Self-Reported Autoimmune Disease by Sex in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study

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People with type 1 diabetes have an increased risk for autoimmune thyroid disease, which is more common in women than in men according to at least one (1) but not all (2) studies. Exposures unique to women, such as pregnancy, exogenous estrogen, and menopause, have been linked to other autoimmune diseases, including rheumatoid arthritis and systemic lupus erythematosus (3). However, studies examining such exposures in women with type 1 diabetes are unavailable.

Because the incidence of type 1 diabetes is increasing worldwide, it is important to determine the factors associated with comorbid conditions (4). We analyzed participants (n = 1,324) in the Diabetes Control and Complications Trial (DCCT), a randomized trial of intensive insulin therapy, and its follow-up, Epidemiology of Diabetes Interventions and Complications (EDIC). With the use of Cox regression models, we estimated hypothyroid risk associated with sex, age, DCCT treatment group, diabetes duration, microvascular complications, and hemoglobin A_{1c} (HbA_{1c}). Among women, we further examined parity, menopause, and estrogen use. We also report the cumulative incidences of other autoimmune diseases by sex.

Year 2 participant characteristics by incident hypothyroidism were similar in terms of BMI, diabetes duration, HbA_{1c}, and microvascular complications. Parity, menopausal status, and estrogen use were also similar among women. By EDIC year 18, more women than men reported incident hypothyroidism (24.6 vs. 11.3%, $P < 0.0001$). Cumulative incidences of other autoimmune conditions, including pernicious anemia (17 women, 4 men) and adrenal disease (2 women, 2 men), were low.

Table 1 presents the risk of incident hypothyroidism associated with sex and other covariates. After multivariable adjustment, women had an increased hazard of hypothyroidism compared with men. Other covariates were not associated with increased hypothyroid risk. Among women, pregnancy, exogenous estrogen, and menopause were not associated with hypothyroidism.

To our knowledge, other studies have not examined female-specific exposures as risk factors for autoimmune disease among women with type 1 diabetes. In the current analysis, increased estrogen exposure was not associated with increased hypothyroid risk. Increased endogenous estradiol, as in pregnancy, or increased exogenous estradiol, as with estrogen use, did not significantly increase risk beyond baseline estradiol production. Other sex-specific exposures not related to sex hormones may also explain these differences.

The strengths of the study include a large cohort, high participant retention, and 18-year follow-up. However, DCCT/EDIC was not designed a priori to assess autoimmune disease. Self-reported disease represents clinically significant disease. However, autoantibody assays and hormone levels were not available to quantify subclinical disease, which leads to an underestimation of autoimmune disease.

In conclusion, in women with type 1 diabetes, the risk for hypothyroidism is not affected by exposure to pharmacologic estrogens, pregnancy, or menopause. Other diabetes-related factors were not associated with increased hypothyroid risk. Further research is needed to examine which exposures may increase this risk in

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**A complete list of participants in the DCCT/EDIC Research Group can be found in N Engl J Med 2011;365:2366–2376.*

Table 1—Risk of incident hypothyroidism

	Adjusted HR (95% CI)*	*P* value
Women (reference = men)	2.40 (1.80–3.20)	<0.01
Age (years)	1.00 (0.98–1.02)	0.59
Smoking (reference = no current smoking)	0.74 (0.50–1.08)	0.12
BMI (kg/m^2)	1.01 (0.97–1.04)	0.69
Intensive therapy arm (reference = conventional arm)	0.95 (0.68–1.33)	0.76
Primary cohort (reference = secondary cohort)	1.05 (0.70–1.58)	0.82
DCCT/EDIC time-weighted HbA_{1c} (%)	1.01 (0.88–1.16)	0.90
Diabetes duration (years)	1.01 (0.97–1.05)	0.65
Proliferative retinopathy†	0.67 (0.28–1.57)	0.35
Neuropathy‡	0.87 (0.62–1.22)	0.42
AER 40–299 mg/24 h (reference <40 mg/24 h)§	0.80 (0.47–1.37)	0.42
AER ≥300 mg/24 h (reference <40 mg/24 h)§	1.16 (0.45–2.98)	0.76
Women only‖		
Ever pregnant	0.88 (0.59–1.31)	0.53
Postmenopausal	1.59 (0.80–3.17)	0.19
Exogenous estrogen use	1.29 (0.86–1.92)	0.22

Risk factors are from EDIC baseline (year 2) unless otherwise indicated. AER, albumin excretion rate; HR, hazard ratio. *Each risk factor in the model is adjusted for all other risk factors in the model. †Retinopathy defined as proliferative diabetic retinopathy or worse on the Early Treatment Diabetic Retinopathy Study scale (≥12) at DCCT closeout. ‡Neuropathy defined using Michigan Neuropathy Screening Instrument. §Nephropathy defined as an AER <40, 40–299, and ≥300 mg/24 h. ‖Models with sex-specific factors include women only.

women and whether such exposures are modifiable. Examination of sex-specific exposures and interactions with HLA types and antibody status to produce disease and how ascertainment for these diseases may differ by sex is needed.

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References

1. Warncke K, Fröhlich-Reiterer EE, Thon A, Hofer SE, Wiemann D, Holl RW; DPV Initiative of the German Working Group for Pediatric Diabetology; German BMBF Competence Network for Diabetes Mellitus. Polyendocrinopathy in children, adolescents, and young adults with type 1 diabetes: a multicenter analysis of 28,671 patients from the German/Austrian DPV-Wiss database. Diabetes Care 2010;33:2010–2012
2. Somers EC, Thomas SL, Smeeth L, Hall AJ. Are individuals with an autoimmune disease at higher risk of a second autoimmune disorder? Am J Epidemiol 2009;169:749–755
3. de Man YA, Dolhain RJ, van de Geijn FE, Willemsen SP, Hazes JM. Disease activity of rheumatoid arthritis during pregnancy: results from a nationwide prospective study. Arthritis Rheum 2008;59:1241–1248
4. DIAMOND Project Group. Incidence and trends of childhood Type 1 diabetes worldwide 1990-1999. Diabet Med 2006;23:857–866