, which in the end may secondarily attenuate placental growth[12,13] (Figure 1A).

In PE patients, the degree of proteinuria correlates to disease severity and to perinatal morbidity,[14–16] and the highest risk (50%–60%) of developing PE is seen in women with diabetic nephropathy.[8,17] We hypothesized that proteinuria could be involved causally in the pathophysiological features of PE. We have shown significantly increased urinary excretion of the serine proteases plasmin and prostasin in nonpregnant diabetes patients and in PE patients without diabetes[18], which correlated with u-albumin.[12,19] Urine from PE- and diabetic nephropathy patients evoked significant amiloride-sensitive inward current in cortical-collecting duct cells. Sensitivity to protease inhibitors indicated proteolytic activation of the ENaC as the mechanism.[12,18] The findings predict that aberrant filtration and activation of plasminogen to plasmin confers proteolytic activity to urine that may cause activation of ENaC in vivo and impair sodium excretion in PE. This, in turn, could explain the association with suppression of the renin angiotensin aldosterone system (RAAS) in PE previously observed.[20–22] Aldosterone acts as a growth factor for placenta, but PE is characterized by small placentas, with thrombotic areas which lead to intrauterine growth restrictions.[23,24] Thus, early suppression of plasma aldosterone by NaCl retention could contribute to the placental dysfunction (Figure 1A).

The present observational study was designed to address the hypothesis that u-plasminogen and p-aldosterone display an inverse relation and that urine plasminogen level predicts the development of PE in a cohort of pregnant T1DM patients with an *a priori* high risk of developing PE. By not including patients with type 2 diabetes and only selecting patients with T1DM, less confounding from differences in BMI, insulin need and peroral antidiabetic pharmacological treatment would be involved. Secondary outcome/effect parameters were to assess the association of plasma aldosterone and the development of PE. To address the hypotheses, urine total plasminogen and plasma aldosterone concentrations were determined in a longitudinal study design throughout pregnancy in women with pre-gestational T1DM from 2 tertiary referral centers for a period of 2 years in Denmark. The association between levels of p-aldosterone and u-plasminogen and development of PE was compared with the established biomarkers: Creatinine Ratio and Association With Development of and HbA_{1C}.

Materials and Methods

The present study was an observational, longitudinal study conducted at 2 Danish centers: Department of Gynecology and Obstetrics at Aarhus University Hospital, Skejby and