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ARTICLE

Pre-eclampsia but not pregnancy-induced hypertension is a risk factor for diabetic nephropathy in type 1 diabetic women

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Abstract
Aims/hypothesis Our aim was to study whether pre-eclampsia and pregnancy-induced hypertension are predictors of diabetic nephropathy in type 1 diabetic women.
Materials and methods A total of 203 type 1 diabetic women, who were pregnant between 1988 and 1996 and followed at the Department of Obstetrics and Gynaecology in Helsinki, were re-assessed after an average of 11 years within the nationwide, multi-centre Finnish Diabetic Nephropathy Study. Diabetic nephropathy was defined as microalbuminuria, macroalbuminuria or end-stage renal disease.
Results Patients with prior pre-eclampsia had diabetic nephropathy more often than patients with a normotensive pregnancy (diabetic nephropathy vs normal albumin excretion rate: 41.9% vs 8.9%; $p<0.001$), whereas patients with a history of pregnancy-induced hypertension did not (10.3% vs 8.9%; $p=0.81$). CHD was more prevalent in patients with a history of pre-eclampsia than in patients with a normotensive pregnancy (12.2% vs. 2.2%; $p=0.03$). Pre-eclampsia (odds ratio [OR] 7.7, 95% CI 1.6-36.1; $p=0.01$) and HbA_{1c} (OR 2.0, 95% CI 1.1-3.8; $p<0.05$) were associated with incident diabetic nephropathy even when adjusted for follow-up time, BMI, smoking, diabetes duration and age.
Conclusions/interpretation These data suggest that a history of pre-eclamptic pregnancy but not pregnancy-induced hypertension is associated with an elevated risk of diabetic nephropathy.

Keywords Coronary heart disease · Diabetic nephropathy · Pre-eclampsia · Pregnancy-induced hypertension · Type 1 diabetes

Abbreviations

ESRD	end-stage renal disease
FinnDiane	Finnish Diabetic Nephropathy Study

Introduction

Pre-eclampsia is an important cause of maternal and fetal morbidity and mortality, and complicates 3–5% of all pregnancies [1–4]. It is characterised by hypertension, proteinuria and endothelial dysfunction during the second half of pregnancy. The incidence of pre-eclampsia in patients with type 1 diabetes is higher than in pregnant non-diabetic women, generally exceeding 10% [5]. Pregnancy-induced hypertension is also twice as common in patients with type 1 diabetes than in non-diabetic women [6].

In patients with type 1 diabetes, pre-pregnancy microalbuminuria and proteinuria are the most important risk

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factors for pre-eclampsia [7–9]. The presence of retinopathy, poor glycaemic control, nulliparity and long duration of diabetes also increases this risk [10]. Although the clinical manifestations of pre-eclampsia disappear after delivery, the endothelial dysfunction seems to persist even years after a pre-eclamptic pregnancy [3, 11].

It is also known that in the general population a history of pre-eclampsia increases the risk of cardiovascular morbidity and mortality [12–14], but only a few studies have focused on the microvascular complications in type 1 diabetes. Pregnancy itself does not seem to be a major factor for diabetic microvascular complications [15]. Lovestam-Adrian et al. showed on the other hand that pre-eclampsia aggravates diabetic retinopathy, but it should be noted that patients in that study were followed for only 6 months after delivery [16]. A small retrospective study showed that proteinuria but not pre-eclampsia is a risk factor for nephropathy in women with type 1 diabetes [17]. Whether pre-eclampsia increases the risk of diabetic nephropathy is still unclear.

Diabetic nephropathy is characterised by an increasing urinary AER [18, 19], elevated blood pressure, a relentless decline in renal function, endothelial dysfunction and increased cardiovascular morbidity and mortality. Approximately one-third of patients with type 1 diabetes are at risk of diabetic nephropathy, which is one of the leading causes of end-stage renal disease (ESRD) in the West [20–22]. Poor glycaemic control, smoking, hypertension and still largely unknown predisposing genes are risk factors for nephropathy in type 1 diabetic patients [23, 24]. Interestingly, many of the factors associated with diabetic microvascular complications are also involved in the pathogenesis of pre-eclampsia suggesting that these entities may be closely linked [25].

The aim of this study was therefore to assess whether pre-eclampsia and pregnancy-induced hypertension predict the development of microvascular complications, with special emphasis on diabetic nephropathy, in women with type 1 diabetes.

Subjects and methods

Baseline (index pregnancy) The patients (n=429) included at baseline were women with type 1 diabetes, who had been followed throughout their pregnancy and delivery at the Department of Obstetrics and Gynaecology, Helsinki University Central Hospital, between 1988 and 1996. This is the only centre responsible for the obstetric care of type 1 diabetic women in the greater Helsinki area with its population of 1.5 million inhabitants. The patients visited the hospital at 2–6-week intervals during pregnancy, starting at 6–10 pregnancy weeks. They were advised to measure their blood glucose at home five times daily on 2–3 days per week. They were prescribed long-acting insulin, one to three times daily, and short-acting insulin at meals in order to achieve good glycaemic control defined as a HbA_{1c}<7.5%.

Blood pressure was measured at each visit after a 10-min rest in the sitting position. Measurements were made with a sphygmomanometer by midwives and nurses and blood pressure was considered elevated when diastolic blood pressure was repeatedly ≥90 mmHg or if it increased by a minimum of 15 mmHg during pregnancy. Urinary protein was measured by a dipstick method at every visit. If the dipstick repeatedly showed a + or a ++ result, suspected proteinuria was confirmed by a 24-h urine collection. Proteinuria was defined as urinary protein excretion of ≥300 mg/24 h.

Pre-eclampsia was defined as elevated blood pressure as described above, accompanied by proteinuria after 20 weeks of pregnancy. Pregnancy-induced hypertension was defined as elevated blood pressure in the absence of proteinuria [26, 27]. Patients with hypertension before 20 weeks of pregnancy were excluded from all analyses and the patients with proteinuria during the first half of pregnancy (White's class F) were excluded from the analyses for nephropathy. Importantly, 57 previous pregnancies from the period before 1988 were further assessed from the medical files in order to detect any possible pre-eclamptic pregnancies prior to the index pregnancy. Three new cases of pre-eclampsia were detected but two of them were classified as White's class F.

HbA_{1c} was measured monthly during pregnancy by HPLC (Diamat; Bio-Rad Laboratories, Hercules, CA, USA). The normal range was defined as a HbA_{1c} between 4.0 and 6.0%. The first HbA_{1c} assessment during pregnancy was carried out between the 7th and 14th week of gestation. The mid-pregnancy value was obtained between the 20th and 25th week, and the third measurement approximately 2 weeks before delivery. The average HbA_{1c} value of each trimester was used in the analysis.

Follow-up study Out of the 429 baseline patients, 366 had one, 46 had two and 17 had more than two childbirths (total number of deliveries 590). Some patients could not be tracked and seven patients had died. Thus the total number of patients invited to the follow-up study was 396, of whom 196 accepted the invitation (Fig. 1). The seven patients who had died were also included in the analyses, using follow-up data retrieved from the hospital medical files. The follow-up visit took place on average 11 years after the index pregnancy, as part of the Finnish Diabetic Nephropathy (FinnDiane) Study, a nationwide, prospective, multicentre study initiated in November 1997. The aim of the FinnDiane study is to find the causes for diabetic late complications, especially nephropathy, in patients with type

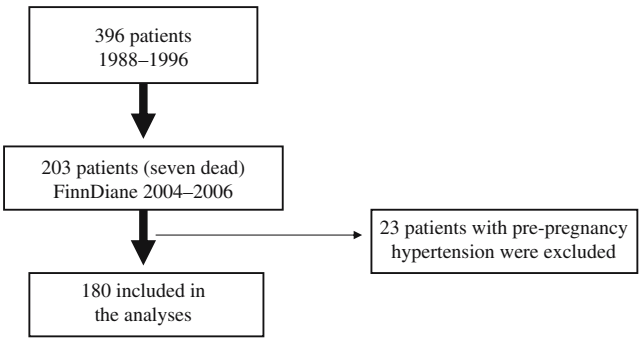

Fig. 1 Flow-chart of patients studied

1 diabetes. The study protocol is in accordance with the Declaration of Helsinki and was approved by the local ethics committees in each participating study centre. Written informed consent was obtained from each patient.

Data on medication, cardiovascular status and diabetic complications were registered by a standardised questionnaire, which was completed by the patient's attending physician and thus immediately verified from the medical files. CHD was defined as a positive history of myocardial infarction, bypass operation, a diagnostic finding in angiography or positive exercise test.

At the follow-up visit, fasting blood samples were drawn, for the determination of HbA_{1c}, lipids, lipoproteins and serum creatinine. HbA_{1c} was analysed by immunoturbidimetry. Serum lipids were measured by automated enzymatic methods using an analyser (Cobas Mira; Hoffman-La Roche, Basel, Switzerland) and serum creatinine by routine enzymatic methods. Urinary AER was assessed from overnight and/or 24-h urine collections by immunoturbidimetry.

The definition of the renal status was based on the AER in at least two out of three urine collections at follow-up. Patients were classified as normoalbuminuric (n=135) if their AER was persistently <20 μg/min in the overnight or <30 mg/24 h in the 24-h urine collection. Microalbuminuria or incipient diabetic nephropathy (n=24) was defined as an AER of 20–200 μg/min or 30–300 mg/24 h, while macroalbuminuria or established diabetic nephropathy (n=9) was defined as an AER >200 μg/min or >300 mg/24 h. Patients who were on renal replacement therapy (dialysis or kidney transplantation) were considered to have ESRD (n=2). The patients with either microalbuminuria, macroalbuminuria or clinical ESRD were pooled and considered to represent diabetic nephropathy in the analyses.

Statistical analyses All analyses were performed with SPSS 12.0.1 (SPSS, Chicago, IL, USA). Baseline characteristics are presented as means±SD for normally distributed values and as median with interquartile range for non-normally distributed values, and percentages. For categorical variables the χ^2 test or Fisher's exact test was used when appropriate. Normally distributed variables were tested with the Student's t test and non-normally distributed with a Kruskal–Wallis test. Logistic regression analysis was used to adjust for age, duration of diabetes, smoking, follow-up time and BMI.

Results

Patient characteristics No clear differences were found in the baseline clinical characteristics of patients who participated in the follow-up study and those who did not (Electronic supplementary material [ESM] Table 1). Clinical characteristics are shown in Table 1. The average time period from the index pregnancy to the follow-up visit was 10.6±2.5 years and ranged from 3.2 to 17.1 years. At the index pregnancy, women with pre-eclampsia were younger and more often nulliparous than patients with uncomplicated pregnancies. Patients with and without pre-eclampsia had similar BMI, whereas patients with pregnancy-induced hypertension had higher BMI than those with normal blood pressure during pregnancy.

Pre-eclampsia and diabetic complications Women with type 1 diabetes and a history of pre-eclampsia had a higher frequency of diabetic nephropathy at follow-up than women with normal blood pressure during pregnancy (41.9% vs 8.9%, p<0.001) (Table 1).

Notably, women with pre-eclampsia were more often on antihypertensive medication (50.0% vs 9.8%, p<0.001) later in life than women with normal blood pressure during pregnancy. Patients with a history of pre-eclampsia were more likely to have CHD (12.2% vs 2.2%, p=0.03). All three patients with a history of myocardial infarction had developed pre-eclampsia during pregnancy.

In the logistic regression analysis, both pre-eclampsia (p<0.001) and HbA_{1c} (all three trimesters) during pregnancy (p<0.05) were independently associated with diabetic nephropathy in a model that also included follow-up time, BMI, smoking, diabetes duration and age (Table 2).

Pregnancy-induced hypertension and diabetic complications Patients with pregnancy-induced hypertension and patients with normal blood pressure during pregnancy did not differ with regard to the development of diabetic nephropathy during follow-up (10.3 vs 8.9%, p=0.81). As expected, patients with pregnancy-induced hypertension used more antihypertensive medication (41.9% vs 9.8%, p<0.001) than those with normal blood pressure during pregnancy (Table 1).

Table 1 Descriptive data of patients by status during pregnancy and at follow-up

	Normotensive pregnancy (n=105)	Pre-eclampsia (n=43)	Pregnancy-induced hypertension (n=32)
Index pregnancy			
Age (years)	31.1±5.2	28.3±4.0[a]	28.6±5.2[b]
BMI (kg/m^2)	22.5±2.8	22.9±2.1	23.8±3.2[b]
Gestational age at delivery (weeks)	37.5±1.4	36.3±1.7[a]	37.1±1.6
Birthweight z-score (SD)	1.2±1.9	1.3±1.9	1.7±1.6
Birthweight (g)	3,725±811	3,433±852	3,811±621
HbA_{1c} pre-pregnancy (%)	7.5±1.1	7.7±0.9	7.3±0.7
HbA_{1c} first trimester (%)	7.5±1.3	8.1±1.2	7.0±1.6
HbA_{1c} second trimester (%)	7.0±1.1	7.3±0.9	7.1±1.3
HbA_{1c} third trimester (%)	7.2±1.2	7.5±1.2	7.4±1.4
Nulliparity (%)	55.2	81.4[b]	75.0
Follow-up			
Age (years)	41.7±6.6	37.9±5.9[b]	39.5±5.6
BMI (kg/m^2)	24.9±4.3	24.6±3.3	25.8±4.2
Duration of diabetes (years)	24.1±8.6	26.8±7.5	24.4±9.6
Systolic BP (mmHg)	128±15	133±14	131±16
Diastolic BP (mmHg)	76±10	80±8[b]	79±8
Total cholesterol (mmol/l)	4.7±0.8	4.7±0.8	4.7±0.7
HDL-cholesterol (mmo/l)	2.0±4.7	1.8±0.5[b]	1.9±0.4
LDL-cholesterol (mmol/l)	2.4±0.6	2.5±0.8	2.4±0.6
Triacylglycerol (mmol/l)	0.7 (0.3–1.6)	0.9 (0.4–3.1)[b]	0.9 (0.3–2.1)[b]
HbA_{1c} (%)	8.6±1.5	8.8±1.3	8.7±1.6
Serum creatinine (μmol/l)	74.7±16.0	93.3±55.5[b]	74.5±12.0
AER (mg/24 h)	16.8 (0.1–116)	43.6 (2–293)	9.9 (4.4–18.0)
Smokers (%)	21.7	15.4	32.3
Antihypertensive treatment (%)	9.8	50.0[a]	41.9[a]
Diabetic nephropathy (%)[c]	8.9	41.9[a]	10.3
CHD (%)	2.2	12.2[bd]	3.2
Myocardial infarction (%)	0	7.3[bd]	3.2

Unless otherwise stated, data are means±SD or median (interquartile range)
[a] $p<0.001$ and [b] $p<0.05$ vs normotensive pregnancy
Patients with pre-pregnancy hypertension were excluded from the analysis (n=23)
[c] White's class F excluded
[d] Fisher's exact test used

Pregnancy characteristics and outcome Poor glycaemic control during pregnancy (irrespective of the trimesters) predicted diabetic nephropathy ($p<0.001$) later in life (Table 3).

A large difference between HbA_{1c} at pregnancy (the third trimester) and follow-up was associated with increased risk of diabetic nephropathy, supporting the role of glucose exposure as a risk factor for diabetic nephropathy (data not shown).

Discussion

The most important finding of this study was that women with type 1 diabetes and pre-eclampsia during pregnancy were much more likely to develop diabetic nephropathy and high blood pressure later in life than women with type 1 diabetes and normal blood pressure during pregnancy. Interestingly, pregnancy-induced hypertension in women with type 1 diabetes was not associated with diabetic nephropathy later in life, which suggests that pre-eclampsia

Table 2 Logistic regression analysis for diabetic nephropathy

	OR	95% CI	p value	Adjusted OR	95% CI	p value
Pre-eclampsia	7.4	2.7–20.5	<0.001	7.7[a]	1.6–36.1[a]	0.01[a]
HbA_{1c} first trimester	3.2	1.5–6.9	0.003	3.2[b]	1.3–7.9[b]	0.01[b]
HbA_{1c} second trimester	3.7	1.8–7.9	<0.001	4.0[b]	1.7–9.8[b]	0.002[b]
HbA_{1c} third trimester	2.1	1.2–3.6	0.01	2.0[b]	1.1–3.8[b]	0.03[b]

[a] Adjusted for BMI, follow-up time, smoking, duration of diabetes, age and the average of the HbA_{1c} measurements during all three trimesters
[b] Adjusted for BMI, follow-up time, smoking, duration of diabetes and age
OR, odds ratio

Table 3 Clinical characteristics of the patients at index pregnancy by kidney status at follow-up

	Normal AER (n=135)	Diabetic nephropathy (n=35)
Index pregnancy		
Age (years)	30.1±5.0	30.0±5.1
BMI (kg/m^2)	22.8±3.0	23.4±2.9
Gestational age at delivery (weeks)	37.3±1.5	35.6±2.1[a]
Birthweight z-score (SD)	1.6±1.7	1.0±1.9
Birthweight of fetus (g)	3,812±718	3,200±902[a]
HbA_{1c} pre-pregnancy (%)	7.3±1.0	7.8±0.8
HbA_{1c} first trimester (%)	7.4±1.3	8.8±0.9[a]
HbA_{1c} second trimester (%)	6.9±1.9	8.1±1.1[a]
HbA_{1c} third trimester (%)	7.1±1.1	8.0±1.3[b]
Pre-eclampsia (%)	18.0	61.9[a]
Pregnancy-induced hypertension (%)	24.1	27.3
Non-hypertensive pregnancy (%)	57.9	10.8[a]

Data are means±SD

[a] $p<0.001$ and [b] $p<0.05$ vs normal AER

Patients with White's class F (or pre-pregnancy hypertension) and patients that could not be appropriately classified for kidney status were excluded from the analysis (n=33)

and pregnancy-induced hypertension are two different diseases. This was also suggested by Hiilesmaa et al. [6], who found that pre-eclampsia but not pregnancy-induced hypertension was associated with glycaemic control during the first half of pregnancy. Notably, poor glycaemic control during pregnancy was a risk factor for subsequent diabetic nephropathy in this study.

Earlier studies indicate that in the general population pre-eclampsia predisposes women to macrovascular complications [12, 13]. This seems to be the case in patients with type 1 diabetes as well, since we found that women with type 1 diabetes and a history of pre-eclampsia had more CHD at follow-up than type 1 diabetic women with normal blood pressure during pregnancy. They also had lower HDL-cholesterol, higher triacylglycerol and elevated diastolic blood pressure.

As far as we know, the only study that shows pre-eclampsia to be a risk factor for diabetic microvascular disease is that by Lowestam-Adrian et al. [16], which suggests an association with retinopathy. The present study indicates that type 1 diabetic women with previous pre-eclampsia have an increased risk of developing diabetic nephropathy.

The diagnosis of diabetic nephropathy deserves some clarification. We pooled all patients with microalbuminuria, macroalbuminuria and ESRD and classified them as representing diabetic nephropathy. Thus although microalbuminuria is a strong predictor of clinical nephropathy in patients with type 1 diabetes [19, 28], further follow-up of our cohort will reveal the true impact of pre-eclampsia on the development of overt proteinuria, and eventually ESRD.

A limitation of the study is that microalbuminuria was not quantitatively measured before and during pregnancy. However, a dipstick test was used at each antenatal visit every 2–4 weeks from weeks 6–10 of pregnancy and onwards. Thus, albuminuria greater than approximately 0.3 g during early pregnancy can be excluded. A definite diagnosis of pre-eclampsia in type 1 diabetic patients with proteinuria during the first half of pregnancy is difficult to make. Therefore, these patients were excluded in the analyses for nephropathy.

The relation between pre-eclampsia and poor glycaemic control is an important, albeit rarely studied issue. Our own experience supports the study by Rudge et al. [29], namely that although poor glycaemic control is associated with pre-eclampsia [6], it does not seem to trigger onset of pre-eclampsia. We cannot, however, rule out the possibility that patients with pre-eclampsia may also have poor glycaemic control after their pregnancy, which would also increase their risk of diabetic nephropathy. Unfortunately, as long as we lack clinical data (e.g. blood pressure, BMI, HbA_{1c}, smoking) from the time period between pregnancy and follow-up visit, this hypothesis cannot be tested. In any case, the HbA_{1c} values measured either prior to pregnancy or at follow-up did not differ between pre-eclamptic patients and those with normotensive pregnancies. In addition, HbA_{1c} was included in the logistic regression analyses for diabetic nephropathy (Table 2) and showed that pre-eclampsia was an independent risk factor for diabetic nephropathy with an odds ratio of 7.7.

An important question that arises is whether non-diabetic women with pre-eclampsia also have a higher risk of kidney disease. In this study we did not have such a group. However, in an earlier study we followed pre-eclamptic women for 5 years and studied their renal and vascular function. None of these women had signs of kidney disease, although they had had massive proteinuria during pregnancy [30].

The mechanisms leading to renal disease in type 1 diabetic patients are not fully understood. One theory is that it has to do with dysfunction of the endothelial lining of the arteries, a phenomenon that has been shown in both pre-eclampsia and diabetic nephropathy [22, 31]. Moreover, an inflammatory process has been observed in both entities [32, 33]. Pre-eclampsia sometimes involves massive proteinuria, which resolves after delivery, but the endothelial dysfunction may remain [11]. However, at the morphological level pre-eclampsia seems to be quite different from diabetic nephropathy. In pre-eclampsia, the glomerular changes are characterised by endothelial swelling and oedema of the glomerular basement membrane, while the glomerulosclerotic lesions tend to be focal, with resem-

blance of lesions seen in different forms of glomerulonephritis [34, 35]. Diabetic nephropathy, on the other hand, is characterised by thickening of the basement membrane and increase in the mesangial matrix. This results in diffuse glomerulosclerosis [36]. It could be speculated that pre-eclampsia causes an insult to the kidney, which predisposes to nephron loss and further to diabetic nephropathy in susceptible individuals.

It can also be speculated that there is a common genetic background for pre-eclampsia [37, 38] and diabetic nephropathy, possibly through endothelial dysfunction, chronic inflammation and insulin resistance. Those diabetic women who develop pre-eclampsia might have a greater risk of developing endothelial dysfunction before pregnancy. No direct measurements of endothelial dysfunction prior to pre-eclamptic pregnancy was performed. However, according to the Steno hypothesis, microalbuminuria could be considered a marker of generalised vascular dysfunction [39]. Since microalbuminuria is a risk factor for pre-eclampsia, this gives indirect evidence for a possible role of endothelial dysfunction [9]. Another possibility is that pregnancy itself, as a state of hypervolaemia, acquired thrombophilia, insulin resistance and low-grade inflammation, could induce pre-eclampsia as the first manifestation of endothelial dysfunction [40]. In any case, pregnancy itself worsens kidney function shortly after delivery, even in persons without kidney disease, but this does not persist in the long term [41–43].

Taken together, our results indicate that type 1 diabetic women with pre-eclampsia require more intensive follow-up after their pregnancies with special emphasis on early detection of microalbuminuria. Once detected, interventions aiming at normoglycaemia, normal blood pressure and a reduced AER should be considered in order to prevent development of diabetic nephropathy.

In conclusion, these data suggest that a history of pre-eclamptic pregnancy but not pregnancy-induced hypertension is associated with an elevated risk of diabetic nephropathy. This suggests that an early start to renoprotective medication in type 1 diabetic women with prior pre-eclampsia could be beneficial.

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