Utilizing HDL Levels to Improve Detection of Celiac Disease in Patients With Iron Deficiency Anemia

Hussein Abu Daya, MD[1,2], Benjamin Lebwohl, MD, MS[2], Scott Smukalla, MD[2], Suzanne K. Lewis, MD[2] and Peter H. Green, MD[2]

doi:10.1038/ajg.2014.30

To the Editor: The majority of patients with celiac disease (CD) in the United States are not diagnosed (1). Although current guidelines (2,3) recommend testing patients with iron deficiency anemia (IDA) for CD, this is infrequently performed (4).

As hypocholesterolemia and low high-density lipoprotein (HDL) levels are common in CD (5,6), we studied the value of using HDL levels to identify a high-risk group of IDA patients who may benefit from CD testing.

This cross-sectional study compared CD patients who presented with IDA with patients who presented with IDA due to non-CD causes at our medical center between 2000 and 2011. CD patients were identified from an IRB-approved database of 1,450 CD subjects, and were included in the study if they presented with IDA and had a lipid profile taken at the time of diagnosis. Each CD patient was matched by age and gender with up to three IDA controls selected from a separate IDA database. IDA was defined as a hemoglobin level < 12 g/dl for women and < 13 for men with serum ferritin < 30 ng/ml.

The two groups were compared by univariate analysis using the Student's *t*-test for continuous variables and the χ^2 analysis or Fisher's exact test for categorical data as appropriate. Sensitivity, specicity, positive predictive value, and likelihood ratios were calculated for various HDL cutoff levels. A receiver operating characteristic curve analysis of HDL was performed to identify the optimal cutoff value predicting CD. Multivariable logistic regression analysis was conducted to assess for an association between the different HDL cutoff values. The sample size provided >90% power with an α level of 0.05. All statistical testing was performed using SPSS (version 18; IBM, New York, NY).

In all, 57 CD patients presenting with IDA were matched to 163 IDA controls. Controls had a significantly higher mean body mass index (BMI) compared with patients with CD (**Table 1**). Hematological parameters were similar in both groups. CD patients had lower B12, folate, total cholesterol, and HDL levels.

We compared the two groups according to four HDL cutoff values (**Table 1**). Of the CD patients, 48% had an HDL level ≤40 mg/dl compared with 24% of controls ($P = 0.001$), and 16% of CD patients had HDL levels ≤25 mg/dl, whereas none of the controls had such a level ($P < 0.0001$).

After adjusting for BMI and the use of lipid-lowering medications, individuals with HDL levels ≤40 mg/dl were more than five times as likely to have CD as those with levels >40 mg/dl (**Table 2**). Those with HDL levels ≤30 mg/dl were eight times as likely to have CD, and the cutoff point was highly predictive of having CD with a posi-

Table 1. Characteristics of the iron deficiency anemia patients with and without celiac disease

	Celiac[a] (57)	Non-celiac[a] (163)	*P* value
Age at diagnoses (years)	45±14	45±13	NS
Female gender	40 (70%)	118 (72%)	NS
Use of lipid-lowering agents[b]	3/48 (6%)	14/120 (12%)	NS
BMI (kg/m^2)	23±4	29±7	<0.0001
Hb (g/dl)	10.5±1.8	10.1±1.7	NS
Hct (%)	33±5	33±4	NS
MCV (fl/cell)	77±9	78±9	NS
Iron (μg/dl)	35±27	32±23	NS
Ferritin (ng/ml)	10±7	12±6	0.04
TIBC (ig/dl)	414±69	402±61	NS
RDW	18±3	17±3	NS
Vitamin B12 (pg/ml)	456±212	545±260	NS
Folate (ng/ml)	12±7	15±4	0.02
ESR (mm/h)	22±19	14±12	0.04
Total cholesterol (mg/dl)	160±30	171±37	0.04
LDL (mg/dl)	97±21	98±32	NS
HDL (mg/dl)	41±14	52±15	<0.0001
TG (mg/dl)	108±69	107±64	NS
HDL ≤25 (mg/dl)	16%	0%	<0.0001
HDL ≤30 (mg/dl)	22%	4%	<0.0001
HDL ≤35 (mg/dl)	30%	13%	0.005
HDL ≤40 (mg/dl)	48%	24%	0.001

BMI, body mass index; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; Hct, hematocrit; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MCV, mean corpuscular volume; NS, nonsignificant; RDW, red blood cell distribution width; TIBC, total iron body capacity; TG, triglycerides.

[a]Celiac: celiac disease patients presenting with iron deficiency anemia; non-celiac: iron deficiency anemia patients due to causes other than celiac disease.

[b]Lipid-lowering medications included statins, fibrates, and niacin.

Table 2. Multivariable logistic regression analysis, sensitivity, specificity, PPV, and positive likelihood ratio of different HDL cutoff values predicting the presence of celiac disease

HDL cutoff value	Adjusted[a] OR	ROC curve analysis for CD prediction	Sensitivity (%)	Specificity (%)	PPV (%)	LR (+)
≤25 mg/dl	NC[b]	AUC=0.9, CI (0.84–0.95) $P<0.0001$	16	100	100	+
≤30 mg/dl	OR=8, CI (2–32) $P=0.004$	AUC=0.7, CI (0.57–0.84) $P=0.004$	22	96	61	6
≤35 mg/dl	OR=4, CI (1–11) $P=0.01$	AUC=0.61, CI (0.5–0.72) $P=0.04$	30	87	42	3
≤40 mg/dl	OR=5, CI (2–12) $P=0.001$	AUC=0.61, CI (0.5–0.7) $P=0.01$	48	77	39	2

AUC, area under the curve; CD, celiac disease; CI, confidence interval; LR, likelihood ratio; NC, not calculated; OR, odds ratio; PPV, positive predictive value; ROC, receiver operating characteristic.

[a]Adjusted for body mass index and the use of lipid-lowering medication.

[b]Since none of the patients in the non-celiac group had HDL ≤25 mg/dl and the specificity was 100%, the multiple logistic regression analysis for this HDL cutoff value could not be calculated.

tive predictive value of 61% and a positive likelihood ratio of 6.

Our study shows that IDA patients with CD have significantly lower HDL levels compared with IDA patients without CD, and that this finding could be used to improve identification of CD. Screening for CD should at least be done for IDA patients who present with HDL levels ≤40 mg/dl with an expectation that those with levels ≤30 mg/dl would have a greatly increased likelihood of CD positivity.

It is notable that total plasma cholesterol levels (TC) were significantly lower in IDA patients with CD than in IDA patients without CD. This is in accordance with previous observations correlating low TC levels with the presence of CD in hypochromic anemia patients, suggesting that it could be used to select anemic patients for CD screening (6). However, after adjusting for age, gender, BMI, and the use of lipid-lowering medications in our study, TC levels, unlike HDL levels, were not significantly associated with the presence of CD in IDA patients.

The limitations to this study include its single-center setting at a tertiary referral center and lack of a validation cohort. The strengths include the use of biopsy-proven CD patients, a sample size providing >90% power, and that the values reported are those at diagnosis. Future studies should prospectively test this approach of case-finding patients with IDA at high risk for CD.

CONFLICT OF INTEREST

Guarantor of the article: Peter H. Green, MD.

Specific author contributions: Hussein Abu Daya: concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis, final approval of the version to be published; Benjamin Lebwohl, Peter H. Green: concept and design, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, final approval of the version to be published; Scott Smukalla: acquisition of data, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, final approval of the version to be published; Suzanne K. Lewis: analysis and interpretation of data, critical revision of the manuscript for important intellectual content, final approval of the version to be published.

Financial support: None.

Potential competing interests: None.

REFERENCES

1. Rubio-Tapia A, Ludvigsson JF, Brantner TL *et al.* The prevalence of celiac disease in the United States. Am J Gastroenterol 2012;107:1538–44; quiz 1537, 1545.
2. Rubio-Tapia A, Hill ID, Kelly CP *et al.* ACG clinical guidelines: diagnosis and management of celiac disease. Am J Gastroenterol 2013;108:656–76.
3. Goddard AF, James MW, McIntyre AS *et al.* Guidelines for the management of iron deficiency anaemia. Gut 2011;60:1309–16.
4. Smukalla SM, Lebwohl B, Mears JG *et al.* How often do hematologists screen for celiac disease? Clin Adv Hematol Oncol 2014;12:100–5.
5. Abu Daya H, Lebwohl B, Lewis SK *et al.* Celiac disease patients presenting with anemia have more severe disease than those presenting with diarrhea. Clin Gastroeneterol Hepatol 2013;11:1472–7.
6. Ciacci C, Cirillo M, Giorgetti G *et al.* Low plasma cholesterol: a correlate of nondiagnosed celiac disease in adults with hypochromic anemia. Am J Gastroenterol 1999;94:1888–91.

[1]Department of Internal Medicine, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA; [2]Celiac Disease Center, Department of Internal Medicine, Columbia University College of Physicians and Surgeons, New York, New York, USA. Correspondence: Peter H. Green, MD, Celiac Disease Center, Department of Internal Medicine, Columbia University College of Physicians and Surgeons, New York, New York 10032, USA.
E-mail: pg11@columbia.edu

Part of this research was submitted to the AGA meeting (DDW) in Orlando 2013.

Genome-Wide Association Study Identifies Two Novel Genomic Regions in Irritable Bowel Syndrome

Elizabeth G. Holliday, PhD, MSc[1], John Attia, MD, PhD[1], Stephen Hancock, MSc[1], Natasha Koloski, PhD[1], Mark McEvoy, PhD[1], Roseanne Peel, MPH[1], Mauro D'Amato, PhD[2], Lars Agréus, MD, PhD[3], Henry Nyhlin, MD, PhD[4], Anna Andreasson, PhD[3,5], Ann E. Almazar, MPH[6], Yuri A. Saito, MD, MPH[6], Rodney J. Scott, PhD[1] and Nicholas J. Talley, MD, PhD[1]

doi:10.1038/ajg.2014.56

To the Editor: Irritable bowel syndrome (IBS) is a common, poorly understood gastrointestinal disorder. Although family