Non-Invasive Monitoring of Intestinal Permeability and Inflammation in a Prospective Serological Diagnosis Study of Pediatric Celiac Disease

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Disclosures

None relevant

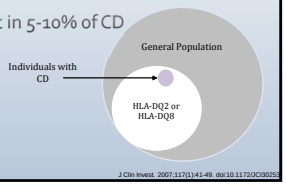
Celiac Disease (CD)

- Gluten sensitive autoimmune enteropathy
- Gluten found in wheat, barley and rye
- 1% prevalence worldwide
- Treatment: Lifelong Gluten Free Diet (GFD)

http://www.scientificamerican.com/article/celiac-disease-insights/

Gene Associations

- HLA-DQ2 & HLA DQ8 predispose to CD
- Genes are necessary but not sufficient
- Both present in 30% of the population
- HLA-DQ2 is found in 95% of CD patients
- HLA-DQ8 is usually present in 5-10% of CD patients



J Clin Invest. 2007;117(1):41-49. doi:10.1172/JCI30253

Celiac Screening

- Serological screening
  - Anti-tissue Transglutaminase (aTTG)
    90-98% Sensitivity, 94-97% Specific
  - Anti-endomysial antibody (EMA)
    85-98% Sensitivity, 97-100% Specific

  (*Farrell et al. Am J Gastro 2001*)
- Genetic Screening
  - Tests the *potential* of having CD
  - Absence of DQ2 and DQ8 excludes diagnosis of CD
    - Negative predictive value of nearly 100%

European Guidelines

- 2012 – ESPGHAN initiated a serological route for diagnosis
  - Symptomatic presentation
  - aTTG 10x upper limit of normal
  - Confirmatory testing (anti-endomysial antibody)
  - Confirmatory genetics
- European Guidelines recommend Genetic screening for:
  - High risk groups
  - Diagnostic conundrums (negative antibodies, Marsh 1)
  - **Symptomatic children where biopsy is not desired**
    (Husby et al. JPGN 2012)

(Husby et al. JPGN 2012)

Diagnostic Controversy

Current North American gold standard is biopsy

Is it being followed?

- Our local laboratory data suggests 17% children <18 yo have positive serology but no biopsy
- 2/3 of those not biopsied had aTTG <100 U/mL
  (Saginur M et al. Pediatrics & Child Health 2012)
- In Europe 44% of surveyed Pediatric GI doctors would prefer to omit biopsy in symptomatic patients
  (Ribes-Koninckx et al. JPGN 2012)

Serological Diagnosis

Accuracy of serological tools raises the questions:

Is serology sufficient to diagnose CD?

- Retrospective studies show aTTG >100 U/mL positive predictive value (PPV) approaching **100%**
  (Mubarak et al. JPGN 2011., Barker et al. Pediatrics 2005., Donaldson et al. J Clin Gastro 2008., Hill et al. Aliment PharmacolTher 2008)
- Our own local study showed aTTG >200 U/mL PPV **100%**
  (Saginur et al. Paediatr Child Health 2013)

Aims

To prospectively pilot serological diagnosis (SD) at our local center

1. Monitoring baseline and follow up aTTG; permeability and fecal calprotectin given serological (SD) vs endoscopic (ED)
2. Assessing if either diagnostic strategy impacted adherence to the GFD
3. Assessing patient and family preference for SD vs ED

Methods

- Recruitment at Stollery CD Clinic – 3-17 year olds without co-morbid diagnosis (e.g. IBD, T1DM)
- Consented to:
  - **SD**: aTTG ≥ 200 U/mL, positive for HLA DQ2 or DQ8
  - **ED**: aTTG > 7 U/mL, positive Marsh 1-3 biopsy findings
- Baseline & Follow up at 12 months:
  - Symptoms, height, weight, aTTG
  - Urine L/M and %Sucrose excretion as permeability markers
  - Stool FC marker as inflammation marker

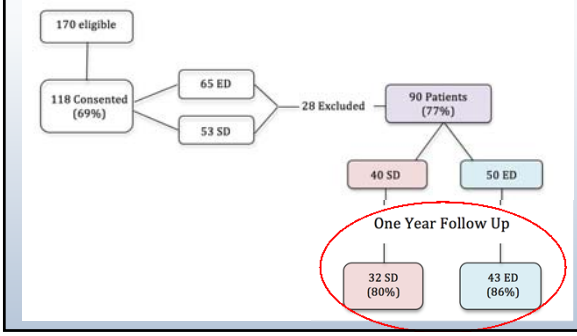
Mucosal Permeability

- Sugar probes: secreted in urine show intestinal leaky
- L/M ratio shows damage throughout the whole gut
  - Estimated 96-100% sensitive
    (Catassi et al. Gut 1997.)
- Sucrose shows proximal intestinal damage
  - Sensitivity 75%, specificity 91%
    (Smecuol et al. Am J Gastroenterol 1999.)
- Increased L/M ratio and FeSucrose in CD patients and recovery to normal levels after GFD
  (Pearson et al. BMJ 1982., Uil et al. Eur J Gastroenterol Hepatol 1996.,Hamilton et al. Gut 1982., Smecuol et al. Gastroenterology 1997.)

Mucosal Inflammation

- Fecal Calprotectin- Calcium binding protein and marker for inflammation
- FC is increased in disorders with mucosal inflammation
  (Costa et al. Dig Liver Dis 2003.)
- FC increase in children with CD related to Marsh score and normalizing with GFD
  (Eretkin et al. J Clin Gastroenterol 2010., Balamtekin et al. Turk J Gastro 2012.)

Enrollment
Jan 2013-Jun 2014



Baseline Demographics

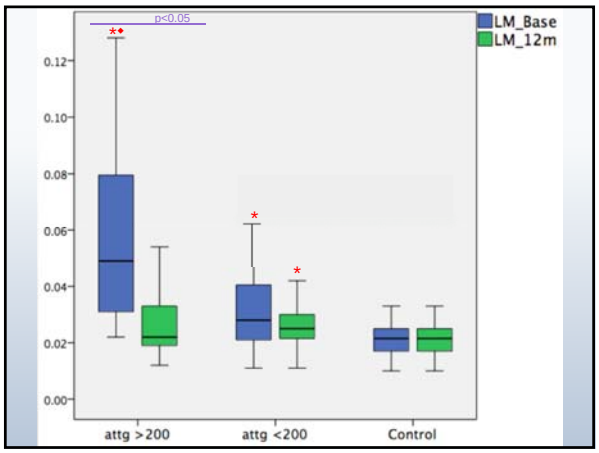
		Serological Diagnosis	Biopsy Diagnosis	p-value
Baseline	Age (years)[1]	8.5(3.4)	9.4(3.5)	>0.05
	Gender (M:F)	14:18	16:27	>0.05
	Height (cm)[1]	131.1(21.4)	133.8(21.1)	>0.05
	Weight (kg)[1]	31.8(15.0)	33.8(16.1)	>0.05
	aTTG (U/ml)[2]	595(230-4100)	51(7.8-2500)	<0.001
	GI symptoms	84.4%	86%	>0.05
	Growth Concerns	46.9%	18.6%	<0.001
	Behavioral Symptoms	46.9%	46.5%	>0.05
	Anemia/Fatigue	59.4%	53.5%	>0.05
	CNS	37.5%	41.9%	>0.05
	Other	12.5%	11.6%	>0.05
	Family History	46.9%	45.2%	>0.05

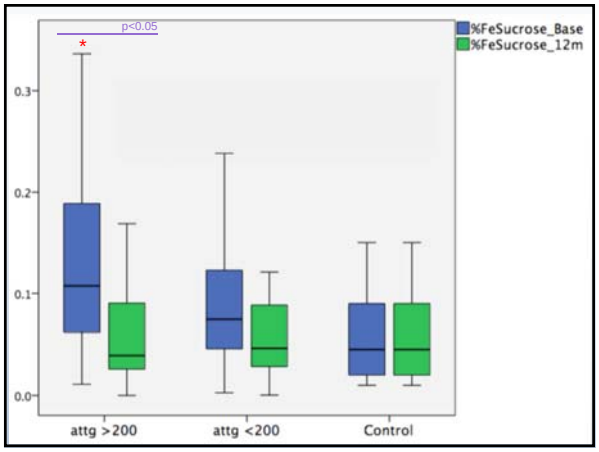
[1]Mean (SD), Significance was shown through T-tests and Mann-Whitney tests ($p<0.05$).

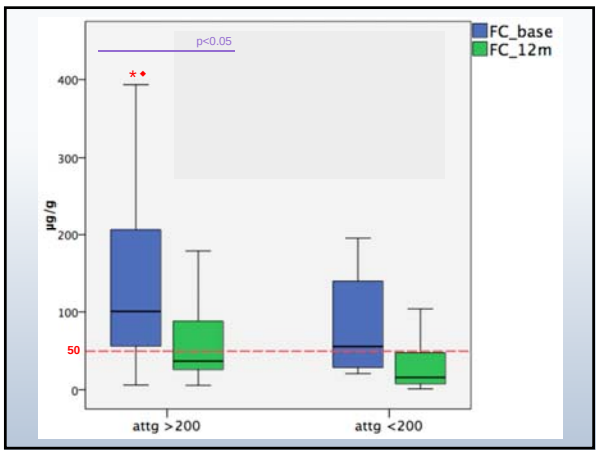
12 Month Demographics

		Serological Diagnosis	Biopsy Diagnosis	p-value
Follow-Up	Diagnosis to follow-up (months)[1]	11.0 (3.8)	11.7 (12.16)	>0.05
	Age (years)[1]	9.5 (3.5)	10 (3.2)	>0.05
	Gender (M:F)	14:18	16:27	>0.05
	Height (cm)[1]	136.6(21.3)	140.5 (20.1)	>0.05
	Weight (kg)[1]	34.6(14.7)	37.6 (16.7)	>0.05
	aTTG (U/ml)[2]	9.4 (1-98)	3.8 (1-420)	<0.005
	% aTTG Decline[2]	98.5 (90.67-99.9)	91.4(-308-99.8)	<0.001
	aTTG <7U/ml	40%	73%	<0.05

[1]Mean(SD), [2]Median(range) . Significance was shown through T-tests and Mann-Whitney tests ($p<0.05$).


p<0.05
LM_Base
LM_12m
0.12
0.10
0.08
0.06
0.04
0.02
0.00
attg >200
attg <200
Control


p<0.05
%FeSucrose_Base
%FeSucrose_12m
0.3
0.2
0.1
0.0
attg >200
attg <200
Control


p<0.05
FC_base
FC_12m
µg/g
400
300
200
100
50
0
attg >200
attg <200

Conclusions

1. Higher aTTG group had increased abnormalities in mucosal permeability and inflammation at baseline
2. Both CD groups showed showed improved intestinal permeability
3. There was no difference in adherence or symptom improvement between the diagnostic groups

Clinical Relevance

- Prospective study designed for the local setting
- Serological diagnosis **did not** disadvantage patients in regards to mucosal healing or adherence to GFD
- Families appreciated having the option of diagnosis route
- Engages family and child early in disease management

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Questions