Original Article



# Significance of red blood cell distribution width in children with celiac disease

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**Background:** In adult studies, red blood cell distribution width (RDW) has been suggested to be a predictor of small intestinal atrophy in celiac disease (CD). Our goal is to assess whether RDW can similarly be used as a reliable marker of compliance and predictor of atrophy in pediatric patients with CD.

**Methods:** We performed a retrospective study of children aged 1–17 years old diagnosed with CD from 2008–2018. We reviewed patient demographics, laboratory parameters prior to CD diagnosis, laboratory findings after management with gluten free diet, and histologic findings at the time of diagnosis.

**Results:** Overall, 128 patients met inclusion criteria. No significant difference in RDW was found prior to diagnosis versus after treatment (13.3 *vs.* 13.1, P=0.590). In addition, RDW did not show clinical significance in detecting villous atrophy (13.4 *vs.* 13.2, P=0.113). However, further analysis revealed a statistically significant association among patients having a RDW >12.9 and presence of atrophy (P=0.04).

**Conclusions:** There is a clear disparity between adult studies and pediatric studies in the usefulness in RDW as a predictive marker for intestinal atrophy and compliance in patients with CD, as RDW did not show clinical significance in detecting villous atrophy or compliance with a gluten free diet.

**Keywords:** Red blood cell distribution width (RDW); red cell distribution width; celiac disease (CD); children

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## Introduction

Celiac disease (CD) is an immune-mediated inflammatory disease of the small bowel secondary to dietary gluten sensitivity in individuals with genetic predisposition. Signs and symptoms vary greatly and range from intestinal symptoms such as diarrhea, abdominal pain or distension, weight loss, and failure to thrive to extraintestinal symptoms such as anemia, osteopenia, and short stature to name a few. However, in a multi-institutional study, prevalence of CD in the United States was noted to be 1:133 among patients with no risk factors or symptoms (1).

As per North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) guidelines, the standard screening test for CD is Tissue Transglutaminase immunoglobulin A (tTG-IgA). Total IgA is additionally obtained to determine if patient has an underlying deficiency. In some clinical scenarios, additional celiac serology such as the Anti-Endomysial IgA

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or the Deamidated Gliadin Peptide is obtained. Diagnosis is confirmed by esophagogastroduodenoscopy. As per NASPHGAN guidelines, 1–2 specimens are obtained from the duodenal bulb and 4 specimens are obtained from the distal duodenum (second or third portion) (2).

Standard management of patients diagnosed with CD consists of gluten-free diet (GFD) (3). Subsequent antibody testing is often performed 4-6 months after treatment has begun. In addition to monitoring growth parameters, other routine laboratory tests, while not universally performed, can include complete blood count (CBC), thyroid stimulating hormone, comprehensive metabolic panel, iron profile, vitamin B12, vitamin D, and folate.

Iron deficiency anemia can be a known complication or initial presentation of CD (4). Ferritin is commonly monitored to screen for iron deficiency anemia in patients with CD as well. With ferritin being an inflammatory marker, it can be falsely negative in patients with inflammatory conditions (5), such as CD. Red blood cell distribution width (RDW) may be a more accurate marker to assess for iron deficiency in patients with CD (6). RDW is the measurement of heterogeneity of red blood cells as well as size variation in peripheral blood, or anisocytosis (7). It is a typically included parameter of a CBC, which is widely available and inexpensive to obtain (6). The value of RDW in assessing clinical outcomes and disease severity has been shown across multiple medical conditions, such as being elevated in patients with iron deficiency anemia (8). Mortality and hospital survival rate assessment have also been shown to be a utility of RDW (9).

In a study of 126 adult patients with CD, Brusco *et al*. found increased RDW to be the most frequent abnormality from a hematologic standpoint (58%) with the next most frequent being anemia (31%) and iron deficiency (29%) (10). Another retrospective study by Harmanci *et al*. comparing RDW values according to presence of intestinal atrophy concluded RDW value >17.25% to be a significant predictor of atrophy (P=0.003) (11). This study included 49 newly diagnosed CD patients. Additionally, RDW was also used to assess response to GFD (11,12). As Mitchell *et al*. showed a significant decrease from initial elevated levels (17.3% *vs*. 13.8%) after 12 months of GFD diet in adult CD patients (12).

Due to increased incidence and prevalence of CD, there is potential utility of simple, inexpensive laboratory tests for diagnosing and monitoring adherence to GFD, especially if additional laboratory workup is equivocal. Our study aims to determine if RDW is a reliable marker of compliance in children treated for CD, like that of the adult counterpart studies. Additionally, we aim to determine if RDW is a reliable prognostic factor in severity of CD in children. We hypothesize that RDW is a useful marker of compliance in children treated for CD and that RDW is a potential predictor of intestinal atrophy in the pediatric CD population. We present the following article in accordance with the STROBE reporting checklist (available at https://pm.amegroups.com/article/view/10.21037/pm-21-24/rc).

## Methods

This study consisted of a retrospective chart review of all children ages 1–17 diagnosed with CD by Children's Hospital of Michigan Gastroenterology division from January 2008 to May 2018. All patients included in the study were required to have documented CBC less than 6 months prior to or at diagnosis, and prior to gluten free diet. Follow-up CBC at 4–12 months was also required for inclusion. Laboratory work reviewed in addition to CBC [specifically RDW, mean corpuscular volume (MCV), hemoglobin, and hematocrit] included tTG-IgA, endomysial antibody, and other labs if available (vitamin D 25-hydroxycholecalciferol, AST, ALT, calcium, phosphorus, albumin, folate, B12, iron, ferritin, and total iron binding capacity). tTG-IgA was reassessed 4–6 months after initial documentation. Specimen findings, as per pathologist report, were reviewed to determine presence of atrophy at diagnosis. Histologic findings were classified as having absence or presence of atrophy. Villous atrophy and CD diagnosis was made by histology and serology. If no atrophy was seen, but other histological features were present such as increased intraepithelial lymphocytes and crypt hyperplasia was present, then appropriate Marsh classification was given (i.e., Marsh type 2) and CD was considered.

Patients were excluded if there was no documented CBC with reviewable lab values prior to diagnosis or if the patient already practiced a gluten free diet. Additional exclusions consisted of the following: patients less than 1 or greater than 17 years of age, documented history of repetitive noncompliance to previous diets recommended by physician, presence of comorbid conditions potentially affecting CBC (i.e., hematologic, oncologic, cardiovascular, renal, inflammatory bowel disease, hepatic), and patients on treatment for previously known anemia. This study was approved by the Wayne State Institutional Review Board as well as Detroit Medical Center Institutional Review

Board (IRB# 045118MP4E, protocol # 1804001374). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Individual consent for this retrospective analysis was waived.

### *Statistical analysis*

Statistical analysis of data was performed using SPSS (Statistical Package for the Social Sciences) for Windows Release 24.0 (SPSS Inc., Chicago, IL, USA). The primary outcome consisting of mean difference in RDW pre- and post-GFD was examined using an independent sample *t*-test. If assumptions of normality and homogeneity of variance were violated, a non-parametric Mann Whitney U test was substituted. A non-parametric Spearman Rho test examined whether a correlation exists between mean difference in RDW and mean difference in tTG-IgA. Exploratory secondary outcomes consisted of analyzing RDW values and determining if a cut-off level led to a significant difference between the presence or absence of atrophy. If assumptions were violated, a non-parametric Kruskal Wallis test was substituted, and pair-wise comparisons were conducted using Mann Whitney U tests. Any comparisons between proportions were examined using a non-parametric Fisher's Exact Test. Significant differences were considered achieved at a P value less than 0.05.

## Results

### *Demographics*

A total of 336 patients were in our study cohort. Among them, 128 patients met inclusion criteria. And 83/128 (65%) were female. Racial demographics: 105/128 (82%) Caucasian, 4/128 (3%) African American, 3/128 (2%) Hispanic/Latino, and 16/128 (13%) races were designated other or unknown. Ages ranged from 1–17 years with mean of 9.0±4.0 years and median of 9.0 years.

### *Serology*

Mean initial RDW prior to GFD was 13.3±0.89, while follow-up RDW mean was 13.1±0.84 (reference range 11.7–14.9). Mean initial tTG-IgA values was 113.1±74.2, while mean at follow-up was 36.7±47.4. Mean tTG-IgA pre-post GFD decreased 77.6±66.1; 95% CI: −89.5 to −65.7; P=0.001. The correlation between mean difference in RDW and mean difference in tTG-IgA was very low (−0.10) and insignificant (P=0.260).

### *Atrophy*

The 79/128 (62%) of patient pathology reports demonstrated presence of atrophy at initial diagnosis. Mean initial RDW was 13.4±0.93 in patients with atrophy, compared to 13.2±0.80 in those patients with no atrophy; this was not found to be significant (P=0.113). Other labs reviewed in relation to villous atrophy are noted in *Table 1*. However, there was a statistically significant association among patients having an initial RDW >12.9 and presence of atrophy (*Table 2*). Pre-GFD, 63.3% of patients with absence of atrophy had RDW values >12.9 in comparison to 79.7% with atrophy. Further, there was also a statistically significant association among patients having a follow-up RDW >12.9 and no atrophy at time of diagnosis. Post-GFD, 36.7% of patients with absence of atrophy had RDW values >12.9 in comparison to 59.5% with atrophy.

There was a significant difference in the tTG-IgA values obtained at the time of diagnosis between patients with and without villous atrophy (129.0 *vs.* 83.0 U/L, P=0.010). However, no significant median differences were found in follow-up tTG-IgA values between the no atrophy group and the atrophy group (10.0 *vs.* 21.0 U/L, P=0.370).

## Discussion

### *Compliance*

The relationship with iron deficiency anemia and CD has been well established. It has been shown that patients with CD can present with iron deficiency due to malabsorption. However, this relationship is poorly understood as patients without villous atrophy can also present with anemia. While anemia does not improve in all patients with dietary modification, it does in the majority. Compliance on a GFD therefore remains of utmost importance.

An iron profile and a CBC are often monitored to assess GFD compliance as well as iron deficiency anemia, with the expectations that they will normalize in patients that are compliant. This may not be accurate given that ferritin may be falsely elevated as it is an inflammatory marker (5). MCV is also potentially not reliable in CD since this condition can cause anemia of chronic disease (13,14). RDW may be a more accurate marker, which is inexpensive and easy to obtain (6). We therefore hypothesized that RDW value difference pre- and post-GFD may potentially be useful

**Table 1** Demographics and initial laboratory parameters in presence of villous atrophy

| Variable | CD, n=128 | No atrophy | Atrophy | P value |
|---|---|---|---|---|
| Demographics | | | | |
| Age, years | 9±4 | | | 0.997 |
| Female | 83 (65%) | | | |
| Race | | | | |
| Caucasian | 105 (82%) | | | |
| African American | 4 (3%) | | | |
| Hispanic/Latino | 3 (2%) | | | |
| Other | 16 (13%) | | | |
| Weight, kilograms | 34±18 | | | 0.728 |
| Lab parameters | | | | |
| RDW | 13.3±0.89 | 13.2±0.80 | 13.4±0.92 | 0.113 |
| Hemoglobin | 13.1±1.21 | 13.1±1.1 | 12.9±1.3 | 0.537 |
| Hematocrit | 38.7±3.9 | 38.6±4.6 | 38.7±3.5 | 0.792 |
| MCV | 83.1±4.6 | 84.0±4.6 | 82.6±4.6 | 0.095 |
| tTG-IgA | 113.1±74.2 | 98.1±84.4 | 122.6±65.7 | 0.072 |
| Iron | 64±34.9 | 74.5±26.2 | 53.5±43.1 | 0.437 |
| Ferritin | 45±22.1 | 57.7±11.6 | 35.5±24.6 | 0.215 |
| TIBC | 336±65.6 | 330±94.9 | 343±29.9 | 0.799 |
| ALT | 25.3±16.6 | 23.5±7.2 | 26.4±20.2 | 0.389 |
| AST | 29.6±18.3 | 28.0±10.3 | 30.5±21.7 | 0.483 |
| Vitamin D 25-OH | 26.5±13.3 | 28.2±13.6 | 25.4±13.3 | 0.565 |
| Calcium | 9.4±0.75 | 9.4±0.49 | 9.4±0.89 | 0.816 |
| Phosphorus | 4.9±0.85 | 5.1±0.57 | 4.7±1.0 | 0.451 |
| Albumin | 4.2±0.47 | 4.3±0.36 | 4.2±0.52 | 0.420 |

CD, celiac disease; RDW, red cell distribution width; MCV, mean corpuscular volume; tTG-IgA, tissue transglutaminase immunoglobulin A; TIBC, total iron binding capacity; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

**Table 2** Analysis of RDW in association with villous atrophy

| RDW >12.9 | No atrophy, n=49 | Atrophy, n=79 | % difference | P value |
|---|---|---|---|---|
| Pre-GFD | 31 (63.3%) | 63 (79.7%) | 16.4% | 0.04 |
| Post-GFD | 18 (36.7%) | 47 (59.5%) | 22.8% | 0.02 |

RDW, red cell distribution width; GFD, gluten free diet.

as a marker of compliance in the pediatric population. Compliance in our study was determined by clinical history and further supported by decrease in tTG-IgA. It should be noted that none of our patients were on iron supplementation, as they all responded to GFD. In our study, the decrease in mean RDW value from diagnosis to follow-up GFD was not found to be statistically significant (P=0.585). Brusco *et al*. found that RDW was the most

prominent hematologic abnormality in an adult CD study of 126 patients (10). Our study of 128 patients, being unique to the pediatric population, did not show consistently abnormal values for RDW. Despite our findings there does appear to be an indirect association given the mean decrease noted. There have been multiple adult studies demonstrating an improvement in RDW after following a GFD (6,11,12). The argument may be made that lab values in the pediatric CD population may not reflect the same level of chronicity as comparatively longstanding disease in adults.

### *Atrophy*

The classic intestinal manifestation of CD seen on small intestinal biopsy is villous atrophy. In the pediatric CD population, atrophy becomes especially relevant due to the impact on nutrition and achievement of maximum growth potential. Our study showed that at diagnosis there was no statistical difference in the mean RDW with or without atrophy (P=0.113). However, further analysis determined that there was a statistically significant association among patients having a RDW >12.9 and presence of atrophy (P=0.04).

This potentially supports the utility of close monitoring of RDW as a predictive marker of atrophy and by extension CD in the appropriate clinical setting. RDW has been suggested to serve as an early sign of intestinal disease even prior to other hematologic parameters. This was noted in a 2002 prospective adult study where there was an increase noted in RDW value in patients with CD when compared to normal individuals, despite normal hemoglobin values (15). Furthermore, in a 2017 prospective pediatric study there were 19 patients defined as having potential or latent CD (positive CD screening but no mucosal atrophy) (16). Knowing that this cohort of patients were either demonstrating signs of CD prior to mucosal changes or would eventually develop mucosal changes, an iron panel was obtained. Among these patients, 0/19 (0%) had low iron, 4/19 (21%) had low ferritin, 3/19 (15%) had anemia. RDW was not mentioned in this study, but we suspect that a larger proportion of patients in this cohort had abnormal RDW. This is suggested by RDW being a more sensitive marker in patients with inflammatory conditions as previously stated. This is our hypothesis and would require further confirmation with additional studies.

It is plausible that early manifestations such as laboratory values in the appropriate clinical setting may lead to earlier CD screening, diagnosis, and treatment. In a climate of strong patient interest in empiric dietary modification, increased identification of latent CD, and high healthcare costs, the utility of routine low-cost testing may be effective in guiding further workup.

To our knowledge this is the first study in the pediatric population to investigate the utility of RDW specifically as a potential predictive marker of both compliance and intestinal atrophy in CD. The strengths of our study include the size of our patient population meeting inclusion criteria. This allowed for more direct comparison between previous adult studies with typically larger patient volumes.

Challenges faced with this study included limited documentation of other lab parameters of interest (i.e., B12, folate, vitamin D, Iron Panel) prior to diagnosis. This limited the ability to conduct more extensive analysis of these potentially relevant nutritional values. Additionally, future prospective studies would be needed to establish a more robust temporal relationship between RDW and atrophy.

In conclusion, RDW did not seem to be as sensitive as a marker for CD patients as compared to adult studies in either severity or compliance. This is an important finding, as the use of RDW is becoming more widespread due to its ease of use, economic feasibility, and significance in assessing a variety of pathologic conditions. Since this is the first pediatric study examining the relationship RDW and CD, more research is needed in this area. However, our data shows that there is disparity between adult studies and pediatric studies in the usefulness in RDW as a predictive marker for intestinal atrophy and compliance in patients with CD.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at https://pm.amegroups.com/article/view/10.21037/pm-21-24/rc

*Data Sharing Statement:* Available at https://pm.amegroups.com/article/view/10.21037/pm-21-24/dss

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*Conflicts of Interest:* All authors have completed the ICMJE

uniform disclosure form (available at https://pm.amegroups.com/article/view/10.21037/pm-21-24/coif). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Wayne State Institutional Review Board as well as Detroit Medical Center Institutional Review Board (IRB# 045118MP4E, protocol # 1804001374). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Individual consent for this retrospective analysis was waived.



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