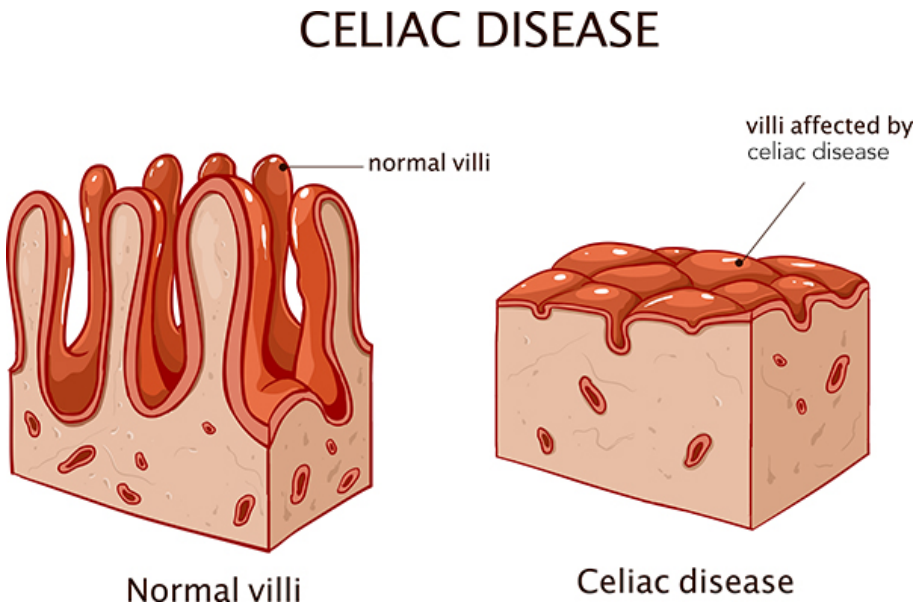
T1DM with Celiac disease
Double Burden for patients in food choices



Case 1 Inter-hospital ENDO 3/2563

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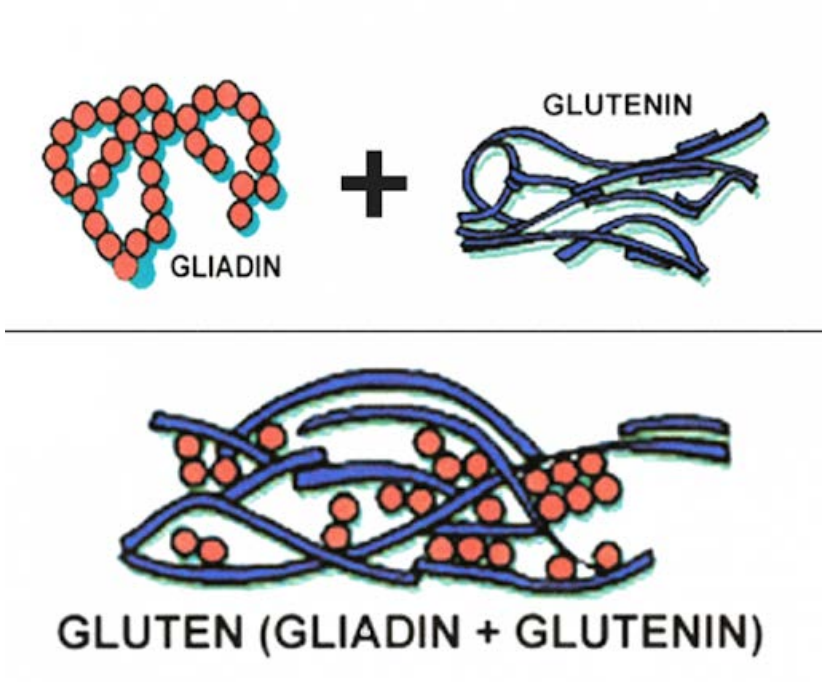
What Is Gluten?

- Gluten is a storage protein found in wheat, barley and rye.
- Gluten gives dough its elasticity, acting like a glue, giving bread its classic chewy, soft texture.



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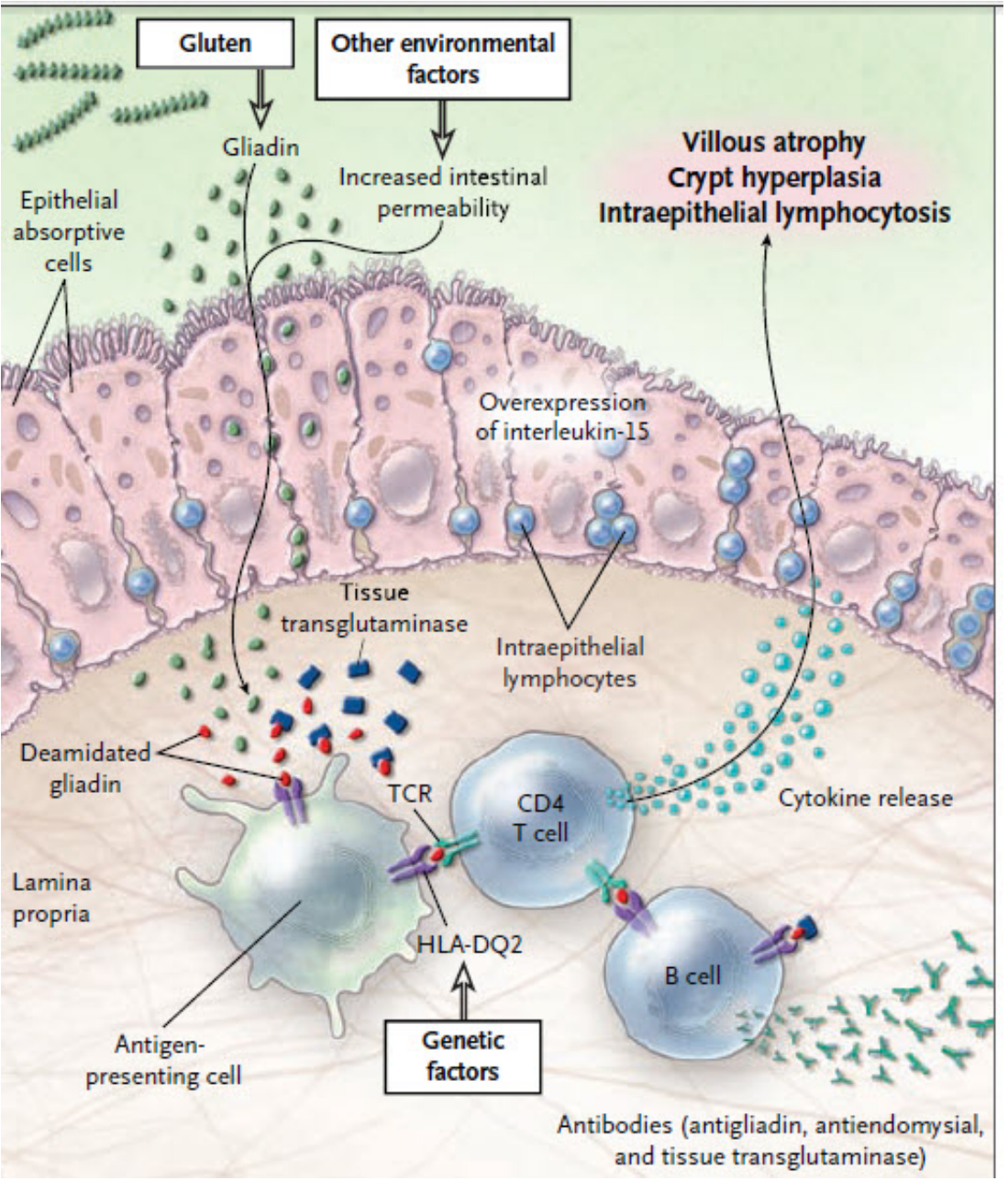

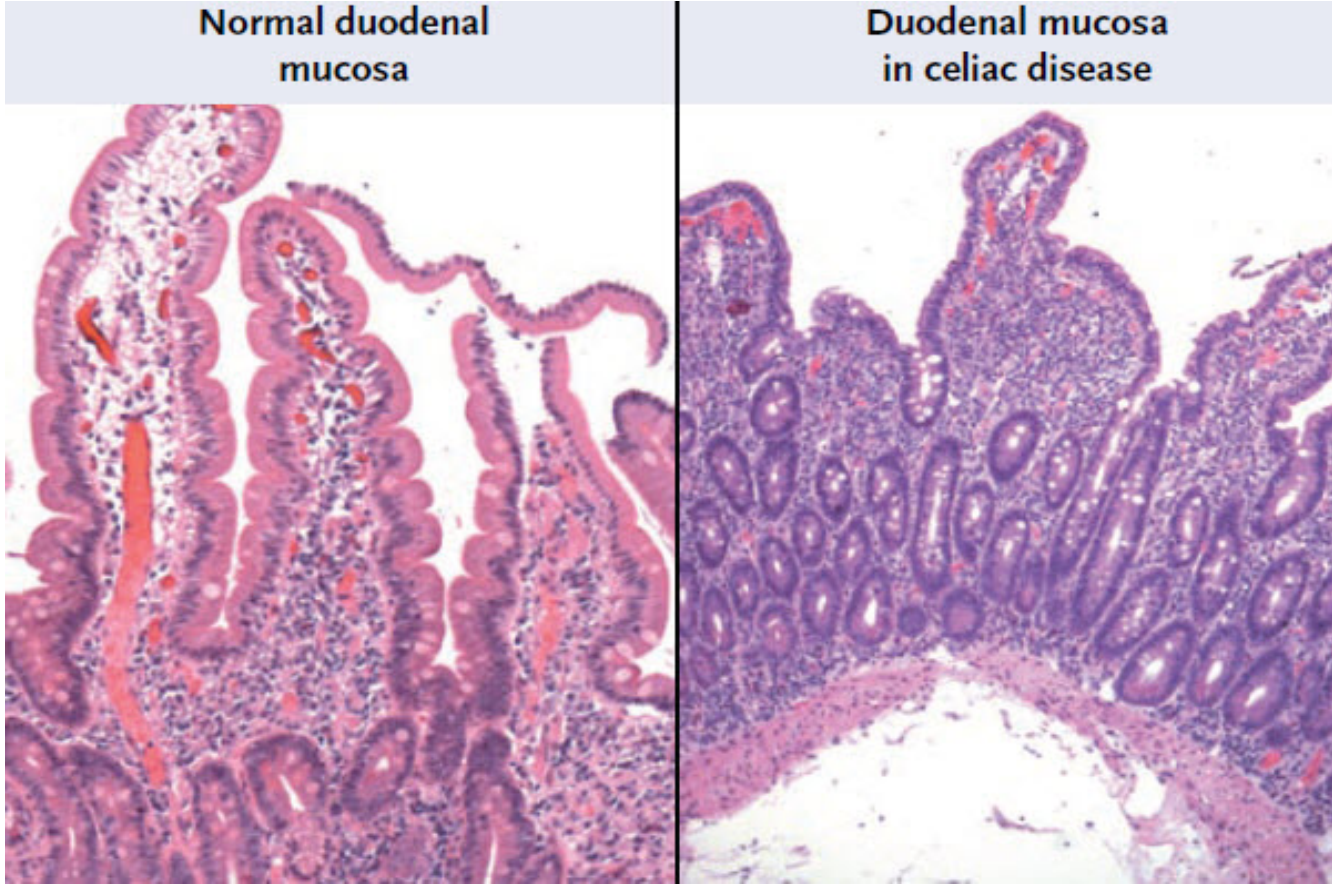

N Engl J Med 2007;357:1731-43.

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High risk populations for celiac disease

Relatives, especially first-degree
Anemia, especially iron deficiency
Osteopenic bone disease
Insulin-dependent diabetes (type 1), especially children
Liver disorders, especially AIH and PBC
Genetic disorders, including Down and Turner's syndrome
Autoimmune endocrinopathy, especially thyroid disease
Skin disorders, particularly dermatitis herpetiformis
Neurological disorders, including ataxia, seizures, MG
Others, including IgA nephropathy

World J Gastroenterol 2010;16:1828-31.

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Celiac disease as a great mimicker

KEY CLINICAL POINTS

CELIAC DISEASE

- Once considered a gastrointestinal disorder that mainly affects white children, celiac disease is now known to affect persons of different ages, races, and ethnic groups, and it may be manifested without any gastrointestinal symptoms.
- Measurement of IgA anti–tissue transglutaminase antibodies is the preferred initial screening test for celiac disease because of its high sensitivity and specificity, but it performs poorly in patients with IgA deficiency (which is more common in patients with celiac disease than in the general population).
- The diagnosis is confirmed by means of upper endoscopy with duodenal biopsy, although recent guidelines suggest that biopsy may not be necessary in selected children with strong clinical and serologic evidence of celiac disease.
- Given the undisputable role of gluten in causing celiac disease enteropathy, the cornerstone of treatment is the implementation of a strict gluten-free diet for life.
- Gluten sensitivity may occur in the absence of celiac disease, and a definitive diagnosis should be made before implementing a lifelong gluten-free diet.

N Engl J Med 2012;367:2419-26.

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Celiac disease as a great mimicker

Table 1. Serum Tests for the Diagnosis of Celiac Disease.*

Test	Sensitivity (Range)	Specificity (Range)	Comments
	percent		
IgA anti-tTG antibodies	>95.0 (73.9–100)	>95.0 (77.8–100)	Recommended as first-level screening test
IgG anti-tTG antibodies	Widely variable (12.6–99.3)	Widely variable (86.3–100)	Useful in patients with IgA deficiency
IgA antiendomysial antibodies	>90.0 (82.6–100)	98.2 (94.7–100)	Useful in patients with an uncertain diagnosis
IgG DGP	>90.0 (80.1–98.6)	>90.0 (86.0–96.9)	Useful in patients with IgA deficiency and young children
HLA-DQ2 or *HLA-DQ8*	91.0 (82.6–97.0)	54.0 (12.0–68.0)	High negative predictive value

* Data are from Husby et al.[28] and Giersiepen et al.[29] DGP denotes deamidated gliadin peptides, and tTG tissue transglutaminase.

N Engl J Med 2012;367:2419-26.

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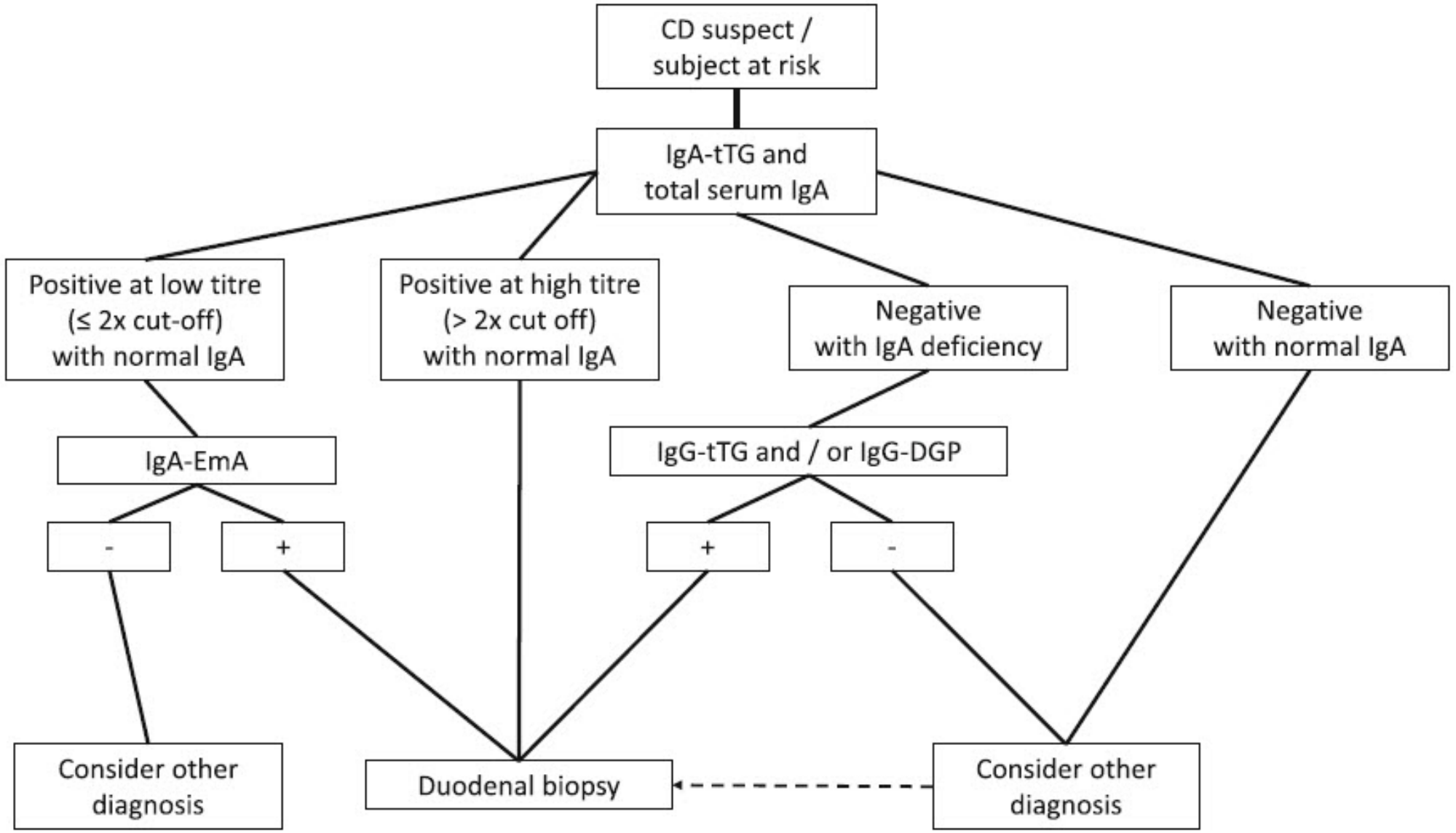

BMC Medicine 2019;17:142.

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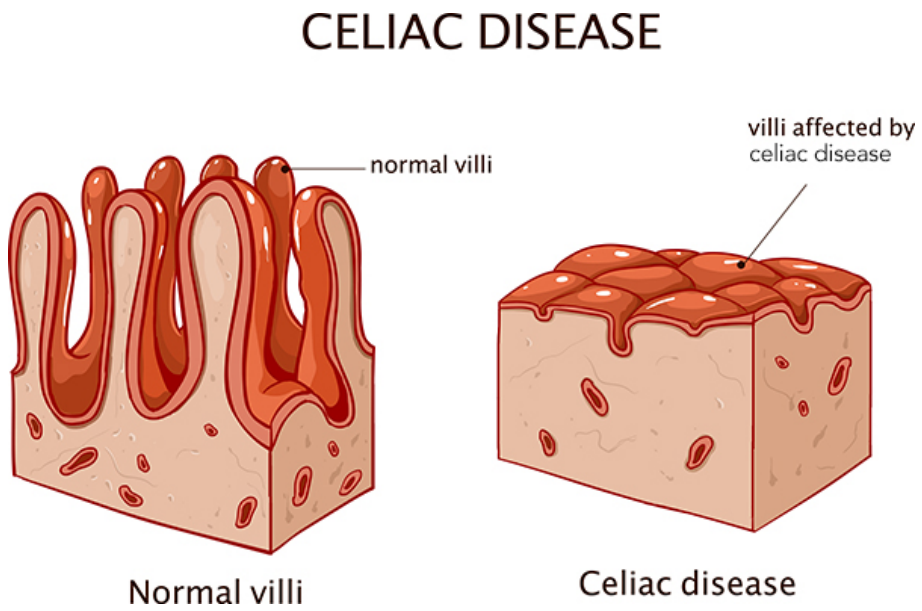
Celiac disease in People with T1DM

- **About 3-8% of people with type 1 diabetes have celiac disease, which is six times higher than the general population.**



Dig Dis 2018;36:399-408.

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Small and Large Bowel: Review

Digestive Diseases

Dig Dis 2018;36:399–408
DOI: 10.1159/000488670

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Published online: July 25, 2018

Interplay between Type 1 Diabetes Mellitus and Celiac Disease: Implications in Treatment

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Dig Dis 2018;36:399-408.

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Prevalence rates of coexistent T1DM and celiac disease in different countries and regions

Dig Dis 2018;36:399-408.

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APJAI
Asian Pacific Journal of
Allergy and Immunology

ORIGINAL ARTICLE

Frequency of HLA-DQB1*0201/02 and DQB1*0302 alleles and tissue transglutaminase antibody seropositivity in children with type 1 diabetes mellitus

Thammarakcharoen T,[1] Hirankarn N,[2] Sahakitrungruang T,[1] Thongmee T,[1] Kuptawintu P,[3] Kanoonthong S,[3] Chongsrisawat V[1]

Abstract

Background: Patients with type 1 diabetes mellitus (T1DM) have an increased risk of celiac disease (CD). Both diseases have a common genetic susceptibility locus in the human leukocyte antigen (HLA) class II alleles. Testing for tissue transglutaminase antibodies (anti-tTG) is highly accurate for a CD diagnosis.

Objective: To determine the frequency of HLA-DQB1*0201/02 and DQB1*0302 alleles and anti-tTG seropositivity in children with T1DM.

Method: Forty-six children with T1DM (male:female=24:22; mean age 12±3.7 years) without significant digestive symptoms were enrolled. The mean duration of diabetes was 5±3.5 years. Serum anti-tTG IgA and IgG as well as

While 29/46 (63.0%) patients carried HLA-DQ2 and/or -DQ8 heterodimers, only 1/46 (2.2%) was positive for anti-tTG IgA (38.5 U/mL; cut-off 15 U/mL).

Asian Pac J Allergy Immunol 2017;35:82-5.

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Classical and non-classical symptoms of T1DM and CD

Type 1 diabetes mellitus	Celiac disease
Hyperglycemia	Abdominal discomfort/bloating
Osmotic symptoms-polyuria, polydipsia, polyphagia	Weight loss, fatigue, growth abnormalities
Vomiting/abdominal discomfort/constipation/headache	Infertility, hypogonadism
Nocturia, pyogenic skin infections, recurrent candida rash	Recurrent aphtous stomatitis
Urine ketones	Low bone mineralization
	Compensatory hyperthyroidism
	Dermatitis herpetiformis
	Dental hypoplasia

Dig Dis 2018;36:399-408.

Nutritional deficiencies of a gluten-free diet

Author	Year	Study design	Population	Study method	Macronutrients/fiber	Micronutrients
Babio et al	2017	Case-control	98 pediatric patients with celiac disease well-controlled on GFD, 98 matched controls	3-day dietary survey	Higher lipid and added sugar, lower dietary fiber intake on GFD	Lower folate, calcium, iron, and magnesium on GFD
Bardella et al	2000	Case-control	71 patients with celiac disease well-controlled on GFD, 142 matched controls	3-day dietary survey	Higher lipid and lower carbohydrate intake on GFD	Not studied
Barone et al	2016	Case-control	39 patients with celiac disease well-controlled on GFD, 39 matched controls	7-day dietary survey	Higher lipid and lower dietary fiber intake on GFD	Not studied
Capristo	2000	Case-control	39 patients with celiac disease well-controlled on GFD, 63 matched controls	7-day dietary survey	Higher lipid intake on GFD	Not studied
Hallert et al.	2002	Cross-sectional	30 patients with celiac disease well-controlled on GFD	Blood sampling, 4-day dietary survey	Not studied	Higher homocysteine, lower folate serum levels, lower vitamin B12 and folate intake on GFD compared to national database
Kinsey et al	2008	Cross-sectional	48 patients with celiac disease well-controlled on GFD	3-day dietary survey	Higher protein and lower lipid consumption on GFD compared to national database	Lower calcium and vitamin D intake on GFD compared to national database
Shepard and Gibson	2013	Case-control	55 patients with celiac disease well-controlled on GFD, 50 newly-diagnosed patients with celiac disease	five 7-day dietary surveys	Higher lipid and lower protein and carbohydrate intake on GFD compared to national database	Lower folate, calcium, iron, and zinc on GFD compared to national database
Thompson et al	2005	Cross-sectional	47 patients with celiac disease well-controlled on GFD	3-day dietary survey	Higher carbohydrate with lower dietary fiber intake on GFD compared to national database	Lower calcium and iron intake on GFD compared to national database
Wild et al	2010	Cross-sectional	93 patients with celiac disease well-controlled on GFD	5-day dietary survey	Higher percentage of carbohydrates consumed as non-milk extrinsic sugars, lower as dietary fiber on GFD compared to national database	Lower magnesium, zinc, iron, manganese, selenium, and folate intake in women, magnesium and selenium intake in men on GFD compared to national database
Zuccotti et al.	2012	Case-control	18 pediatric patients with celiac disease well -controlled on GFD, 18 matched controls	Food frequency + 24-h dietary survey	Higher mean energy and carbohydrate, lower fat intake on GFD	Not studied

Curr Gastroenterol Rep 2017;19:54.

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Hematologic manifestations of Celiac disease

Hematologic manifestations of CD	Prevalence	Proposed mechanisms
Iron deficiency anemia	Very common	Malabsorption GI bleed (less likely)
Anemia secondary to Vitamin B12 deficiency	Less common than folate and IDA	Severe ileal atrophy Lack of pancreatic secretion stimulation Intrinsic factor deficiency
Anemia secondary to folate deficiency	11–49%	Malabsorption
Thrombocytosis	60% upon diagnosis	IDA Functional hyposplenism Inflammatory mediators
Thrombocytopenia	Less common than thrombocytosis	Autoimmunity Haplotypes other than HLA-DQ2 or HLA-DQ8 Folic acid deficiency
Leukopenia	Rarely reported	Deficiency of both folic acid and copper
Thromboembolism	Modest increase in prevalence compared to general population	Hyperhomocysteinemia Magnesium deficiency Thrombocytosis Protein C and S deficiency Associated autoimmune disease or malignancy Elevated levels of TAFI Genetic predisposition
Coagulopathy	Up to 70% of untreated adults	Associated liver dysfunction Isolated thrombocytopenia ITP Vitamin K malabsorption
IgA deficiency	2.6% of patients with CD	Shared haplotype: HLA-A1, Cw&, B8, DR3, DQ2
Hyposplenism	16–77%	See Table I
Lymphoma	N/A Highly increased risk with RCD	Increased intestinal permeability of environmental carcinogens Chronic inflammation Chronic antigenic stimulation Release of proinflammatory cytokines Immune surveillance problems Nutritional deficiencies

Scan J Gastroenterology 2012;47:1401-11.

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Every Fifth Individual With Type 1 Diabetes Suffers From an Additional Autoimmune Disease: A Finnish Nationwide Study

*Sari Mäkimattila,[1] Valma Harjutsalo,[2,3,4,5] Carol Forsblom,[2,3,4] and Per-Henrik Groop,[2,3,4,6] on behalf of the FinnDiane Study Group**

https://doi.org/10.2337/dc19-2429

Of individuals with T1D, 22.8% had at least one additional AD, which included 31.6% of women and 14.9% of men

OBJECTIVE

The aim of this study was to quantify the excess risk of autoimmune hypothyroidism and hyperthyroidism, Addison disease, celiac disease, and atrophic gastritis in adults with type 1 diabetes (T1D) compared with nondiabetic individuals in Finland.

RESEARCH DESIGN AND METHODS

Diabetes Care 2020;43:1041-7.

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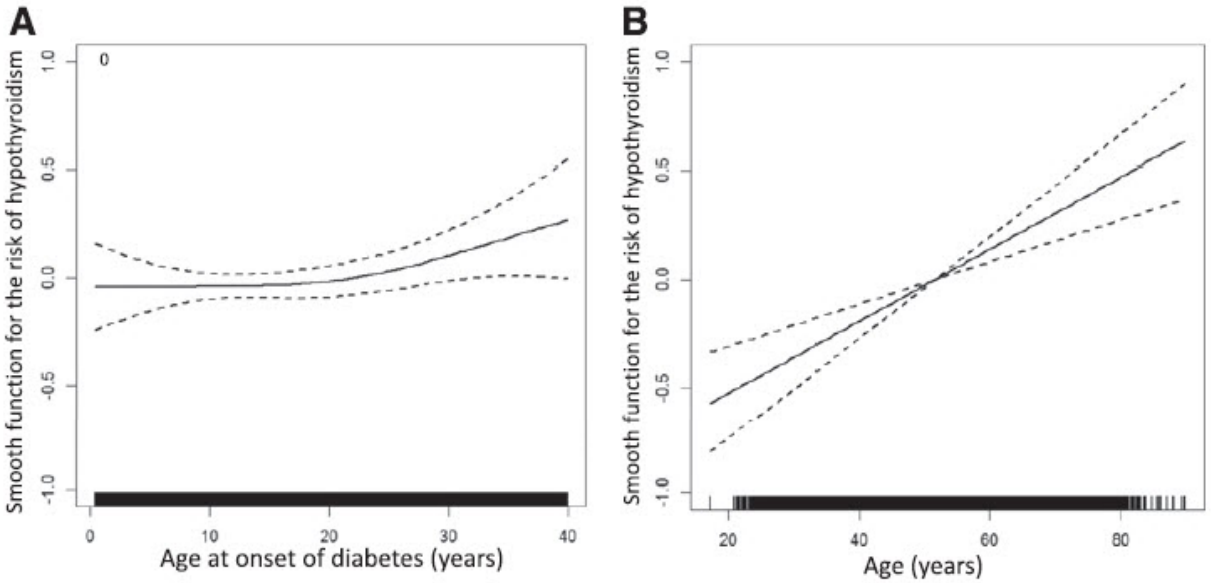

Figure 1—Plots of estimated smoothing splines of the association between the risk of hypothyroidism and the age at diagnosis of diabetes (*A*) and age (*B*). Dashed lines represent 95% CI. The area above zero represents increased risk, and the area under zero represents decreased risk.

Opposite to hypothyroidism, the risk of celiac disease was 1.5% higher for each decreasing year of age at onset of diabetes

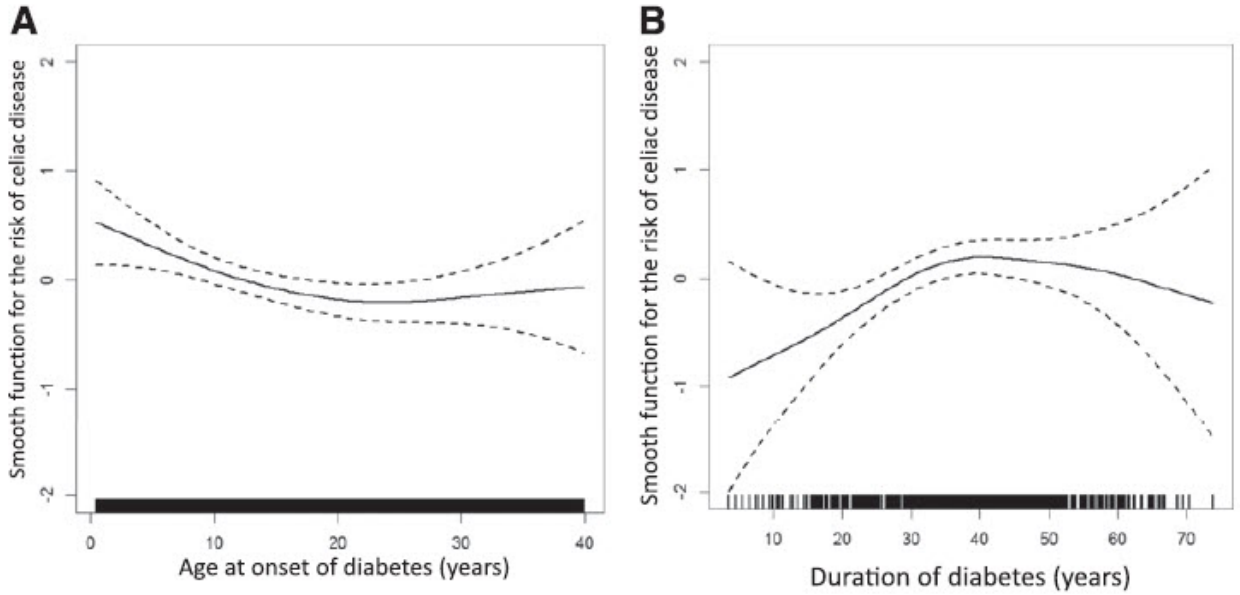

Figure 2—Plots of estimated smoothing splines of the association between the risk of celiac disease and the age at diagnosis of diabetes (*A*) and duration of diabetes (*B*). Dashed lines represent 95% CI. The area above zero represents increased risk, and the area under zero represents decreased risk.

Diabetes Care 2020;43:1041-7.

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Screening and Treatment Outcomes in Adults and C With Type 1 Diabetes and Asymptomatic Celiac Dise: CD-DIET Study

https://doi.org/10.2337/dc19-1944

OBJECTIVE

To describe celiac disease (CD) screening rates and glycemic outcomes of a gluten-free diet (GFD) in patients with type 1 diabetes who are asymptomatic for CD.

RESEARCH DESIGN AND METHODS

Asymptomatic patients (8–45 years) were screened for CD. Biopsy-confirmed CD participants were randomized to GFD or gluten-containing diet (GCD) to assess changes in HbA_{1c} and continuous glucose monitoring over 12 months.

RESULTS

Adults had higher CD-seropositivity rates than children (6.8% [95% CI 4.9–8.2%, N = 1,298] vs. 4.7% [95% CI 3.4–5.9%, N = 1,089], P = 0.035) with lower rates of prior CD screening (6.9% vs. 44.2%, $P < 0.0001$). Fifty-one participants were randomized to a GFD (N = 27) or GCD (N = 24). No HbA_{1c} differences were seen between the groups (+0.14%, 1.5 mmol/mol; 95% CI −0.79 to 1.08; P = 0.76), although greater postprandial glucose increases (4-h +1.5 mmol/L; 95% CI 0.4–2.7; P = 0.014) emerged with a GFD.

CONCLUSIONS

CD is frequently observed in asymptomatic patients with type 1 diabetes, and clinical vigilance is warranted with initiation of a GFD.

OBJECTIVE

Toronto, Toronto, Ontario, Canada

Diabetes Care 2020;43:1553-6.

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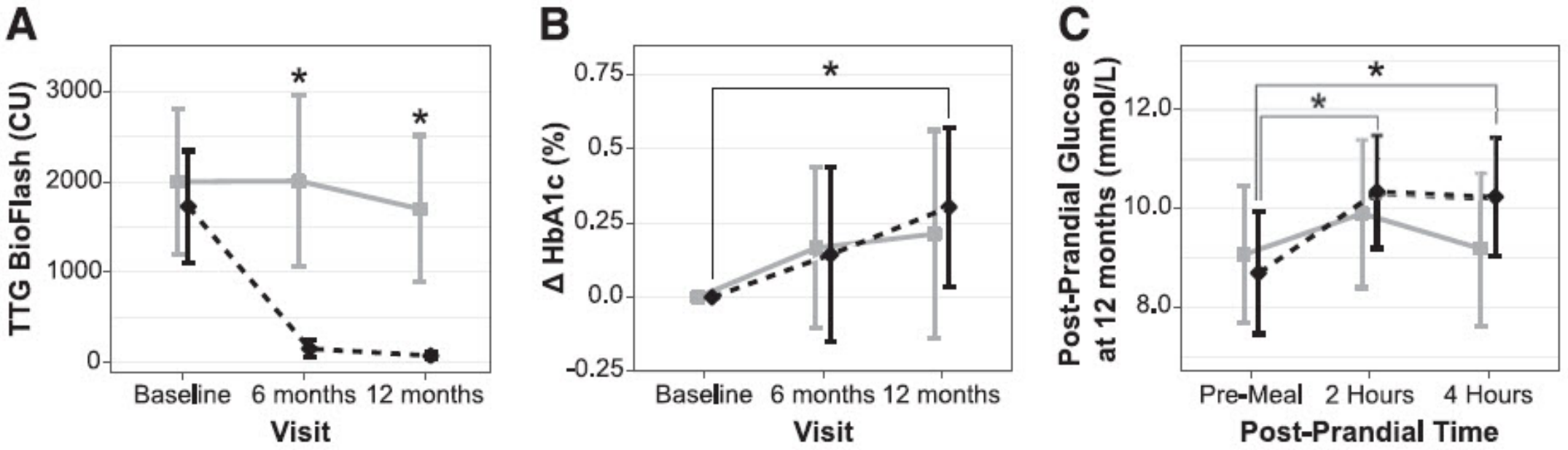

Figure 2—The results from the CD-DIET Dietary Intervention Trial. Data from the GFD arm shown in black with a dashed line (■), while data from the GCD are shown with solid gray line (■). *A*: Dietary adherence to assigned group was assessed using serial serologic testing. TTG-IgA antibody titers were similar in the GCD and the GFD groups at baseline. They appropriately decreased in the GFD arm by 6 months and continued to drop among GFDs, resulting in a significant difference between GCDs (1,698.0 ± 1,834.0 CU) and GFDs (73.4 ± 83.9 CU) at 12 months ($P < 0.0001$). *B*: The change in HbA_{1c} between study groups. No difference in HbA_{1c} was seen between the the GFD group relative those on a GCD over the 12 months (+0.14% [1.5 mmol/mol], $P = 0.76$); however, within the GFD group, HbA_{1c} increased (+0.30% [3.3 mmol/mol], 95% CI 0.04–0.57%, $P = 0.028$). *C*: Changes in postprandial glucose assessed by CGM. Postprandial glycemia in the GFD was higher compared with premeal levels at both the 2-h time point (+1.6 mmol/L [29 mg/dL]; $P = 0.0015$) and 4-h time point (+1.5 mmol/L [27 mg/dL]; $P = 0.014$), while glucose levels of the GCD arm returned to premeal levels ($\Delta = 0.1$ mmol/L [1.8 mg/dL]). Error bars represent 95% CIs. *Significant differences below $P < 0.05$.

Diabetes Care 2020;43:1553-6.

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Learning points in this patient

- Thoroughly history taking including detailed family history is the key.
- Brittle DM was coined in 1930s and then became a convenient word. **BUT** it should find out what cause the brittleness of glycemic control.

- Listen to the patient who knows best for his/her symptoms.
- Multi-disciplinary team is necessary in the difficult cases.

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THANK YOU VERY MUCH FOR YOUR ATTENTION

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