# Micronutrient Deficiencies in Patients With Typical and Atypical Celiac Disease

*Jorge E. Botero-López, *Magdalena Araya, *Alejandra Parada, *Marco A. Méndez, *Fernando Pizarro, †Nelly Espinosa, ‡Paulina Canales, and §Teresa Alarcón

**ABSTRACT**

**Objective:** The extent of the digestive/absorptive involvement in atypical presentation of celiac disease (CD) is not always clear. The aim of the study was to assess nutritional status of iron (Fe), copper (Cu), and zinc (Zn) in patients with typical CD (TCD) and atypical CD (ACD).

**Patients and Methods:** A cross-sectional study was done in patients with TCD, ACD, and healthy controls (HC). Hemoglobin, serum ferritin, free erythrocyte protoporphyrin, Fe, Cu, ceruloplasmin, Zn, anti-endomysial antibodies, and anti-tissue transglutaminase antibodies were measured. Data were analyzed by Kruskal-Wallis, principal component analysis, and linear discriminant analysis.

**Results:** One hundred nine individuals were studied (54 TCD, 19 ACD, 36 HC); mean age ± standard deviation was 23 ± 15.8 (range 1.6–75.4) years. Median and range of hemoglobin were 12.8 g/dL (8.1–17.6) in TCD, 12.4 g/dL (10.5–14.5) in ACD, and 13.6 g/dL (11.1–16.7) in HC ($P < 0.0001$); serum ferritin was 17.7 μg/L (2.9–157), 10.8 μg/L (2.7–39.8), and 28.7 μg/L (4.5–127.2), respectively ($P < 0.01$). Cu was 105 μg/dL (60–185), 97.5 μg/dL (40–130), and 125 μg/dL (80–205), respectively ($P < 0.05$). Ceruloplasmin was 21.6 mg/dL (14.2–73.2), 22.6 mg/dL (0.9–34.3), and 32.1 mg/dL (5.8–72.6), respectively ($P < 0.01$). There were no differences in Fe, free erythrocyte protoporphyrin, and Zn. Principal component analysis showed that 58% of observed variability was explained by Fe and Cu indicators. Linear discriminant analysis revealed differences between CD and HC ($P < 0.0001$), with high values of correct classification for TCD (73%) and HC (72%), but not ACD (16%), which were mostly classified as TCD (79%).

**Conclusions:** Deficiency of micronutrients was found both in typical as well as in atypical cases.

**Key Words:** atypical celiac disease, copper, iron, typical celiac disease, zinc

(*JPGN* 2011;53: 265–270)

Celiac disease (CD) is an autoimmune condition induced by gluten in susceptible individuals, characterized by enteropathy that manifests different degrees of intestinal malabsorption (1–4). Known prevalence of the disease has increased greatly in recent years as a consequence of the massive use of anti-endomysial and anti-transglutaminase antibodies, which led to the recognition of atypical forms of the condition (5–7). Typical presentations consist mainly of apparent and often intense digestive symptoms (1,8,9); instead, digestive clinical manifestations in atypical presentations may be minimal or not apparent (1,3,8). In some cases, the presence of anemia or short stature suggests long-lasting nonapparent malabsorption syndrome, but this is not clear, especially when referred to subclinical malabsorption of nutrients other than proteins, lipids, and carbohydrates (10,11). Few reports refer to minerals; it has been reported that copper (Cu) deficiency may cause clinical neurological manifestations in chronic, poorly treated patients with CD (12,13); this situation was also reported in patients after many years of bariatric surgery, a condition in which nonapparent malabsorption of macro- and micronutrients is also possible (14).

In the present study, we aimed at assessing mineral status in patients with different forms of CD, setting 2 objectives: to measure the frequency of iron- (Fe), Cu-, and zinc- (Zn) deficient status and to assess to what extent the status of these minerals may be useful to differentiate typical from atypical forms of CD.

## PATIENTS AND METHODS

### Subjects and Design

The 200 patients diagnosed as having CD by the gastroenterology services of hospitals San Juan de Dios, Exequiel González Cortés, Pontificia Universidad Católica, and Militar of Santiago, Chile, between 1990 and 2008, formed the universe from which cases were obtained. Our present study was conducted between July 2008 and February 2009; 156 of 200 clinical charts were recovered; 55 did not answer the contact telephone number and 28 patients did not complete the study (did not return to consultation, received micronutrients supplement before or at the time of the study, other gastrointestinal pathologies with malabsorption or acute infectious illnesses were diagnosed). Thus, 73 patients were analyzed; they had positive immunoglobulin A (IgA) anti-endomysial antibodies (EMA) and/or anti-tissue transglutaminase (anti-tTG) antibodies, serum IgA concentration as expected for age, and duodenal biopsy exhibiting histological alterations compatible with CD at the time of diagnosis.

Data were obtained from clinical charts and a semistructured interview, during which we collected information about clinical and laboratory characteristics at the time of diagnosis, follow-up, and the present study. This included age at the beginning of symptoms, clinical symptoms and signs, age at diagnosis, current weight and height, results of EMA/tTG antibodies, intestinal histology at the time of diagnosis, and adherence to a gluten-free diet (GFD).

### Ethical Aspects

The protocol was approved by the Committee on Ethics for Human Research of the Institute of Nutrition and Food Technology,

Received October 5, 2009; accepted August 26, 2010.

From the *Institute of Nutrition and Food Technology INTA, University of Chile, the †Hospital Militar, the ‡Hospital Exequiel González Cortés, and the §Hospital San Juan de Dios, Chile.

Address correspondence and reprint requests Magdalena Araya, MD, PhD, Institute of Nutrition and Food Technology INTA, Macul 5540, Santiago 11, Chile (e-mail: maraya@inta.cl).

The study was partially funded by projects Fondecyt 1070595.

The authors report no conflicts of interest.



DOI: 10.1097/MPG.0b013e3181f988fc

University of Chile, and the institutional review board 1 only of the participating hospitals. Informed consent of patients and of parents or guardians in children younger than 12 years old was obtained before enrollment in the protocol.

## Anthropometric Indicators

The $z$ score of weight for height was calculated in children younger than 6 years old and percentile of body mass index for age in participants 6 to 18 years old; nutritional status was classified according to the National Center for Health Statistics/World Health Organization reference values (15). Nutritional status in individuals older than 18 years was defined by body mass index (16). Short stature in those younger than 18 years was defined by height for age $<-2$ standard deviations (SD), after correcting for sex (17).

## Procedures

A 6-mL venous blood sample collected from the antecubital arm between 8 and 9 AM was used to measure hematological, biochemical, serological, and mineral indicators. It is generally accepted that mineral indicators used in medical practice have some limitations; in the present study we used them as follows: hemoglobin (Hb), serum ferritin (SF), free erythrocyte protoporphyrin (FEP), and serum Fe concentration as indicators of Fe status; serum Cu and ceruloplasmin (Cp) concentration to assess Cu status; and Zn serum concentration as an indicator of Zn status. Hb was determined by an electronic counter (CELL-DYN 1700, Abbott Diagnostics, Abbott Park, IL); Cu, Fe, and Zn by atomic absorption spectrophotometry (Perkin Elmer, Model SIMAA 6100, Perkin-Elmer Corporation, Norwalk, CT); Cp by nephelometry (Array Protein System; Beckman Instruments, Brea, CA); SF by a sandwich enzyme immunoassay (18); FEP as Zn protoporphyrin (ZP Hematofluorometer Model 206D, AVIV Biomedical Inc, Lakewood, NJ); C-reactive protein (CRP) as an indicator of acute inflammation by a turbidimetric technique (Turbox, Orion Diagnostics, Espoo, Finland). Because chronic patients followed by our public health services may have poor adherence to treatment and follow-up, we also measured present status of CD by measuring IgA EMA by indirect immunofluorescence (IMMCO Diagnostics Inc, Buffalo, NY), and IgA anti-tTG by enzyme immunoassay (IMMCO Diagnostics).

## Operational Definitions

Forms of CD were defined by the symptoms present at diagnosis; typical CD (TCD) by the presence of diarrhea, abdominal distension, and weight loss and/or poor growth as symptoms leading to diagnosis; and atypical celiac disease (ACD) by anemia and/or short stature ($<-2$ SD height for age) of unknown cause, in the absence of the symptoms defined in the first group. Controls were apparently healthy individuals with no history suggestive of CD (including constipation, abdominal pain, and anemia); negative EMA and anti-tTG tests; and normal total serum IgA, matched by sex. Present status of the disease was defined by negative (in remission) and positive (active) serological studies.

Deficient Cu nutritional status was defined operationally by serum Cu concentration $<70$ μg/dL in men, $<70$ μg/dL in girls younger than 12 years of age, and $<80$ μg/dL in women older than 12 years and/or Cp $<17$ mg/dL (19). Deficient Fe nutritional status was defined by Hb concentration below cutoff ($<11$ g/dL in children younger than 5 years, $<11.5$ g/dL in children 5 to 12 years, $<13$ g/dL in men, and $<12$ g/dL in women older than 12 years) (20); FEP cutoff was $>70$ μg/dL red blood cells (21); for serum Fe this was $<70$ μg/dL in children younger than 12 years, $<70$ μg/dL in men, and $<60$ μg/dL in women older than 12 years; and/or SF $<12$ μg/L (18). Deficiency of Zn was defined by serum Zn concentration $<74$ μg/L in men and $<70$ μg/L in women (22). CRP cutoff was defined following the manufacturer's instructions ($>10$ mg/L).

## Sample Size and Statistical Analysis

Sample size to detect 1 SD difference between 2 celiac and 1 control groups (23), with an alpha value of 0.05 and power of 0.8, was 15 subjects per group. A total of 73 patients with CD participated in the study, divided into group TCD (n = 54), group ACD (n = 19), and healthy control (HC) group (n = 36).

First data analysis was carried out by Shapiro-Wilk test, which showed asymmetric distribution of most variables assessed. Groups were compared for clinical presentation (TCD, ACD, and HC) and serological status (positive and negative) using $\chi^2$ test for categorical variables and Kruskal-Wallis test for continuous variables. Principal component analysis (PCA) was chosen for multivariate analysis because Fe, Cu, and Zn have several interactions in their metabolism, and this analysis allows the simultaneous assessment of all the variables, giving a weight (loading) to each of them, independent of their interactions. Linear discriminant analysis (LDA) was used to assess the relation between the classification groups and the micronutrients indicators as a whole, and the jackknife procedure as a resample technique to obtain a classification matrix, which allowed determination of the individuals correctly classified in the groups originally defined.

Differences were considered significant at $P < 0.05$. Data are presented as median and range for continuous variables and as frequency and percentage in categorical variables. Statistical analysis was performed using SYSTAT 11.0 software (SYSTAT, Inc, Evanston, IL).

# RESULTS

Age in the 109 individuals studied (54 TCD, 19 ACD, 36 HC) ranged between 1.6 and 75.4 years (mean $23 \pm 15.8$ years). Distribution by age and sex was not different in the 3 studied groups (Table 1); 26% of cases were younger than 12 years; nutritional status was not related to clinical presentations, low weight was not found in the ACD group and was present in 13% of TCD and 5% of HC ($P = 0.16$); 26% of TCD, 42% of ACD, and 36% of HC were overweight/obese ($P = 0.35$). As expected, in cases with CD younger than 18 years short stature was more frequent than in controls (16% in TCD, 50% in ACD, and 5% in HC; $P = 0.016$). Of all of the patients, 69.9% declared that they adhered to a gluten-free diet, but 53.4% had positive EMA and/or anti-tTG. Comparing symptoms reported at the time of diagnosis and those declared on present evaluations, 3 and 2 cases of ACD had developed abdominal pain and constipation, respectively, and 38.4% reported at least 1 symptom (Table 2).

Analyzing the total group of patients with CD, indicators revealed deficient Fe nutritional status in 65.8% (32.9% low Hb, 43.8% low FS, 4.4% low serum Fe, and 45.8% increased FEP); Zn status (as measured by serum Zn concentration) was deficient in 20% and Cu status in 15% (6.8% low serum Cu and 10.9% low serum Cp). No significant differences were found among individuals with micronutrient deficiencies by age and/or sex, except for Cp deficiency, which was more frequent in boys older than 12 years (men 33.3% vs women 7.7%, $P = 0.02$) and for Hb, which was more frequent in women older than 12 years (men 13.3% vs women 41%, $P = 0.045$). Analyses both by clinical presentation and by serological status showed that deficient Fe nutritional status (low Hb and low SF) was significantly more frequent in patients

TABLE 1. Sex and age distribution by clinical presentation

| | TCD (n = 54) | | ACD (n = 19) | | HC (n = 36) | | Total (n = 109) | |
|---|---|---|---|---|---|---|---|---|
| Sex | M | W | M | W | M | W | M | W |
| n* | 16 | 38 | 6 | 13 | 10 | 26 | 32 | 77 |
| Age, y** | 22 ± 20.6 (2.1–75.4) | 26.4 ± 17.2 (1.9–65.7) | 26.8 ± 17.2 (8.6–50.9) | 24.1 ± 16 (1.6–51.2) | 15.5 ± 8.4 (4–28.1) | 20.1 ± 11.2 (1.8–40) | 21.2 ± 17.2 (2.1–75–4) | 23.8 ± 15.5 (1.6–65.7) |

Values expressed as mean ± 1 SD (range). ACD = atypical celiac disease; HC = healthy controls; TCD = typical celiac disease. *$\chi^2$ test $P = 0.96$. **Kruskal-Wallis test, $P = 0.31$.

with CD (and patients with active CD) as compared with controls, but differences were not significant when comparison was between typical and atypical forms of the disease (Table 3, panel A). The same result was obtained when median serum concentrations of Hb, SF, and Cu indicators were compared (Table 3, panel B). When cases with CRP >10 mg/L were excluded, serum Cp concentrations also became significant, with a median of 21.6 mg/dL (14.2–73.2 mg/dL) in TCD, 22.6 mg/dL (0.9–34.3 mg/dL) in ACD, and 32.1 mg/dL (5.8–72.6 mg/dL) in HC ($P = 0.02$); in the latter analysis, differences in Hb, SF, and serum Cu remained significant.

Multivariate analysis included all of the indicators measured in the 3 groups assessed. PCA showed that 6 components explained 100% of the observed variability; the first component (highest loading value that explains the observed results) was formed by indicators of Fe nutritional status (Hb, SF, and Fe) and the second component (second highest loading value) by indicators of copper status (Cu and Cp), both explaining 58% of the variance. Using the matrix obtained with the 6 PCA components and defining clinical presentations as the classification variable, LDA revealed significant differences among the 3 study groups (TCD, ACD, and HC groups) (Wilks' lambda = 0.6424; $F = 3.9211$; $df = 12–190$; $P < 0.0001$). Discriminant classification matrix by jackknife procedure yielded high values of correct classifications for TCD (73%) and HC (72%) but not for ACD (16%), which were mostly classified as TCD (79%). LDA was repeated using serological status as the classification variable, showing similar significant differences among groups with positive (active CD) and negative antibodies and HC group (Wilks' lambda = 0.6136; $F = 4.3796$ $df = 12–190$; $P < 0.0001$). The classification matrix by jackknife procedure in this second analysis showed that correct classification was 62% for positive serology, 53% for negative serology, and 75% for HC (Table 4).

TABLE 2. Frequency of symptoms at the time of current assessment in patients grouped by their initial clinical presentation

| Symptoms | TCD (n = 54) n (%) | ACD (n = 19) n (%) |
|---|---|---|
| Abdominal pain | 15 (27.8) | 3 (15.8) |
| Abdominal distension | 11 (20.4) | — |
| Diarrhea | 10 (18.5) | — |
| Weight loss | 7 (13) | — |
| Constipation | 4 (7.4) | 2 (10.5) |
| Vomiting | 4 (7.4) | — |
| Dental enamel defects | 3 (5.6) | — |
| Dermatitis herpetiformis | — | 2 (10.5) |
| Edema | 1 (1.9) | — |
| Asymptomatic | 31 (57.4) | 14 (73.7) |
| Short stature (in younger than 18 y) | 4/25 (16) | 4/8 (50) |

ACD = atypical celiac disease; TCD = typical celiac disease.

## DISCUSSION

Results show that classical indicators of micronutrient status differentiate cases with CD from controls, but not patients with TCD from patients with atypical clinical presentations. Our findings show that micronutrient deficiencies are detectable in both clinical presentations, a clinically relevant result that indicates that patients with atypical presentations should receive the same supplementation management as patients with typical symptoms and that intestinal malabsorption should be sought actively and systematically in them.

Overweight and obesity have been reported in patients with CD by some authors in recent years (5,24–27). That this diagnosis is reached earlier probably explains the low frequency of malnutrition/low weight. In the present study, the frequency of overweight/obesity in all of the groups is in the range described in the local general population (28). It is interesting that in patients with obesity, clinical manifestations were diverse, with presentations both typical and atypical. Other authors have reported similar findings, describing symptoms leading to diagnosis such as gastrointestinal symptoms, anemia, vitamin $B_{12}$ deficiency, or diagnosis derived from active screening because the patient had a positive case in the family (24,25,27). Dickey and Kearney (26) assessed 371 patients with CD and found low weight in 5% of them and 39% with overweight/obesity. In our study, 9.6% of patients had low weight, 70% of these did not comply with the diet. Atypical presentations predominated among overweight/obese patients, but there was no statistical difference among the 3 groups (data not shown). It was unexpected that the frequency of mineral deficiencies was not different among patients with low weight ($\chi^2$, $P > 0.5$, data not shown).

It is interesting that analysis by clinical presentation (typical/atypical) and by serology (positive EMA/tTG found in 53.4% of study cases) yielded similar results; although the number of individuals when doing the latter analysis is smaller, these findings suggest that mineral deficiencies are present both in active and treated cases of TCD and ACD. This interpretation is supported by the multivariate analysis.

Assessments of minerals in patients with CD are few and refer mainly to individuals with classic presentations (29–31). In the present study, the frequency of individuals with deficient Hb and SF values was significantly higher in both celiac groups when compared with controls (Table 3, panel A) and the differences remained significant when comparisons were made by the groups' medians (Table 3, panel B). Fe deficiency being frequent, it is

TABLE 3. Micronutrient status by clinical presentation and by serological status expressed as frequency of cases with deficiency (panel A) and median serum concentration per group (panel B)

| | | Clinical presentation | | | Serological status | | |
|---|---|---|---|---|---|---|---|
| Panel A | HC (n = 36) | TCD (n = 54) | ACD (n = 19) | $P^{*}$ | Positive (n = 39) | Negative (n = 34) | $P^{*we}$ |
| Hb | 2.8 | 31.5 | 36.8 | 0.002 | 46.2 | 17.6 | <0.0001 |
| SF | 22.2 | 40.7 | 52.6 | 0.05 | 51.3 | 35.3 | 0.02 |
| Fe | — | 6.0 | — | — | 5.3 | 3.2 | 0.39 |
| FEP | 27.8 | 50 | 36.8 | 0.14 | 50 | 41.9 | 0.18 |
| Cu | — | 6.1 | 10.5 | — | 5.4 | 9.7 | 0.18 |
| Cp | 11.1 | 7.4 | 21.1 | 0.26 | 12.8 | 8.8 | 0.86 |
| Zn | 13.9 | 19.6 | 21.1 | 0.73 | 23.7 | 15.6 | 0.5 |
| Panel B | | | | $P^{**}$ | | | $P^{**}$ |
| Hb, g/dL | 13.6 (11.1–16.7) | 12.8 (8.1–17–6) | 12.4 (10.5–14.5) | 0.0001 | 12.2 (8.1–17.6) | 12.9 (10.5–14.6) | 0.0001 |
| SF, μg/L | 28.7 (4.5–127.2) | 17.7 (2.9–157) | 10.8 (2.7-39-8) | 0.007 | 11 (2.7–157) | 21 (2.9–68.6) | 0.0011 |
| Fe, μg/dL | 145 (80–290) | 150 (35–280) | 150 (75–245) | 0.79 | 132.5 (35–280) | 175 (55–255) | 0.01 |
| FEP, μg/dL RBC | 62.8 (31.4–103) | 68.5 (42.8–237) | 68.6 (45.7-108-7) | 0.065 | 71.5 (42.8–237) | 62.9 (45.2–97) | 0.049 |
| Cu, μg/dL | 122.5 (80–205) | 105 (60–185) | 105 (40–190) | 0.009 | 105 (40–185) | 105 (60–190) | 0.009 |
| Cp, mg/dL | 32.4 (5.8–72.6) | 31.6 (11–73.2) | 31.6 (0.9–57.6) | 0.38 | 30.6 (6.7–68.7) | 31.6 (0.9–73.2) | 0.95 |
| Zn, μg/dL | 90 (60–125) | 85 (55–145) | 80 (65–135) | 0.13 | 80 (55–145) | 85 (55–130) | 0.18 |

ACD = atypical celiac disease; Cp = ceruloplasmin; Cu = copper; Fe = iron; FEP = free erythrocyte protoporphyrin; Hb = hemoglobin; HC = healthy control; RBC = red blood cell; SF = serum ferritin; TCD = typical celiac disease; Zn = zinc.

Panel A: Values expressed in percentages. $^{*}\chi^2$ test. For cutoff values, see text.

Panel B: Values expressed in median and range. $^{**}$Kruskal-Wallis test.

TABLE 4. Jackknife classification matrix using clinical presentation and serological status as classification variables (in rows cases as originally classified)

| | Clinical presentation | | | |
|---|---|---|---|---|
| | TCD | ACD | HC | %* |
| TCD (n = 48) | 35 | 1 | 12 | 73 |
| ACD (n = 19) | 15 | 3 | 1 | 16 |
| HC (n = 36) | 10 | 0 | 26 | 72 |
| Total (n = 103) | 60 | 4 | 39 | 62 |
| | Serological status | | | |
| | Positive | Negative | HC | %* |
| Positive (n = 37) | 23 | 6 | 8 | 62 |
| Negative (n = 30) | 10 | 16 | 4 | 53 |
| HC (n = 36) | 6 | 3 | 27 | 75 |
| Total (n = 103) | 39 | 25 | 39 | 64 |

ACD = atypical celiac disease; HC = healthy controls; TCD = typical celiac disease.
* Percentage of concordance between original classification and discriminant classification.

relevant to mention that the figures of low Hb and ferritin detected in our controls are similar to those published in apparently healthy local population of the same age and sex (32–35). Bergamaschi et al (36) assessed anemia prevalence in 132 patients with CD (whose clinical presentation was not mentioned in the article) and found low Hb in 34%, with higher prevalence in women (21% in men vs 41% in women, $P = 0.021$). We found a similar frequency in 32.9% of the assessed patients with CD, which is 12 times more frequent than in controls; in the present study, there were significant differences by sex in patients older than 12 years (13.3% in men vs 41% in women, $P = 0.045$). Anemia can result from intestinal malabsorption of several micronutrients necessary for normal hematopoiesis (37), including Cu (11). Cu deficiency has been described in patients with TCD (15,29) and it is a known cause of anemia and thrombocytopenia (11,13). To what extent anemia was the result of malabsorption or inflammation in our patients cannot be clarified in the present study. Of the patients with CD, 6.8% had low serum Cu, independent of their clinical presentation, whereas all of the controls had normal values. Cu deficiency was independent of Hb and SF, a finding that is difficult to explain considering that Fe and Cu share transporters and a number of proteins in their metabolism and that Cu is needed for the formation of Hb molecules (38,39); the low number of cases with Cu deficiency may explain at least part of this result. Chronic Cu deficiency without anemia is relevant because, being asymptomatic, it may remain undiagnosed and patients may develop neurological symptoms in the long term; this can be treated, but there is evidence that at least part of the damage is not reversible (12,14,40). Zn status measured as serum Zn concentration revealed that cases had a higher frequency of deficient values than controls, but the differences did not reach statistical significance; significant differences in serum Zn concentration by serological status also were not found, a finding that is consistent with data recently published by Högberg et al (41).

One of the exclusion criteria in the present study was that participants should be free of known acute and chronic clinical infectious and inflammatory conditions; therefore, we expected that the values of serum Cu, Cp, and ferritin would reflect Cu and Fe status; however, in 23.3% of all of the patients CRP was above the cutoff (18.5% and 36.8% of TCD and ACD, respectively); we interpret this as a consequence of the inflammatory status present in some patients with CD. This idea was supported by the significantly higher frequency of CRP above the cutoff among patients with positive serology ($\chi^2$, $P < 0.05$, data not shown).

A relevant contribution of the present study derives from the multivariate analysis, which showed significant differences among groups compared by both clinical presentation and serological results; LDA differentiated between patients with CD and controls, but not between typical and atypical patients, confirming the results found by univariate analysis. On the contrary, the same analyses using serological status as the classification variable differentiated between patients with positive serology, patients with negative serology, and controls ($P < 0.0001$); yet, using serological status as the classification variable, the jackknife procedure yielded lower values than by clinical presentation. We do not have an explanation for the low number of patients who having negative serology were classified as HCs (4/30 cases).

In summary, the results show that mineral deficiency is present in both typical and atypical forms of CD, active search of mineral deficiency should be conducted in all of the cases, and the patients with atypical forms of CD should receive mineral supplements as part of their treatment, just as patients with typical presentations do.

## REFERENCES

1. Fasano A. Clinical presentation of celiac disease in the pediatric population. *Gastroenterology* 2005;128:S68–73.
2. Kagnoff MF. Overview and pathogenesis of celiac disease. *Gastroenterology* 2005;128:S10–8.
3. Mearin ML. Celiac disease among children and adolescents. *Curr Probl Pediatr Adolesc Health Care* 2007;37:86–105.
4. Green P, Cellier C. Celiac disease. *N Engl J Med* 2007;357:1731–43.
5. Telega G, Bennet TR, Werlin S. Emerging new clinical patterns in the presentation of celiac disease. *Arch Pediatr Adolesc Med* 2008; 162:164–8.
6. Abu-Zekry M, Kryszak D, Diab M, et al. Prevalence of celiac disease in Egyptian children disputes the east-west agriculture-dependent spread of the disease. *J Pediatr Gastroenterol Nutr* 2008;47:136–40.
7. Catassi C, Fasano A. Celiac disease. *Curr Opin Gastroenterol* 2008; 24:687–91.
8. Fasano A, Catassi C. Coeliac disease in children. *Best Pract Res Clin Gastroenterol* 2005;19:467–78.
9. Dewar DH, Ciclitira PJ. Clinical features and diagnosis of celiac disease. *Gastroenterology* 2005;128:S19–24.

10. Puri AS, Garg S, Monga R, et al. Spectrum of atypical celiac disease in north indian children. *Indian Pediatr* 2004;41:822–7.
11. Halfdanarson TR, Litzow MR, Murray JA. Hematologic manifestations of celiac disease. *Blood* 2007;109:412–21.
12. Henri-Bhargava A, Melmed C, Glikstein R, et al. Neurologic impairment due to vitamin E and copper deficiencies in celiac disease. *Neurology* 2008;71:860–1.
13. Halfdanarson TR, Kumar N, Hogan WJ, et al. Copper deficiency in celiac disease. *J Clin Gastroenterol* 2009;43:162–4.
14. Griffith DP, Liff DA, Ziegler TR, et al. Acquired copper deficiency: a potentially serious and preventable complication following gastric bypass surgery. *Obesity* 2009;17:827–31.
15. World Health Organization. *The World Health Organization Child Growth Standards. http://www.who.int/childgrowth/en/.* Published 2006. Accessed April 15, 2008.
16. World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO consultation on obesity. WHO/NUT/NCD/98.1.1998. Geneva: World Health Organization; 1998.
17. American Association of Clinical Endocrinologists. Medical guidelines for clinical practice for growth hormone use in adults and children. *Endocr Pract* 2003;9:64–76.
18. International Anemia Consultative Group. *Measurement of Iron Status*. Washington DC: The Nutrition Foundation; 1985.
19. Elin RJ. Reference intervals and laboratory values. In: Goldman L, Ausiello DA, eds. *Cecil Textbook of Medicine.* 22th ed. Philadelphia: WB Saunders; 2004:2496–505.
20. World Health Organization. Iron deficiency anaemia: assessment, prevention, and control. A guide for programme managers. WHO/NHD/01.3.2001. Geneva: World Health Organization; 2001.
21. Gleason G, Scrimshaw N. An overview of the functional significance of iron deficiency. In: Kraemer K, Zimmermann MB, eds. *Nutritional Anemia.* Basel, Switzerland: Sight and Life Press; 2007: 45–57.
22. International Zinc Nutrition Consultative Group. Assessment of the risk of zinc deficiency in populations and options for its control. *Food Nutr Bull* 2004;25:S91–204.
23. Rodriguez A, Soto G, Torres S, et al. Zinc and copper in hair and plasma of children with chronic diarrhea. *Acta Pediatr Scand* 1985;74:770–4.
24. Furse RM, Mee AS. Atypical presentation of coeliac disease. *BMJ* 2005;330:773–4.
25. Oso O, Fraser NC. A boy with coeliac disease and obesity. *Acta Paediatr* 2006;95:618–9.
26. Dickey W, Kearney N. Overweight in celiac disease: prevalence, clinical characteristics, and effect of a gluten-free diet. *Am J Gastroenterol* 2006;101:2356–9.
27. Arslan N, Esen I, Demircioglu F, et al. The changing face of celiac disease: a girl with obesity and celiac disease. *J Paediatr Child Health* 2009;45:317–8.
28. Ministerio de Salud de Chile PUC. Encuesta Nacional de Salud Chile 2003. Santiago, Chile: Ministerio de Salud; 2003.
29. Goyens P, Brasseur D, Cadranel S. Copper deficiency in infants with active celiac disease. *J Pediatr Gastroenterol Nutr* 1985; 4:677–80.
30. Kemppainen T, Kröger H, Janatuinen E, et al. Bone recovery after a gluten-free diet: a 5-year follow-up study. *Bone* 1999;25:355–60.
31. Ince AT, Kayadibi H, Soylu A, et al. Serum copper, ceruloplasmin and 24 h urine copper evaluations in celiac patients. *Dig Dis Sci* 2008;53:1564–72.
32. Hertrampf E, Olivares M, Pizarro F, et al. Impact of iron fortified milk in infants: evaluation of effectiveness [abstract]. *Ann Nutr Metab* 2001;45 (suppl):117.
33. Olivares M, Hertrampf E, Pizarro F, et al. Hemoglobin fortified biscuits: bioavailability and its effect on iron nutriture in school-children. *Arch Latinoamer Nutr* 1990;40:209–20.
34. Grebe G, Lira P, Legues ME, et al. Estudio de las reservas de hierro en una población de adultos sanos en Chile. *Rev Med Chile* 1984; 112:884–92.
35. Olivares M, Hertrampf E, Capurro MT, et al. Prevalence of anemia in elderly subjects living at home: role of micronutrient deficiency and inflammation. *Eur J Clin Nutr* 2000;54:834–9.
36. Bergamaschi G, Markopoulos K, Albertini R, et al. Anemia of chronic disease and defective erythropoietin production in patients with celiac disease. *Haematologica* 2008;93:1785–91.
37. Hershko C, Patz J. Ironing out the mechanism of anemia in celiac disease. *Haematologica* 2008;93:1761–5.
38. Manoharan PT, Alston K, Rifkind JM. Interaction of copper (II) with hemoglobins in the unliganded conformation. *Biochemistry* 1989;28:7148–53.
39. Bonomo RP, De Flora A, Rizzarelli E, et al. Copper (II) complexes encapsulated in human red blood cells. *J Inorg Biochem* 1995; 59:773–84.
40. Bilic E, Bilic E, Sepec BI, et al. Stiff-person syndrome in a female patient with type 1 diabetes, dermatitis herpetiformis, celiac disease, microcytic anemia and copper deficiency: just a coincidence or an additional shared pathophysiological mechanism? *Clin Neurol Neurosurg* 2009;111:644–5.
41. Högberg L, Danielsson L, Jarleman S, et al. Serum zinc in small children with coeliac disease. *Acta Paediatr* 2009;98:343–5.