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SHORT REPORT

Celiac Disease and Incident Dupuytren's Contracture: A Matched Nationwide Cohort Analysis

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Abstract: This study explored the association between celiac disease (CeD) and Dupuytren's contracture (DC) using data from the Swedish ESPRESSO cohort. We analyzed 49,699 CeD patients and 245,267 matched controls, identifying 1420 incident DC cases. CeD patients had a 1.21-fold increased risk of DC compared to controls, with a more pronounced risk in women and older individuals. Further research is needed to understand the underlying mechanisms of this relationship.

Plain Language Summary: Dupuytren's contracture is characterized by hard nodules in the palm, leading to finger flexion and impairing activities like writing and cooking. The disease has been linked to a higher prevalence among individuals with immune-mediated diseases but there are little data on the association with celiac disease. In this study we used register-based data to follow-up some 49,000 individuals with celiac disease and 245,000 individuals from the general population. A higher proportion of individuals with celiac disease developed Dupuytren's contracture, corresponding to a 21% increased risk.

Keywords: celiac disease, Dupuytren's contracture, immune-mediated disorders, cohort analysis

Introduction

Dupuytren's contracture (DC) is a disease where small hard nodules in the palm are followed by flexed fingers. In the long-term, patients with DC have difficulties with writing and cooking. Traditionally, the disease has been seen as a disease among white males of Caucasian origin and used to be called "Viking disease". One recent meta-analysis suggested that almost one in twelve individuals develop DC.[1] Importantly, DC may have been especially common among individuals with immune-mediated diseases such as type 1 diabetes[2] and rheumatoid arthritis.[1] In addition, anti-tumor necrosis factor therapy has been found to soften and reduce nodules size among participants with early-stage DC in a phase 2b, randomized, double-blind, placebo-controlled trial.[3]

Celiac disease (CeD) is another immune-mediated disease.[4] This disease has been linked to a wide range of extraintestinal complications, including several immune-related disorders.[5–7] Until recently, data on the co-occurrence of CeD and DC have been rare. However, our Mendelian randomization analysis demonstrated a potential association between CeD and DC using genetic data from two large-scale studies.[6] In this study, we used nationwide registers to examine the association between CeD and a clinical diagnosis of DC.

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Materials

We conducted a prospective matched cohort analysis using data from the Swedish ESPRESSO cohort.[8] The cohort included 50,000 patients with CeD diagnosed by biopsy records from pathology departments in Sweden during 1969–2017. Specifically, topography codes for the small intestine (excluding the ileum) and Systematized Nomenclature of Medicine (SNOMED) codes corresponding to villus atrophy were used for CeD definition with a positive predictive value of 95% in a validation study utilizing medical record review for a previous query of these data[9] and a positive predictive value of 99% in recent biopsy reports.[10] Each CeD patient was matched with five comparators based on birth year, sex, calendar year, and county of residence from the general population by Statistics Sweden. Medical and demographic statistics for CeD patients and matched comparators were obtained from diverse Swedish national registers including Swedish national registers, including the National Patient Register, the Total Population Register, and the longitudinal integrated database for health insurance and labor market studies.

Incident DC was our outcome and defined through International Classification of Diseases (ICD)-7, 8, 9, and 10 codes (ICD-7: 744,20; ICD-8: 733,9; ICD-9: 728G; and ICD-10: M72.0) in the Swedish National Patient Register. Individuals with DC already at baseline (index date; the diagnosis date for CeD and matching date for comparators) were removed. Remaining study participants were followed up from the index date until the diagnosis of DC, death, emigration, or December 31, 2021. Education level was used as a proxy for socioeconomic status and grouped into compulsory school (0–9 years), upper secondary (10–12 years), college or university (≥13 years), and unknown (missing data). Further covariates included country of birth (Sweden, other Nordic countries, and other parts of the world), and the Charlson Comorbidity Index (CCI) assessed up to 6 months prior to the index date.[8] To approximate regular healthcare-seeking behavior, the frequency of healthcare visits occurring between 2 years and 6 months before the index date was obtained from the Swedish national patient register, categorized into five groups: 0, 1, 2, 3–6, and ≥7 times.

The Cox proportional hazards regression conditioned on matching factors (age, sex, county, and calendar year) was used to estimate the association between CeD and the risk of incident DC, with adjustment for education levels, country of birth, and the CCI. To examine surveillance bias, we performed a sensitivity analysis with additional adjustment for healthcare visits between 2 years and 6 months before index date. We used the Schoenfeld residual test to examine the proportionality assumption and found it satisfied (P = 0.357). The analysis was conducted using R 4.4.1. Statistical significance was determined at a two-sided P-value of ≤ 0.05.

This project was approved by the Stockholm ethics review board.

Results

After excluding individuals with data unavailable and irregularities, death on the index date, previous DC diagnosis, and lack of index case for the comparators; the main analysis included 49,699 patients with CeD and 245,267 comparators. Individuals developing incident DC were older at baseline, they were more often males, had lower education levels and had a higher CCI. During a total follow-up of 856,286 person-years in patients with CeD (median 16.2 years interquartile range 10.4–23.3) and 4,308,964 person-years in comparators (median 16.5 years interquartile range 10.7–23.7), 1420 individuals developed DC (280 celiac patients and 1140 comparators) with incidence rates of 327 and 265 per 100,000 person-years, respectively. Among individuals who developed DC, the median age at diagnosis was similar in both groups (67.2 years in CeD vs 67.4 years in controls). After adjusting for confounders, CeD was associated with a 1.21-fold increased risk of DC (95% CI 1.05–1.38). The association appeared to be more pronounced in women (hazard ratio 1.38; 95% CI 1.10–1.73) compared with men (hazard ratio 1.12; 95% CI 0.95–1.33) and increased with older diagnosed age (Table 1). The association persisted in the analysis with additional adjustment for healthcare visits (hazard ratio 1.17; 95% CI 1.02–1.34) and in the analysis excluding data in the first year after the index date (hazard ratio 1.21; 95% CI 1.05–1.40).

Table 1 Association between Celiac Disease (CeD) and Incident Dupuytren's Contracture (DC) in a Swedish Nationwide Matched Cohort

Population	CeD		Comparators		HR	95% CI	*P*
	Case	Person-Years	Case	Person-Years			
Overall	280	856,286	1140	4,308,964	1.21	1.05–1.38	0.007
Sex							
Men	175	311,983	785	1,575,428	1.12	0.95–1.33	0.186
Women	105	544,303	355	2,733,536	1.38	1.10–1.73	0.006
Diagnosis age							
< 18 y	6	385,377	22	1,928,936	1.09	0.39–3.04	0.868
≥18-<60 y	175	368,524	720	1,859,382	1.16	0.98–1.38	0.082
≥60 y	99	102,386	398	520,646	1.26	0.99–1.61	0.063
Start year of follow-up							
1969–1989	34	128,770	157	655,416	1.07	0.72–1.58	0.749
1990–1999	100	313,849	385	1,594,860	1.39	1.10–1.75	0.006
2000–2009	118	310,709	489	1,545,994	1.13	0.92–1.40	0.253
2010–2017	28	102,959	109	512,694	1.18	0.77–1.82	0.451

Note: The analysis was adjusted for education levels, birth country, and Charlson Comorbidity Index assessed up to 6 months prior to the baseline.
Abbreviations: CI, confidence interval; HR, hazard ratio.

Discussion

This population-based study confirmed earlier Mendelian randomization data demonstrating a link between CeD and DC.[6] Underlying mechanism of this association is unknown. DC is more common in people with lower body mass index,[11] a feature it shares with CeD,[12] which may partly explain our findings. Another possible mechanism for this association may involve the upregulation of tissue transglutaminase in CeD, which can cross-link or deamidate external or structural proteins, creating neoepitopes that trigger immune responses. This immune activation may contribute to the development of secondary autoimmune or fibrotic conditions, including DC, as previously proposed in the context of extraintestinal manifestations of CeD.[13,14] Among the limitations of our study is the lack of data on lifestyle factors and occupational history. Specifically, we were unable to adjust for smoking, alcohol consumption, or participants' occupation and work-related physical activity. However, the observed association remained stable after adjustment for education level, which we used as a proxy for socioeconomic status. In conclusion, the present findings confirm earlier Mendelian randomization data suggesting a modest association between CeD and DC.

Abbreviations

CCI, Charlson Comorbidity Index; CeD, Celiac disease; DC, Dupuytren's contracture; ICD, International Classification of Disease.

Ethics Details

The study was approved by the Stockholm Ethics Review Board on 27 August 2014 (#2014/1287-31/4) with amendments (#2018/972-32).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in the drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

Dr Ludvigsson has coordinated an unrelated study on behalf of the Swedish IBD quality register (SWIBREG). That study received funding from Janssen corporation. Dr Ludvigsson has also received financial support from MSD developing a paper reviewing national healthcare registers in China. Dr Ludvigsson has an ongoing research collaboration on celiac disease with Takeda. Dr Leffler is an employee of Takeda. The authors report no other conflicts of interest in this work.

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