

Menopause in Type 1 Diabetic Women

Is it Premature?

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Women with type 1 diabetes have a delayed menarche and a greater prevalence of menstrual disorders than women without diabetes. However, little is known about the menopause transition among type 1 diabetic women. The Familial Autoimmune and Diabetes (FAD) Study recruited both adult individuals who were identified from the Children's Hospital of Pittsburgh Type 1 Diabetes Registry for the years 1950–1964 and their family members. Unrelated nondiabetic control probands and their relatives were also evaluated. Women with type 1 diabetes ($n = 143$) compared with nondiabetic sisters ($n = 186$) or unrelated control subjects ($n = 160$) were more likely to have an older age at menarche (13.5, 12.5, and 12.6 years, respectively, $P < 0.001$), more menstrual irregularities before 30 years of age (45.7, 33.3, and 33.1%, respectively, $P = 0.04$), and a younger age at menopause (41.6, 49.9, and 48.0 years, respectively, $P = 0.05$). This resulted in a 6-year reduction in the number of reproductive years (30.0, 37.0, and 35.2 years, respectively, $P = 0.05$) for women with type 1 diabetes. Risk factors univariately associated with earlier menopause included type 1 diabetes (hazard ratio [HR] 1.99, $P = 0.04$), menstrual irregularities before 30 years of age (HR 1.87, $P = 0.04$), nulliparity (HR 2.14, $P = 0.01$), and unilateral oophorectomy (HR 6.51, $P < 0.0001$). Multivariate analysis confirmed that type 1 diabetes (HR 1.98, $P = 0.056$), menstrual irregularities by 30 years of age (HR 2.36, $P = 0.01$), and unilateral oophorectomy (HR 9.76, $P < 0.0001$) were independent determinants of earlier menopause in our cohort. We hypothesize that an earlier menopause, which resulted in a 17% decrease in reproductive years, is a major unstudied complication of type 1 diabetes. *Diabetes* 50:1857–1862, 2001

Young women with type 1 diabetes have a delayed age at menarche and are at higher risk for having menstrual irregularities than nondiabetic women of similar age (1–3). Of the women with type 1 diabetes, >30% report problems, such as amenorrhea, polymenorrhea, and oligomenorrhea throughout their reproductive years. This is approximately double the prevalence of menstrual disorders observed among women without the disease (2), with differences most pronounced when diabetes occurs before puberty (2,3). Type 1 diabetic women are also more likely to have adverse pregnancy outcomes than nondiabetic women (4–6). Spontaneous abortions (4), stillbirths, and congenital anomalies (5) characterize the reproductive histories of type 1 diabetic women with poor glycemic control. With advances in intensive insulin therapy, women with type 1 diabetes are now able to maintain better glycemic control and have successful pregnancies and healthy children (6,7). However, little is known about late reproductive events, such as the menopause transition, among women with type 1 diabetes.

Although the prognosis associated with type 1 diabetes has improved dramatically in recent decades, affected individuals remain at high risk for premature morbidity (8,9) and mortality (10,11) from cardiovascular, cerebrovascular, and peripheral vascular diseases (PVDs). More than one-half of the deaths that currently occur among affected individuals between 25 and 40 years of age are a result of vascular disorders (11). This reflects an approximate 20-fold increased risk compared with the rates for nondiabetic individuals of the same age. Moreover, the sex differences in cardiovascular disease risk observed for the general population, with lower rates among women than men, are reduced among individuals with type 1 diabetes (10,11). Although this may be related to metabolic disturbances (e.g., hyperglycemia, hypertension, etc.), such abnormalities are unlikely to explain the magnitude of the increased prevalence of atherosclerotic diseases in type 1 diabetic subjects compared with nondiabetic subjects.

The early occurrence of vascular complications is only one of the characteristics of premature aging that are frequently observed among individuals with type 1 diabetes. Other changes include accelerated thickening of muscle basement capillary membrane (12) and stiffening of connective tissue (13). These generally occur in nondiabetic subjects >50 years of age but are commonly observed among young adults with type 1 diabetes, particularly

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FAD; Familial Autoimmune and Diabetes; HR, hazard ratio; IRB, Institutional Review Board; OC, oral contraceptive; PCOS, polycystic ovarian syndrome; PVD, peripheral vascular disease; RA, rheumatoid arthritis.

those with long disease duration. Diabetes also increases the risk for cataracts (14). In addition, a reduced cell-population doubling time has been noted among type 1 diabetic patients compared with nondiabetic individuals of comparable age (15,16). Collectively, these data suggest that individuals with type 1 diabetes experience accelerated senescence. Therefore, one would expect other indicators of biological age, such as the occurrence of the menopause transition, to begin prematurely among women with type 1 diabetes (17). To our knowledge, there is only one anecdotal report in the very early literature to support this hypothesis (18). Thus, the current analyses were undertaken to begin to explore the menopause transition in a unique and representative cohort of adult Caucasian women with type 1 diabetes, their sisters, and unrelated nondiabetic control subjects.

RESEARCH DESIGN AND METHODS

The Familial Autoimmune and Diabetes (FAD) Study, which is the basis of this study, recruited a cohort of men and women ($n = 656$) who were retrospectively defined in 1981 for a study of type 1 diabetes mortality. Individuals were eligible if they were on insulin therapy at diagnosis between 1950 and 1964, <17 years of age at disease onset, and seen at the Children's Hospital of Pittsburgh within 1 year of type 1 diabetes onset. During 1990, registered patients were recontacted to update the data collected in 1981. Information was obtained for 86% ($n = 561$) of the registered patients. Compared with nonrespondents ($n = 95$), no significant differences in age, sex, duration of diabetes, or cigarette smoking at baseline were observed.

Beginning in 1993, living patients who completed the 1990 survey ($n = 375$) were recruited for the FAD Study. Not unexpectedly, the group of probands who had died ($n = 181$) or were ineligible because of imprisonment and/or mental illness ($n = 5$) were older than survivors (mean birth year 1949 vs. 1951, $P < 0.001$) and in 1990 had a longer duration of diabetes (32.9 vs. 31.5 years, $P < 0.001$) than survivors. After obtaining informed consent, 71% of those eligible ($n = 265$) participated. Compared with nonparticipants ($n = 110$), no significant differences were observed with regard to age, sex, race, duration of diabetes, cigarette smoking, or prevalence of self-reported autoimmune disease from the 1990 survey. In addition, parents and siblings of enrolled probands ($n = 868$) were contacted and asked to participate. Those recruited ($n = 635$, 73.6%) were evaluated using protocols identical to those used for the probands.

A total of 96 healthy control probands and their parents and siblings were examined during the same time period for the FAD Study. Approximately 32,000 letters of invitation were sent using mass mailings to individuals residing in similar zip codes as the case subjects; the case subjects and control subjects were group-matched by age, sex, race, and duration of residence in the Pittsburgh area. In accordance with Institutional Review Board (IRB) procedures, the investigations were blinded to the names, addresses, and specific characteristics of the subjects. Of those who responded, 18% were eligible and were actively recruited. No additional information was obtained for ineligible subjects, per IRB recommendations. However >90% of eligible subjects enrolled in the study. The target sample size for the control families, which was based on power calculations to test major study hypothesis, was 100.

Study protocol. All participants received a clinical evaluation that included an assessment of autoimmune diseases, blood pressure, and BMI. They also donated a blood sample for laboratory evaluations (e.g., lipids, HbA_{1c}, and autoantibodies) and genetic studies (e.g., HLA-DQ molecular typing). In addition, they completed several questionnaires regarding their current and past medical history (e.g., macro- and microvascular complications), lifestyle factors (e.g., smoking, physical activity, nutrition, and socioeconomic status), and reproductive histories (e.g., pregnancies, infertility, and hormone use). The diagnosis of autoimmune thyroid disease was based on the clinical evaluation, medical history, assessment of signs and symptoms, and laboratory determinations as previously described (19,20). The diagnosis of rheumatoid arthritis (RA) was also based on the clinical and laboratory evaluations. Classification of RA was according to the 1987 Revised American Rheumatism Association Criteria (21). The presence of other autoimmune diseases (e.g., pernicious anemia, vitiligo, etc.) was determined by medical history.

Menstrual and menopausal events were self-reported using survey instruments as described above. The questions included were based on those used

by the Healthy Women Study, which was conducted by one of the coauthors (L.H.K.) and followed >500 premenopausal women from western Pennsylvania through the menopause transition (22,23). The FAD Study participants were asked whether they used birth control pills, estrogen pills, vaginal creams/injections/patches, and progestins during each of the five age-groups that represent the entire reproductive period, ranging from 20–24 years of age to ≥ 50 years of age. FAD Study participants were also asked to indicate whether their menstrual periods were regular or irregular, the number of days of flow, whether they experienced heavy bleeding, and the length of their menstrual cycles during these same year-age intervals. For the current analyses, menstrual irregularities were defined as one or more of the following disturbances before 30 years of age, when premenopausal status could most likely be confirmed: 1) menstruating >5 days per cycle, 2) menstrual cycles >31 days, or 3) heavy menstrual flow. Menopausal status was based on women's responses to the question, "Have you gone through natural menopause or change of life?" Women who responded "yes" were asked to report their age at menopause.

Statistical analyses. Statistical analyses for categorical variables shown in Table 1 were performed using χ^2 tests. Exact methods were used when the expected value of any cell was <5. For continuous variables, *t* tests and analysis of variance were used. For data that were not normally distributed, such as age at menopause, the nonparametric Mann-Whitney rank order test was used. This test examines the rank order of the values but not the values themselves; therefore, it is robust to lack of normality. Women reporting either hysterectomy or bilateral oophorectomy were excluded from all but the descriptive analysis.

Time to menopause was evaluated using product-limit methodology and Cox Proportional Hazards analysis, which included "diabetes status" as the independent variable (24). Although all women will eventually experience menopause, these methods censor those who are premenopausal at their current age. The Breslow statistic was used to test for statistically significant differences in the time to menopause curves. This approach was conservative; it gives more weight to the first part of the curve, where the estimates are more precise because of heavy censoring at the curve's tail.

RESULTS

Clinical and reproductive characteristics. Approximately 98% of the FAD Study cohort was Caucasian. Among women, the mean age at diagnosis of type 1 diabetes was 8.1 ± 5.1 years, and their mean diabetes duration at the time of the exam was 34.5 ± 5.5 years.

The clinical and reproductive characteristics of the women with type 1 diabetes, their nondiabetic sisters, and unrelated nondiabetic control subjects are illustrated in Table 1. Women with type 1 diabetes were statistically significantly more likely to have Hashimoto's thyroiditis than nondiabetic sisters or control subjects. No differences in the prevalence of Graves' disease or definite RA were observed. However, the prevalence of possible RA was significantly higher among type 1 diabetic women compared with their nondiabetic sisters or control subjects (19.6, 8.1, and 6.3%, respectively, $P = 0.0003$). Other reported autoimmune diseases were rarely observed (<2%), with no differences among the three groups.

As expected, the mean age at menarche was statistically significantly older for type 1 diabetic women compared with nondiabetic women. In addition, statistically significantly more type 1 diabetic women reported irregular menstrual cycles before 30 years of age than nondiabetic women, and they were statistically significantly less likely to have ever taken oral contraceptives (OCs) but not other estrogen medications. Although there was no difference in reported infertility, statistically significant differences in parity and mean number of pregnancies were observed, particularly between type 1 diabetic women and their sisters.

A similar proportion of type 1 diabetic and nondiabetic women had a hysterectomy or a bilateral or unilateral

TABLE 1
Characteristics of women with and without type 1 diabetes

Characteristic	With diabetes (<i>n</i> = 143)	Without diabetes		<i>P</i>
		Sisters (<i>n</i> = 186)	Control subjects (<i>n</i> = 160)	
Mean age at exam (years)	42.6	42.4	41.3	0.26
Hashimoto's thyroiditis	42.7	30.4	19.4	<0.001
Graves' disease	5.0	3.8	3.1	0.71
RA	0.7	2.2	0.0	0.11
Mean age at menarche (years)	13.5	12.5	12.6	<0.001
Menstrual irregularities (<30 years of age)	45.7	33.3	33.1	0.04
OC use	44.0	79.0	80.0	<0.001
Estrogens other than OC	17.7	22.6	16.3	0.29
Infertility	16.9	17.7	17.0	0.97
Nulliparous	35.5	19.9	36.3	<0.001
Mean number of pregnancies	1.8	2.5	1.8	<0.001
Hysterectomy	16.2	10.8	9.4	0.16
Bilateral oophorectomy	2.2	2.7	1.9	0.93
Unilateral oophorectomy	5.9	3.3	2.5	0.29
Natural menopause	12.5	12.7	10.4	0.80
Mean age at menopause* (years)	41.6	49.9	48.0	0.05
Mean reproductive years	30.0	37.0	35.2	0.05
Ever smoked	41.8	48.4	50.6	0.29
Mean BMI	24.6	25.2	27.8	0.002
College attendance	64.6	65.6	75.6	0.07
Income >\$40,000/year	40.8	59.1	52.7	0.006

Data are % unless otherwise indicated. *These analyses excluded women with a premenopausal hysterectomy or bilateral oophorectomy and were based on 120, 165, and 144 women, respectively, of whom 15, 21, and 15 experienced natural menopause.

oophorectomy (Table 1). Among those who had surgery, the mean ages were similar among type 1 diabetic women, nondiabetic sisters, and control subjects for hysterectomy (35.2, 39.2, and 35.2 years of age, respectively, $P = 0.09$), bilateral oophorectomy (39.3, 38.6, and 27.3 years of age, respectively, $P = 0.14$), and unilateral oophorectomy (35.9, 35.2, and 28.8 years of age, respectively, $P = 0.56$). After excluding women with a premenopausal hysterectomy or bilateral oophorectomy among type 1 diabetic women, nondiabetic sisters, and control subjects, 120, 165, and 144 women, respectively, could experience natural menopause, which was reported by 15, 21, and 15 women, respectively. Although a similar proportion of type 1 diabetic and nondiabetic women reported a natural menopause, the mean age at natural menopause was statistically significantly younger for type 1 diabetic women compared with nondiabetic sisters or control subjects (Table 1). Interestingly, five women with type 1 diabetes but only one nondiabetic sister and one nondiabetic control subject reported having natural menopause before 40 years of age. Because of their older age at menarche and younger age at menopause, type 1 diabetic women had an average of 6 fewer reproductive years than their sisters or control subjects. This difference was statistically significant.

As illustrated in Table 1, type 1 diabetic women also had a statistically significantly lower mean BMI and a lower annual income than nondiabetic sisters or control subjects. They were also somewhat less likely to attend college. However, no statistically significant differences in cigarette smoking were observed among the three groups. **Early menopause and type 1 diabetes.** Among women with type 1 diabetes, those with early menopause (defined as self-report natural menopause ≤ 47 years of age) (25)

were somewhat younger at type 1 diabetes onset (8.6 vs. 12.6 years of age, $P = 0.10$). However, the mean level of HbA_{1c} at exam was virtually the same (8.5 vs. 8.4%, $P = 0.78$). The mean units of required insulin per day were also similar (35.3 vs. 31.9 units, $P = 0.40$) among type 1 diabetic women with early versus later menopause. In addition, no statistically significant differences were observed in reported macrovascular complications (cardiovascular disease and PVD, 56.6 vs. 42.1%, $P = 0.69$), microvascular complications (retinopathy and nephropathy, 77.8 vs. 57.9%, $P = 0.42$), hypertension (42.9 vs. 20.0%, $P = 0.59$), or lipid levels (mean triglycerides 141.3 vs. 134.4 mg/dl, $P = 0.59$, mean HDL 59.0 vs. 65.0 mg/dl, $P = 0.31$). However, potential problems with statistical power as a result of the small sample size ($n = 28$) for these analyses may have masked important clinical effects that will become more apparent as our follow-up continues.

Univariate analyses: time to menopause. Survival analysis confirmed the difference in time to menopause for type 1 diabetic and nondiabetic women ($P = 0.02$) (Fig. 1).

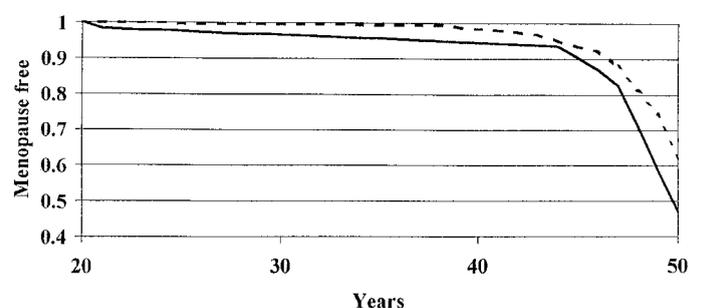


FIG. 1. Time to menopause. —, Type 1 diabetic women; - - -, nondiabetic women.

TABLE 2
Univariate Cox proportional hazard analysis: time to menopause

Risk factor	HR	P	95% CI
Type 1 diabetes	1.99	0.04	(1.02–3.88)
Hashimoto's thyroiditis	1.34	0.33	(0.75–2.41)
Any autoimmune disease*	1.26	0.44	(0.71–2.24)
Age at menarche	1.11	0.29	(0.92–1.31)
Menstrual irregularities <30 years of age	1.87	0.04	(1.04–3.35)
Nulliparous	2.14	0.01	(1.20–3.84)
OC use	0.72	0.27	(0.41–1.28)
Unilateral oophorectomy	6.51	<0.0001	(2.84–14.9)
DQA1*0301-DQB1*0302	1.85	0.04	(1.02–3.35)
DQA1*0501-DQB1*0201	0.74	0.33	(0.40–1.37)
Family history of early menopause	2.12	0.14	(0.78–5.73)
Ever smoked	1.23	0.48	(0.69–2.17)
Duration smoking \geq 1 pack/week	1.00	0.91	(0.98–1.02)
Alcohol consumption (drinks/week)	0.96	0.34	(0.87–1.05)
BMI	1.01	0.82	(0.95–1.07)
College attendance	1.27	0.46	(0.67–2.43)
Income >\$40,000/year	0.90	0.34	(0.72–1.12)

*Hashimoto's thyroiditis, Graves' disease, rheumatoid arthritis.

Cox proportional hazards analysis was then performed to examine potential risk factors reported for early menopause (25–33) in this cohort. As illustrated in Table 2, women with diabetes were approximately twice as likely to have experienced menopause earlier than similar nondiabetic women. However, no differences for Hashimoto's thyroiditis, Graves' disease, or RA were observed. Women who reported menstrual irregularities before 30 years of age and those who were nulliparous were also statistically significantly more likely to have an earlier menopause. Age at menarche and OC use were not related to time to menopause in this cohort. As expected, women with a unilateral oophorectomy had a highly significantly increased risk for earlier menopause compared with those who did not have ovarian surgery.

Possible genetic and lifestyle factors known to impact the reproductive experience of nondiabetic women were also examined. Women who carried the DQA1*0301-DQB1*0302 haplotype, which is in linkage disequilibrium with DR4, were approximately twice as likely to have an earlier menopause than women without this haplotype. However, no statistically significant associations were observed between time to menopause and the DQA1*0501-DQB1*0201 haplotype (in linkage disequilibrium with DR3), family history of early menopause, cigarette smoking, alcohol consumption, BMI, education, or income.

Multivariate analyses: time to menopause. Multivariate Cox proportional hazards analysis was performed to examine relations among the factors associated with time to menopause. The potential independent risk factors considered for the models were those that were univariately and biologically associated with age at menopause (Table 2). The final regression model contained only three statistically significant variables: type 1 diabetes (hazard ratio [HR] 1.98, $P = 0.056$), menstrual irregularities before 30 years of age (HR 2.36, $P = 0.01$), and unilateral oophorectomy (HR 9.76, $P < 0.0001$). These data indicate that type 1 diabetic women are nearly twice as likely to have a younger age at menopause than nondiabetic women after adjusting for other factors, and they confirm

the importance of type 1 diabetes as a statistically significant risk factor for early age at menopause in our cohort.

DISCUSSION

To our knowledge, this is the first formal report of a statistically significantly earlier age at menopause among type 1 diabetic compared with nondiabetic women. A clinical report from 1954 suggested that menopause may occur slightly earlier in women who developed diabetes as adults (18). However, these results were based on a very small number of patients and lacked an appropriate control group. We also found only one study of type 2 diabetic women that reported similar mean ages at menopause for diabetic patients and nondiabetic control subjects (34). Because so little is known about the menopause transition in diabetic women, we recently received funding from the National Institutes of Health to prospectively follow the FAD Study cohort through the perimenopausal years with clinical and laboratory evaluations.

A younger age at menopause for type 1 diabetic women can have great clinical significance. First, it dramatically reduces the number of childbearing years among women whose reproductive experience is already compromised. It has been well established that women with type 1 diabetes, particularly those in poor metabolic control, are at high risk for perinatal morbidity and mortality (4–6). Thus, the observed 6-year average reduction in childbearing years, caused by late menarche and early menopause, clearly illustrates the significant decrease in the reproductive potential of type 1 diabetic women.

Secondly, premenopausal type 1 diabetic women are already at high risk of developing cardiovascular disease. Therefore, an earlier menopause transition may exacerbate their likelihood of developing these complications during their postmenopausal years. Among nondiabetic women, menopause is associated with more atherogenic lipid profiles (22,23,35), lower bone mineral densities (36,37), increased risks for cardiovascular disease (38,39), osteoporosis (40), and early mortality (17,41). Such conditions appear to improve with hormone replacement therapy in the general population (42,43). To our knowledge, there are no comparable data for type 1 diabetic women. This confirms the importance of future prospective studies of the menopause transition among women with type 1 diabetes.

In addition to type 1 diabetes, menstrual irregularities before 30 years of age and unilateral oophorectomy were independently associated with earlier menopause in our cohort. The association with unilateral oophorectomy was particularly strong. It has been reported that a subgroup of hysterectomized women without bilateral oophorectomy have a significantly earlier age of ovarian failure than women who experience natural menopause (44). Possible explanations include a compromised vascular supply to the ovary postsurgery and/or the need for an endocrine contribution from the uterus to ensure normal ovarian function. Thus, hysterectomy with the removal of one rather than two ovaries may have similar but less dramatic effects. Whether this is also true for women with type 1 diabetes who frequently suffer from microvascular complications remains to be confirmed, but it represents an important area of future investigation.

Interestingly, cigarette smoking was not associated with time to menopause. The lack of relationship with cigarette smoking could reflect a selection bias as a result of an association between smoking and mortality. However, further exploration of this issue revealed no significant differences in the prevalence or duration of cigarette smoking among type 1 diabetic participants compared with nonparticipants for either the 1990 survey or the FAD Study. In fact, there was a suggestion that more participants were current smokers than nonparticipants. Because previous research of the determinants of earlier menopause have been primarily based on nondiabetic women, it may be that in type 1 diabetic populations the effects of other potential risk factors, such as cigarette smoking, are obscured.

Although our findings were based on self-reported age at menopause, previous investigations have demonstrated that such data are quite reproducible, particularly when ascertained soon after the occurrence of menopause (45,46). For example, several studies reported that ~70–80% of women were able to correctly report their age at menopause to within 1 year on two separate questionnaires administered 7–9 years apart. Proportions were even higher for recalling age at surgical menopause. In addition, validation analysis revealed very high agreement between self-report age at hysterectomy or bilateral oophorectomy and the age noted in medical records. Given the young and comparable ages of the type 1 diabetic women, their sisters, and nondiabetic control subjects, it is unlikely that information bias was a problem with this investigation.

One explanation for an early menopause among type 1 diabetic women may be related to prolonged hyperglycemia and/or other long-term complications of the disease. In addition, peripheral hyperinsulinemia and insulin resistance occurs among approximately one-half of individuals with type 1 diabetes (47,48). Hyperinsulinemia is associated with the polycystic ovarian syndrome (PCOS) and is characterized by hyperandrogenemia and amenorrhea (49–51). Because insulin and androgen levels are highly correlated in women with PCOS, one may speculate that the young age at menopause in women with type 1 diabetes may be mediated, in part, through peripheral hyperinsulinemia and/or hyperandrogenemia. However, the occurrence of PCOS in women with type 1 diabetes has rarely been reported (1). Thus, factors unrelated to long-term diabetes may also be important determinants of the menopause transition. One such variable may be autoimmunity.

Several reports have suggested that early menopause has an autoimmune etiology (52–55). Approximately 20–40% of women with premature ovarian failure also have autoimmune disorders, particularly autoimmune thyroid disease (56–58). In addition, circulating anti-ovarian autoantibodies have been observed with a greater frequency among subjects who experienced premature ovarian failure compared with healthy control subjects, even though they had no evidence of overt autoimmune disease. Thus, there appears to be a strong positive association between autoimmunity and premature menopause. Although we did not observe a stronger relationship with earlier menopause among women with type 1 diabetes and another

autoimmune disorder (compared with those with only type 1 diabetes), our sample size was small. Thus, it remains to be determined whether the clustering of autoimmune diseases within individuals is an independent risk factor for earlier menopause.

Given the well-documented associations between the HLA region of chromosome 6 and type 1 diabetes risk, the genetic factors that increase the risk of autoimmune disorders may also influence age of menopause. It has been shown that HLA-linked genes contribute to the levels of sex hormones in men (59) and age at menarche in women (60). In addition, associations between premature ovarian failure and HLA-DR3 (61) and HLA-DR4 (62), which confer susceptibility to type 1 diabetes, have been observed. We also noted that time to menopause was associated with the DR4-DQA1*0301-DQB1*0302 haplotype but not the DR3-DQA1*0501-DQB1*0201 haplotype in our univariate analysis. Whether this association is independent of type 1 diabetes will be confirmed with continued follow-up.

The FAD Study follow-up is now underway and provides a unique opportunity to prospectively evaluate the menopause transition among type 1 diabetic women. To our knowledge, such an investigation has never been conducted and will reveal critical information about premature aging, autoimmunity, and early menopause among women with type 1 diabetes.

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