Short communication

Urinary albumin excretion and 24-hour blood pressure as predictors of pre-eclampsia in Type I diabetes

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Abstract

Aims/hypothesis. To evaluate the value of 24-h blood pressure monitoring compared to office blood pressure and urinary albumin excretion in predicting pre-eclampsia in Type I (insulin-dependent) diabetes mellitus.

Methods. The study included 136 consecutive pregnancies in Caucasian women with Type I diabetes before gestation without diabetic nephropathy, anamnestic hypertension or early abortion. Values of urinary albumin excretion and office blood pressure before pregnancy and the HbA_{1C} value at the time of conception were obtained. Microalbuminuria was defined as urinary albumin excretion of 30–300 mg/24 h in two out of three consecutive urine samples. Single measurements of 24-h urinary albumin excretion, office blood pressure and HbA_{1C} were done five 5 times during pregnancy. In a subgroup of 74 women 24-h blood pressure measurements were done at 10 and 28 weeks of gestation. Pre-eclampsia was defined as office blood pressure higher than 140/90 mmHg ac-

companied by proteinuria above 0.3 g/24 h later than 20 weeks of gestation.

Results. Urinary albumin excretion and systolic blood pressure were higher before and throughout pregnancy in 14 women developing pre-eclampsia compared with women remaining normotensive ($p < 0.001$; $p < 0.05$, respectively). By logistic regression analysis the best predictor for pre-eclampsia was microalbuminuria before pregnancy ($p < 0.05$) with no additive predictive effect of 24-h blood pressure or office blood pressure measurement. The night:day ratio of blood pressure was similar in the two groups.

Conclusion/interpretation. Microalbuminuria before pregnancy is the strongest predictor of pre-eclampsia in Type I diabetes. Measuring 24-h blood pressure early in pregnancy did not improve the ability to identify women at risk. [Diabetologia (2000) 43: 927–931]

Keywords Urinary albumin excretion, ambulatory blood pressure monitoring, blood pressure, pregnancy, pre-eclampsia, pregnancy-induced hypertension, haemoglobin A_{1C}, Type I diabetes.

The incidence of pre-eclampsia in women with diabetes before gestation is considerably higher (10–20%) than in the background population (4–5%). Pre-eclampsia is characterised by a rise in blood pressure (BP) and simultaneous development of proteinuria. Whether pathophysiological changes in BP mea-

sured by 24-h blood pressure (24-h BP) monitoring or slightly increased urinary albumin excretion in the microalbuminuric range contribute to the increased risk of developing pre-eclampsia in Type I (insulin-dependent) diabetes mellitus is not well established.

The aim of our study was to evaluate the value of 24-h BP monitoring compared with office BP and urinary albumin excretion in predicting pre-eclampsia in Type I diabetes.

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Abbreviations: BP, Blood pressure

Subjects and methods

Out of 161 consecutive Caucasian women with pregestational Type I diabetes, admitted to our obstetric clinic before 17 weeks of gestation with a living foetus, 158 (98%) were included in the study. Women with diabetic nephropathy ($n = 8$), known hypertension ($n = 2$) or early abortions ($n = 12$) were excluded. The women were admitted non-selected to the obstetric clinic from a well-defined geographical area covering approximately 2 million inhabitants. Apart from insulin seven women were treated with levothyroxine, hydrocortisone or antiepileptics or a combination of these during pregnancy.

Management of the diabetic pregnancies accorded with routine procedures of the Obstetric Clinic at the National University Hospital (Rigshospitalet) [1]. The women were asked to measure blood glucose at home at least four times daily and adjust insulin doses accordingly, aiming at preprandial blood glucose concentrations of 3–6 mmol/l. They were seen at the obstetric clinic or the local diabetes centres or both at intervals of 1–2 weeks. Labour was induced 1–2 weeks before term based on individual evaluation.

Values of urinary albumin excretion and office BP within the last 2 years before pregnancy and the haemoglobin A_{1C} (HbA_{1C}) value closest to the time of conception (2–6 weeks of gestation) were obtained from local records. Microalbuminuria was defined as urinary albumin excretion of 30–300 mg/24 h in two out of three consecutive urine samples [2]. The women were classified as smokers when smoking 1 or more cigarettes a day.

At 10, 14, 20, 28 and 34 weeks of gestation single measurements of 24-h urinary albumin excretion, office BP and HbA_{1C} were made. In a subgroup of 74 women we obtained 24-h blood pressure (24-h BP) measurements at the booking visit (8–14 weeks) and at 28 weeks of gestation.

Urine samples were analysed for albumin by ELISA [2] or by a turbidimetric method using the same antibodies and buffers. Haemoglobin A_{1C} was analysed by high-performance liquid chromatography or by antibody immunoassay (normal range 4.1–6.4%). Office BP was measured after 5–10 min rest in a sitting position. Measurements of 24-h BP were done using Takeda Medical (A&D Co, Tokyo, Japan) TM-2420/TM-2421 ambulatory blood pressure monitors [3]. The 24-h BP device was programmed to measure BP half-hourly during daytime (07:00–23:00) and hourly during night-time (23:00–7:00). A 24-h BP recording was considered successful if 70% of the readings were valid. The actual awake and sleep time from the women's diaries were used to calculate the night:day ratio of BP for each woman [4].

The diagnosis of pre-eclampsia was based on office BP higher than 140/90 mmHg (three measurements) accompanied by proteinuria above 0.3 g/24 h (two urine samples) later than 20 weeks of gestation. Pregnancy-induced hypertension without proteinuria was defined as development of BP higher than 140/90 mmHg later than 20 weeks of gestation with dipstick negative urine or urinary albumin excretion less than 190 mg/24 h or both. Women who met neither of these criteria were categorised as normotensive. Blunted decline in nocturnal BP was defined as a nocturnal decrease in BP less than 10%.

Statistical analysis. Normally distributed variables are given as means $\pm$ SD and urinary albumin excretion as geometric means and range. Student's *t* test and Fisher's exact test were used for comparison between groups. Logistic regression analysis was applied to identify variables independently associated with development of pre-eclampsia. Presence of microalbu-

minuria before pregnancy, urinary albumin excretion above 30 mg/24 h early in pregnancy and the upper quartile for systolic office BP (120 mmHg) in the normotensive group were used as a cut-off levels for calculating adjusted odds ratios. We considered *p* less than 0.05 to be significant.

Results

Of the women 136 delivered later than 24 weeks of gestation. There were 14 women (10%) who developed pre-eclampsia between 24 and 36 weeks of gestation. In 12 out of the 14 women antihypertensive treatment was initiated shortly after pre-eclampsia was diagnosed. Three women developed thrombocytopenia ($< 100 \times 10^9/l$) and seven developed increased serum uric acid concentrations (> 0.35 mmol/l). They were admitted to hospital 14 (range 4–31) days before delivery. Of these women 12 (86%) delivered preterm (27–37 weeks) compared with 42 (36%) of the normotensive women ($p < 0.001$). The perinatal mortality was 1 (7%) out of 14 and 2 (2%) out of 116 births, respectively (NS). Two (17%) of the singleton infants of mothers developing pre-eclampsia were small for date (< 10 centile) compared with three (2%) of the singleton infants of normotensive mothers (NS). Six women (4%) developed pregnancy-induced hypertension without proteinuria. Five were treated with antihypertensives. The prevalences of preterm birth, low birth weight and perinatal deaths were similar to those of the normotensive group.

Baseline characteristics of women developing pre-eclampsia and women developing pregnancy-induced hypertension without proteinuria compared with the women remaining normotensive are given in Table 1. Early in pregnancy both systolic office BP and systolic 24-h daytime BP were slightly raised in women developing pre-eclampsia. The night:day ratio of BP was similar in all three groups. Blunted nocturnal decline in BP was found in four (50%) out of eight developing pre-eclampsia, two (40%) out of five developing pregnancy-induced hypertension without proteinuria and 17 (29%) out of 56 women remaining normotensive (NS).

At 28 weeks of gestation the 24-h daytime BP was 124(10)/73(6) mmHg in women remaining normotensive ($n = 33$) compared with 142(24)/72(9) mmHg in women developing pre-eclampsia ($n = 6$) ($p < 0.01$ /NS). Out of five women in the pre-eclamptic group four (80%) had blunted nocturnal decline in BP compared with ten (32%) out of 31 normotensive women ($p < 0.05$). Seven women (9%) could not tolerate the 24-h BP device and 38 women (51%) noted a pronounced disturbing effect on their sleep.

Urinary albumin excretion was increased before and throughout pregnancy with a steep increase from 20 weeks of gestation in women developing

Table 1. Baseline data on 136 pregnant women with Type I diabetes: women developing pre-eclampsia and women developing pregnancy-induced hypertension (PIH) without proteinuria compared with normotensive women

	Normotensive	Pre-eclampsia	PIH without proteinuria
Number (<i>n</i>)	116	14	6
Age (years)	29 (4)	32 (5) ^a	30 (6)
Duration of diabetes (years)	13 (8)	19 (9)	6 (4)
Body mass index (kg/m ²)	24 (4)	25 (4)	22 (2)
HbA _{1C} at gestation (%)	7,6 (1,1)	8,0 (0,9)	7,2 (0,9)
Early systolic office BP (mm Hg)	115 (12)	124 (13) ^a	118 (13)
Early diastolic office BP (mm Hg)	69 (8)	72 (7)	70 (13)
Systolic 24-h daytime BP (mm Hg) ^d	120 (9)	131 (14) ^b	119 (7)
Diastolic 24-h daytime BP (mm Hg) ^d	72 (7)	70 (7)	74 (7)
Night:day ratio of systolic BP (%) ^e	87 (6)	89 (7)	89 (6)
Night:day ratio of diastolic BP (%) ^e	85 (6)	85 (7)	82 (3)
Pre-pregnancy microalbuminuria (<i>n</i>) ^f	7 (7%)	7 (58%) ^c	0
Early pregnancy UAE > 30 mg/24 h (<i>n</i>) ^g	10 (10%)	6 (46%) ^c	0
Retinopathy (<i>n</i>)	44 (39%)	9 (64%)	0
Nullipara (<i>n</i>)	55 (47%)	9 (64%)	5 (83%)
Smokers (<i>n</i>)	28 (24%)	7 (50%) ^a	1 (17%)
Whites classification B + C/D + R (<i>n</i>)	65/51	5/9	6/0 ^a

Values are means ± (SD) or numbers and (percentage).
^a $p < 0.05$, ^b $p < 0.01$, ^c $p < 0.001$ compared with normotensive.
 The 24-h blood pressures are measured in early pregnancy (8–14 weeks of gestation). ^d 57, 9, and 5 respectively;

^e $n = 56$, 8, and 5 respectively; ^f $n = 101$, 12 and 4, respectively;
^g $n = 102$, 13 and 5, respectively. UAE, urinary albumin excretion

pre-eclampsia compared with the normotensive group ($p < 0.001$; Fig. 1). A higher systolic office BP was observed before and throughout the pregnancy ($p < 0.01$) with a further increase from 28 weeks of gestation in women developing pre-eclampsia ($p < 0.001$; Fig. 1). Haemoglobin A_{1C} values were higher from 14 to 28 weeks of gestation in the women developing pre-eclampsia ($p < 0.05$). Women developing pregnancy-induced hypertension without proteinuria had urinary albumin excretions, office BP and HbA_{1C} values similar to the women remaining normotensive until 34 weeks of gestation (data not shown).

Microalbuminuria before pregnancy ($p < 0.01$) and older age ($p < 0.05$) were the only variables independently and positively associated with development of pre-eclampsia. When systolic 24-h daytime BP early in pregnancy was substituted for systolic office BP ($N = 69$) the best predictor for pre-eclampsia was still microalbuminuria before pregnancy ($p < 0.05$) with no additive effect of 24-h BP measurement. The adjusted odds ratio for microalbuminuria prior to pregnancy as predictor of pre-eclampsia was 25 (CI 4–165). The adjusted odds ratios for urinary albumin excretion above 30 mg/24-h, systolic office BP higher than 120 mm Hg and systolic 24-h daytime BP higher than 120 mm Hg in early pregnancy were 9 (CI 2–46), 2 (CI 0.2–11) and 7 (CI 0.5–80), respectively.

The sensitivity of microalbuminuria before pregnancy for predicting pre-eclampsia was 58%, the specificity was 93% and the positive predictive value was 50%.

Discussion

Our study shows that microalbuminuria before pregnancy is the strongest independent predictor of pre-eclampsia in Type I diabetes even when BP is measured carefully with a 24-hour BP device.

Reliable values of urinary albumin excretion before pregnancy obtained from local records were available for 86% of the women. The high intraindividual day-to-day variation (40%) in the 24-h urinary albumin excretion was met by requiring at least two consecutive urine samples of urinary albumin excretion to classify a woman as having persisting microalbuminuria. Early pregnancy proteinuria of 190–499 mg a day has previously been described as associated with increased risk of developing pre-eclampsia [5]. Using measurement of urinary albumin excretion, progression from microalbuminuria before pregnancy to nephrotic proteinuria in late pregnancy has been described [6]. In our study, persisting microalbuminuria before pregnancy was strongly associated with the development of pre-eclampsia. A single measurement of 24-h urinary albumin excretion early in pregnancy is also useful in predicting pre-eclampsia. The apparent higher adjusted odds ratio for increased urinary albumin excretion measured before compared with early in pregnancy as predictor of pre-eclampsia was probably due to more solid documentation before pregnancy.

In our preliminary study, microalbuminuria was superior to office BP before pregnancy in predicting pre-eclampsia [7]. In the present study we found increased systolic BP early in pregnancy in the group

Fig. 1A–C. Urinary albumin excretion, office blood pressure and haemoglobin A_{1c} before and during pregnancy in 130 women with Type I diabetes. **A** Urinary albumin excretion in relation to development of pre-eclampsia (■, $n = 14$) or a normotensive pregnancy (●, $n = 116$). Dotted lines limit the microalbuminuric range. Data are geometric means $\pm$ 95% CI of means. **B** Systolic/diastolic office blood pressure in relation to development of pre-eclampsia (■/□) or a normotensive pregnancy (●/○). Data are means $\pm$ SEM. **C** Haemoglobin A_{1c} in relation to development of pre-eclampsia (■) or a normotensive pregnancy (●). Data are means $\pm$ SEM

of women developing pre-eclampsia. The BP was, however, still within the normal range, the absolute differences were small and the overlap between the pre-eclamptic group and the normotensive group was large. The best predictor for pre-eclampsia remained microalbuminuria before pregnancy with no additive effect of 24-h BP measurement. This is in accordance with the findings in healthy primigravid women where 24-h BP measurement between 18 and 24 weeks of gestation could not predict development of hypertension [8]. In early pregnancy the nocturnal decline in BP in our study was similar in women developing pre-eclampsia and women remaining normotensive. Preserved diurnal rhythm at 18 weeks of gestation has also been described in non-diabetic women developing pregnancy-induced hypertension [9]. In addition, 24-h BP monitoring was resource intensive and rather unpleasant for the women.

Poor metabolic control has been reported to be associated with a higher incidence of pre-eclampsia in diabetic pregnancies [10]. We found a tendency towards higher HbA_{1c} values early in pregnancy in women developing pre-eclampsia compared with the normotensive group and the difference became statistically significant from 14–28 weeks of gestation. This supports the concept, that ensuring good glycaemic control is important.

The presence of microalbuminuria before pregnancy was the strongest predictor of development of pre-eclampsia in Type I diabetes. Measurement of 24-h BP early in pregnancy did not improve the ability to identify women at risk.

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