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Prevalence of Celiac Disease in Patients with Iron Deficiency Anemia – a Systematic Review with Meta-analysis

Srihari Mahadev^{1,*}, Monika Laszkowska^{1,*}, Johan Sundström², Magnus Björkholm³, Benjamin Lebwohl¹, Peter HR Green¹, Jonas F Ludvigsson^{#,1,4,5,6}

¹Celiac Disease Center, Department of Medicine, Columbia University College of Physicians and Surgeons, New York, New York, USA

²Department of Medical Sciences, Uppsala University, and Uppsala Clinical Research Center, SE-751 85 Uppsala, Sweden

³Department of Medicine, Division of Hematology, Karolinska University Hospital and Karolinska Institutet, SE-171 76 Stockholm, Sweden

⁴Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, SE-171 77 Stockholm, Sweden

⁵Department of Pediatrics, Örebro University Hospital, SE-701 85 Örebro, Sweden

⁶Division of Epidemiology and Public Health, School of Medicine, University of Nottingham, Nottingham, UK

Abstract

Background & Aims—Anemia is common in patients with celiac disease and a frequent presentation. Guidelines recommend screening iron-deficient patients with anemia for celiac disease. However, the reported prevalence of celiac disease among patients with iron-deficiency anemia (IDA) varies. We performed a systematic review to determine the prevalence of biopsy-verified celiac disease in patients with IDA.

#Correspondence and reprint requests: Jonas F Ludvigsson, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, 171 77 Stockholm, Sweden, Phone: +46 (0) 19- 6021000, Fax: +46 (0) 19-187915, jonasludvigsson@yahoo.com.

***Contributed equally.**

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*Appendix 4 is the PRISMA checklist and is not cited in the paper.

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Methods—We performed a systematic review of manuscripts published in PubMed Medline or EMBASE through July 2017 for the term celiac disease combined with anemia or iron-deficiency. We used fixed-effects inverse variance-weighted models to measure the pooled prevalence of celiac disease. Meta-regression was used to assess subgroup heterogeneity.

Results—We identified 18 studies comprising 2998 patients with IDA for inclusion in our analysis. Studies originated from the United Kingdom, United States, Italy, Turkey, Iran, and Israel. The crude unweighted prevalence of celiac disease was 4.8% (n=143). Using a weighted pooled analysis, we demonstrated a prevalence of biopsy-confirmed celiac disease of 3.2% (95% CI, 2.6%–3.9%) in patients with IDA. However, heterogeneity was high ($I_2 = 67.7\%$). The prevalence of celiac disease was not significantly higher in studies with a mean participant age older or younger than 18 years, nor in studies with a mixed-sex vs female-predominant (60%) population. On meta-regression, year of publication, the proportion of females, age at celiac disease testing, and the prevalence of in the general population were not associated with the prevalence of celiac disease in patients with IDA. In the 8 studies fulfilling all our quality criteria, the pooled prevalence of celiac disease was 5.5% (95% CI, 4.1%–6.9%).

Conclusions—In a systematic review and meta-analysis, we found that approximately 1 in 31 patients with IDA have histologic evidence of celiac disease. This prevalence value justifies the practice of testing patients with IDA for celiac disease.

Keywords

celiac; coeliac; iron deficiency; meta-analysis

Key terms

celiac (American spelling); coeliac (British spelling); fracture; gluten; anemia

INTRODUCTION

Celiac disease (CD) occurs in about 1 in 100 patients in the Western world¹. It is an immune-mediated disease triggered by the exposure to gluten. While environmental factors are important, recent data highlight the importance of genetic factors^{2, 3}. Patients with CD are at increased risk of a number of disorders including lymphoma⁴ and autoimmunity^{5–7}.

Typically, patients with CD demonstrate small intestinal inflammation and villous atrophy⁸, and this may result in malabsorption of both calories and micronutrients including iron. Major guidelines for both management of CD^{9–11} and iron-deficiency anemia (IDA)¹² point out the association between these two diseases and the need to test patients with unexplained IDA for CD. The highly-cited systematic review by Dube et al in 2005¹³ reported a CD prevalence of between 2.9% and 6% in patients with asymptomatic IDA, increasing to 10–15% when patients with IDA and concomitant gastrointestinal symptoms were screened¹³. However, since the publication of the paper by Dube et al¹³, a large number of publications on IDA and CD have appeared, with CD prevalence varying between 1.8%¹⁴ and 20%^{15, 16}. Despite this we are unaware of any up-to-date systematic review aiming to quantitatively combine prevalence data for CD in IDA.

The aim of this study was to investigate the prevalence of CD in patients with IDA, and to determine if CD prevalence differed by IDA subgroups.

METHODS

We used the PRISMA guidelines¹⁷ when planning and executing this paper. We did not publish any pre-specified protocol prior to the study.

Search

The library of Karolinska Institutet searched PubMed and EMBASE for CD (celiac disease or coeliac disease or gluten or non-tropical sprue) combined with “anemia” or “anaemia” or “iron-deficiency”, up until May 2016. We then updated our search in July 2017. The search was limited to English-language publications. SM and ML conducted the review of all search hits with assistance from JFL.

After initial review of abstracts and titles, 68 papers were read in detail. Eighteen papers were then included in the final analysis ((Table 1) and Appendix 1 (flowchart for study inclusion))^{14–16, 18–32}. For case-control studies we restricted the extracted information to those patients with IDA.

Celiac disease

Small intestinal biopsy was required for the CD diagnosis. Most biopsy-confirmed patients with available serology data had a positive CD serology but this was not a requirement for diagnosis in our study. Where authors did not report the prevalence of Marsh I–III, we assumed that “biopsy-verified CD” required at least Marsh II–III; where Marsh categories were presented, grade I was not accepted as CD. It is well-known from other studies that the prevalence of CD will increase when Marsh I is accepted as proof of CD or even when biopsy-negative patients are regarded as CD positive. In a sub-analysis, we examined the risk of CD in IDA where it was explicitly stated that Marsh III was required.

Anemia

The definition of anemia varied among the studies, with most studies requiring a hemoglobin (Hb) below 135 g/L in males and 120 in females, but both stricter^{20, 27} and looser²² inclusion criteria were applied (see Table 1 for details on anemia definition in individual studies). A “low Hb cut-off level” for anemia is sometimes relevant (eight of the studies included patients <18 years and some focused on younger children where Hb levels are generally lower than in an adult population and the mean/median ages in the different studies ranged from 5.3 years¹⁵ to 63 years¹⁸). The majority of studies drew patients from tertiary referral hospitals, although one study looked at screening of blood donors¹⁶, and another at blood specimens obtained from primary care providers²³. Characteristics of the included studies are given in Table 1, with definitions of iron-deficiency anemia summarized in Appendix 2.

Upper and lower 95% confidence intervals (Cis) and standard errors based on the proportions reported in each paper were calculated.

Data items and risk of bias

Data on the following variables were extracted: (i) year of publication, (ii) age at screening (child<18 years, adult, mixed), (iii) country, and (iv) Marsh stage³³. The prevalence of CD in the general population differs³⁴. For this reason we examined the prevalence of CD in IDA in relationship to the underlying CD prevalence in each country (Italy³⁵; US³⁶; UK³⁵; Iran³⁷; Northern Ireland (we used UK data³⁵); Israel³⁸, and Turkey³⁹).

We used the Munn, et al critical appraisal tool to grade the quality of our prevalence studies⁴⁰ (Appendix 3). Since a funnel plot (eFigure 1) indicated that publication bias could not be ruled out, we carried out a separate analysis restricted to studies with a standard error 0.02. While random-effects models tend to give greater relative weight to imprecise results,⁴¹ especially where heterogeneity is present, we carried out such an analysis restricted also to studies with a standard error 0.02.

Summary measures, analysis method and heterogeneity

To calculate a weighted prevalence of CD among patients with IDA we used a fixed-effect model. This prevents smaller and imprecise studies from impacting the summary estimate unduly⁴². We report all estimates with 95% CIs. We also calculated the heterogeneity between studies as I^2 . Given the high heterogeneity observed in this study (67.7%) we explored the prevalence of CD in subgroups based on geographic region, study size, age and gender. Studies were grouped according to country of origin, classified as North America, Europe, Turkey, or Asia (Iran and Israel). We defined subgroups of study size (199 vs. 200) and gender (<60 vs. 60% females; the average proportion of females in the 16 studies with available data was 64%). In addition, we carried out four meta-regression analyses to examine the association of CD prevalence in IDA with: (i) study size, (ii) publication year, (iii) proportion of females and (iv) underlying CD prevalence. All these factors can potentially explain the variance of CD prevalence.

Statistics software

Stata 13 was used for all analyses.

RESULTS

Titles and abstracts were read for 2057 papers published up until May 2016 (Flowchart). In July 2017 the search was updated. Since the Karolinska Institutet Library was only able to perform searches for full years, the second search started from Jan 2016 up until July 2017 (167 hits) and therefore overlapped with the first search but yielded no additional relevant papers.

Sixty-eight papers were identified as potentially relevant for our meta-analysis, and were read in detail. Any disagreement between SM and ML was solved through consensus, or through mediation with JFL. Reasons for exclusion of the 50 excluded papers were: unclear inclusion criteria (definition of CD or IDA, n=15^{43–57}); looked at refractory IDA or anemia of obscure origin (n=10^{58–67}); full-text unavailable or not available in English (n=7^{68–74}); high risk of selection bias (n=6^{32, 75–79}); looked at iron deficiency without anemia, or

anemia not explicitly part of criteria ($n=4^{80-83}$); looked at anemia in general, not IDA ($n=3^{84-86}$); or other reason (small intestinal biopsy not performed ($n=1^{87}$), case report ($n=1^{88}$), examined prevalence of IDA in patients with CD ($n=1^{89}$), not original research ($n=1^{90}$), examined CD in general population not IDA ($n=1^{91}$)).

In the quantitative part of the analysis, we hence included 18 relevant studies with 2998 patients with IDA (Table 1)^{14-16, 18-32}. Of these 2998 patients, 143 had CD, yielding an unweighted proportion of 4.8%. The median size of the 18 studies was 104 patients. Three studies contributed more than 400 patients each^{14, 23, 31}. The median prevalence of CD was 5.0%. Eight studies had taken place in Europe.

Prevalence of CD in anemia

The pooled prevalence of CD in patients with IDA was 3.2% (95% CI=2.6–3.9%)(Figure 1). The heterogeneity was high ($p<0.001$; $I^2 = 67.7\%$). We therefore performed subgroup analyses and meta-regressions to examine this heterogeneity.

The pooled prevalence of CD in IDA was similar in studies that enrolled patients with an average age <18 years at publication (4.0%; 95%CI=2.1–5.8%)^{15, 27, 32}, as compared to those with a mean age ≥ 18 years (3.1%; 95%CI=2.5–3.8%)^{14, 16, 18-26, 28-31}. Excluding two studies^{14, 23} where the mean age was ≥ 18 but exact values were not possible to extract, we found no relationship between age at testing for CD and prevalence of CD in IDA (Figure 2a, $p=0.461$, see Figure legend for mean vs. median age).

The CD prevalence in IDA varied by continent ($p=0.002$ for subgroup analysis). The CD prevalence was 4.6% (95%CI=1.6–7.5%) in North America^{25, 26}. The prevalence in Europe (without Turkey)^{14, 16, 18, 19, 21-24} was 2.5% (95%CI=1.7–3.3%), with Turkey^{15, 27-29, 32} (4.1%; 95%CI=2.5–5.7%) and other Asian countries^{20, 30, 31} (6.4%; 95%CI=4.4–8.3%) showing the highest prevalence.

Two studies did not report the proportion of women^{14, 23}. In IDA studies where at least 60% of participants were women^{18-20, 22, 24, 25, 28-31} the CD prevalence was 5.5% (95%CI=4.2–6.7%), as opposed to 4.2% (95%CI=2.6–5.7) in studies with a more mixed population or a majority of males^{15, 16, 21, 26, 27, 32}. The CD prevalence in the two studies without data on sex distribution was 2.0% (95%CI=1.2–2.8%). In a meta-regression, we found no association between the proportion of women and the prevalence of CD in IDA (Figure 2b, $p=0.726$).

Several studies have reported an increase in the prevalence of CD over time^{92, 93}; for this reason we examined the association between CD prevalence in IDA according to year of publication. A meta-regression could not demonstrate any association with year of publication (Figure 2c, $p=0.377$). Fourteen studies had included consecutive patients with IDA for CD screening^{14, 16, 19-26, 28-30}. Restricting the analysis to these studies, the CD prevalence was 2.9% (95%CI=2.2–3.6%). Seven studies explicitly reported that they required Marsh 3 for the CD diagnosis^{15, 16, 21, 23, 28, 31, 32}. The prevalence of CD when requiring Marsh III (3.7%; 95%CI=2.1–3.8%) did not differ from that of other studies ($p=0.267$) where the prevalence was 2.9% (95%CI=2.3–3.9%). In eleven studies, all patients

with positive antibodies had undergone biopsies^{14–16, 20, 22, 25, 26, 28–31}. Smaller studies (< 199 participants) showed higher prevalence of CD in IDA ($p=0.007$)(4.8%; 95% CI=3.5–6.0%) compared to large studies (≥ 200 participants)(2.7%; 95% CI=2.0–3.5%). We also investigated if the underlying population prevalence of CD was associated with the CD prevalence in patients with IDA. We were unable to demonstrate any such association (Figure 2d; $p=0.829$). Restricting our dataset to studies with a standard error < 0.02, the CD prevalence in IDA was 2.8% (95% CI=2.1–3.4%). Using a random-effects model applied to studies with a standard error < 0.02, the CD prevalence in IDA was 3.3% (95% CI=2.2–4.3%).

Finally, we examined the prevalence of CD in IDA studies^{20, 22, 24–26, 28, 30, 31} fulfilling all quality criteria (except the criterion concerning the identification of subpopulations, Appendix 3)⁴⁰. In these eight studies, the CD prevalence was 5.5% (95% CI=4.1–6.9%).

DISCUSSION

In this systematic review with meta-analysis of 2998 individuals, we found that biopsy-proven CD is a relatively frequent finding in patients with IDA, with a prevalence of roughly 1 in 31. The CD prevalence in IDA was not influenced by the proportion of females, the average age, or the baseline prevalence of CD in the populations studied. This is notable given that IDA is more common in certain subgroups, such as premenopausal women. Our findings suggest that IDA is an important risk factor for CD irrespective of patient demographics, and that endoscopic small bowel biopsy should be a part of the diagnostic workup for the condition, even in persons in which other etiologies may be suspected.

To our knowledge, this is the first meta-analysis to report a pooled estimate for the overall prevalence of biopsy-proven CD in patients with IDA. Prior studies have shown highly varying prevalence data for CD in IDA. Only one prior systematic review has addressed the question specifically, examining the CD prevalence in iron-deficient individuals as a subgroup of Western European populations,¹³ including 6 of the studies we also reviewed.^{18, 20, 22, 24, 94, 95} A meta-analysis was not conducted in this prior review. The prevalence of biopsy-confirmed CD in IDA was reported to be between 2.9% and 6%, which is consistent but slightly higher than our pooled estimate of 3.2% (95% CI=2.6–3.9%). It is possible that restriction to Western European individuals in Dube et al. 2005 may have accounted for the slightly higher prevalence estimates, although we did not identify an association between the baseline risk of CD in the population studied and the prevalence of CD in IDA on meta-regression.

The prevalence of IDA in the overall population varies markedly by sex and age, being most prevalent in females of reproductive age and in infancy in both sexes, likely due to higher iron requirements and poor dietary intake.⁹⁶ As CD is a genetic disorder, it might be expected that the prevalence of CD might be lower in studies in which the population was more likely to have other acquired etiologies of IDA, such as in female-predominant cohorts. However, we found no relationship between the average participant age and the prevalence of CD in IDA in our meta-regression ($p=0.461$), or between the proportion of females in the sample and the prevalence of CD in IDA ($p=0.726$). We cannot, however rule out that CD

may be more common in childhood IDA. The prevalence of CD in the latter population was 4.0% although only based on three studies (27 cases of CD in 446 children with IDA, non-weighted data)^{15, 27, 32}. One reason for a higher prevalence of CD in children with IDA could be that other causes of IDA (including gastrointestinal bleeding and cancer) are less frequent in children. While IDA may occur in up to a third of CD patients, CD has also been associated with other causes of anemia such as folate and B12 deficiency as well as anemia of chronic disease^{97, 98}. Both malnutrition and ongoing inflammation likely contribute to anemia in CD patients. In CD patients with IDA, a gluten-free diet alone has been shown to induce improvement in ferritin levels and reversal of anemia without iron supplementation, underscoring the link between the two conditions.⁹⁹ Our findings do suggest that testing for CD is warranted in all patients with IDA, without exclusion of groups that have a high prevalence of other IDA etiologies.

One explanation for the significant variation in reported CD prevalence may be publication bias. Smaller studies in our meta-analysis yielded higher prevalence figures (pooled weighted estimates of 4.8% as opposed to 2.7%). Considering that small studies are more difficult to publish, publication bias is likely on the basis of our funnel plot. In this analysis, 2 of the 3 smallest studies both reported that 1 in 5 tested patients with IDA had CD, compared to distinctively lower proportions in the largest studies (1 in 37 patients with IDA in studies of 200 participants had CD). In order to avoid giving undue weight to smaller studies we used a fixed-effect model. Data from other fields suggest that exclusion of unpublished data (as in our study) may overestimate the pooled estimates¹⁰⁰. We approached this potential limitation by restricting our dataset to studies with a standard error 0.02 in a subanalysis. This yielded a pooled prevalence of 2.8%, similar to the overall pooled prevalence of our study (3.2%) and in line with estimates from Dube et al¹³.

Another kind of bias that may have pushed up the CD prevalence in some earlier screenings studies is if patients with concomitant gastrointestinal symptoms and IDA were more likely to undergo endoscopy as part of their assessment than asymptomatic IDA patients. We excluded studies where IDA patients with symptoms from the digestive tract were tested, and in another attempt to eliminate selection bias specifically examined studies where patients were (explicitly) included consecutively. This did not influence the results notably (2.9%).

Significant heterogeneity was observed which could not be explained by the examined characteristics. We performed meta-regressions to examine the interaction between the age, sex, and prevalence of CD in the general population and the prevalence of CD in IDA, none of which were explanatory. We also restricted our dataset to studies fulfilling all quality criteria, with a slight increase in the pooled CD prevalence (5.5%). We found no association between baseline CD prevalence and CD prevalence in IDA ($p=0.829$), but when merging data from different countries, the pooled CD prevalence in IDA patients from Asia (Israel and Iran) outside Turkey was 6.4%. We urge caution when interpreting these data, however, since they were based on only three studies^{20, 30, 31}. Of note, most previous research on biopsy-verified CD in IDA is limited to few countries (mainly Italy and Turkey), and there are little data from elsewhere. For this meta-analysis we only identified two studies from the US^{25, 26}.

Strengths of the present study include a large pool of identified studies, drawn from two different databases (PubMed and EMBASE). This large number of studies allowed us to restrict the analysis to histologically-confirmed, rather than serologically-diagnosed CD which is frequently reported but which can overestimate the true prevalence of CD. It also afforded subgroup analysis and meta-regression with examination of important demographic variables as interacting factors.

The observed heterogeneity without explanatory factors is a significant limitation of our study, and impacts on interpretation of the pooled estimate. We had limited data on patients from many parts of the world, including Asia and Africa, and no information on the ethnicity of study participants. While our funnel plot indicated a degree of publication bias that may have overestimated CD prevalence, critical appraisal of study quality suggested that in high-quality studies, more than 1 in 20 IDA patients may have CD. We were unable to examine the linear relationship between hemoglobin levels and prevalence of CD. We also did not have complete antibody data, and were unable to examine the prevalence of biopsy-negative CD in IDA. Recently the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) developed a non-biopsy pathway to CD diagnosis in patients with repeatedly positive celiac-specific serology, positive HLA-DQ2/DQ8 and symptoms consistent with CD¹⁰¹, however within these guidelines patients evaluated with anemia would require biopsy.

In conclusion, this meta-analysis found that approximately 1 in 31 patients with IDA had biopsy-verified CD, and that the prevalence of CD in IDA did not vary by the average age, proportion of females, or baseline CD prevalence. While no major gastroenterology society advocates for screening the general population for CD, there is a consensus that testing should be performed in patients with IDA^{9, 10, 12}. Our findings strongly support this recommendation, and further highlight the importance of endoscopy with histologic evaluation for CD in the diagnostic workup for patients with this condition, even in populations where other etiologies of IDA are common.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CD	Celiac disease
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GFD	Gluten-free diet
IDA	iron-deficiency anemia
VA	Villous atrophy

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PRISMA 2009 Flow Diagram¹

¹From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 6(6): e1000097. doi:10.1371/journal.pmed1000097. For more information, visit www.prisma-statement.org.

1. Medline (Ovid)

Date of Search: 2016-05-31	Field labels:
Number of hits: 1,393	
Comments:	
1. exp Celiac Disease/ 2. exp Glutens/ 3. (celiac* or celiak* or coeliac* or coeliak* or gluten or non-tropical sprue or nontropical sprue).ti,ab,kf. 4. 1 or 2 or 3 5. Anemia, Iron-Deficiency/ 6. (anemi* or anaemi* or iron).ti,ab,kf. 7. 5 or 6 8. 4 and 7 9. remove duplicates from 8	

2. Embase (embase.com)

Date of Search: 2016-05-31	Field labels:
Number of hits: 1,837	
Comments:	
No. Query	Results
#11 #9 AND ('article'/ti OR 'article in press'/ti OR 'editorial'/ti OR 'erratum'/ti OR 'letter'/ti OR 'note'/ti OR 'review'/ti OR 'short survey'/ti)	1,837
#9 #4 AND #8	2,698
#8 #5 OR #6 OR #7	324,467
#7 anemi*.ab,ti OR anaemi*.ab,ti OR iron.ab,ti	317,688
#6 'iron deficiency'/exp	12,387
#5 'iron deficiency anemia'/exp	22,687
#4 #1 OR #2 OR #3	42,347
#3 celiac*.ab,ti OR celiak*.ab,ti OR coeliac*.ab,ti OR coeliak*.ab,ti OR gluten.ab,ti OR 'non-tropical sprue'.ab,ti OR 'nontropical sprue'.ab,ti	35,206
#2 'gluten'/exp	7,117
#1 'celiac disease'/exp	26,266

Figure 1.
Prevalence of biopsy-verified celiac disease in iron-deficiency anemia

Figure 2.

a. Meta-regression: Relationship between age at CD investigation and CD prevalence in iron-deficiency anemia.

Y-axis: Percentage (%) of celiac disease among patients with iron-deficiency anemia among. X-axis: Age in years when tested for CD ($p=0.461$). Age represents median age for the following three studies^{21, 22, 24} and otherwise mean age.

b. Meta-regression: Relationship between proportion of women and CD prevalence in iron-deficiency anemia.

Y-axis: Percentage (%) of celiac disease among study participants with iron-deficiency anemia. X-axis: Percentage of females in each individual study ($p=0.726$).

c. Meta-regression: Relationship between year of publication and CD prevalence in iron-deficiency anemia.

Y-axis: Percentage (%) of celiac disease among study participants with iron-deficiency anemia. X-axis: Year of study publication ($p=0.377$).

d. Meta-regression: Relationship between CD prevalence in the general population and CD prevalence in iron-deficiency anemia.

Y-axis: Percentage (%) of celiac disease among study participants with iron-deficiency anemia. X-axis: Prevalence of CD in the general population ($p=0.829$).

Table 1

Papers included in the systematic review on celiac disease prevalence in iron-deficiency anemia

Study and Year	Country	Percentage	Celiac patients, N	Patients with IDA, N
McIntyre, 1993 ¹⁸	UK	2.7	3	111
Corazza, 1995 ¹⁹	Italy	5.0	10	200
Ackerman, 1996 ²⁰	Israel	12.1	11	91
Carroccio, 1998 ²¹	Italy	5.9	5	85
Annibale, 2001 ²²	Italy	5.6	4	71
Ransford, 2002 ²³	UK	2.3	11	484
Annibale, 2003 ²⁴	Italy	8.5	5	59
Mandal, 2004 ¹⁴	UK	1.8	9	504
Karnam, 2004 ²⁶	USA	2.9	3	105
Grisolano, 2004 ²⁵	USA	8.7	9	103
Kalayci, 2005 ²⁷	Turkey	2.2	3	135
Ferguson, 2007 ¹⁶	Northern Ireland	20.0	6	30
Gonen, 2007 ²⁸	Turkey	3.0	3	100
Ucardag, 2009 ²⁹	Turkey	7.8	6	77
Emami, 2012 ³⁰	Iran	5.4	7	130
Ertekin, 2013 ¹⁵	Turkey	21.3	13	61
Baghbanian, 2015 ³¹	Iran	6.0	24	402
Karaman, 2016 ³²	Turkey	4.4	11	250