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Sex Differences in Autoimmune Multimorbidity in Type 1 Diabetes Mellitus and the Risk of Cardiovascular and Renal Disease: A Longitudinal Study in the United States, 2001–2017

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Abstract

Background: Autoimmune diseases are usually more prevalent in women. The risks of cardiovascular and renal disease in those with multiple autoimmune diseases have not been fully described.
Materials and Methods: Using a national database from a large health insurer in the United States (years 2001–2017) containing ~75 million members, we calculated age- and sex-specific co-prevalence of 12 autoimmune disorders for individuals with type 1 diabetes. We then evaluated whether concomitant autoimmune diseases were associated with renal failure, ischemic stroke, and myocardial infarction.
Results: Of the 179,248 people diagnosed with type 1 diabetes, 1 in 4 had a concomitant autoimmune disease (27.03%; 95% confidence interval [CI] = 26.83%–27.24%), with hypothyroidism, rheumatoid arthritis, and celiac disease being the most common. The prevalence of autoimmune disease was 1.9 times greater in female than male patients ($p < 0.001$). In female patients with type 1 diabetes, one in three had another autoimmune disease (35.62%; 95% CI = 35.30%–35.94%) compared with one in five male patients (19.17%; 95% CI = 18.92%–19.42%). The risk of renal failure, ischemic stroke, and myocardial infarction increased with a greater number of concomitant autoimmune diseases ($p < 0.001$, test for trend for both female and male patients). Patients with type 1 diabetes who had multiple sclerosis or myasthenia gravis experienced an approximate threefold increase in risk of ischemic stroke (odds ratio [OR] = 3.57, OR = 3.22, respectively). Patients with type 1 diabetes and Addison's disease had a threefold increased risk of renal failure.
Conclusions: Patients with type 1 diabetes, particularly women, frequently have coexisting autoimmune diseases that are associated with higher rates of renal failure, ischemic stroke, and myocardial infarction. Additional study is warranted, as are preventive efforts in this high-risk population.

Keywords: sex, autoimmunity, type 1 diabetes, multimorbidity

Introduction

In the United States, 1 in 4 noninstitutionalized older adults (≥65 years of age) have at least 2 or more chronic medical conditions and, for younger adults (18–44 years), it is 1 in 20.[1] Long-term multimorbidity (*i.e.*, multiple coexisting chronic conditions) is associated with decreased health-related quality of life and increased physical and cognitive impairment, disability, and mortality even among young and middle-aged adults.[2–4] The burden of a lifetime spent with the daily challenges of coping with multimorbidity is particularly poignant for those who develop chronic diseases at an early age. Type 1 diabetes mellitus is one such disease, the incidence of which is greatest in children.[5] Rates of type 1 diabetes, an autoimmune disease, often cluster with other autoimmune diseases such as celiac disease and thyroid disorders.[6–9] In the Type 1 Diabetes Registry, 34% of female and 19% of male patients with type 1 diabetes had additional autoimmune diseases.[6] In a study of adults with type 1 diabetes using a nationwide patient database, 30% of women and

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15.8% of men had an additional autoimmune disease, with thyroid disease being the most common.[7] In a pediatric study, one-third of children with type 1 diabetes had autoantibodies for common autoimmune disorders and 6% were diagnosed with another autoimmune disease within several months after the onset of type 1 diabetes.[9]

Although both microvascular and macrovascular complications of type 1 diabetes have been described,[10,11] population-based studies of the influence of multiple autoimmune diseases on subsequent cardiovascular and renal disease have not been fully investigated. Because the United States has the largest population with type 1 diabetes,[12] we used a nationwide sample to investigate the co-prevalence of autoimmune diseases. We were particularly interested in the ages when such autoimmune diseases manifested and sex differences in prevalence. Although autoimmune diseases, in general, tend to be more common in female than male patients, type 1 diabetes is unusual in that it is more common in male than female patients, particularly after puberty.[13] With this national database, we answered the following questions: (1) for a patient with type 1 diabetes of a given age and sex, what is the likelihood of concomitant autoimmune disease? and (2) are persons with multiple autoimmune disorders more likely to have severe morbidities such as renal failure, myocardial infarction, and ischemic stroke?

Materials and Methods

Data source

The data source was an integrated relational database from a nationwide health insurer serving all 50 states in the United States. Longitudinal data were extracted from January 1, 2001 through June 30, 2017 from the Clinformatics® Data Mart Database (available through OptumInsight, Eden Prairie, MN). This nationwide database contains integrated health information on ~75 million American infants, children, and adults with private health insurance, encompassing demographic and membership information, diagnoses and procedures, outpatient and inpatient services, pharmacy records, and laboratory data.

Subjects

Data were extracted on patients with type 1 diabetes using a validated algorithm with the ratio of type 1 to type 1 and type 2 diabetes diagnoses set at ≥0.6. In previous analyses, this yielded a positive predictive value of 98.7% for individuals ≥10 years of age (slightly more accurate than setting the ratio at ≥0.5) and of 98.7% for those <10 years of age.[14] An additional criterion was the use of insulin; because all patients with type 1 diabetes must use insulin to live, those patients who never used insulin were excluded.[15] No restrictions were made regarding age or sex. There were 0.02% ($n = 35$) values missing for sex and these individuals were excluded.

The 12 most common autoimmune diseases in those with type 1 diabetes in the database were chosen for greater review. These were hypothyroidism (including Hashimoto's disease), rheumatoid arthritis, celiac disease, psoriasis, Grave's disease, inflammatory bowel disease, pernicious anemia, Addison's disease, systemic lupus erythematosus, multiple sclerosis, Sjögren's syndrome, and myasthenia gravis. Information regarding autoimmune diseases was extracted using previously defined diagnostic codes from both outpatient and inpatient files.[16] For hypothyroidism, we excluded those with postsurgical, postablative, iodine, or iatrogenic hypothyroidism.

Statistical analyses

Initially, the age- and sex-specific prevalence of concomitant autoimmune disease in those with type 1 diabetes was calculated. The numerator was the number of patients with type 1 diabetes who had evidence of the autoimmune disease diagnoses from inpatient and/or outpatient records. The denominator was the number of patients with type 1 diabetes. Results were stratified by sex and 5-year age groups. For example, for women with type 1 diabetes who were 35–39 years of age, what percentage had rheumatoid arthritis? This prevalence was calculated for each age–sex group and reflects the likelihood of diagnosis and treatment during that time period. Of importance, the age- and sex-specific prevalence does not reflect the prevalence of autoimmune disease throughout the entire lifespan of the individual; rather, it reflects the diagnosis and treatment of that disease during a specific age period. Exact binomial 95% confidence intervals (CIs) were calculated.

The burden of multimorbidity was explored further by examining whether renal and cardiovascular diseases differ in frequency depending upon the presence of other autoimmune diseases. Outcomes of interest were severe, potentially irreversible disease including renal failure, ischemic stroke, and myocardial infarction. Logistic regression was used, with the specific renal/cardiovascular disease as the dependent variable and the number of concurrent autoimmune diseases as the explanatory variable of interest. Results were stratified by sex, and adjusted for age at the time of enrollment. Odds ratios (ORs) and 95% CIs were calculated, as were post-regression predicted probabilities for each outcome (*i.e.*, probability that the event occurred in that particular group), which were calculated using the ''margins'' command after fitting the logit model. In secondary analyses, all 12 autoimmune diseases were simultaneously entered as independent variables in a logit model for each of the 3 adverse outcomes (renal failure, ischemic stroke, and myocardial infarction). Alpha was set at 0.05, two-tailed. Analyses were conducted using Stata/MP 15.1 (College Station, TX).

Results

Characteristics of the study participants

Over the entire study period (2001–2017), there were 179,248 individuals with type 1 diabetes, 85,690 of whom were female patients and 93,558 were male patients (Table 1). The mean age at enrollment was 35.2 years and the mean follow-up period was 3.4 years. Overall, one in four individuals with type 1 diabetes had at least one of the 12 autoimmune diseases (27.03%; 48,457/179,248; 95% CI = 26.83%–27.24%). The prevalence of autoimmune disease was 1.9 times greater in female than in male patients ($p < 0.001$). In female patients with type 1 diabetes, 35.62% had another autoimmune disease (30,523/85,690; 95% CI = 35.30%–35.94%) and, in male patients, 19.17% did (17,934/93,558; 95% CI = 18.92%–19.42%).

Table 1. Characteristics of Individuals with Type 1 Diabetes

Characteristic	*Female*	*Male*	*Total*
Individuals, *n* (%)	85,690 (47.8)	93,558 (52.2)	179,248 (100)
Age when enrolled, mean (SD)	35.7 (19.4)	34.7 (18.6)	35.2 (19.0)
Years enrolled, mean (SD)	3.4 (3.2)	3.4 (3.1)	3.4 (3.1)
Residence, *n* (%)			
New England, New Jersey	4711 (5.5)	5156 (5.5)	9867 (5.5)
New York, Pennsylvania	3905 (4.6)	4393 (4.7)	8298 (4.6)
Middle Atlantic	8732 (10.2)	9409 (10.1)	18,141 (10.1)
Southeast	15,991 (18.7)	16,491 (17.6)	32,482 (18.1)
Michigan, Indiana, Ohio, Kentucky	9683 (11.3)	10,395 (11.1)	20,078 (11.2)
North Central	7524 (8.8)	8860 (9.5)	16,384 (9.1)
Middle Central	8324 (9.7)	9131 (9.8)	17,455 (9.7)
South Central	11,328 (13.2)	12,172 (13.0)	23,500 (13.1)
Mountain	8018 (9.4)	9060 (9.7)	17,078 (9.5)
Pacific	7474 (8.7)	8491 (9.1)	15,965 (8.9)
Concomitant autoimmune disease, *n* (%)			
Rheumatoid arthritis	2498 (2.9)	1012 (1.1)	3510 (2.0)
Celiac disease	1944 (2.3)	1328 (1.4)	3272 (1.8)
Inflammatory bowel disease	823 (1.0)	762 (0.8)	1585 (0.9)
Pernicious anemia	772 (0.9)	415 (0.4)	1187 (0.7)
Hypothyroidism	25,764 (30.1)	14,004 (15.0)	39,768 (22.2)
Graves' disease	1400 (1.6)	665 (0.7)	2065 (1.2)
Addison's disease	501 (0.6)	348 (0.4)	849 (0.5)
Psoriasis	1372 (1.6)	1191 (1.3)	2563 (1.4)
Systemic lupus erythematosus	584 (0.7)	113 (0.1)	697 (0.4)
Multiple sclerosis	455 (0.5)	200 (0.2)	655 (0.4)
Sjogren's syndrome	346 (0.4)	60 (0.1)	406 (0.2)
Myasthenia gravis	85 (0.1)	57 (0.1)	142 (0.1)

SD, standard deviation.

Of the 48,457 individuals with type 1 diabetes who had concomitant autoimmune diseases, 85.59% had only one concomitant disease ($n=41,476$), 12.23% had two concomitant diseases ($n=5928$), 1.84% had three ($n=891$), and 0.33% ($n=162$) had four or more. The most common autoimmune diseases occurring together were hypothyroidism with rheumatoid arthritis.

Age-specific prevalence of concomitant autoimmune disease in female and male patients

Overall, there were considerable age and sex differences in the prevalence of concomitant autoimmune diseases in patients with type 1 diabetes. The pattern of occurrence varied for each of the diseases. Age- and sex-specific prevalence of concomitant autoimmune diseases for patients with type 1 diabetes are listed in Table 2 (females) and Table 3 (males). For example, a 45-year-old woman with type 1 diabetes has a 33% chance of having hypothyroidism, a 3% chance of having rheumatoid arthritis, and a 1% chance of having celiac disease, psoriasis, Graves' disease, inflammatory bowel disease, or pernicious anemia.

The overall prevalence of hypothyroidism in individuals with type 1 diabetes was 22.19% (95% CI = 21.99%–22.38%). Diagnosis and treatment for hypothyroidism was most prevalent in middle-aged and older adults with type 1 diabetes. However, even in adolescents (ages 15–19 years), 1 in 7 female (14.41%) and 1 in 14 male patients (6.94%) had hypothyroidism. The prevalence was significantly greater ($p<0.001$) in female (30.07%; 95% CI = 29.76%–30.37%) than in male patients (14.97%; 95% CI = 14.74%–15.20%).

The diagnosis of rheumatoid arthritis increased with age in patients with type 1 diabetes, until approximately 60–64 years of age and then decreased somewhat at the oldest age. The overall prevalence of rheumatoid arthritis in individuals with type 1 diabetes was 1.96% (95% CI = 1.89%–2.02%) and was significantly ($p<0.001$) greater in female (2.92%; 95% CI = 2.80%–3.03%) than in male patients (1.08%; 95% CI = 1.02%–1.15%).

Celiac disease occurred in 1.83% of persons with type 1 diabetes (95% CI = 1.76%–1.89%). Diagnosis and treatment of celiac disease was greatest in children and adolescents 5–19 years of age and was quite low in older adults. Celiac disease occurred in 2.27% of female patients with type 1 diabetes (95% CI = 2.17%–2.37%) and 1.42% of male patients with type 1 diabetes (95% CI = 1.34%–1.50%) ($p<0.001$).

Adults with type 1 diabetes who were in their 50th and 60th decade of life were most likely to be diagnosed with psoriasis. Overall, 1.43% (95% CI = 1.38%–1.49%) of those with type 1 diabetes had psoriasis, with a greater prevalence in female (1.60%; 95% CI = 1.52%–1.69%) than in male patients (1.27%; 95% CI = 1.20%–1.35%) ($p<0.001$). The diagnosis of psoriasis was low at the very youngest age, increased somewhat in middle adulthood, and declined somewhat at the oldest age.

Graves' disease was most common in middle-aged adults with type 1 diabetes. Overall, Graves' disease occurred in 1.15% (95% CI = 1.10%–1.20%) of individuals with type 1 diabetes. The prevalence was significantly ($p<0.001$)

Table 2. Age-Specific Prevalence of Autoimmune Diseases in Female Patients with Type 1 Diabetes

Age, years	*Patients* (n)	*Rheumatoid arthritis (%)*	*Celica disease (%)*	*Inflammatory bowel disease (%)*	*Pernicious anemia (%)*	*Hypo-thyroidism (%)*	*Graves' disease (%)*	*Addison's disease (%)*	*Psoriasis (%)*	*Lupus (%)*	*Multiple sclerosis (%)*
Youth											
<5	2738	0.18	1.50	0.07	0.00	1.17	0.07	0.04	0.26	0.07	0.00
5–9	6577	0.35	3.71	0.08	0.02	5.06	0.30	0.09	0.29	0.06	0.02
10–14	10,458	0.38	4.06	0.12	0.02	10.30	0.48	0.13	0.45	0.07	0.00
15–19	11,593	0.66	3.40	0.34	0.06	14.41	0.74	0.22	0.65	0.24	0.03
Young adults											
20–24	12,648	0.84	2.10	0.55	0.19	16.48	1.00	0.21	0.73	0.28	0.11
25–29	14,343	0.96	1.31	0.56	0.22	19.96	1.24	0.28	1.01	0.30	0.24
30–34	13,747	1.43	1.20	0.54	0.36	24.51	1.52	0.36	1.19	0.45	0.36
35–39	13,291	2.28	1.16	0.65	0.50	27.62	1.60	0.42	1.28	0.69	0.48
Middle-aged adults											
40–44	12,729	2.73	1.09	0.64	0.76	31.26	1.48	0.49	1.34	0.69	0.63
45–49	11,998	3.29	1.30	0.88	0.91	32.86	1.35	0.54	1.40	0.78	0.67
50–54	10,919	3.81	1.08	1.09	1.01	35.28	1.72	0.60	1.61	0.68	0.77
55–59	9213	4.17	1.17	1.02	1.03	37.46	1.51	0.85	1.69	0.82	0.76
60–64	6808	4.72	1.13	1.01	1.34	38.66	1.29	0.81	1.67	0.75	0.75
Older aged adults											
65–69	5587	3.88	0.84	1.13	1.22	35.67	0.98	0.70	1.79	0.55	0.54
70–74	3919	2.96	0.41	1.07	1.43	31.28	0.77	0.51	1.17	0.59	0.59
75–79	2908	3.61	0.38	0.79	1.93	31.67	0.79	0.34	0.86	0.31	0.45
80–84	1586	2.96	0.32	0.76	1.89	35.25	0.57	0.76	0.82	0.50	0.38
85+	566	3.71	0.00	0.71	2.47	31.10	0.35	1.06	1.06	0.00	0.35

Table 3. Age-Specific Prevalence of Autoimmune Diseases in Male Patients with Type 1 Diabetes

Age, years	*Patients* (n)	*Rheumatoid arthritis (%)*	*Celiac disease (%)*	*Inflammatory bowel disease (%)*	*Pernicious anemia (%)*	*Hypothyroidism (%)*	*Graves' disease (%)*	*Addison's disease (%)*	*Psoriasis (%)*	*Lupus (%)*	*Multiple sclerosis (%)*
Youth											
<5	3093	0.10	0.84	0.10	0.00	0.61	0.06	0.03	0.16	0.00	0.00
5–9	7148	0.15	2.73	0.15	0.00	2.62	0.18	0.13	0.24	0.01	0.00
10–14	11,360	0.22	2.61	0.17	0.01	5.32	0.21	0.17	0.44	0.01	0.00
15–19	13,429	0.22	2.36	0.27	0.06	6.94	0.37	0.15	0.44	0.04	0.04
Young adults											
20–24	14,710	0.25	1.13	0.40	0.12	7.85	0.37	0.20	0.46	0.02	0.06
25–29	16,549	0.34	0.66	0.45	0.05	8.50	0.37	0.25	0.64	0.04	0.05
30–34	15,534	0.48	0.59	0.55	0.12	10.06	0.43	0.23	0.86	0.06	0.15
35–39	15,141	0.70	0.54	0.61	0.14	12.10	0.67	0.22	1.06	0.07	0.17
Middle-aged adults											
40–44	14,518	0.90	0.65	0.71	0.23	13.83	0.69	0.19	1.21	0.13	0.24
45–49	13,741	1.13	0.68	0.82	0.41	15.73	0.65	0.33	1.27	0.10	0.23
50–54	12,196	1.41	0.67	0.98	0.49	17.44	0.64	0.42	1.39	0.11	0.29
55–59	9864	1.54	0.63	0.81	0.56	18.47	0.84	0.41	1.44	0.19	0.24
60–64	7078	1.81	0.59	1.00	0.69	19.94	0.52	0.40	1.47	0.23	0.37
Older aged adults											
65–69	5523	1.83	0.62	0.89	0.89	17.83	0.62	0.40	1.20	0.05	0.25
70–74	3560	1.46	0.42	0.93	1.26	17.70	0.31	0.42	1.29	0.17	0.20
75–79	2275	1.27	0.35	1.14	1.85	17.45	0.35	0.31	1.32	0.18	0.22
80–84	986	1.62	0.51	0.71	1.83	20.79	0.30	0.41	0.71	0.00	0.51
85+	271	1.11	0.42	1.48	0.74	24.72	0.00	0.00	0.37	0.00	0.37

greater in female (1.63%; 95% CI = 1.55%–1.72%) than in male patients (0.71%; 95% CI = 0.66%–0.77%).

Diagnosis and treatment of inflammatory bowel disease occurred in 0.88% (95% CI = 0.84%–0.93%) of individuals with type 1 diabetes. It occurred most often in middle-aged and older adults. The prevalence was greater in female (0.96%; 95% CI = 0.90%–1.03%) than in male patients (0.81%; 95% CI = 0.76%–0.87%) ($p = 0.001$), although difference was not as marked as in the other autoimmune disorders.

Pernicious anemia occurred in 0.90% of female patients with type 1 diabetes (95% CI = 0.84%–0.97%) and 0.44% in male patients with type 1 diabetes (95% CI = 0.40%–0.49%) ($p < 0.001$). Overall, the prevalence of pernicious anemia was 0.66% (95% CI = 0.63%–0.70%) and was greater in older adults.

The prevalence of Addison's disease was greater in adults with type 1 diabetes and overall, was 0.47% (95% CI = 0.44%–0.51%). Female patients were more likely to have Addison's disease (0.58%; 95% CI = 0.53%–0.64%) than male patients (0.37%; 95% CI = 0.33%–0.41%) ($p < 0.001$).

Systemic lupus erythematosus occurred most often in middle-aged women with type 1 diabetes. The prevalence was lower in children and in the oldest adults. The prevalence of lupus was markedly greater in female (0.68%; 95% CI = 0.63%–0.74%) than in male patients (0.12%; 95% CI = 0.10%–0.15%) ($p < 0.001$).

Multiple sclerosis occurred in 0.37% (95% CI = 0.34%–0.39%) of those with type 1 diabetes. Similar to lupus, it occurred more often in middle-aged women. The prevalence was 0.53% in female (95% CI = 0.48%–0.58%) and 0.21% in male patients (95% CI = 0.19%–0.25%) with type 1 diabetes ($p < 0.001$).

Sjögren's syndrome was principally a condition seen in women with type 1 diabetes; the prevalence was quite low in men. The prevalence of Sjögren's syndrome was 0.23% overall (95% CI = 0.21%–0.25%), but was 0.40% (95% CI = 0.36%–0.45%) in female and 0.06% (95% CI = 0.05%–0.08%) in male patients ($p < 0.001$).

The prevalence of myasthenia gravis was quite low overall (0.08%; 95% CI = 0.07%–0.09%). The prevalence in female patients with type 1 diabetes was 0.10% (95% CI = 0.08%–0.12%) and in male patients it was 0.06% (95% CI = 0.05%–0.08%) ($p = 0.004$).

Association with renal and cardiovascular morbidities

Renal failure occurred in 18,350 of the persons with type 1 diabetes and was more frequent in those with concomitant autoimmune disease (15.1% with vs. 8.4% without; $p < 0.001$). Table 4 provides the ORs for the association between the number of concomitant autoimmune diseases and the outcomes (renal failure, ischemic stroke, myocardial infarction). As the number of additional diseases increased, so did the odds of renal failure ($p < 0.001$, test for trend in both female and male patients). For those with four or more concomitant autoimmune diseases, the OR was 4.77 in female and 5.02 in male patients. The predicted probability of renal failure ranged from 0.12 in female patients with one concomitant autoimmune disease to 0.27 in female patients with four or more concomitant autoimmune diseases.

TABLE 4. ASSOCIATION BETWEEN NUMBER OF CONCOMITANT AUTOIMMUNE DISEASES AND RENAL FAILURE, ISCHEMIC STROKE, AND MYOCARDIAL INFARCTION IN PATIENTS WITH TYPE 1 DIABETES

	Renal failure				*Ischemic stroke*				*Myocardial infarction*			
No. of concomitant autoimmune diseases	*Odds ratio**	*95% CI*	p	*Predicted probability*	*Odds ratio*[a]	*95% CI*	p	*Predicted probability*	*Odds ratio*[a]	*95% CI*	p	*Predicted probability*
Females												
0	1.00	(Baseline)		0.08	1.00	(Baseline)		0.04	1.00	(Baseline)		0.02
1	1.53	1.46–1.61	<0.001	0.12	1.77	1.65–1.89	<0.001	0.06	1.59	1.44–1.77	<0.001	0.02
2	2.35	2.15–2.56	<0.001	0.17	2.78	2.48–3.11	<0.001	0.09	2.61	2.22–3.08	<0.001	0.04
3	3.66	3.07–4.36	<0.001	0.23	4.96	4.00–6.14	<0.001	0.14	3.77	2.75–5.16	<0.001	0.05
≥4	4.77	3.30–6.88	<0.001	0.27	6.90	4.49–10.62	<0.001	0.17	5.12	2.78–9.44	<0.001	0.07
Males												
0	1.00	(Baseline)		0.09	1.00	(Baseline)		0.04	1.00	(Baseline)		0.02
1	1.51	1.43–1.59	<0.001	0.13	1.83	1.70–1.98	<0.001	0.06	1.60	1.44–1.78	<0.001	0.03
2	2.41	2.14–2.72	<0.001	0.19	2.72	2.31–3.20	<0.001	0.09	2.54	2.04–3.15	<0.001	0.04
3	4.34	3.16–5.96	<0.001	0.29	4.73	3.13–7.14	<0.001	0.13	3.19	1.78–5.72	<0.001	0.05
≥4	5.02	1.99–12.62	0.001	0.31	20.77	7.75–55.66	<0.001	0.31	7.27	2.02–26.16	0.002	0.10

[a]Adjusted for age.
CI, confidence interval.

The corresponding probabilities for male patients were 0.13–0.31, respectively.

Ischemic stroke ($n = 8616$) occurred in 8.3% of those with concomitant autoimmune disease, but in 3.5% of those with type 1 diabetes without another autoimmune disorder ($p < 0.001$). The odds of ischemic stroke increased with the number of concomitant autoimmune diseases ($p < 0.001$, test for trend in both sexes). The predicted probability of ischemic stroke was 0.04 in patients with type 1 diabetes without concomitant autoimmune disease, but rose to 0.17 in female and 0.31 in male patients who had four or more concomitant autoimmune diseases (Table 4).

Myocardial infarction ($n = 3711$) was more likely to occur in patients with type 1 diabetes who had another autoimmune disease (3.4%) compared with 1.6% in those without ($p < 0.001$). The ORs for the number of concomitant autoimmune diseases and myocardial infarction increased with the increasing number of concomitant autoimmune diseases ($p < 0.001$, test for trend in both female and male patients). The predicted probabilities for myocardial infarction were lower than those for ischemic stroke in both sexes (Table 4).

There were no statistically significant interactions between sex and the number of concomitant autoimmune diseases for renal failure and myocardial infarction (interaction term, $p = 0.277$ for renal failure, $p = 0.205$ for myocardial infarction). However, the risk of ischemic stroke rose more dramatically in male patients as the number of concomitant autoimmune diseases increased compared with female patients ($p = 0.002$, interaction term), as given in Table 4.

The association between specific concomitant autoimmune diseases and renal/cardiovascular morbidities are listed in Table 5. Individuals with type 1 diabetes who had Addison's disease were at considerably elevated risk of renal failure (OR = 3.19), ischemic stroke (OR = 2.24), and myocardial infarction (OR = 2.34). Similarly, concomitant systemic lupus erythematosus was associated with approximately twofold greater risk of renal failure, ischemic stroke, and myocardial infarction. Individuals with type 1 diabetes and myasthenia gravis were at particularly greater risk of ischemic stroke (OR = 3.22), as were patients with multiple sclerosis (OR = 3.57).

Although renal and cardiovascular morbidities were less common in children than adults, there were some children and adolescents with these outcomes. The OR for renal disease, comparing individuals with and without concomitant autoimmune disease, was 1.85 (95% CI = 1.62–2.10) in patients who were <20 years of age. For ischemic stroke, the corresponding OR was 2.11 (95% CI = 1.44–3.10). For myocardial infarction, there was no association in patients <20 years ($p = 0.134$ comparing with and without concomitant autoimmune disease).

Discussion

Multimorbidity of autoimmune disease is common in women with type 1 diabetes—occurring in one in three patients—and is associated with substantially greater frequencies of renal failure, ischemic stroke, and myocardial infarction. Concomitant autoimmune disease in male patients with type 1 diabetes was less frequent, occurring in one in five male patients, but also was strongly associated with renal and cardiovascular outcomes. The greater the number of autoimmune diseases, the greater the risk. Patients with type 1 diabetes who also had Addison's disease, systemic lupus erythematosus, multiple sclerosis, or myasthenia gravis were at particular risk.

Studies using large patient registries also found a high prevalence of concomitant autoimmune diseases in persons with type 1 diabetes, although there is some variation in prevalence across studies.[6,7] In a large study of autoimmune disease in adults with type 1 diabetes, one in five patients with type 1 diabetes had thyroid disease, although the authors used a broader definition of thyroid disease that combined hypothyroidism and hyperthyroidism of unspecified etiologies.[7] Our study differs in that we included both children and adults. Our findings demonstrate that certain autoimmune conditions occur more often in children with type 1 diabetes, such as celiac disease, but others such as pernicious anemia are more frequent in older adults.

Our study highlights the importance of taking a comprehensive history of autoimmune disorders, particularly in

Table 5. Association Between Specific Concomitant Autoimmune Diseases and Renal Failure, Ischemic Stroke and Myocardial Infarction in Patients with Type 1 Diabetes

Concomitant autoimmune disease	*Renal failure*		*Ischemic stroke*		*Myocardial infarction*	
	Odds ratio[a]	*95% CI*	*Odds ratio*[a]	*95% CI*	*Odds ratio*[a]	*95% CI*
Rheumatoid arthritis	1.47	1.35–1.61	1.79	1.60–1.99	1.68	1.43–1.96
Celiac disease	1.16	1.02–1.33	1.28	1.04–1.56	1.33	1.01–1.76
Inflammatory bowel disease	2.17	1.92–2.45	1.82	1.54–2.16	1.34	1.03–1.74
Pernicious anemia	2.16	1.89–2.46	2.14	1.82–2.50	1.99	1.61–2.47
Hypothyroidism	1.38	1.33–1.43	1.63	1.55–1.71	1.46	1.36–1.56
Graves' disease	1.04	0.91–1.20	1.16	0.96–1.40	1.44	1.12–1.84
Addison's disease	3.19	2.73–3.73	2.24	1.80–2.77	2.34	1.76–3.11
Psoriasis	1.19	1.06–1.33	1.26	1.08–1.48	1.28	1.03–1.60
Systemic lupus erythematosus	2.55	2.14–3.04	2.15	1.71–2.71	1.97	1.42–2.73
Multiple sclerosis	1.92	1.59–2.32	3.57	2.88–4.42	1.91	1.35–2.69
Sjogren's syndrome	1.25	0.98–1.60	1.58	1.18–2.11	0.71	0.42–1.20
Myasthenia gravis	1.85	1.26–2.73	3.22	2.11–4.91	2.07	1.14–3.76

[a]Adjusted for age.

women with type 1 diabetes. All 12 concomitant autoimmune diseases occurred more frequently in female patients, although there was variation in the age in which specific diseases occurred. Other investigators have also found a greater prevalence of concomitant autoimmune diseases in female with type 1 diabetes compared with male patients.[6,7] We found that the degree of the female predominance depends upon the age of the patient and the specific type of concomitant disease.

At present, the components of the comprehensive diabetes medical evaluation of patients with type 1 diabetes indicate that the presence of autoimmune diseases be ascertained at medical visits.[17] For laboratory evaluation, screening for autoimmune thyroid disease and celiac disease are recommended soon after the diagnosis of type 1 diabetes.[17] Our findings underscore the importance of these recommendations and suggest that this evaluation is especially pertinent to girls and women with type 1 diabetes, who are at greater risk for all of the concomitant autoimmune diseases studied here.

Of importance, concomitant autoimmune diseases were associated with renal failure, ischemic stroke, and myocardial infarction. With each additional autoimmune disease, the likelihood of renal failure, stroke, and myocardial infarction increased. In previous research, there was a fourfold increased risk of death in those with both diabetes and Addison's disease, usually from cardiovascular disease.[18] Coronary heart disease including myocardial infarction occurred in 7.4% of those with both type 1 diabetes and Addison's disease, whereas it in 4.9% in those with type 1 diabetes only.[18] In a different investigation, the incidence of myocardial infarction was 13.0 per 1000 person-years in those with both diabetes and rheumatoid arthritis, which was higher than in those with diabetes alone (8.1/1000 person-years) or in those with rheumatoid arthritis alone (5.7/1000 person-years).[19]

It is unknown whether the risk of renal and cardiovascular disease in persons with multiple autoimmune disease is because of the complexities of underlying pathophysiology or whether subsequent chronic conditions render management of type 1 diabetes more difficult. Additional information is necessary to determine whether there are particular aspects of diabetes management that are challenging given the presence of another condition. Previous research has shown that in some instances (*e.g.*, type 1 diabetes with celiac disease), treatment of celiac disease with a gluten-free diet decreased hypoglycemic episodes but then increased the need for larger doses of insulin.[20,21] Other studies indicate that treatment for the autoimmune disorder (*e.g.*, Addison's disease, rheumatoid arthritis) with corticosteroids may result in hyperglycemia.[22] This can pose challenges to the daily management of glucose levels and may impact long-term risk of diabetic complications.

There are limitations of this study. Information regarding HbA1c and duration of type 1 diabetes were only available on a subset of individuals and therefore, are not included in this study. In addition, we did not capture all autoimmune diseases among persons with type 1 diabetes; we concentrated on the 12 most frequent conditions in this population. In patients with type 1 diabetes, there also may be other nonautoimmune-related comorbidities beyond those studied here. Therefore, it is likely that the overall burden of multimorbidity may be greater. However, the conditions captured here are among those associated with the worst physical health-related quality of life and mortality risk.[2]

Strengths of this study include the precision of the estimates owing to the large sample size and the inclusion of individuals of all ages. Because of this, we incorporated data on patients with several rare chronic conditions such as multiple sclerosis. In previous studies, autoimmune conditions such as multiple sclerosis had devastating effects on physical health-related quality of life.[2] The prevalence and prognosis of such rare conditions are often underestimated because large national studies in the United States do not obtain these data. In addition, the inclusion of all age groups adds to the body of literature on multimorbidity because most published studies are of older adults—not fully capturing the impact of chronic conditions that originate earlier in life. Although renal/cardiovascular outcomes are rarer in young patients, children with type 1 diabetes and concomitant autoimmune disease were at increased risk of renal failure and ischemic stroke.

In conclusion, we found that the presence of concomitant autoimmune disease in patients with type 1 diabetes was common, occurring in one of every three women and one of every five men. Multimorbidity in patients with type 1 diabetes was strongly associated with renal failure, ischemic stroke, and myocardial infarction. Because concomitant autoimmune disease is more frequent in women than men with type 1 diabetes, these renal and cardiovascular diseases affect greater numbers of women. We recommend periodic screening for autoimmune diseases throughout the lifespan of patients with type 1 diabetes. We encourage initiatives to evaluate the effectiveness of more intensive preventive treatments to decrease the incidence of renal failure, ischemic stroke, and myocardial infarction in patients with type 1 diabetes.

Authors' Contributions

All authors contributed to the concept and design. M.A.M.R. and J.M.L. acquired the data. M.A.M.R. analyzed the data. All authors participated in drafting the article or revising it critically for intellectual content. All authors approved of the final version.

Author Disclosure Statement

No competing financial interests exist.

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