Review Article

Is Celiac Disease (CD) Prevalent in Patients with Multiple Sclerosis (MS): A Systematic Review and Meta-Analysis

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Background. Celiac disease (CD) is an autoimmune disease, and its prevalence reported variously in different studies. The goal of this study is to evaluate the pooled prevalence of CD in subjects with MS.

Methods. PubMed, Scopus, EMBASE, Web of Science, and Google Scholar along with gray literature were systematically searched. The search included all relevant studies which were published up to October 2022. Two researchers independently searched all databases and also references of included studies.

Results. We found 8211 articles by literature search, and after deleting duplicates, 5594 remained. Fifteen articles remained for meta-analysis. Totally, 31418 patients were evaluated, and the total number of possible/confirmed cases was 124. Studies were published between 2004 and 2020, and the most published studies were from Italy. Five studies provided information regarding controls. The total number of controls was 22394, of whom 22 had CD. Mean age ranged from 35 to 55 years. The pooled prevalence of CD in MS patients was 0 (I² = 88.2%, p < 0.001). The pooled odds of CD in subjects with MS are 0.46 (95% CI: 0.19–1.1) (I² = 0, p = 0.9).

Conclusion. The pooled prevalence of this systematic review showed that CD is not prevalent in MS cases.

1. Introduction

Multiple sclerosis (MS) is an autoimmune disease of central nervous system (CNS) [1, 2], affecting youth all over the world. The exact etiology of the disease is unknown, but multiple putative etiologic factors have been considered to play a role in development of MS [3].

Accompanying with a wide range of autoimmune diseases, such as hypothyroidism, inflammatory bowel disease, rheumatoid arthritis, and diabetes, could highlight common genetic or environmental exposures between MS and other autoimmune diseases [3, 4]. Epidemiological studies showed an increased susceptibility for developing another autoimmune diseases in subjects with a single autoimmune disease [5–8].

Celiac disease (CD) is an autoimmune gluten-sensitive enteropathy, which results in small intestinal lesions and malabsorption in affected cases [9]. The pathogenesis of CD is based on genetic factors and mucosal immune response [10]. Almost all affected patients with CD have HLA DR3-
DQ2 and/or the DR4-DQ8 [11–13]. These HLA class II haplotypes show strong association with MS [14, 15].

On the other hand, CD is associated with neurological manifestations and diseases such as ataxia, epilepsy, neuropathy, and multiple sclerosis (MS) [16].

In some previous studies, the increased levels of anti-gliadin and gluten antibodies were detected in MS cases while another study failed to confirm this finding [9, 17, 18].

As there is no systematic review and meta-analysis regarding the prevalence of CD in MS cases, we designed this study to evaluate the prevalence of CD in MS cases.

2. Methods

2.1. Search Strategy. PubMed, Scopus, EMBASE, Web of Science, and Google Scholar along with gray literature were systematically searched. The search included all relevant studies which were published up to October 2022.

Two researchers independently searched all databases and also references of included studies.

2.2. The Syntax Which Was Used in MeSH Is as Follows. ((Sclerosis AND multiple) OR (sclerosis AND disseminated) OR “disseminated sclerosis” OR “multiple sclerosis” OR “acute fulminating”) AND (“Celiac Disease” OR (Disease AND Celiac) OR “Gluten Enteropathy” OR (Enteropathies AND Gluten) OR (Enteropathies AND Gluten-Sensitive) OR “Gluten Sensitive Enteropathy” OR “Gluten-Sensitive Enteropathies” OR “Gluten-Sensitive Enteropathy” OR (Enteropathies AND Gluten-Sensitive) OR (Enteropathy AND Gluten-Sensitive) OR “Gluten Sensitive Enteropathy” OR “Gluten-Sensitive Enteropathies” OR (Sprue AND Celiac) OR (Sprue AND Nontropical) OR “Nontropical Sprue” OR “Celiac Sprue” OR Sprue).

Inclusion criteria were cross-sectional studies/case, articles which had been published in the English language. We included studies only in which the diagnostic criteria were biopsy of duodenum.

Exclusion criteria are letter to editors, case reports, and RCT studies.

2.3. Data Extraction. Two independent researchers extracted data. In the case of discrepancies, they asked another
<table>
<thead>
<tr>
<th>Author</th>
<th>Continent</th>
<th>Region</th>
<th>Year</th>
<th>Study design</th>
<th>Total MS cases</th>
<th>Female cases</th>
<th>Male cases</th>
<th>Age mean (SD)</th>
<th>EDSS mean (SD) or median (range)</th>
<th>Total celiac case</th>
<th>Total control</th>
<th>Female control</th>
<th>Male control</th>
<th>Total celiac control</th>
<th>Quality assessment*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lo et al. [22]</td>
<td>Australia</td>
<td>Australia</td>
<td>2021</td>
<td>Cohort</td>
<td>1518</td>
<td>1204</td>
<td>309</td>
<td>55.7 (11.2)</td>
<td>NR</td>
<td>15</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>7/9</td>
</tr>
<tr>
<td>Lo et al. [23]</td>
<td>Australia</td>
<td>Australia</td>
<td>2021</td>
<td>Cross-sectional</td>
<td>902</td>
<td>709</td>
<td>193</td>
<td>55.8 (11.4)</td>
<td>NR</td>
<td>10</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>7/10</td>
</tr>
<tr>
<td>Piccini et al. [24]</td>
<td>Europe</td>
<td>Italy</td>
<td>2020</td>
<td>Cohort</td>
<td>2050</td>
<td>1579</td>
<td>471</td>
<td>28.8 (10.8)</td>
<td>RRMS: 1251</td>
<td>NR</td>
<td>9</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>7/9</td>
</tr>
<tr>
<td>Lorence et al. [25]</td>
<td>Europe</td>
<td>Italy</td>
<td>2018</td>
<td>Cross-sectional</td>
<td>286</td>
<td>205</td>
<td>81</td>
<td>42.4 (10.6)</td>
<td>NR</td>
<td>2.7 (1.8)</td>
<td>4</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>7/10</td>
</tr>
<tr>
<td>Laroni et al. [26]</td>
<td>Europe</td>
<td>Italy</td>
<td>2017</td>
<td>Cohort</td>
<td>1877</td>
<td>1218</td>
<td>659</td>
<td>35.3 (11.3)</td>
<td>NR</td>
<td>2.1 (1.1)</td>
<td>12</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>7/9</td>
</tr>
<tr>
<td>Zanchi et al. [27]</td>
<td>Europe</td>
<td>Italy</td>
<td>2017</td>
<td>Cross-sectional</td>
<td>601</td>
<td>403</td>
<td>198</td>
<td>43.9</td>
<td>RRMS: 487 SPMS: 103 PRMS: 11</td>
<td>2 (1.0-9.0)</td>
<td>47</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>8/10</td>
</tr>
<tr>
<td>de Oliveira et al. [28]</td>
<td>Latin America</td>
<td>Brazil</td>
<td>2016</td>
<td>Cross-sectional</td>
<td>249</td>
<td>176</td>
<td>73</td>
<td>NR</td>
<td>NR</td>
<td>1</td>
<td>211</td>
<td>163</td>
<td>48</td>
<td>3</td>
<td>8/10</td>
</tr>
<tr>
<td>Farez et al. [29]</td>
<td>Latin America</td>
<td>Argentina</td>
<td>2014</td>
<td>Case control</td>
<td>211</td>
<td>163</td>
<td>48</td>
<td>40.4 (10)</td>
<td>NR</td>
<td>1 (0-8.5)</td>
<td>211</td>
<td>163</td>
<td>48</td>
<td>3</td>
<td>7/10</td>
</tr>
<tr>
<td>Levinthal et al. [30]</td>
<td>America</td>
<td>USA</td>
<td>2013</td>
<td>Cross-sectional</td>
<td>218</td>
<td>170</td>
<td>48</td>
<td>47.6 (10)</td>
<td>RRMS: 154 SPMS: 24 PRMS: 9 Undefined: 32</td>
<td>NR</td>
<td>2</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>7/10</td>
</tr>
<tr>
<td>Khoshbaten</td>
<td>Asia</td>
<td>Iran</td>
<td>2012</td>
<td>Cross-sectional</td>
<td>100</td>
<td>68</td>
<td>32</td>
<td>33.1 (8.8)</td>
<td>RRMS: 78 SPMS: 14</td>
<td>3.9 (1.9)</td>
<td>0</td>
<td>121</td>
<td>75</td>
<td>46</td>
<td>6/10</td>
</tr>
<tr>
<td>Rodrigo et al. [31]</td>
<td>Europe</td>
<td>Spain</td>
<td>2011</td>
<td>Cross-sectional</td>
<td>72</td>
<td>60</td>
<td>12</td>
<td>43 (10)</td>
<td>RRMS: 72</td>
<td>1.7 (1.1)</td>
<td>8</td>
<td>Check</td>
<td></td>
<td></td>
<td>7/10</td>
</tr>
<tr>
<td>Nicoletti et al. [16]</td>
<td>Europe</td>
<td>Italy</td>
<td>2008</td>
<td>Case control</td>
<td>217</td>
<td>130</td>
<td>87</td>
<td>40.2 (10.2)</td>
<td>RRMS: 193 SPMS: 21 PRMS: 3</td>
<td>NR</td>
<td>0</td>
<td>200</td>
<td>123</td>
<td>77</td>
<td>8/10</td>
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<tr>
<td>Nielsen et al. [32]</td>
<td>Europe</td>
<td>Denmark</td>
<td>2008</td>
<td>Cohort</td>
<td>12403</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>1</td>
<td>20798</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>4</td>
</tr>
<tr>
<td>Eaton et al. [33]</td>
<td>Europe</td>
<td>Denmark</td>
<td>2007</td>
<td>Cohort</td>
<td>9961</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>6</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Edwards and Constantinescu [34]</td>
<td>Europe</td>
<td>UK</td>
<td>2004</td>
<td>Case control</td>
<td>658</td>
<td>454</td>
<td>204</td>
<td>45</td>
<td>NR</td>
<td>3</td>
<td>1064</td>
<td>NR</td>
<td>NR</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Salvatore et al. [17]</td>
<td>Europe</td>
<td>Italy</td>
<td>2004</td>
<td>Cross-sectional</td>
<td>95</td>
<td>NR</td>
<td>NR</td>
<td>41.3 (21-63)</td>
<td>RRMS: 76 SPMS: 16 PRMS: 3</td>
<td>NR</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>6/10</td>
</tr>
</tbody>
</table>
Overall ($I^2 = 88.29\%$, $p = 0.00$)

Zanchi (2017)
Piccini (2020)
Nielsen (2008)
Levinthal (2013)
Nicoletti (2008)
Khoshbaten (2012)
Oliveira (2016)
Eaton (2007)
Pangan Lo (2020)
Nicoletti (2008)
Salvatore (2004)
Rodrigo (2011)
Oliveira (2016)
Nielsen (2008)
Khoshbaten (2012)
Overall ($I^2 = 0.0\%$, $p = 0.923$)

**Figure 2:** The pooled prevalence of CD in MS patients.

<table>
<thead>
<tr>
<th>Study</th>
<th>ES (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edwards (2004)</td>
<td>0.00 (0.00, 0.01)</td>
<td>1.09</td>
</tr>
<tr>
<td>Levintharl (2013)</td>
<td>0.01 (0.00, 0.03)</td>
<td>0.19</td>
</tr>
<tr>
<td>Piccini (2020)</td>
<td>0.00 (0.00, 0.01)</td>
<td>3.88</td>
</tr>
<tr>
<td>Lorefsce (2018)</td>
<td>0.01 (0.01, 0.04)</td>
<td>0.16</td>
</tr>
<tr>
<td>Farez (2014)</td>
<td>0.00 (0.00, 0.03)</td>
<td>0.35</td>
</tr>
<tr>
<td>Marie (2020)</td>
<td>0.01 (0.01, 0.02)</td>
<td>0.81</td>
</tr>
<tr>
<td>Laroni (2017)</td>
<td>0.01 (0.00, 0.01)</td>
<td>2.11</td>
</tr>
<tr>
<td>Zanchi (2017)</td>
<td>0.08 (0.06, 0.10)</td>
<td>0.07</td>
</tr>
<tr>
<td>Eaton (2007)</td>
<td>0.00 (0.00, 0.00)</td>
<td>17.68</td>
</tr>
<tr>
<td>Pangan Lo (2020)</td>
<td>0.01 (0.01, 0.02)</td>
<td>0.63</td>
</tr>
<tr>
<td>Nicoletti (2008)</td>
<td>0.00 (0.00, 0.02)</td>
<td>20.31</td>
</tr>
<tr>
<td>Salvatore (2004)</td>
<td>0.00 (0.00, 0.04)</td>
<td>15.90</td>
</tr>
<tr>
<td>Rodrigo (2011)</td>
<td>0.11 (0.06, 0.20)</td>
<td>0.01</td>
</tr>
<tr>
<td>Oliveira (2016)</td>
<td>0.00 (0.00, 0.02)</td>
<td>0.48</td>
</tr>
<tr>
<td>Nielsen (2008)</td>
<td>0.00 (0.00, 0.00)</td>
<td>20.08</td>
</tr>
<tr>
<td>Khoshbaten (2012)</td>
<td>0.00 (0.00, 0.04)</td>
<td>16.25</td>
</tr>
<tr>
<td>Overall ($I^2 = 88.29%$, $p = 0.00$)</td>
<td>0.00 (0.00, 0.00)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

**Figure 3:** The pooled odds of CD in subjects with MS.

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edwards (2004)</td>
<td>0.37 (0.11, 1.30)</td>
<td>48.84</td>
</tr>
<tr>
<td>Farez (2014)</td>
<td>0.33 (0.03, 3.20)</td>
<td>15.01</td>
</tr>
<tr>
<td>Nicoletti (2008)</td>
<td>0.92 (0.06, 14.83)</td>
<td>10.03</td>
</tr>
<tr>
<td>Nielsen (2008)</td>
<td>0.42 (0.05, 3.75)</td>
<td>16.13</td>
</tr>
<tr>
<td>Khoshbaten (2012)</td>
<td>1.21 (0.07, 19.63)</td>
<td>9.99</td>
</tr>
<tr>
<td>Overall ($I^2 = 0.0%$, $p = 0.923$)</td>
<td>0.46 (0.19, 1.10)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis.
in subjects with MS are 0.46 (95% CI: 0.19-1.1) (Figure 3). As the odds of CD in subjects with MS are not high, there is a need to determine heterogeneity, inconsistency ($I^2$) was calculated. As the $I^2$ was more than 50%, we used random effects for pooling the data. We reported pooled prevalence with 95% CI.

3. Results

We found 1113 articles by literature search, and after deleting duplicates, 519 remained. Sixteen articles remained for meta-analysis (Figure 1).

Totally, 31418 patients were evaluated and total number of possible/confirmed cases was 124. Studies were published between 2004 and 2020, and the most published studies were from Italy. Five studies provided information regarding controls. The total number of controls was 22394, of whom 22 had CD.

Mean age ranged from 35-55 years. The quality assessment score ranged between 4 and 10 (table 1).

The pooled prevalence of CD in MS patients was 0 ($I^2 = 88.2\%, p < 0.001$) (Figure 2). The pooled odds of CD in subjects with MS are 0.46 (95% CI: 0.19-1.1) ($I^2 = 0$, $p = 0.9$) (Figure 3).

4. Discussion

This is the first systematic review and meta-analysis evaluating the prevalence of celiac disease in MS patients.

The results show that the prevalence is near zero in MS, and the odds of CD in subjects with MS are not high.

Patients with MS suffer from a wide range of gastrointestinal manifestations such as dysphagia, constipation, and/or fecal incontinence [35–38]. Dyspeptic symptoms and pain are also common in MS cases which impair quality of life and interfere with daily activities [30].

de Oliveira et al. assessed 249 MS patients and reported CD in only one [28] which was along with findings of Nielsen et al. who evaluated gluten-sensitive enteropathy in 12403 MS cases and found it in only one (RR = 0.6, 95% CI: 0.1-4.6) [32].

Rodrigo et al. included 72 MS cases and 123 healthy controls and found the antibodies (IgA-anti-transglutaminase-2) in 10% of MS cases and 2.4% ($p < 0.05$) (OR = 5.3) while HLA-DQ2 markers did not significantly differ between patients and healthy subjects [31]. In their study, 32% of first degree had CD.

In Germany in 2001, 75 children with CD were evaluated by electroencephalogram, computed tomography (CT scan), and magnetic resonance imaging (MRI) of the brain and reported white matter lesions in 15 cases [39].

CD has a clear etiology which is autoimmunity and is the consequence of gluten intolerance. Genetics play an important role [31] and mostly occurs at adolescence [40]. The relationship between MS and CD is considered in some studies while the pathogenesis of both diseases’ T-cells plays an important role, and Matheson found that patients with MS benefit from gluten free diet [41]. Shor et al. and Reichelt and Jensen reported the decrease in number of demyelinating lesions in MS cases who were treated with gluten free diet [42, 43]. They also share common HLABs [14, 15]. The prevalence of CD in different general populations is estimated between 0.2% and 0.7% [44–47].

It has been shown that CD is related with other neurological diseases such as peripheral neuropathies, seizure, ataxia, and cognitive impairment. One suggestion is that antibodies to gliadin or a peptide sequence of gliadin are neurotoxic and precede neurological manifestation in CD [48].

This systematic review had some limitations. There were studies that used serologic evaluation for CD diagnosis which were excluded. There were no reports from some countries. The control groups were different; as in some studies, the control group was healthy subjects, and in others, the control group was patients with other diseases except MS. Larger multicentric studies from lots of countries are reported.

5. Conclusion

The pooled prevalence of this systematic review showed that CD is not prevalent in MS cases.

Conflicts of Interest

The authors declare that they had no conflict of interest.

References


