Diabetologia (2016) 59:472–480
DOI 10.1007/s00125-015-3816-0

ARTICLE

Age at menarche and the risk of diabetic microvascular complications in patients with type 1 diabetes

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Received: 6 August 2015 / Accepted: 2 November 2015 / Published online: 25 November 2015

Abstract
Aims/hypothesis The aim of this study was to evaluate the relationship among age at onset of diabetes, age at onset of menarche and risk of diabetic nephropathy and laser-treated retinopathy in type 1 diabetes.
Methods Data related to age at menarche were collected through questionnaires and were available for 1,304 women who participated in the Finnish Diabetic Nephropathy Study (FinnDiane). A possible association between age at menarche and diabetic nephropathy and retinopathy was investigated.
Results There was an inverse relationship between the age at onset of diabetes and age at menarche: the younger the age at onset of diabetes, the higher the age at menarche ($p < 0.0001$). A non-linear relationship between the age of menarche and risk of diabetic microvascular complications was found in patients with diabetes onset before menarche, but there was no such association in patients with diabetes onset after menarche. Women with delayed menarche (> mean age+2 years) had a 2.30 (95% CI 1.27, 4.17; $p < 0.006$) times higher risk of nephropathy compared with the women who underwent menarche at the mean age±2 years. Delayed menarche also increased the risk of retinopathy (OR 2.34 [95% CI 1.36, 4.01]). After excluding patients with nephropathy, the OR for retinopathy was 2.11 (95% CI 1.15, 3.90). Earlier menarche (< mean age−2 years) did not have any effect on this risk.
Conclusions/interpretation Delayed menarche was associated with an increased risk of diabetic nephropathy and retinopathy, whereas early menarche was not. Delayed menarche may be used as a new tool to identify women at risk of diabetic microvascular complications.

Keywords Age at menarche · Age at onset of diabetes · Delayed menarche · Diabetic nephropathy · Diabetic retinopathy · Puberty · Type 1 diabetes

Electronic supplementary material The online version of this article (doi:10.1007/s00125-015-3816-0) contains peer-reviewed but unedited supplementary material, which is available to authorised users.

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Abbreviations

ESRD	End-stage renal disease
FinnDiane	Finnish Diabetic Nephropathy Study
GAM	Generalised additive modelling
HPG	Hypothalamus–pituitary–gonadal
SBP	Systolic BP

Introduction

Previous studies have shown that age at onset of type 1 diabetes has an effect on the risk of microvascular complications, including diabetic nephropathy [1, 2] and diabetic

proliferative retinopathy [3]. Diabetic end-organ complications rarely occur before puberty, and the onset of puberty accelerates microvascular complications [4–7]. These observations suggest an association between sex hormones and diabetic end-organ complications. Providing further support for a close relationship between the development of diabetic complications and sex hormones, especially in women with type 1 diabetes, is the fact that these women commonly experience reproductive health issues including delayed menarche and puberty, an increased rate of menstrual irregularities, hyperandrogenism, a reduced ability to conceive, a high risk of adverse pregnancy outcomes (including spontaneous abortions, stillbirths and congenital anomalies), and premature menopause [8–12]. What remains unclear is whether any of these complications related to the reproductive system can contribute to the risk of other, non-reproductive organ complications associated with diabetes, such as diabetic nephropathy and diabetic retinopathy. Women with type 1 diabetes exhibit a much higher incidence of renal disease compared with non-diabetic women [13]. One of the factors contributing to this observation may be the abnormal regulation of sex hormone concentrations associated with diabetes. Indeed, both clinical and experimental data suggest that type 1 diabetes may be associated with reduced circulating estradiol levels [14–16]. These observations, coupled with the fact that puberty accelerates renal dysfunction, support the notion of a correlation between reproductive and renal abnormalities in type 1 diabetes.

Several studies have reported delayed menstruation in young women with type 1 diabetes [17–19]. While some studies concluded that delayed menarche is related to poor glycaemic control, other studies have reported that menarche in type 1 diabetes is still delayed when there is good metabolic control [20–22]. In contrast, some studies show no association between the age at menarche and diabetes [23, 24], suggesting that there is still no clear understanding of whether or not the presence of diabetes affects the onset of menstruation and whether this relationship might be dependent on the age at onset of type 1 diabetes. Interestingly, over the years, the age of menarche has progressively been declining and this secular trend has also been observed in girls both with and without type 1 diabetes throughout the world [25].

Thus, since studies suggest that type 1 diabetes may affect the age at menarche and that both the age at onset of type 1 diabetes and pubertal changes affect the risk of diabetic microvascular complications, we hypothesised that age at onset of menarche may be an important determinant of the risk of diabetic nephropathy and retinopathy in type 1 diabetes. Therefore, the aim of this study was to evaluate the effect of the combined type 1 diabetes–puberty-driven cascade on the risk of diabetic microvascular complications. We aimed to first, evaluate the effect of age at onset of diabetes on the timing of menarche in a large continuum of ages at onset of diabetes and, second, evaluate the risk of microvascular complications after dividing the study population into groups with diabetes onset before and after the onset of menarche.

Methods

Data used for the analyses were derived from the Finnish Diabetic Nephropathy Study (FinnDiane). FinnDiane is a nationwide, comprehensive multicentre study with the aim of identifying genetic and environmental risk factors for diabetic complications, with a special emphasis on diabetic nephropathy in patients with type 1 diabetes. A detailed description of the FinnDiane recruitment protocol was previously reported [24]. Briefly, all adult (age ≥18 years) patients with type 1 diabetes from 21 university and central hospitals, 33 district hospitals, and 26 primary health-care centres across Finland were asked to participate; the participation rate was 78%. The age range of patients at the baseline visit was 18–76 years. Type 1 diabetes was defined by an age at onset of diabetes of <40 years with insulin treatment initiation within 1 year of diagnosis.

At the baseline visit between 1994 and 2011, study patients underwent a throughout clinical examination at a regular visit to their attending physician at each FinnDiane centre. During this visit, their BP was measured and blood samples collected for lipid, HbA_{1c} and other measurements. Data regarding the presence of microalbuminuria, macroalbuminuria or end-stage renal disease (ESRD), as well as laser photocoagulation of eyes, were obtained from the medical files by the attending physician using a standardised questionnaire. In the present study, the diagnosis of macroalbuminuria or ESRD was defined as diabetic nephropathy and laser photocoagulation as severe retinopathy.

Data related to reproductive health history and related health issues were collected in the year 2011 and onwards through a questionnaire obtained from 1,325 women. The self-administered study questionnaire included questions about reproductive health including age at menarche. Of these patients, 21 could not provide information on the age of menarche, leaving 1,304 eligible study participants. These patients were divided according to the decade of their birth; 1944 or before, 1945–1954, 1955–1964, 1965–1974, 1975–1984 and 1985 or after; deviation in the age at menarche from the group mean was determined for each birth decade. The association between deviation from the group mean and risk of diabetic nephropathy and severe retinopathy was studied.

Statistical analysis The relationship between age at menarche and age at onset of diabetes was first studied using the generalised additive modelling (GAM) without a priori assumptions about type of relationship. Similarly, the relationship between

age at menarche and risk of diabetic nephropathy and severe retinopathy was studied using GAM. Because data on the diagnosis of nephropathy or retinopathy were not available for all patients, the binary response variable of whether the patients had diabetic nephropathy or severe retinopathy at the baseline was used. GAM was thus conducted under binomial distribution and the link function was logit. GAM is an extension of the generalised linear model that allows the inclusion of non-parametric smoothing functions to identify potential non-linearity in the relationship between the independent and the dependent variables [26, 27]. The generalised cross-validation function was used as a criterion for the selection of the smoothing parameters to determine an appropriate level of smoothing. The *df* values indicating the smoothing level were 4.14, 3.37 and 1.16 for diabetic nephropathy, retinopathy, and retinopathy when patients with nephropathy were excluded, respectively. Partial residual plots are provided to show the relationship between age at menarche and the risk of microvascular complications.

Logistic regression analyses were performed to quantify the effect of delayed menarche on the risk of diabetic microvascular complications. Based on the results drawn from GAM, data were divided into three groups relative to the mean age at menarche: mean age±2 years (reference group); less than the mean age−2 years; and more than the mean age+2 years. Multivariable analyses were conducted by adjusting for the following well-defined key risk factors: age at onset of diabetes; duration of diabetes; BMI; smoking status; HbA_{1c}; systolic BP (SBP); HDL-cholesterol and triacylglycerol levels. HbA_{1c} was measured once at the baseline evaluation; therefore, the effect of metabolic control on age of menarche could not to be taken into account. All analyses were performed using SAS statistical software (version 9.3, SAS Institute, Cary, NC, USA) and R open source software (www.r-project.org). GAM models were fitted using the mgcv library in R [28].

The ethics committees of all participating centres approved the study protocol. Written informed consent was obtained from each patient and the study was performed in accordance with the Declaration of Helsinki as revised in the year 2000.

Results

Information on 1,304 women was available for inclusion in the analyses. The age range at the time of questionnaire collection was 18–85 years (mean age 47.7±11.5). Of the 1,304 participants, 600 had diabetes onset before menarche (pre-menarcheal diabetes) and 704 after (post-menarcheal diabetes). A total of 117 (19.5%) patients in the pre-menarcheal diabetes group and 50 (7.1%) patients in the post-menarcheal diabetes groups were diagnosed with diabetic nephropathy at the baseline visit. The corresponding numbers were 236 (39.3%) and 96 (13.6%), respectively, for severe retinopathy.

The age at menarche varied from 9 to 18 years. The clinical characteristics of patients grouped by pre- and post-menarcheal diabetes onset are shown in Table 1. Pre-menarcheal diabetes was associated with a shorter stature, worse glycaemic control and blood lipid profiles, and a higher prevalence of antihypertensive medication. Table 2 shows the clinical characteristics of patients with pre-menarcheal type 1 diabetes according to the age at menarche. Pre-menarcheal diabetes shifts the distribution towards an older age at menarche and slightly distorts the normal distribution of age at menarche. Patients with a delayed menarche had the worst SBP, but the difference in SBP was no longer significant after adjustment for age and duration of diabetes. However, the frequency of antihypertensive medication remained significant after adjustment. Early and delayed menarche were both associated with a shorter stature.

The mean (± SD) age at menarche was higher in women with pre-menarcheal diabetes (13.82±1.65 years) compared with post-menarcheal diabetes patients (12.89±1.43 years; $p<0.0001$; Table 1). There was a decreasing trend in the age at menarche with advancing decade of birth: the mean ages were 13.80±1.46, 13.54±1.52, 13.30±1.72, 13.26±1.62, 13.06±1.42 and 12.96±1.25 in the birth cohorts of 1944 or before, 1945–1954, 1955–1964, 1965–1974, 1975–1984 and 1985 or after ($p<0.0001$ for the trend). Mean age at menarche decreased in both the pre-menarcheal and post-menarcheal diabetes groups (Fig. 1). It should also be noted that the difference in the mean age of menarche between pre-menarcheal and post-menarcheal onset of diabetes decreased with advancing decade of birth.

There was an inverse relationship between the age at onset of diabetes and the age at menarche (Fig. 2): a younger age at onset of diabetes was associated with an older age at menarche. The age at menarche decreased linearly with increase of onset of diabetes until age 20 years.

Risk of diabetic nephropathy and severe retinopathy according to age of menarche A non-linear relationship between the age of menarche and the risk of diabetic nephropathy was found in patients with pre-menarcheal type 1 diabetes ($p=0.004$ for non-linearity; Fig. 3a). If age at menarche was delayed by more than 2 years (corresponding to age >15 years at menarche), then the risk of diabetic nephropathy increased. Specifically, women with a delayed menarche (> mean age+2 years) had 2.50 times higher risk of diabetic nephropathy compared with women whose age at menarche was within ±2 years of the mean (OR 2.50 [95% CI 1.54, 4.04]; $p<0.001$). Women with an earlier menarche (< mean age−2 years) did not have a significantly different risk of diabetic nephropathy (OR

Table 1 Clinical characteristics of patients in the pre-menarcheal and post-menarcheal type 1 diabetes groups at the time of evaluation (1994–2011)

Characteristic	Diabetes diagnosed before onset of menarche	Diabetes diagnosed after onset of menarche	*p* value for difference[a]
n	600	704	
Age (years)			
At baseline visit	32.5 (23.9–41.5)	40.2 (32.3–48.1)	<0.0001
At onset of diabetes	8.9 (5.9–10.7)	21.1 (16.1–27.5)	<0.0001
At menarche (years)	13.82±1.65	12.89±1.43	<0.0001
Duration of diabetes (years)	24.7 (16.6–32.8)	18.0 (9.3–25.3)	<0.0001
BMI (kg/m^2)	24.9±3.6	24.8±3.8	0.48
WHR	0.67±0.07	0.68±0.06	0.51
Height (cm)	163.8±6.5	165.3±6.1	<0.0001
HbA_{1c} (%)	8.5±1.4	8.2±1.4	0.004
HbA_{1c} (mmol/mol)	69.5±15.4	66.7±15.7	
Total cholesterol (mmol/l)	4.90±0.89	4.88±0.84	0.15
HDL-cholesterol (mmol/l)	1.41±0.37	1.49±0.38	<.0001
Triacylglycerol (mmol/l)	0.93 (0.71–1.30)	0.87 (0.68–1.20)	<.0001
SBP (mmHg)	128.9±17.5	129.5±17.1	0.16[b]
DBP (mmHg)	76.8±8.9	77.9±9.2	0.17[b]
Antihypertensive medication (%)	38.8	29.4	0.046[b]
eGFR (ml/min/1.73 m^2)	85.7±30.0	87.3±22.2	0.53[b]
Laser-treated retinopathy (%)	39.3	13.6	<0.0001
Diabetic nephropathy (%)	19.5	7.1	<0.0001

Data are expressed as mean (± SD), median (interquartile range) or percentages; *p* value refers to ANOVA, Kruskal–Wallis test or χ^2 test

[a] Adjusted for duration of diabetes when applicable

[b] Adjusted for age and duration of diabetes

DBP, diastolic BP; eGDR, estimated GFR, calculated using the Chronic Kidney Disease Epidemiology Collaboration equation [47]

1.71 [95% CI 0.65, 4.55]; $p=0.28$). The effect was not much attenuated when adjusted for conventional risk factors for diabetic complications such as age at onset of diabetes, duration of diabetes, HbA_{1c}, systolic BP, HDL, cholesterol and triacylglycerol levels, history of smoking, and BMI (OR 2.30 [95% CI 1.27, 4.17]; Table 3). Age at menarche did not have an effect on the risk of diabetic nephropathy in women with post-menarcheal type 1 diabetes (Table 3).

Similar to diabetic nephropathy, the risk of severe diabetic retinopathy increased if the delay in menarche was more than 2 years (Fig. 3b). Delayed menarche had an increasing effect on the risk of severe retinopathy (OR 2.84 [95% CI 1.82, 4.44]) in the univariate analysis. In the multivariable analysis, the OR was 2.34 (95% CI 1.36, 4.01; Table 3). When patients with diabetic nephropathy were excluded from the analysis, the effect of increasing age at menarche remained a significant predictor of severe retinopathy ($p=0.01$), but the relationship was rather linear (Fig. 3c). The OR was 1.17 (95% CI 1.04, 1.33) in the multivariable analysis for each increasing year of age at menarche. The comparable OR was 2.11 (95% CI, 1.15, 3.90) for the group in which menarche was delayed by more than the mean age+2 years (Table 3) and the only significant predictors were duration of diabetes and age at onset of menarche.

Discussion

This is, to the best of our knowledge, the first study to analyse the association between age at menarche and risk of diabetic nephropathy and severe retinopathy in women with type 1 diabetes. Our study shows that women with pre-menarcheal type 1 diabetes and delayed menarche have an increased risk of diabetic microvascular complications.

This study confirms an earlier observation that menarche is delayed in patients with pre-menarcheal type 1 diabetes. Previous studies have reported that if the age at onset of diabetes is less than 10 years, then menarche is delayed [17, 19, 29]. We found an inverse linear relationship between the age at onset of diabetes and age at menarche, i.e. the younger the age at onset of diabetes, the older the age at menarche.

There has been debate about whether a delay in menarche still exists because diabetes management has vastly improved over the years. Recent studies, however, found that, despite intensive insulin treatment and good metabolic control, the

Table 2 Clinical characteristics of the patients with pre-menarcheal type 1 diabetes at time of evaluation (1994–2011) according to the age at menarche

Characteristic	Age at menarche<mean−2 years (range 9–11 years)	Age at menarche=mean±2 years (range 11–15 years)	Age at menarche>mean+2 years (range 15–18 years)	*p* value for difference[a]
n	33	466	101	
Age (years)				
At baseline visit	28.2 (21.0–36.3)	31.5 (23.5–40.5)	39.0 (31.7–45.8)	<0.0001
Onset of diabetes	9.0 (6.8–9.8)	8.8 (5.9–10.7)	9.1 (5.8–11.5)	0.65
At menarche	10.88±0.42	13.46±1.07	16.44±0.71	<0.0001
Duration of diabetes (years)	18.9 (14.4–27.9)	23.8 (15.4–31.8)	30.7 (22.0–38.2)	<0.0001
BMI (kg/m^2)	25.5±3.7	24.9±3.6	24.6±3.5	0.25
WHR	0.67±0.06	0.69±0.09	0.67±0.07	0.14
Height (cm)	161.4±7.1	164.6±6.3	161.4±6.8	<0.0001
HbA_{1c} (%)	8.4±1.3	8.6±1.4	8.2±1.2	0.10
HbA_{1c} (mmol/mol)	68.3±14.1	70.4±15.8	65.6±13.4	
Total cholesterol (mmol/l)	4.64±0.75	4.91±0.89	4.97±0.86	0.26
HDL-cholesterol (mmol/l)	1.36±0.31	1.41±0.37	1.40±0.38	0.42
Triacylglycerol (mmol/l)	0.91 (0.70–1.30)	0.95 (0.71–1.32)	0.90 (0.70–1.18)	0.41
SBP (mmHg)	124.5±14.8	128.3±17.3	133.0±18.6	0.88[b]
DBP (mmHg)	77.5±8.6	75.9±9.4	76.5±8.9	0.96[b]
Antihypertensive medication (%)	27.3	36.1	57.0	0.05[b]
eGFR (ml/min/1.73 m^2)	90.0±24.4	88.1±29.6	73.3±31.1	<0.08[b]
Laser-treated retinopathy (%)	29.0	36.8	62.4	0.02
Diabetic nephropathy (%)	18.2	17.1	28.8	<0.001

Data are expressed as mean (± SD), median (interquartile range) or percentages; *p* value refers to ANOVA, Kruskal–Wallis test or χ^2-test. There is overlap in the range of age at menarche between the groups because the age at menarche was centred to the group mean by decade

[a] Adjusted for duration of diabetes when applicable

[b] Adjusted for age and duration of diabetes

DBP, diastolic BP; eGFR, estimated GFR, calculated with the Chronic Kidney Disease Epidemiology Collaboration equation [47]

menarche is still delayed for type 1 diabetes patients, but this delay does not appear to be as great as previously observed [10, 18, 30]. The researchers concluded that factors other than glycaemic control might contribute to the menarcheal delay. Patients in our study were born over a wide time span (i.e. 1930s to 1980s). Consistent with previous observations, a significant difference in the delay in menarche between pre- and post-menarcheal diabetes patients still existed in the cohort born in 1975–1984, but was diminished compared with those born in earlier decades. Owing to small sample size in the post-menarcheal group in the youngest cohort (born 1985 or later), it was not possible to make any conclusions regarding differences in age at menarche. However, comparison between patients with pre-menarcheal diabetes and a Finnish background population showed that these patients still had a slightly delayed menarche. In Finnish women without diabetes, the mean age at menarche has decreased from 14.9 years in the early 1900s to 12.7 years in the 1970s or later [31], as also seen worldwide [25].

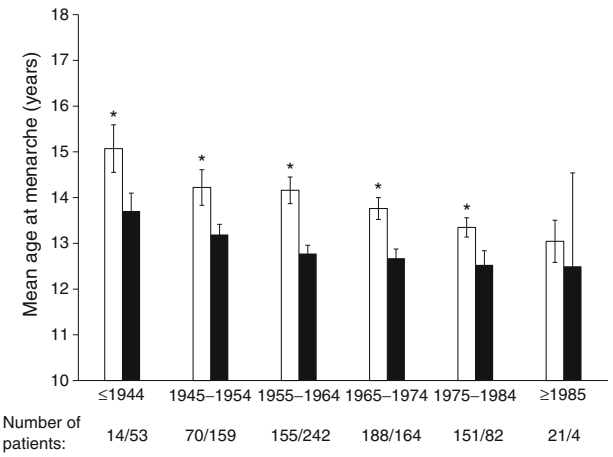

Fig. 1 Mean age at menarche in pre-menarcheal (white bars) and post-menarcheal (black bars) women with type 1 diabetes according to birth cohort. Error bars show the 95% CI. *$p<0.0001$ for difference. The numbers below the graph denote number of patients in the pre-menarcheal group/number of patients in the post-menarcheal group

One of the most important observations in the present study was that delayed menarche was associated with an increased risk of diabetic nephropathy and severe retinopathy. Unfortunately, we cannot compare our results to those of

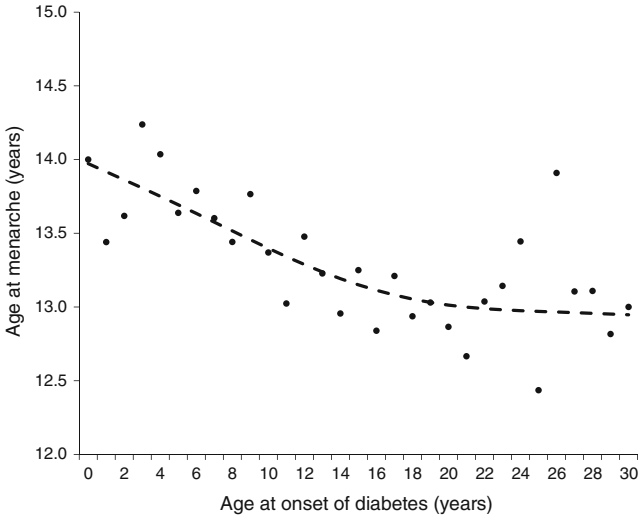

Fig. 2 Relationship between age at onset of diabetes and age at menarche in women with type 1 diabetes. Black circles denote the mean age at menarche and the dashed line (best fit) denotes the predicted age at menarche

previous studies because no comparable studies have been reported. However, delayed menarche has been associated with other diseases and conditions such as irregular menstruation and other gynaecological disturbances [17]. In the general population, menarcheal age has been associated with several other conditions, such as pre-eclampsia, decreased bone mineral density, type 2 diabetes, breast cancer and cardiovascular disease [32–34]. Puberty is known to accelerate microvascular complications. Our previous study showed that women with pubertal and prepubertal type 1 diabetes had a risk of ESRD and diabetic proliferative retinopathy that was almost equal to that of men, but that the risk diverged after puberty [1]. These data suggest that female sex as a protective factor against the development of microvascular complications may be abolished if diabetes onset is before or during puberty, thus implicating hormonal changes associated with puberty in the development of microvascular complications. Puberty is characterised by changes in the hypothalamus–pituitary–gonadal (HPG) axis, including pituitary growth hormone, insulin-like growth factor I, gonadotrophins, luteinising hormone and follicle-stimulating hormone [35]. Type 1 diabetes has been shown to cause disturbances in the HPG axis; in girls with type 1 diabetes, these disturbances are associated with

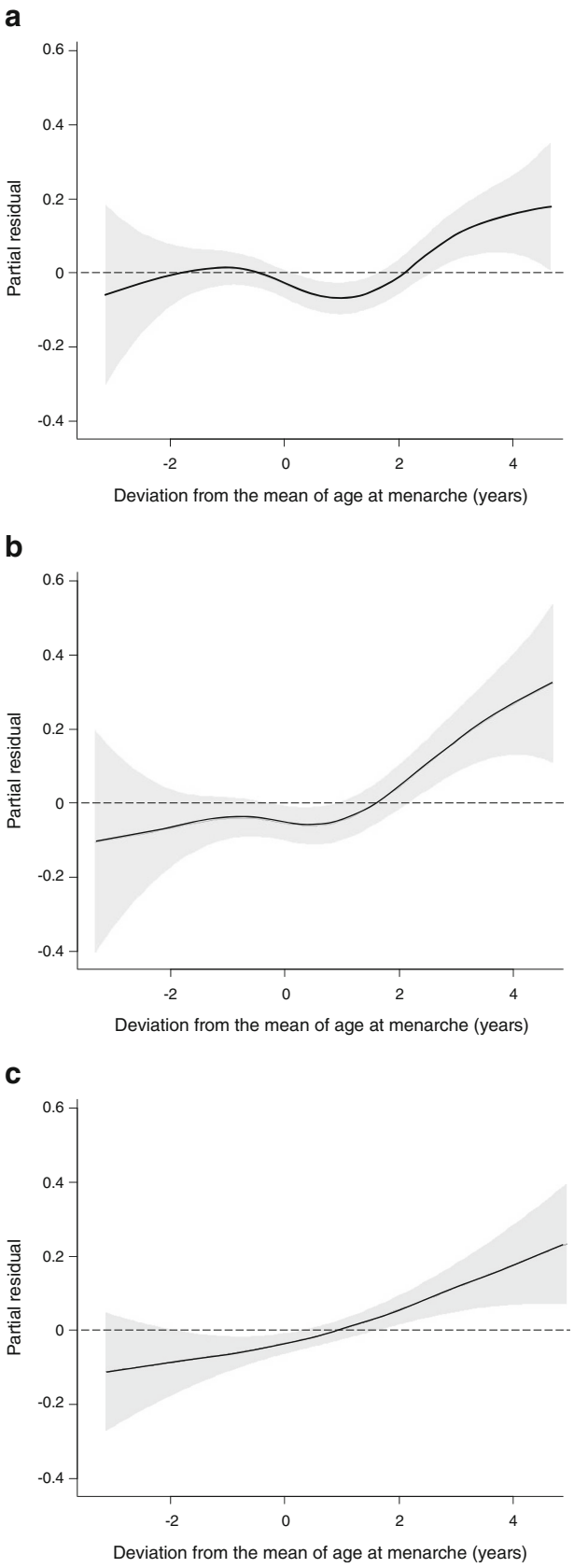

Fig. 3 Partial residual plots for GAM analyses in women with premenarcheal diabetes, showing the combined effect of linear and non-parametric contributions to deviation from the mean age at menarche (black line) on the risk of (**a**) diabetic nephropathy (n=600), (**b**) severe diabetic retinopathy (n=600, including patients with diabetic nephropathy) and (**c**) severe diabetic retinopathy (n=495, excluding patients with diabetic nephropathy). Shaded areas represent 95% CIs. The area above the dotted line at zero represents increased risk and the area under the dotted line represents a decreased risk

Table 3 Multivariable logistic regression analysis for the prevalence of diabetic nephropathy, laser-treated retinopathy (diabetic nephropathy included), laser-treated retinopathy (diabetic nephropathy excluded) in women with type 1 diabetes by age at menarche

Type 1 diabetes diagnosis	Diabetic nephropathy		Laser-treated retinopathy (nephropathy included)		Laser-treated retinopathy (nephropathy excluded)	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Pre-menarcheal						
Age at menarche<(mean−2), years	2.09 (0.76, 5.72)	0.15	0.93 (0.38, 2.30)	0.88	0.69 (0.22, 2.19)	0.53
Age at menarche>(mean+2), years	2.30 (1.27, 4.17)	0.006	2.34 (1.36, 4.01)	0.002	2.11 (1.15, 3.90)	0.02
Post-menarcheal						
Age at menarche<(mean−2), years	0.73 (0.28, 1.94)	0.53	0.65 (0.31, 1.39)	0.27	0.64 (0.27, 1.53)	0.32
Age at menarche>(mean+2), years	0.30 (0.02, 3.65)	0.34	0.11 (0.02, 1.12)	0.06	0.23 (0.03, 2.04)	0.19

delayed ovarian maturation and sex hormone production, leading to delayed menarche [35]. Thus, there appears to be a strong link between sex hormones, delayed menarche and the development of diabetic microvascular complications associated with type 1 diabetes [36]. Further evidence for a link between hormonal status and risk of microvascular complications associated with type 1 diabetes was provided by a study showing that women with diabetic retinopathy and nephropathy undergo menopause at an earlier age [37].

Several experimental studies have demonstrated a renoprotective role for exogenous oestrogens in models of type 1 diabetic retinopathy and nephropathy [38–40]. It is possible that early onset of diabetes impairs the ovarian production of oestrogen, thus becoming permissive for the development of organ complications later in life. Indeed, in both streptozotocin-induced diabetic mice and rats, smaller ovarian preovulatory follicles and delayed oocyte maturation with increased apoptosis of ovarian follicular cells have been observed [41, 42]. Even though hyperglycaemia may cause ovarian follicle changes regardless of the age at onset, it is likely that the early onset of diabetes may not only impair oestrogen production but also permanently reduce the number of available follicles for oestrogen production later in life. Supporting this notion is a report that adult streptozotocin-induced diabetic rats exhibit decreased circulating levels of oestrogen and an imbalance in the expression of renal oestrogen receptors [43].

In the present study, patients with a delayed menarche had the best glycaemic control. In addition, it should be noted that, while our data indicate that women with delayed menarche had the best HbA_{1c} values at the baseline visit, these values represent glycaemic control several years, or even decades, after puberty. The reason for delayed menarche may be poor metabolic control during the second decade of life, which is a critical time for the development of chronic complications. Menarche is one of the final events of puberty, and delayed puberty and menarche may indicate diminished oestrogen levels during puberty. Therefore, worse metabolic control may leads to mild hypogonadism, delayed puberty and delayed menarche.

It is widely accepted that the substantial variation in age at menarche among individuals may be due to genetic factors [44]. A recent large genome-wide association study detected 106 genomic loci involving in pubertal timing and age at menarche [45]. While it is unlikely that age at menarche per se is a causal factor for diabetic nephropathy or retinopathy, it may be a marker of an underlying process that confers an increased risk. Recently, our study group belonging to the GENIE ('GEnetics of Nephropathy an International Effort') consortium identified the first sex-specific genetic variant to be strongly associated with ESRD in type 1 diabetes in women but not in men [46]. Interestingly, the variant is located between the *SP3* and *CDCA7* genes, and *SP3* encodes a transcription factor that directly interacts with oestrogen receptor alpha (ER-α).

Finally, some limitations need to be considered. As with any study that uses self-reported data on questionnaires, recall bias may exist. Another limitation is that the HbA_{1c} values used in the present study were measured at the baseline visit, i.e. years or even decades after menarche. It is therefore not possible to rule out the possibility that patients with delayed menarche had worse glycaemic control during the pubertal period.

Conclusions

Our study shows that age at onset of type 1 diabetes contributes to the age at menarche and, in turn, to the risk of diabetic nephropathy and severe retinopathy later in life. Specifically, the relation between age at menarche and the risk of diabetic nephropathy and severe retinopathy was J-shaped, i.e. delayed menarche was associated with an increased risk of diabetic nephropathy and severe retinopathy but early menarche was not. Delayed menarche may thus be used as a new tool to

identify women at risk of diabetic microvascular complications. It is, however, possible that in the future a shorter delay than 2 years could be used as a sign of delayed menarche and thus as a marker of increased risk of diabetic microvascular complications.

Acknowledgements The authors would like to acknowledge all of the physicians and nurses at each of the FinnDiane centres that participated in patient recruitment and characterisation (see the electronic supplementary material [ESM1].

Funding This research was funded by grants from the Folkhälsan Research Foundation, the Academy of Finland (134379), the Wilhelm and Else Stockmann Foundation, the Liv och Hälsa Foundation and the Novo Nordisk Foundation. The funding bodies were not involved in the design or conduct of the study.

Duality of interest statement P-HG has received lecture honorariums from AbbVie, Boehringer Ingelheim, Cebix, Eli Lilly and Company, Genzyme, Novartis, Novo Nordisk, MSD and Medscape, and research grants from Eli Lilly and Company and Roche. P-HG is also an advisory board member of Boehringer Ingelheim, Eli Lilly and Company and Novartis. All other authors declare that there is no duality of interest associated with their contribution to this manuscript.

Contribution statement VH was responsible for study and questionnaire design, statistical analyses and first draft of the manuscript. CM-B contributed to the study and questionnaire design and to the writing and critical revision of the manuscript. CF contributed to the questionnaire design, data acquisition and critical revision of the manuscript. P-HG was the principal investigator of the study and participated in interpretation of the results and critical revision of the manuscript. All authors contributed to the final version. P-HG is responsible for the integrity of the work as a whole.

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