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Patients With Celiac Disease Have a Lower Prevalence of Non–Insulin-Dependent Diabetes Mellitus and Metabolic Syndrome

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See related article, Wakim–Fleming J et al, on page 511 in *CGH*.

BACKGROUND & AIMS: We investigated whether risk for non–insulin-dependent diabetes mellitus (NIDDM) and metabolic syndrome are affected by celiac disease. We examined the prevalence of NIDDM and metabolic syndrome among adults with celiac disease, compared with matched controls. **METHODS:** We assessed medical records of 840 patients with biopsy-proven celiac disease for diagnoses of NIDDM, hypertension, or hyperlipidemia; body mass index (BMI); lipid profile; and levels of glucose or glycosylated hemoglobin, to identify those with metabolic syndrome. Patients without celiac disease were matched for age, sex, and ethnicity (n = 840 controls). The prevalence of NIDDM and metabolic syndrome in the celiac disease cohort was compared with that of the controls and subjects included in the National Health and Nutrition Examination Survey. **RESULTS:** Twenty-six patients with celiac disease (3.1%) had NIDDM compared with 81 controls (9.6%) ($P < .0001$). Similarly, the prevalence of metabolic syndrome was significantly lower among patients with celiac disease than controls (3.5% vs 12.7%; $P < .0001$). The mean BMI of patients with celiac disease was significantly lower than that of controls (24.7 vs 27.5; $P < .0001$). However, celiac disease was still associated with a lower risk of NIDDM, after controlling for BMI. **CONCLUSIONS: The prevalence of NIDDM and metabolic syndrome are lower among patients with celiac disease than in matched controls and the general population. These differences are not explained by differences in BMI. Studies are needed to determine the mechanisms by which celiac disease affects the risk for NIDDM and metabolic syndrome.**

Keywords: NHANES; Gluten Sensitivity; Type 2 Diabetes; Obesity.

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The association between celiac disease (CD) and the risk of insulin-dependent diabetes mellitus (IDDM) was established more than 30 years ago.[1] The reported prevalence of CD in IDDM patients ranges from 1.8% to 8.4%[1–4] compared with approximately 1% in the general population.[5,6] Consequently, screening for CD in IDDM patients is a common practice given the potential benefits of the gluten-free diet.[7] Despite multiple studies on the association between CD and IDDM, the literature search does not yield any studies examining the association between CD and either non–insulin-dependent diabetes mellitus (NIDDM) or metabolic syndrome, although these conditions affect far more adults than IDMM.[8,9] Any potential modulation of the risk of NIDDM or metabolic syndrome in the CD population is important to recognize because these conditions are associated with significantly increased mortality and morbidity from cardiac and noncardiac complications.[10–12]

The incidence of NIDDM is known to increase with age, and higher body mass index (BMI) and is linked closely to both diet and ethnicity.[9–11] For example, 12.6% of non-Hispanic blacks in the United States who are 20 years or older have NIDDM compared with only 7.1% of age-matched, non-Hispanic whites.[9] In addition, the prevalence of NIDDM is higher in individuals older than age 65 compared with those between 45 and 65 years (26.9% vs 13.7%).[9] Similarly, individuals with a higher BMI are more likely to have NIDDM, with the prevalence exceeding 20% in obese subjects.[13]

In general, the BMI of CD patients is lower than that of the general population.[14–16] Compared with the general population, fewer celiac patients are overweight or obese and more are underweight or have a normal weight.[14] Although CD appears to be protective against being overweight, treatment with the gluten-free diet (GFD) may increase intestinal absorption. Furthermore, the GFD is often higher in fat and caloric density than similar gluten-containing foods.[15] Thus, treatment of CD may increase

Abbreviations used in this paper: BMI, body mass index; CD, celiac disease; GFD, gluten-free diet; IDDM, insulin-dependent diabetes mellitus; NHANES, National Health and Nutrition Examination Survey; NIDDM, non–insulin-dependent diabetes mellitus; PPARG, peroxisome proliferator-activated receptor γ; tTG, tissue transglutaminase.

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risks for obesity, NIDDM, and metabolic syndrome. For these reasons, we hypothesized that differences in the prevalence of NIDDM and metabolic syndrome might be seen in CD either at diagnosis or during treatment with the GFD. The aim of this study was to determine the prevalence of NIDDM and metabolic syndrome in a large CD cohort compared with age-, sex-, and ethnicity-matched controls and national population data and to determine any potential effect of the GFD on the incidence of NIDDM and metabolic syndrome.

Patients and Methods

The Celiac Center at Beth Israel Deaconess Medical Center maintains a secure database (Microsoft Access, Redmond, WA) of all patients with known or suspected celiac disease, including demographic information and age.

Electronic records of 840 adults with biopsy-confirmed celiac disease were reviewed for documented history of hypertension, NIDDM, or hyperlipidemia, and for plasma glucose levels or glycosylated hemoglobin percentages, blood pressure recordings, lipid profiles, and BMI measurements (body weight in kg/height in m^2). These conditions were elicited routinely on visits to gastroenterology clinics as well as other clinics and all internal and available external records and laboratory results were reviewed. In addition, our medical center has implemented a robust system of universal medication reconciliation and all records were reviewed for medications used to treat hypertension, hyperlipidemia, and diabetes. In addition, the dates of initiation of the GFD were recorded for analysis of possible correlation between duration on GFD and NIDDM incidence.

A total of 840 age-, sex-, and ethnicity-matched controls were picked at random from a list of matched individuals presenting to their primary care physician for an annual health maintenance visit in the same time period as the celiac patient being matched. Controls were chosen without any a priori knowledge of comorbidity or quality of information in the medical record. Controls found to have CD were excluded (Supplementary Figure 1). BMI measurements were classified per the World Health Organization criteria as underweight ($<$18.5), normal (18.5–24.9), overweight (25–29.9), or obese ($\geq$30).[17] NIDDM was defined as a fasting blood glucose level of 126 or greater, glycosylated hemoglobin level of 6.5% or greater, or a blood glucose level of 200 mg/dL or greater at 2 hours during an oral glucose tolerance test. The International Diabetes Federation definition of metabolic syndrome[18] was adopted including obesity and any 2 of the following: (1) triglyceride levels higher than 150, high-density lipoprotein levels less than 40 in men, or high-density lipoprotein levels less than 50 in women; (2) diagnosis of hypertension, or systolic blood pressure greater than 135 or diastolic blood pressure greater than 85; or (3) fasting plasma glucose level of more than 100 mg/dL or an established diagnosis of NIDDM. In addition, the criteria of the National Health and Nutrition Examination Survey (NHANES) for age classification were adopted as follows: young adults (20–45), middle-aged adults (45–65), and senior adults ($\geq$65).[19,20]

The prevalence of NIDDM in the celiac cohort also was compared with the NHANES population for reference. This survey included 5514 individuals who were interviewed over the period of 1999 through 2004.[19]

Statistical analysis was performed using SPSS for Windows (release 13.0; SPSS, Inc, Chicago, IL) and SAS (version 9.3; SAS Institute, Inc, Cary, NC). Tests of associations of the matching variables were performed at the pair level. Associations between categoric variables and CD diagnosis were assessed using conditional logistic regression models that adjusted for matching. Multivariate conditional logistic regression models adjusted for BMI and smoking. Associations between continuous variables and CD diagnosis were assessed using Wilcoxon signed-rank tests. Associations of variables with CD diagnosis for subgroups (eg, subjects with metabolic syndrome or obese subjects) were assessed using logistic or linear regression models, with adjustment for matching through the use of generalized estimating equations and through covariate adjustment for the matching variables.

Comparisons of proportions across subgroups of the CD population and between the CD population and the NHANES cohort were conducted using chi-square tests with Yates correction for discrete variables and the Student *t* test as appropriate. We used Cox regression with time-varying covariates to analyze risk of NIDDM before and after CD diagnosis, and before and after initiation of a gluten-free diet. Specifically, we modeled time on the age scale and included all subjects in the model, whether or not they received a diagnosis of CD. Celiac status was treated as a time-dependent variable, and for the controls, it remained coded at the baseline level (ie, as negative for celiac disease). The coding of this variable for the cases, however, switched to positive at the age of celiac diagnosis. The event was diagnosis of NIDDM. Study entry was defined as the date at which the subjects' charts were reviewed and time 0 was defined as the subject's day of birth. At study entry, the subject may or may not have been diagnosed previously with NIDDM. If not, then the subject was treated as censored at their age at study entry. If the subject had been diagnosed with NIDDM, then his/her age at diagnosis was the event time. The model specified that all subjects were comparable with respect to hazard for NIDDM until a diagnosis of CD occurred. At that age, the hazard for that subject was allowed to change. Furthermore, the hazard was allowed to change with the onset of a GFD. We further adjusted for all covariates, including the matching variables, in the model. This modeling approach assumes no or minimal survival bias as a result of NIDDM or CD diagnosis. This study was approved by the Beth Israel Deaconess Medical Center Institutional Review Board.

Table 1. Demographics of Case-Control Pairs

	Total pairs N = 840	Male (%) 231 (27.5%)	Female (%) 609 (72.5%)	*P* value for association with sex
Age, *y* (SD)	49.4 (16.5)	53.6 (17.8)	47.7 (15.7)	<.0001
Mean BMI	24.7	—	—	<.0001
Race, n (%)				.66
White	746 (88.8%)	200 (86.6%)	546 (89.7%)	—
Black	6 (0.7%)	2 (0.9%)	4 (0.7%)	—
Hispanic	16 (1.9%)	5 (2.1%)	11 (1.8%)	—
Asian (%)	8 (1%)	3 (1.3%)	5 (0.8%)	—
Unreported (%)	64 (7.6%)	21 (9.1%)	43 (7.0%)	—

Results

Demographics

The celiac cohort and control group mainly were white (88.9%) and female (72.5%). The male matched pairs were significantly older than the female pairs (53.6 vs 47.7 y; $P < .0001$) (Table 1). Hispanics were the second largest ethnic group in the study (2.0%), whereas Asians and African Americans constituted 1% and 0.7%, respectively. A total of 7.4% of the study subjects declined to report ethnicity. All celiac subjects had documentation of presenting symptoms at diagnosis as well as date of initiation of the GFD. A total of 85.4% of all celiac subjects had an assessment of dietary compliance as documented by a specialized dietitian. The mean duration of time on the GFD was 84.11 months.

Prevalence of NIDDM and Metabolic Syndrome

Twenty-six individuals in the celiac group were found to have NIDDM (3.1%) compared with 81 subjects in the control group (9.6%; $P < .0001$) (Table 2). The prevalence of NIDDM in the celiac cohort also was significantly lower than the estimated national prevalence derived from the NHANES population (3.1% vs 9.8%; $P < .0001$). The prevalence of NIDDM in our control group was similar to the NHANES (9.6% vs 9.8%; $P = 1.0$). Similarly, the CD cohort had a lower prevalence of metabolic syndrome compared with the control group (3.5% vs 12.7%; $P < .0001$) (Table 3).

Prevalence of NIDDM by Age Group

The prevalence of NIDDM in both the celiac cohort and the control groups increased with advancing age as expected (Table 2). When segregated into the NHANES age groups (20–44, 45–64, and ≥65 y), we found that the prevalence of NIDDM in the celiac cohort was significantly lower than our matched controls in all 3 age groups (Table 2). Similarly, the prevalence of NIDDM in the celiac cohort was significantly lower than the general US population as represented by the NHANES cohort (Table 2).

Distribution of NIDDM by BMI Categories

The mean BMI of the celiac cohort was significantly lower than that of controls (24.7 vs 27.5; $P < .0001$). (Table 2) The distribution of the celiac cohort and control group differed significantly by BMI categories overall ($P < .0001$), with significant differences between each of the underweight and normal categories vs the obese category ($P < .0001$), but not between the overweight and obese categories ($P = .056$). More subjects in the celiac group were underweight compared with the control group (5.4% vs 2.1%). A total of 56.8% of patients in the celiac cohort were in the normal BMI range compared with 36.9% in the control group. In addition, controls were more likely to be overweight (34.2% vs 23.6%) and obese (26.8% vs 14.2%). There was no difference in BMI between celiac patients with NIDDM and matched controls with NIDDM (31.6 vs 32.3; $P = .69$, based on diabetic pairs only; and $P = .43$ based on a generalized estimating equation model using all diabetic subjects with adjustment for sex, race, and age). The prevalence of NIDDM increased in both CD patients and controls in higher weight categories. None of the underweight subjects in the celiac cohort or controls had NIDDM. In the normal weight category, 1.0% of the celiac group had NIDDM compared with 3.5% in the control group ($P = .02$). In the overweight group the prevalence of NIDDM increased to 4.0% in the celiac group and 8.7% in the control group ($P = .045$). The highest NIDDM prevalence rates were in the obese category with 10.8% of the celiac group and 20% ($P = .03$) of the controls affected (Table 4).

Table 2. Prevalence of NIDDM by Age Groups

Age group	Celiac cohort (%) N = 840	Controls (%) N = 840	NHANES population[a] (N = 5514)	*P* value between celiac cohort and controls	*P* value between celiac cohort and NHANES population	*P* value between controls and NHANES population
20 to <45	0/343 (0%)	12/343 (3.5%)	3.7%	.003	.0001	1.0
45 to <65	10/326 (3.1%)	36/326 (11%)	13.7%	<.0001	<.0001	.2
≥65	16/17 1(9.3%)	33/171 (19.3%)	26.9%	.01	<.0001	.03

[a]1999–2004 National Health and Nutrition Examination Survey.

Table 3. Prevalence and Demographics of Subjects With Metabolic Syndrome

	Celiac cohort (%) N = 840	Controls (%) N = 840	*P* value
Prevalence	3.5%	12.7%	.004
% females	75.9%	63.6%	.15[a]
Mean age, *y*	60.4	59.0	.46[b]
Mean BMI	36.1	36.2	.80[c]

[a]Based on a generalized estimating equation logistic regression model with adjustment for white race, BMI, and age.
[b]Based on a generalized estimating equation linear regression model with adjustment for race category, sex, and BMI.
[c]Based on a generalized estimating equation linear regression model with adjustment for race category, sex, and age.

Compared with the NHANES population, the prevalence of NIDDM in the CD cohort was significantly lower in the normal weight and overweight categories (Table 4). In addition, the prevalence rates of NIDDM in our control cohort and the NHANES population were comparable in all BMI categories (Table 4).

Subgroup Analysis

To control for potential ascertainment bias, we conducted a subgroup analysis of subjects in the celiac cohort who had a primary care physician affiliated with our medical center (the pool from which the controls were drawn) and compared them with their matched controls. In total, 398 celiac subjects had an internal primary care physician, of whom 85.9% were screened for NIDDM and 86.4% were screened for hyperlipidemia. Among the 398 coupled matched controls, 90.5% and 92% were screened for NIDDM and dyslipidemia, respectively. In this subgroup analysis, the prevalence of NIDDM was lower in celiac subjects (6.5%) compared with controls (13.1%) ($P = .001$). The mean age in the 2 subgroups was 56.2 years. Similarly, the prevalence of dyslipidemia in the celiac group was significantly lower compared with the controls (18.3% vs 34.9%; $P < .0001$). Finally, 93.7% of the 840 controls had screening laboratories for NIDDM compared with 71.8% of the celiac cohort. Limiting the analysis to screened subjects alone, 4.5% of the celiac subjects had NIDDM compared with 10.5% of the controls.

Effect of CD Diagnosis, Presenting Symptoms, and GFD Duration on NIDDM Incidence

We were also able to use this cohort to study the potential effects of CD diagnosis, presenting clinical symptoms, and duration on the GFD on the incidence of NIDDM in individuals with CD. Twenty-one of the 26 patients (80.8%) with both celiac disease and NIDDM were diagnosed with CD after being diagnosed with NIDDM. The mean time difference from diagnosis of NIDDM to CD in these subjects was 1.9 years.

To assess for a potential effect of malabsorption on NIDDM risk in CD we examined the prevalence of NIDDM in CD subjects who had documented intestinal healing on repeat endoscopy. In this analysis, we defined intestinal healing as the improvement of the initial biopsy from Marsh III pathology to normal or Marsh I (increased intraepithelial lymphocytes) pathology. In total, 289 celiac subjects had a follow-up endoscopy after adoption of a GFD. On follow-up biopsy, 115 (39.8%) had normal pathology (mean duration on GFD, 42.0 mo) compared with 174 (60.2%) with ongoing intestinal inflammation (mean duration on GFD, 26.5 mo). Five of the 115 subjects who had documented intestinal healing had NIDDM and, of these 5, none were diagnosed with NIDDM after intestinal healing was documented. Similarly, 5 of the 174 subjects who had ongoing intestinal damage had NIDDM, of whom 1 was diagnosed with NIDDM after the diagnosis of CD. The overall prevalence of NIDDM in the cohorts with and without ongoing enteropathy was 2.9% and 4.3%, respectively ($P = .5$). These findings are similar to analysis based on time on the GFD as a surrogate of intestinal healing.[21] In this analysis, we compared celiac subjects who have been on a GFD for less than 2 years with subjects on the GFD for 2 years or more. The prevalence of NIDDM in the group on a GFD for less than 2 years was not statistically different from those on a GFD for a longer duration (1.4% vs 3.3%; $P = .7$). Both groups had a similar mean BMI (24.6 vs 24.8; $P = .7$), but the cohort on a longer-duration GFD was significantly older (39.5 vs 50.3; $P < .0001$). In addition, we compared presenting symptoms in celiac subjects with and without NIDDM. A total of 363 of 814 (44.6%) celiac subjects without NIDDM had malabsorptive symptoms (diarrhea, weight loss, or steatorrhea) at CD diagnosis compared with 19 of 26 (73.1%) of the celiac subjects with NIDDM ($P = .0047$).

Multivariate Analyses

To further evaluate the association between CD and the diagnosis of NIDDM and metabolic syndrome, we performed multivariate conditional logistic regression

Table 4. Prevalence of NIDDM by BMI Category

BMI category	Celiac cohort (%) (N = 840)	Controls (%) (N = 840)	NHANES population[a] (N = 5514)	*P* value between celiac cohort and controls	*P* value between celiac cohort and NHANES population	*P* value between control and NHANES population
All	3.1%	9.6%	9.8%	<.0001	<.0001	1.0
<18.5	0/45 (0%)	0/18 (0%)	2.1%	1.0	1.0	1.0
18.5–24.9	5/477 (1.0%)	11/310 (3.5%)	4.9%	.02	<.0001	.3
25–29.9	8/198 (4.0%)	25/287 (8.7%)	8.5%	.045	.03	.9
≥30	13/120 (10.8%)	45/225 (20%)	16.8%	.03	.1	.2

[a]Analysis of participants in the National Health and Nutrition Examination Survey (1999–2004).

models controlling for BMI and smoking. After controlling for these variables, there remained a significantly ($P = .008$) negative association between CD and NIDDM (odds ratio, 0.49; 95% confidence interval, 0.29–0.83) and a significantly negative association ($P = .014$) between CD and metabolic syndrome (odds ratio, 0.51; 95% confidence interval, 0.30–0.87). In addition, we fit a Cox model on the age scale, in which we allowed the hazard for NIDDM diagnosis to change at CD diagnosis, and then to be multiplied by an exponential function of the time on the GFD from the time of its initiation. We adjusted for sex, BMI, smoking, and race in these models. Both the diagnosis of CD and the time on GFD negatively correlated with NIDDM, suggesting a protective effect. The hazard ratio for NIDDM diagnosis after CD diagnosis relative to that before CD diagnosis was not significantly different and was estimated as 0.49 ($P = .080$), and the hazard ratio for NIDDM diagnosis after 10 years on a GFD relative to that before CD diagnosis was estimated as 0.48 ($P = .101$). The associated log hazard parameter for time on a GFD also was not significant ($P = .96$). We also fit a model in which we allowed the hazard for NIDDM diagnosis to change at CD diagnosis and then again at initiation of GFD, without including a multiplier for time on GFD. The model additionally adjusted for race, BMI, smoking status, and sex. The results from this model suggest that the hazard for NIDDM is lower for individuals with CD vs those without, adjusting for all other covariates, but that the hazard ratio increases from 0.36 ($P = .022$) after CD diagnosis to 0.55 ($P = .108$) after initiation of GFD. The associated log hazard parameter for initiation of GFD was not significant ($P = .235$).

Discussion

In our literature search we did not come across studies that examine associations between NIDDM, metabolic syndrome, and CD despite the fact that NIDDM and metabolic syndrome are very common and significant disorders. By conducting this study in a large celiac cohort, we aimed to evaluate any possible association between NIDDM, metabolic syndrome, and CD, allowing for control of the confounding effect of differential BMI distribution between the cohorts. In addition to analyzing US population data (from NHANES) we also compared our celiac cohort with age-, sex-, and ethnicity-matched controls to account for possible regional factors that otherwise could affect study results. The fact that the prevalence of NIDDM in our control group was similar to estimated US rates by age and weight as reported by NHANES supports the adequacy of our control populations. In addition, given the fact that the majority of the celiac subjects in our cohort were white, we limited the comparison of NIDDM rates with NHANES non-Hispanic whites. This subanalysis confirmed a significantly lower prevalence in celiac subjects (3.1% vs 7.1%; $P < .0001$).

The primary novel and important finding of our study was the significantly lower prevalence of NIDDM in CD patients compared with the general population and matched controls. The possible explanation that the lower rate of NIDDM in individuals with CD was caused by different BMI distribution was not supported by our study data because the lower prevalence of NIDDM in CD remains significant after controlling for BMI. Furthermore, although the expected trend for increasing NIDDM prevalence with advancing age and increased BMI are seen in the CD cohort, the substantial differences between CD and control cohorts remain even after adjusting for age and BMI. Further, because NIDDM is a major driver of morbidity in individuals who are overweight or have metabolic syndrome, protection from NIDDM may reduce the risks associated with weight gain in the celiac population.

The mechanisms by which individuals with CD are protected from NIDDM and metabolic syndrome are not clear at this time, however, possible explanations include altered pancreatic function,[22–24] impaired nutrient absorption,[22] and changes in gastrointestinal endocrine function.[22] Decreased absorption as a result of enteropathy is one apparent explanation for the lower risk of NIDDM and metabolic syndrome in patients with CD. However, this explanation is not supported by our findings that rates of NIDDM and metabolic syndrome are independent of BMI, and that the prevalence of NIDDM was not altered by status of follow-up intestinal histology or by duration on the GFD. Furthermore, most of the diabetic subjects in our celiac cohort were diagnosed with NIDDM before being diagnosed with CD or starting a GFD. This suggests that making the CD diagnosis or starting the GFD does not increase the consequent incidence of NIDDM and is supported by the protective but nonsignificant hazard ratios on COX model analysis. However, these hazard ratios need to be interpreted with caution because the analysis might have lacked enough power given that only 5 celiac subjects had their NIDDM diagnosis after CD diagnosis and initiation of the GFD. Finally, signs and symptoms of malabsorption (diarrhea, weight loss, and iron-deficiency anemia) were significantly more common in patients with CD and NIDDM compared with those with CD without NIDDM, suggesting that protection from NIDDM is not related to malabsorption. One alternate possibility is that there is overlap between the genes predisposing to celiac disease and protective against NIDDM. Tissue transglutaminase (tTG) drives inflammation in CD via the down-regulation of peroxisome proliferator-activated receptor γ (PPARG).[25] On the other hand, PPARG up-regulation has been implicated in NIDDM susceptibility.[26] Therefore, the down-regulation of PPARG in CD may be implicated in decreased risk of NIDDM.

Although our study was large and reached highly significant and novel findings, we do note that it had limitations. The International Diabetes Federation includes central obesity as one criterion for metabolic syndrome. Most of our patients did not have available waist circumference measurements and therefore we instead included patients with BMI measurements of 30 and greater. Although this might have

affected the prevalence of metabolic syndrome in our study, we expect its impact on our analysis to have been minor. Moreover, BMI was used for all study groups, minimizing the risk of differential bias. Further, restricting the analysis to the obese category, only 31.7% (38 of 120) of the obese celiac subjects met other criteria for the metabolic syndrome compared with 47.6% (107 of 225) of the obese control group ($P = .004$). In addition, our study included mostly white patients who live in a limited geographic region. However, our control group, which was selected from the same ethnic and regional population, was very similar to national survey populations, providing 2 independent control comparisons with consistent results. Another limitation of our study was that most subjects did not have endoscopic follow-up after starting the GFD and intestinal healing could be assessed directly in only 34.4% of celiac subjects. However, most patients were compliant with the GFD (78.5%) as documented by a specialized dietitian. Moreover, 91.2% of these subjects had clinical improvement as well as normalization of their tTG titers, which increased the likelihood of histologic improvement or remission. On further analysis, we found no effect of intestinal healing on follow-up biopsy, dietitian-reported GFD adherence, or tTG normalization on risk of subsequent development of NIDDM.

In conclusion, NIDDM and the metabolic syndrome are less prevalent in patients with CD. The reasons for this finding are unknown but do not appear to depend solely on BMI. Genetic factors may be important given the strong genetic contributions to both disorders. Our findings indicate a novel and potentially important protective effect for CD that is especially notable given the increasing morbidity and mortality associated with NIDDM and the metabolic syndrome in many parts of the world where CD also increasingly is recognized. Further studies are warranted to understand the mechanisms by which CD patients are protected against NIDDM and the metabolic syndrome.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2013.01.033.

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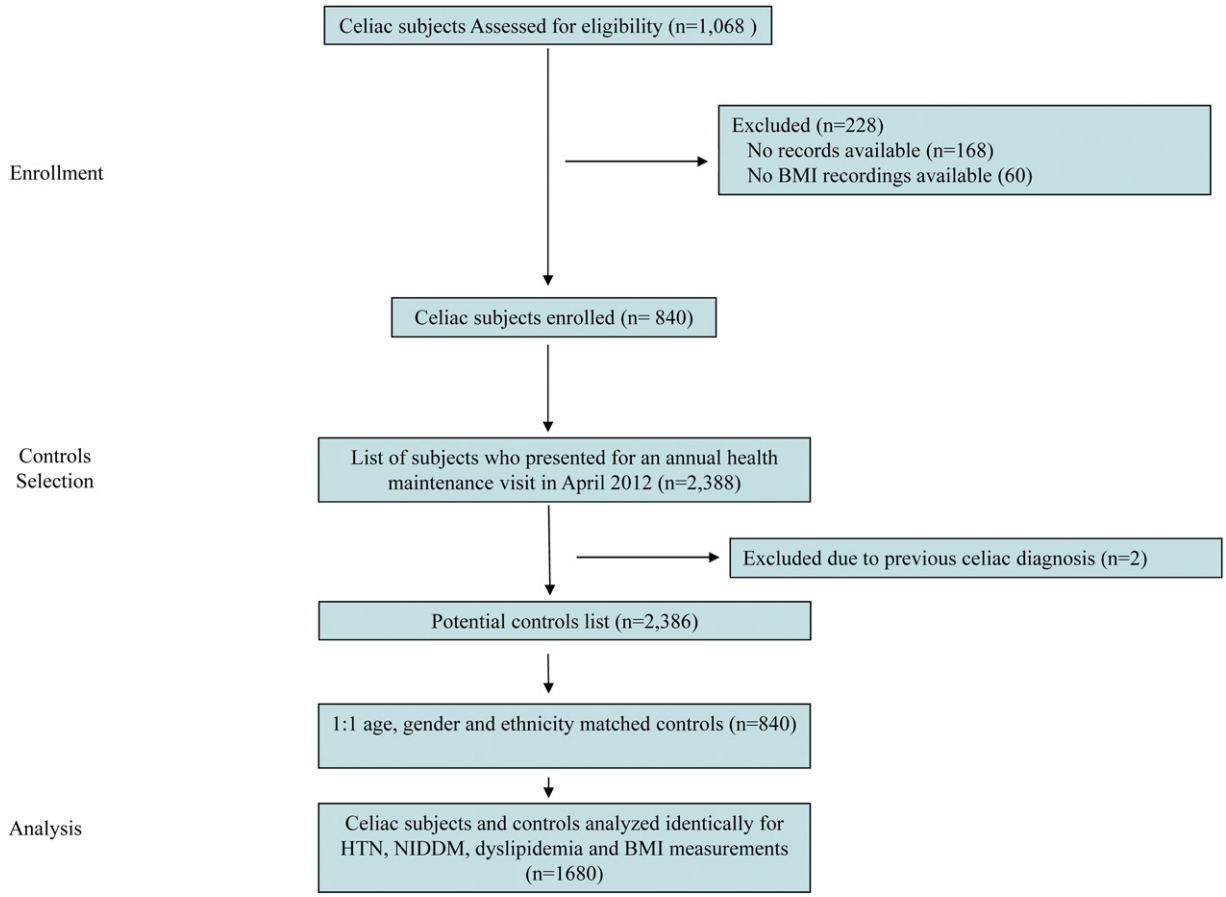
Conflicts of interest

The authors disclose no conflicts.



Supplementary Figure 1. Consort chart for selection of celiac subjects and controls. HTN, Hypertension; PCP, primary care physician.