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1 **Increased rate of abdominal surgery both before and after** 2 **diagnosis of Celiac Disease**

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43 atrophy

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ABSTRACT

46 **Background:** The detection of celiac disease (CD) is suboptimal.

47 **Aims:** We hypothesized that misdiagnosis is leading to diagnostic delays, and examine this
48 assertion by determining if patients have increased risk of abdominal surgery before CD
49 diagnosis.

50 **Methods:** Through biopsy reports from Sweden's 28 pathology departments we identified all
51 individuals with CD (Marsh stage 3; n=29,096). Using hospital-based data on inpatient and
52 outpatient surgery recorded in the Swedish Patient register, we compared abdominal surgery
53 (appendectomy, laparotomy, biliary tract surgery, and uterine surgery) with that in 144,522
54 controls matched for age, sex, county and calendar year. Conditional logistic regression
55 estimated odds ratios (ORs).

56 **Results:** 4,064 (14.0%) individuals with CD and 15,760 (10.9%) controls had a record of earlier
57 abdominal surgery (OR=1.36, 95%CI=1.31-1.42). Risk estimates were highest in the first year
58 after surgery (OR=2.00; 95%CI=1.79-2.22). Appendectomy, laparotomy, biliary tract surgery,
59 and uterine surgery were all associated with having a later CD diagnosis. Of note, abdominal
60 surgery was also more common after CD diagnosis (hazard ratio=1.34; 95%CI=1.29-1.39)

61 **Conclusions:** There is an increased risk of abdominal surgery both before and after CD
62 diagnosis. Surgical complications associated with CD may best explain these outcomes. Medical
63 nihilism and lack of CD awareness may be contributing to outcomes.

64 **Keywords:** appendix, autoimmunity, celiac, gall bladder, inflammation, surgery

65

66

67 INTRODUCTION

68 Celiac disease (CD) is an immune mediated small bowel enteropathy, which affects 1 in 100
69 people.^{1,2} It occurs in genetically susceptible individuals and is triggered by gluten, which is a
70 protein found in wheat, barley and rye. The commonest age for diagnosis is between 40 and 60
71 years old, however it can occur at any age, with women 1.5 to 2 times more likely to develop the
72 condition than men.³ Diagnostic delays in CD have been widely reported, ranging between 10-13
73 years from symptom onset to diagnosis.⁴⁻⁸ Recent reports from Finland, Sweden and the UK
74 suggest these diagnostic delays are improving.^{4,9,10} This is supported by improvements in CD
75 detection, with the ratio of clinically diagnosed CD cases to undetected cases improving in the
76 UK from 1 in 8 in 1999 to 1 in 4 in 2011.^{11,12} Although these findings are encouraging they are
77 not universal, with data from the Canadian Celiac Health Survey showing no improvements in
78 diagnostic delays over recent years.¹³

79
80 These diagnostic delays can have significant consequences to patients. Individuals with CD have
81 increased healthcare costs, higher usage rates of healthcare services and use more drugs before
82 having a diagnosis of CD.¹⁴⁻¹⁶ Health related quality of life (HRQoL) can also be affected, with a
83 recent study from Sweden showing HRQoL in undiagnosed patients to be comparable to that of
84 stroke patients.^{4,10} Delays in diagnosis may also influence morbidity, and potentiate the
85 development of celiac-related complications^{6,17-20}, however overall mortality does not appear to
86 be influenced.²¹

87
88 The protean clinical manifestations of CD may be responsible for the delays in diagnosis.
89 Patients with CD can present to varying healthcare professionals, with an array of clinical
90 symptoms and signs. These include gastrointestinal symptoms, weight loss, anaemia, reduced
91 bone mineral density, or in association with other autoimmune diseases.¹ Other individuals may

92 present more insidiously for example with ataxia, or peripheral neuropathy or could be
93 asymptomatic, having been identified through screening of high-risk population groups.²² These
94 diverse presentations create diagnostic challenges to clinicians, which could be influencing CD
95 detection rates.

96
97 Alternative reasons as to why CD detection rates remain low are that clinicians do not consider
98 the diagnosis of CD or ignore the diagnosis (medical nihilism). Collectively, this could be
99 termed diagnostic inertia, which is a derivation of clinical inertia where a patient fulfils the
100 diagnostic criteria for a particular disorder, but is not diagnosed by their physician as having the
101 disorder.^{23, 24} Diagnostic inertia in CD has been shown to exist in both primary and secondary
102 care settings.^{7, 25} The type of clinician the patient encounters also influences diagnostic
103 outcomes, with gastroenterologists and more experienced physicians more likely to consider and
104 diagnose CD.^{6, 7, 26} Diagnostic inertia in CD has implications to patients, culminating in
105 misdiagnosis, unnecessary interventions and potentially the prescription of inappropriate
106 medications.^{5, 27}

107
108 These concerns lead to our hypothesis that patients with CD have higher rates of abdominal
109 surgery before their CD diagnosis as a consequence of diagnostic inertia. Our hypothesis is
110 tested in this large population-based study by examining abdominal surgery and the risk of
111 having a later diagnosis of CD.

112

113 **MATERIALS AND METHODS**

114 Through Sweden's 28 pathology departments we obtained data on CD through small intestinal
115 biopsies with villous atrophy (Marsh III). We then used the Swedish personal identity number²⁸
116 to link biopsy data to surgery recorded in the Swedish Patient register.²⁹

117
118 *Exposure – Surgery*
119 We defined abdominal surgery as either of laparotomy, appendectomy, biliary tract surgery or
120 uterine surgery according to relevant international classification of disease (ICD) code in the
121 Swedish Patient Register (*see appendix*). We did not include uterine surgery that was specifically
122 carried out for infertility reasons, as it has been suggested that patients with CD have a decreased
123 fertility³⁰, although this has been debated.³¹ We have previously examined CD and
124 appendectomy³², but that paper was restricted to individuals with an inpatient diagnosis with
125 CD, and we have since found that risk estimates based on biopsy data on CD can be substantially
126 different.^{33,34}

127 The Swedish Patient register started in 1964. It became nationwide in 1987, adding day-surgery
128 data in 1997, and hospital-based outpatient care in 2001. The positive predictive value of most
129 diagnoses in this registry is between 85% and 95%.²⁹

130

131 *Outcome measure - Celiac disease*

132 IT personnel at Sweden's 28 pathology departments identified individuals with small intestinal
133 villous atrophy (VA; histopathology stage Marsh 3³⁵) from computerized biopsy reports. The
134 data collection took place in 2006-08 but the biopsies themselves had been performed in 1969-
135 2008. Data on personal identity number, topography (duodenum and jejunum), morphology
136 (according to SnoMed histopathology codes, for a list see our earlier publication³⁶), and date of
137 biopsy were delivered to the researchers. We then reviewed the patient charts of 114 randomly
138 selected individuals with VA and 108 (95%) had CD. The biopsy reports were based on average
139 of three tissue specimen³⁷, which should, according to Pais et al, detect 95% of all CD.³⁸
140 Throughout the study period, biopsy was requested for CD diagnosis in Sweden.

141

142 *Controls*

143 Each patient with CD was matched with up to five controls by *Statistics Sweden* using the
144 Swedish Total population register.³⁹ Matching criteria were sex, age, county, and calendar year.
145 Removal of data irregularities and duplicates left us with 29,096 individuals with CD and
146 144,522 matched controls, i.e. an identical data-set as in our earlier paper on mortality in CD.⁴⁰

147

148 *Statistics*

149 We calculated odds ratios (ORs) for later CD in patients undergoing abdominal surgery using
150 conditional logistic regression (thereby comparing strata with one CD patients and his/her
151 matched controls). Through the conditional approach we automatically considered age, sex,
152 county and calendar year. Of note, uterine surgery calculations were only performed in women
153 (18,005 with CD and 89,544 controls).

154 A priori we decided to examine the association between abdominal surgery (and its components)
155 according to age at CD (≤ 19 years; 20-39 years; 40-59 years; ≥ 60 years), sex, and calendar
156 period (1997-2004; 2005-2008). We also examined the risk of CD according to time since
157 abdominal surgery (< 1 , 1-4, and ≥ 5 years). In a separate analysis we adjusted for country of birth
158 (Nordic vs. not Nordic) and education using four a priori-defined categories.⁴¹ Four percent of
159 study participants lacked data on education and were fitted into a separate fifth category in the
160 multivariate analysis.

161 Finally we examined the temporal relationship between abdominal surgery and CD and used Cox
162 regression to calculate the risk of abdominal surgery *after* CD. This analysis was based on
163 individuals without a prior record of abdominal surgery at date of CD diagnosis (and
164 corresponding date in matched controls): CD: n=25,030; controls: n=120,610.

165

166 We used SPSS 22 (SPSS, Inc. Chicago, IL, USA) for the statistics. ORs with 95% confidence
167 intervals that did not include one were regarded as statistically significant.

168 *Ethics*

169 Our study was approved by the Ethics Review board of Stockholm, Sweden. According to the
170 board's decision no study participant was contacted as the study is strictly register-based.⁴²

171

172 **RESULTS**173 *Background data*

174 Almost two thirds of our study participants were female (Table 1), and some 41% had received
175 their diagnosis in childhood (Table 1). The median year of CD diagnosis (and entry year of study
176 for the participants) was 1998 (range: 1969-2008). The median age at CD diagnosis was 30 years
177 (range: 0-95). More than 90% of the study participants were born in the Nordic countries.

178

179

180 *Main findings*

181 Of 29,096 individuals with CD, 4,064 (14.0%) had undergone abdominal surgery prior to celiac
182 diagnosis, compared to 15,760/144,522 (10.9%) of matched controls. This corresponded to an
183 OR of 1.36 (95%CI=1.31-1.42). Adding level of education and country of origin to our model
184 did not influence our risk estimates (1.35; 1.30-1.40). CD was more common in the first year
185 after abdominal surgery (OR=2.00; 95%CI=1.79-2.22), than after 1-4 years (OR=1.31;
186 95%CI=1.22-1.42) or after 5 years or more (OR=1.23; 95%CI=1.18-1.29).

187 Stratified analyses found increased risk of CD after abdominal surgery in both males and
188 females, in all age groups and in all calendar periods although risk estimates varied (results and
189 interaction tests are presented in Table 2).

190

191 *Specific conditions*

192 A laparotomy was associated with a 58% increased risk of later CD (95% CI 1.48-1.69).
193 Similarly we found a positive association also with appendectomy (1.42; 1.34-1.50), biliary tract
194 surgery (1.26; 1.18-1.34) and uterine surgery (1.13; 1.06-1.21) and later CD. Results of stratified
195 analyses for the above conditions are presented in Table 3. Final diagnosis after undergoing
196 surgery was assessed in a post-hoc analysis using relevant ICD codes, where the proportion of
197 appendicitis, cholecystitis and uterine myoma was explored in those having inpatient
198 appendectomy, biliary surgery and uterine surgery respectively. Restrictions were made to only
199 inpatient diagnoses, as the Patient Register did not include both outpatient procedure codes and
200 diagnostic codes before 2001. For all these surgical procedures, patients with CD were less
201 likely to have appendicitis ($p=0.001$), cholecystitis ($p<0.001$) and uterine myoma ($p<0.001$) at
202 surgery than controls.

203

204 *Prospective analysis*

205 In order to examine the temporal relationship between abdominal surgery and CD we also
206 carried out a Cox regression on CD and future risk of abdominal surgery. In this analysis we
207 compared 25,030 CD patients and 120,610 matched controls without a record of abdominal
208 surgery prior to CD diagnosis (and corresponding date in matched controls). 3536 (14.1%) of
209 CD patients vs. 13,279 (11.0%) controls had later abdominal surgery corresponding to a Hazard
210 ratio of 1.34 (95%CI=1.29-1.39).

211

212 **DISCUSSION**

213 In this large nationwide case-control study we demonstrate that patients with CD have an
214 increased risk of abdominal surgery both before and after diagnosis of CD, compared to sex and
215 age-matched controls. The highest ORs for developing CD were seen just after abdominal
216 surgery. The most plausible explanation is that abdominal surgery occurs as a complication to
217 both undiagnosed and diagnosed CD. This notion is supported by some recent work evaluating
218 512 CD patients where 36% of CD patients had operative interventions, of which 12% were
219 directly for CD related problems (e.g. dysmotility, pain, malignancy).⁴³

220
221 An alternative explanation for the increased surgical rates before CD diagnosis may be
222 misdiagnosis. Misdiagnosis is recognized and frequent in celiac patients.⁴⁴ Although biliary
223 disorders have been described in the context of CD, possibly needing surgical intervention, it is
224 possible that the misdiagnosis of abdominal pain and iron-deficiency anaemia culminated in
225 inappropriate abdominal surgical interventions such as appendectomy and laparotomy.⁴⁵
226 The lack of histological outcomes from the surgically removed specimens in our cohort does
227 limit our ability to establish definitively whether misdiagnosis occurred, however the frequency
228 of normal pathological specimens following surgical removal has previously been described,
229 with 25.7% (64/249) of patients in a recent study having a normal appendix following
230 appendectomy for suspected appendicitis.⁴⁶ Our assessment of final diagnoses in inpatients after
231 surgery would also support our assumptions of misdiagnosis. Review of this data permitted
232 calculations of absolute risk differences between CD patients and controls, suggesting that 1 in
233 24 appendectomies, 1 in 11 biliary surgeries and 1 in 16 uterine surgeries may be occurring due
234 to unawareness of CD and its symptoms. These findings collectively support the potential of
235 diagnostic inertia occurring in CD, contributing to identified diagnostic delays.

236

237 This study has several strengths, including its population-based design and the independent
238 ascertainment of cases from national health registers. The Swedish National Patient Register has
239 been validated repeatedly, and the majority of diagnoses have a high positive predictive value
240 (85–95%).²⁹ Furthermore, CD was identified through biopsy records showing villous atrophy.
241 During the study period, biopsy remained the gold standard for diagnosis in both children and
242 adults, and $\geq 96\%$ of all pediatricians and gastroenterologists in Sweden reported performing a
243 small intestinal biopsy before diagnosis.³⁶ A patient chart review found that 95% of all samples
244 with villous atrophy represented CD, a higher positive predictive value than physician-assigned
245 diagnosis for CD in the Swedish National Patient register.⁴⁷ In addition, villous atrophy in
246 Sweden is rarely explained by diagnoses other than CD (0.3% of individuals with villous atrophy
247 had inflammatory bowel disease).³⁶ Although positive CD serology was not included within the
248 definition of CD, it has been demonstrated that 88% of those with available CD serology data
249 have positive antibodies at the time of first biopsy.³⁶

250
251 Limitations to this work are that the Swedish Patients Registry does not include individual-based
252 data on symptoms. This means that we are unable to accurately decipher symptoms of
253 undiagnosed CD patients at the time of a surgery, which could enhance our assertion of
254 diagnostic inertia. A previous subset analysis of CD patients within our biopsy database suggests
255 diarrhea (36%) and anemia (35%) are the most common clinical characteristics seen at the time
256 of diagnosis. Given that risk of CD is highest within 1 year of abdominal surgery, it is highly
257 likely that undiagnosed CD patients are presenting to surgical teams with ‘classical CD’
258 symptoms.

259
260 This study compares favourably to a previous study demonstrating increased surgical risk in
261 undiagnosed CD patients (n=476).⁴⁸ Our current study is significantly larger than that previous
262 work, helping to establish high statistical precision and calculation of important subanalyses,

263 including stratified analyses according to sex, age and calendar period of CD diagnosis. Our
264 work also draws comparisons to work in inflammatory bowel disease, with a recent study from
265 China highlighting increased rates of abdominal surgery before the diagnosis of Crohn's
266 disease.⁴⁹

267
268 As undiagnosed CD is common and misdiagnosis frequent, our findings should provide the
269 impetus for enhanced CD testing in patients with abdominal symptoms. Previous work has
270 suggested that undiagnosed CD patients presenting with surgical abdominal pain are being
271 missed.⁵⁰ Furthermore, this association is recognized in patients labelled with Irritable Bowel
272 Syndrome.⁵¹ We suggest that if a patient is considered not to have acute abdominal pain
273 warranting surgical intervention, this should alert clinicians to consider the diagnosis of CD. The
274 use of a celiac serology is cheap and minimally invasive compared to the potential costs of
275 surgery, which are both psychological and financial (e.g. median cholecystectomy cost =
276 \$15,651 (13,787 EUR)).⁵² Through recognizing or questioning for celiac associated symptoms in
277 this group of patients the detection of CD could be improved.

278
279 In conclusion this is the largest study to date showing that patients with CD have increased rates
280 of abdominal surgery both before and after CD diagnosis. Although CD is likely to be associated
281 with surgical complications, our work emphasizes the need for clinicians to be mindful of the
282 protean manifestations of CD. This could help improve detection, reduce unnecessary medical
283 interventions and ease psychological burden to CD patients.

284

285

286

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411 **Table 1** Characteristics of study participants

412 **Table 2.** Abdominal surgery and risk of later Celiac disease

413 **Table 3.** Subanalyses: Abdominal surgery and risk of later Celiac disease.

414 APPENDIX – online only supplement

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