Non-celiac gluten sensitivity (NCGS)

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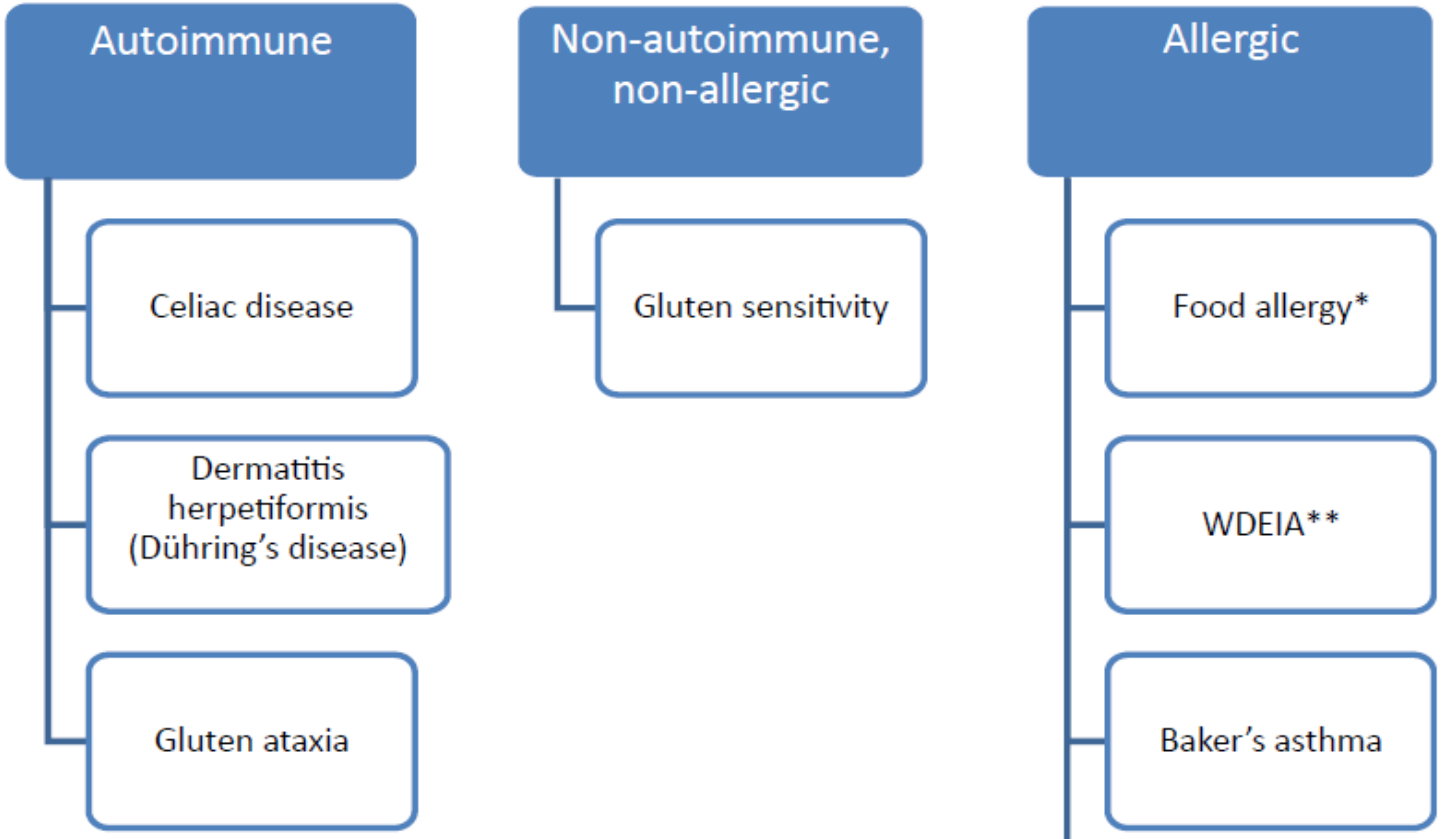
Wheat related disorders



* IgE-mediated and non-IgE-mediated

**wheat dependent exercise induced anaphylaxis

Fig. 2. Classification of gluten-related disorders.

History

The first comprehensively documented case of "gluten sensitivity" (in a non-celiac disease/wheat allergy patient) was reported in 1980[6]. That report described eight adult women suffering from incapacitating abdominal pain and chronic diarrhea which rapidly remitted when a gluten-free diet was initiated, with symptomatic relapse after re-exposure to a gluten containing diet (GCD). Jejunal biopsies

TABLE 1. Symptoms in Patients With Nonceliac Gluten Sensitivity

Gastrointestinal	Extraintestinal
Bloating	"Foggy" mind
Diarrhea	Tiredness
Constipation	Fatigue
Abdominal pain	Joint pain
Nausea	Depression
Vomiting	Numbness
Anal fissures	Loss of balance
	Eczema
	Anemia
	Weight fluctuations
	Rash
	Headaches



GI symptom

Non GI symptoms

- Migraine
- Headache



Non GI symptoms

- Autoimmune diseases in 25 % of subjects , autoimmune thyroiditis
- Iron deficient anemia (IDA)
- Headache, chronic fatigue , foggy mind, fibromyalgia, dermatitis , joint pain

Definition

- Symptoms triggered by gluten ingestion during hours or few days
- Resolution of symptoms on GFD during hours or few days

- Absence of celiac Disease (Normal TTG and normal histology)
- Absence of wheat allergy

Nutrients 2013 Sapone

Prevalence

The prevalence of NCGS remains unknown in many regions around the world.

The prevalence of NCGS is **0.6% - 13%** in Western populations

Young females are more involved than males (3:1)

Prevalence

- Prevalence in 4 years old children in Stockholm,s was 4%

- In recent UK study prevalence of self reported NCGS 13%

Acta paediatr 2008 ,97,85-90

بیماری سلیاک

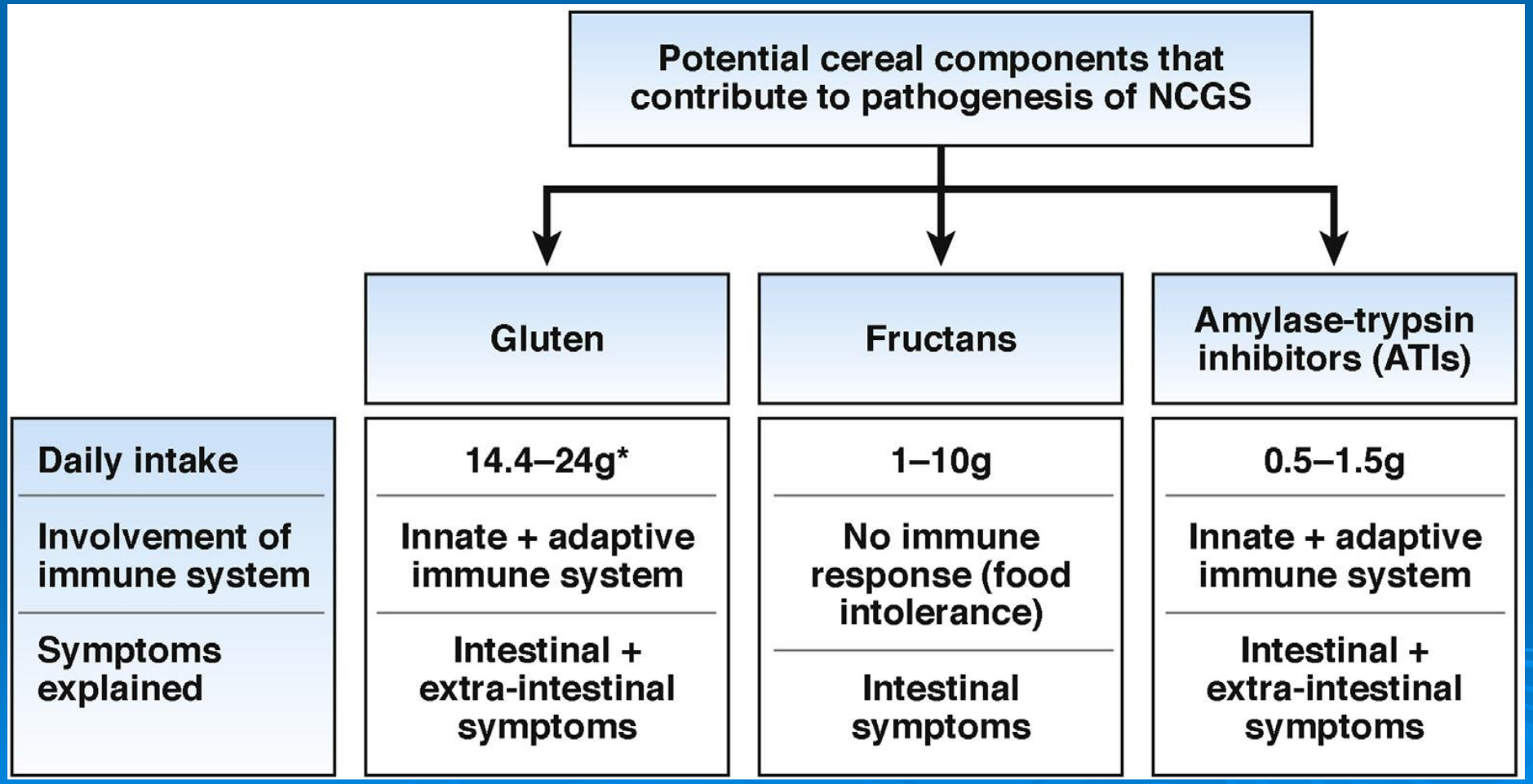


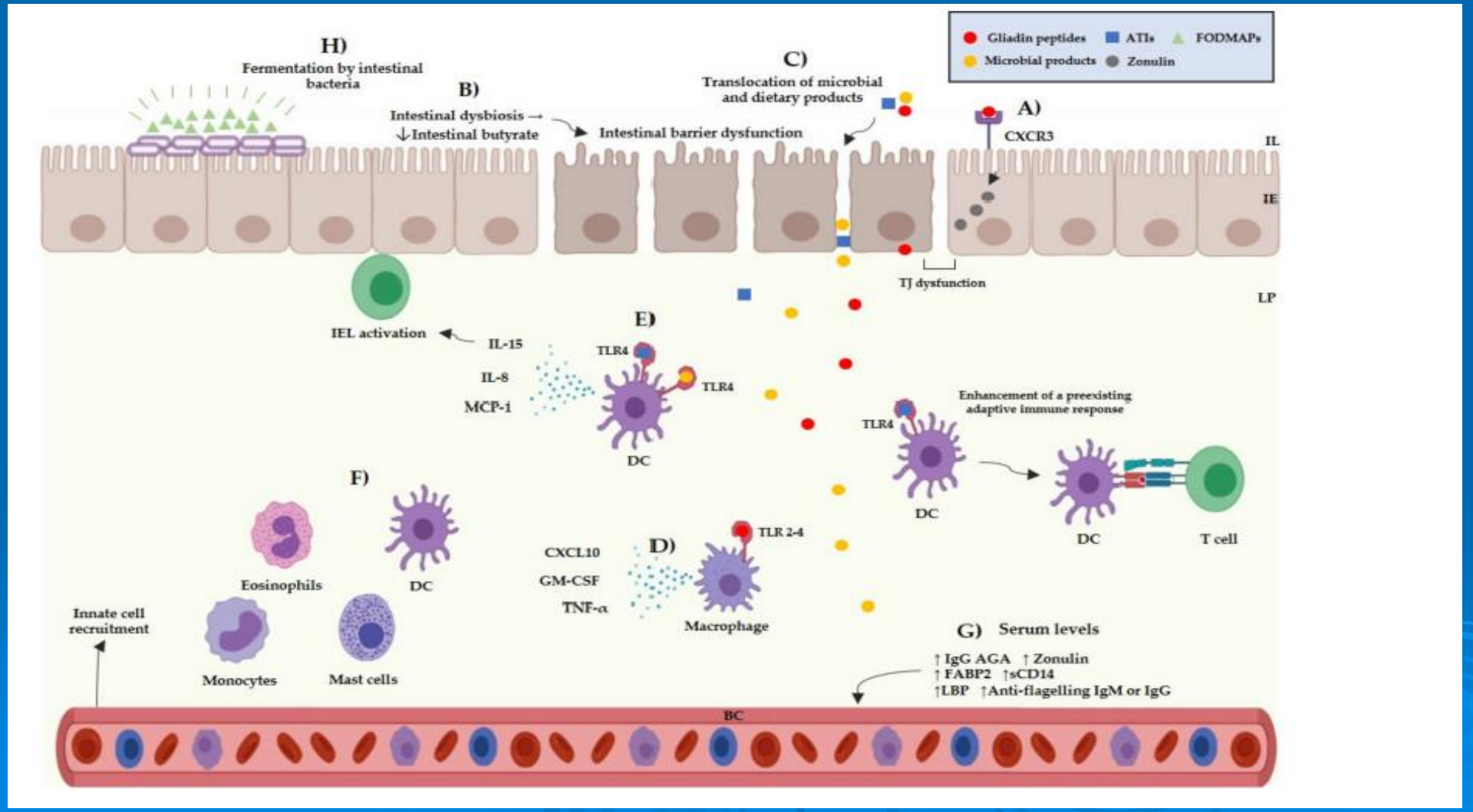
New biomarker

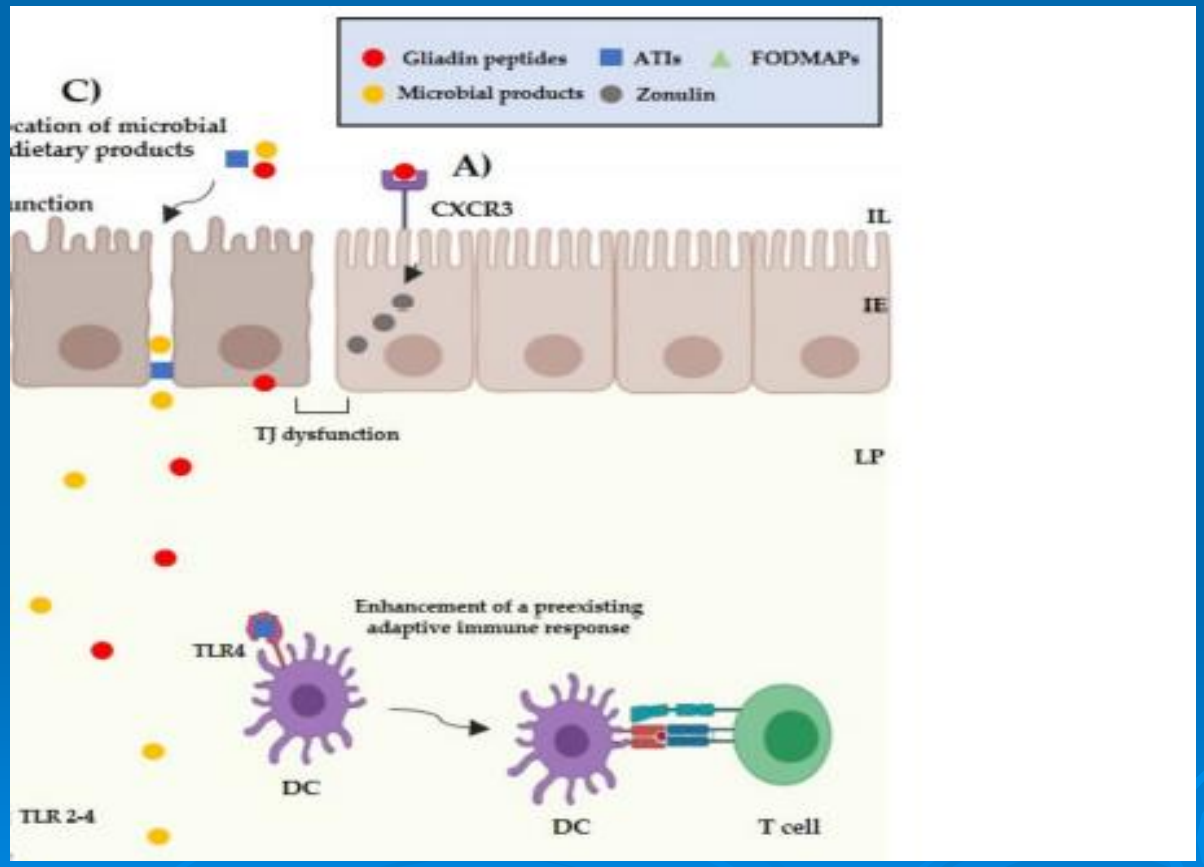
- Zonulin protein that increase permeability tight junction lead leaky gut
- In recent Italian study accuracy of zonulin level in 59 patients was 81%
- But utility of zonulin measurement in clinical practice remains to be stablished

N.C.G.S c.catassi 2023

Etiology


Potential cereal components that contribute to pathogenesis of NCGS
Gluten
Fructans
Amylase-trypsin inhibitors (ATIs)
Daily intake
Involvement of immune system
Symptoms explained
14.4–24g*
Innate + adaptive immune system
Intestinal + extra-intestinal symptoms
1–10g
No immune response (food intolerance)
Intestinal symptoms
0.5–1.5g
Innate + adaptive immune system
Intestinal + extra-intestinal symptoms


Gliadin peptides
ATIs
FODMAPs
Microbial products
Zonulin
H)
Fermentation by intestinal bacteria
B)
Intestinal dysbiosis →
↓Intestinal butyrate
C)
Translocation of microbial and dietary products
Intestinal barrier dysfunction
A)
CXCR3
IL
IE
LP
TJ dysfunction
IEL activation
IL-15
E)
TLR4
IL-8
MCP-1
TLR4
DC
Enhancement of a preexisting adaptive immune response
TLR4
DC
DC
T cell
F)
Eosinophils
DC
CXCL10
GM-CSF
TNF-α
D)
TLR 2-4
Macrophage
Innate cell recruitment
Monocytes
Mast cells
G) Serum levels
↑IgG AGA ↑Zonulin
↑FABP2 ↑sCD14
↑LBP ↑Anti-flagelling IgM or IgG
BC


Gliadin peptides
ATIs
FODMAPs
Microbial products
Zonulin
C)
cation of microbial
dietary products
unction
A)
CXCR3
IL
IE
TJ dysfunction
LP
Enhancement of a preexisting
adaptive immune response
TLR4
DC
TLR 2-4
DC
T cell

Pathogenesis

- Data show that there is a predominant role of **the innate immune system**
- Increased expression of toll-like receptor (TLR) 4 &2 and decreased expression of the T-regulatory cell marker
- Up-regulated levels of interleukin (IL) 8, transforming growth factor (TGF)
- evidence suggests that **both the innate and adaptive** immune systems trigger the intestinal inflammation

Pathology

- Mild duodenal inflammation
- MO but (median IEL is higher than 14)
- MI slight increase of intraepithelial lymphocytes like celiac
- No villous atrophy

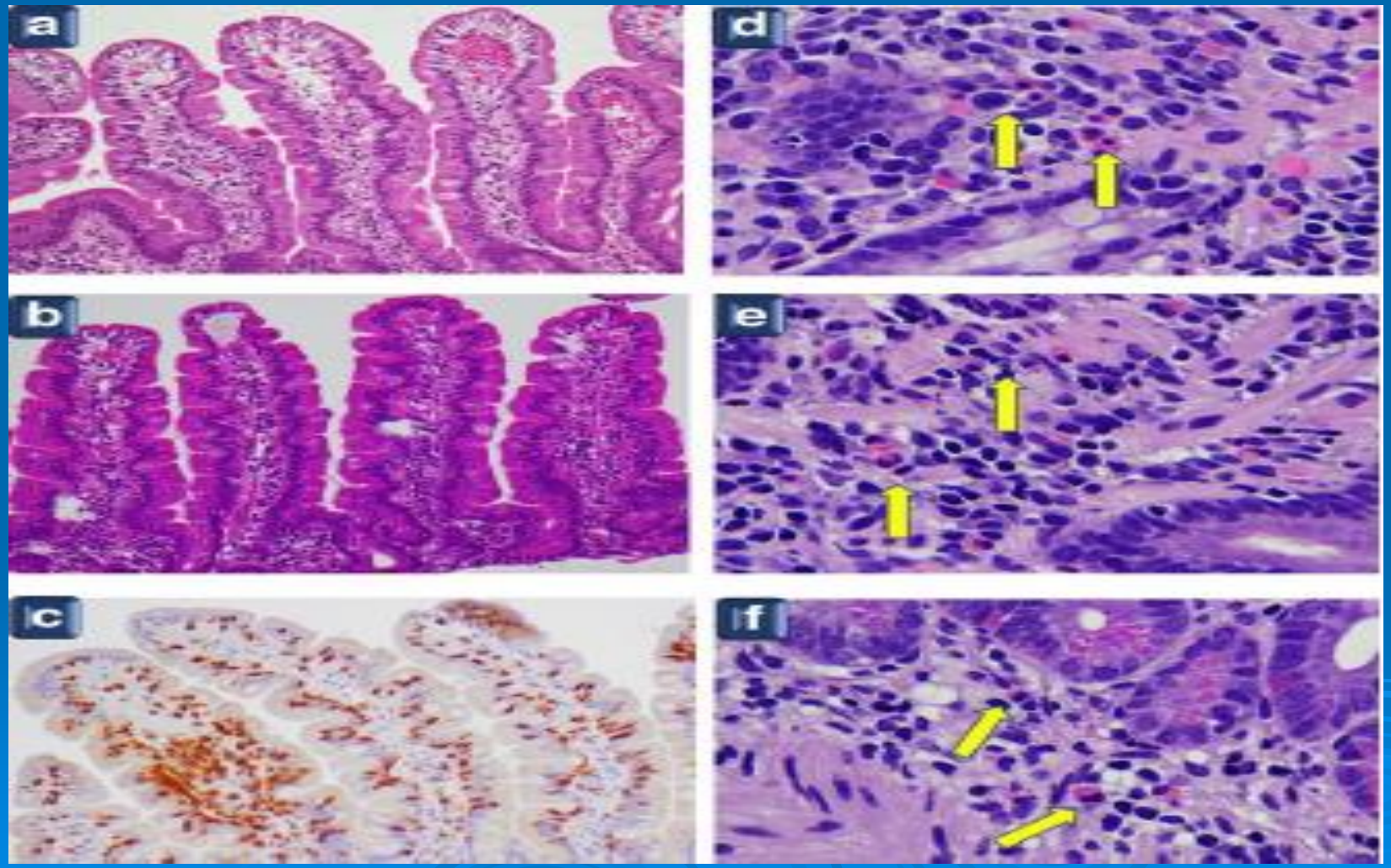
- Increased levels of eosinophils, and lamina propria T cells

Histopathology of NCGS

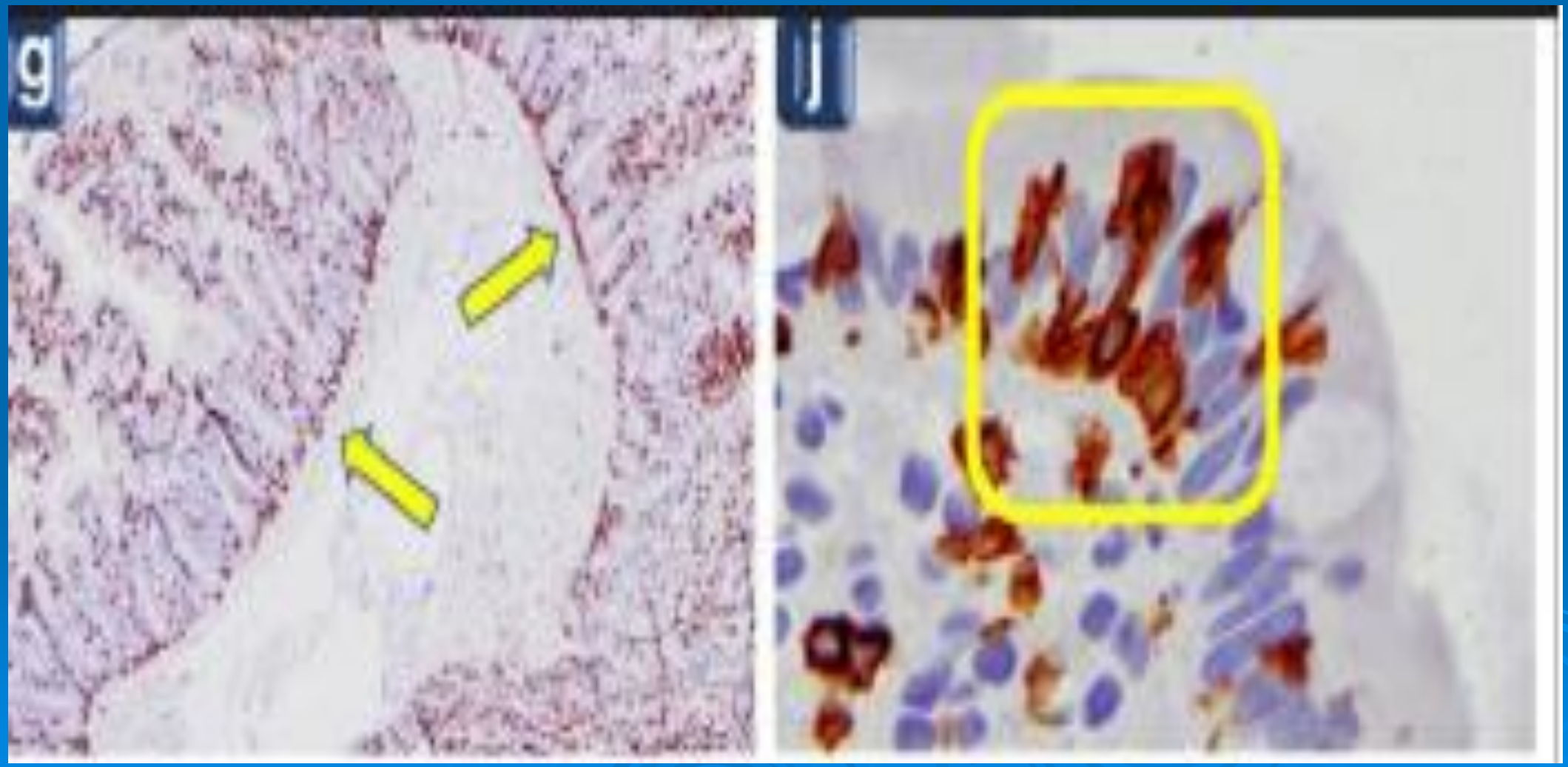
- Increase in **intraepithelial lymphocytes and eosinophils** (Marsh I)

- Increase the number of eosinophils

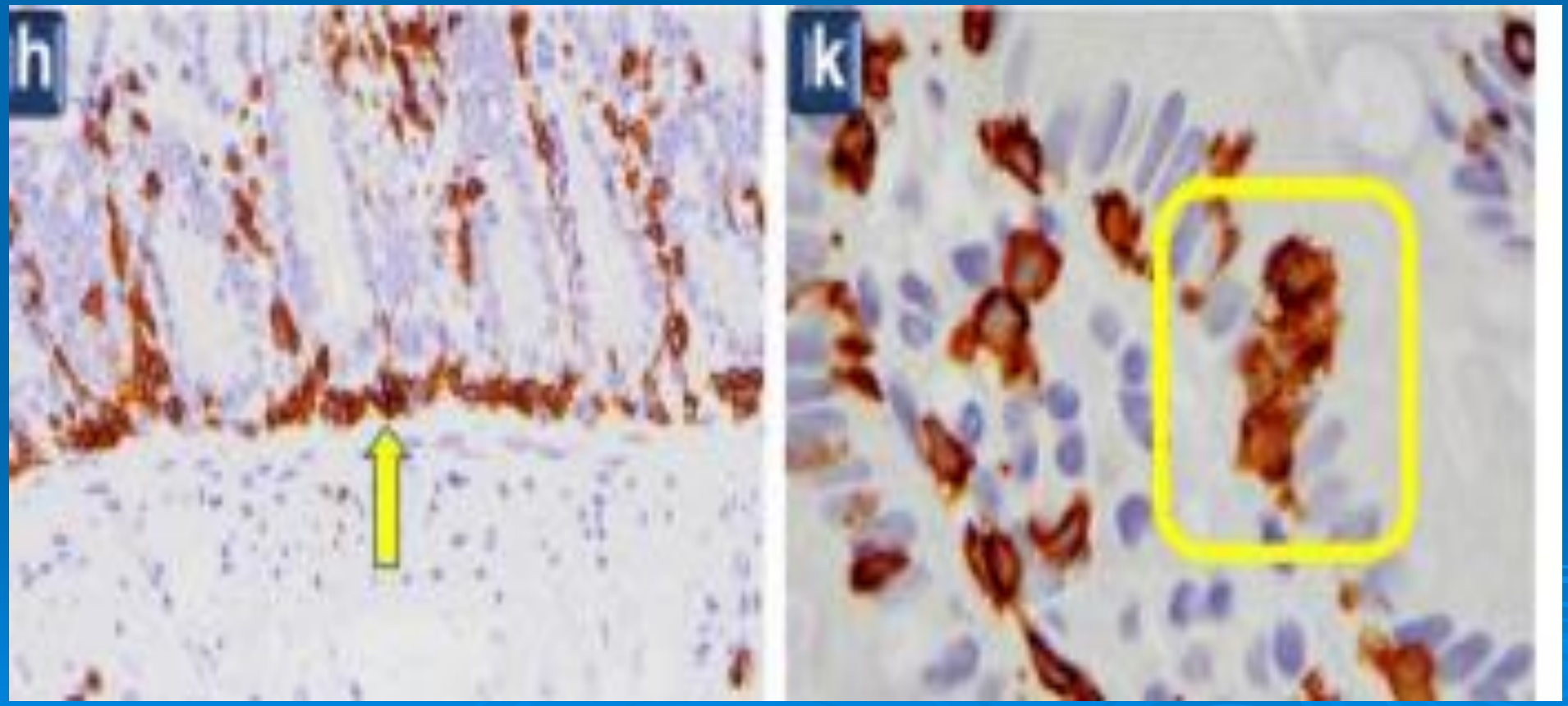
Pathology



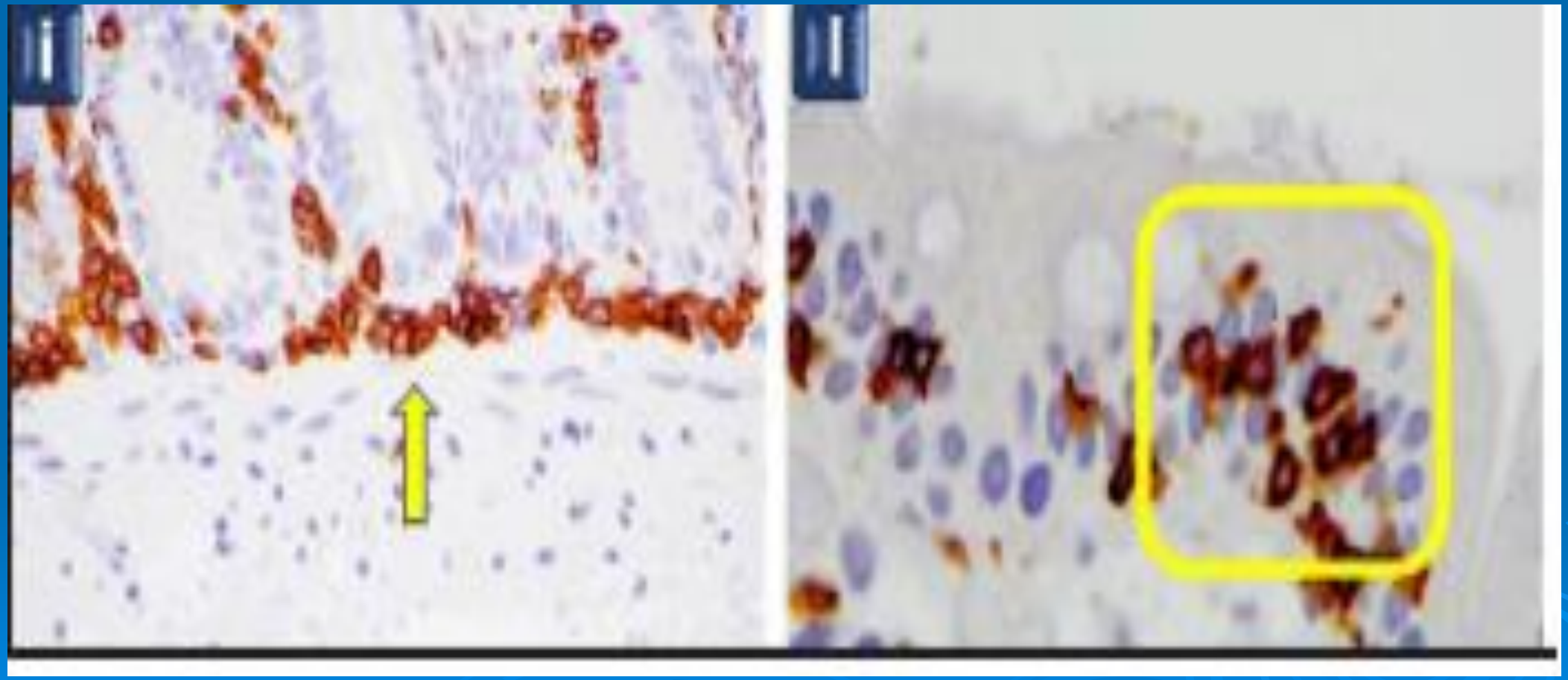
Pathology



Pathology



Pathology



Serology

- No specific lab marker yet identified
- Up to 50% AGA IgG is positive
- HLA DQ 2 & DQ 8 are present up to 50%

NCGS Diagnosis

- lack of sensitive and specific biomarkers for the diagnosis of NCGS

- Exclusion of CD
- Exclusion of wheat allergy by serum IgE levels
- Gluten elimination diet at least for 6 weeks
- Salreno expert's criteria

Nutrients – April 2015

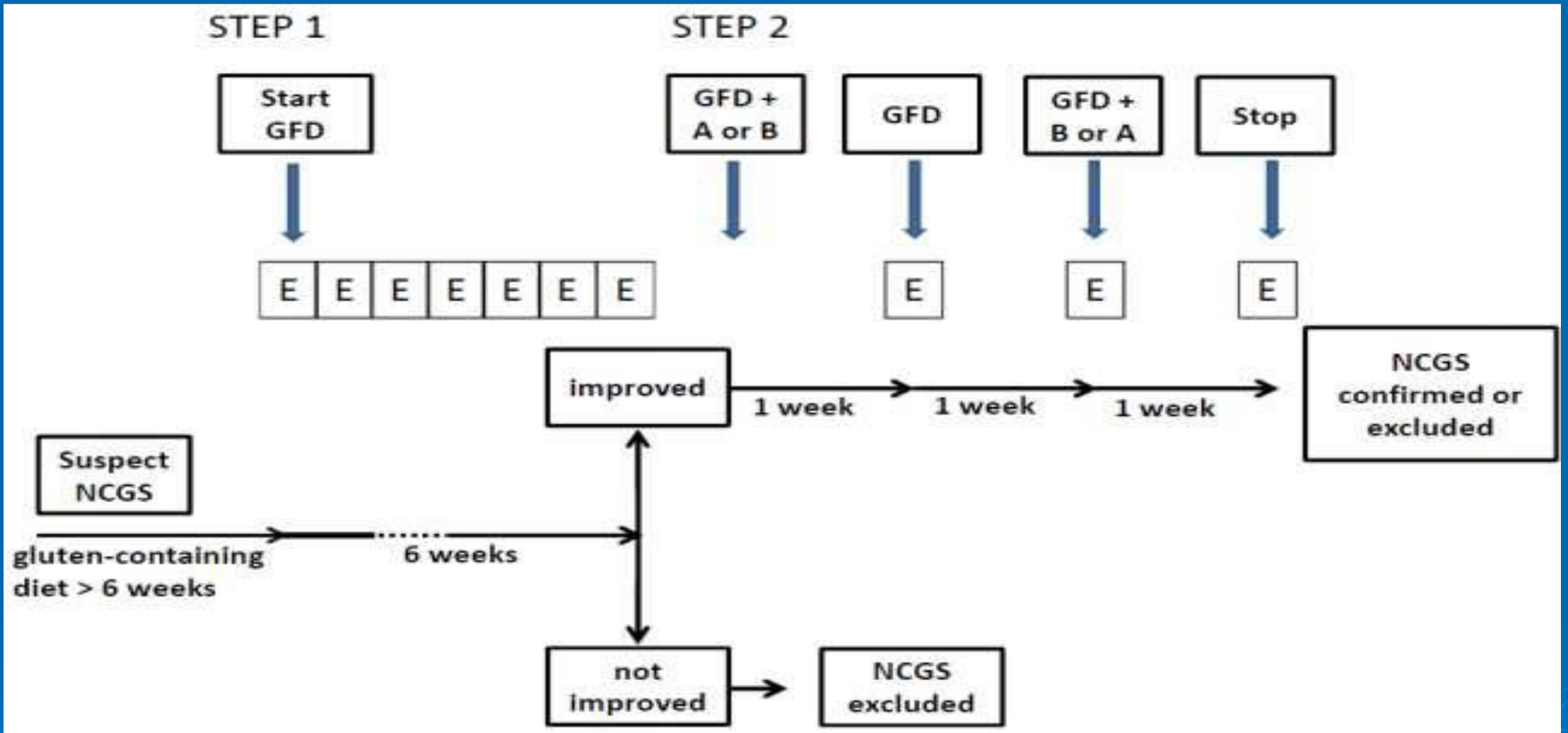


Figure 2. The flow diagram of the NCGS diagnostic process. GFD = gluten-free diet; A = product A (gluten or placebo); B = product B (placebo or gluten); E = evaluation (questionnaire). The evaluation is performed weekly during Step 1 and daily during Step 2.

Wheat related disorders

	NCGS	CD	WA
Trigger	Gluten, ATIs, FODMAPs	Gluten	Wheat proteins
Prevalence	0.49–14.9%	1%	1%
Pathogenesis	Predominant role of the innate immunity	Autoimmune	IgE-mediated allergenic reaction
HLA DQ2/DQ8	50% carry HLA DQ2/DQ8 haplotypes	>95% carry HLA DQ2/DQ8 haplotypes	No HLA DQ2/DQ8 restricted
Serological biomarkers	There is a lack of serological biomarkers (50% cases are IgG AGA positive)	IgA EMA, IgA tTG, IgG DGP	IgE against wheat-proteins
Histology	Marsh 0 to I	Marsh I to IV	Normal
Type of symptoms	Intestinal and extraintestinal	Intestinal and extraintestinal	Intestinal and extraintestinal
Onset of symptoms	Hours to days	Days to weeks	Minutes to hours
Symptoms intensity	Mild	Low to High	Low to High
Complications	Unknown	Long-term complications	Anaphylaxis
Diagnosis	DBPCGC	HLA DQ2/DQ8, antibodies and biopsy	IgE against wheat, skin-prick test and wheat challenge
Treatment	GFD, low-FODMAP diet	GFD	Wheat-free diet
Treatment duration	Unknown	Life-long	Life-long

NCGS & IBS

	NCGS	IBS
Food trigger	Gluten, ATIs, FODMAPs	Not restricted to wheat components found in gluten-containing cereals
Prevalence	0.49–14.9%	1.1–35.5%
HLA DQ2/DQ8	50% presents HLA DQ2/DQ8 haplotypes	No HLA DQ2/DQ8 restricted
Histology	Marsh 0 to I	Normal
Clinical manifestations	Intestinal and extraintestinal	Intestinal
Diagnosis	DBPC gluten challenge	Rome IV criteria
NvI	>1	<1
Treatment	GFD, low-FODMAP diet	Multi-approach treatment (may benefit with a GFD and low-FODMAP diet)

Management & Natural history

- GFD Symptoms usually disappear soon with withdrawal of gluten and relapse following challenge with in hours or few days
- Rechallenge after 1-2 years of GFD
- No major complications of untreated NCGS described unlike CD

Role of NCGS in Refractory Functional dyspepsia

A Randomized Double-Blind, Placebo-Controlled Trial

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MOHAMMAD M FANAEIAN, MD
TEHRAN UNIVERSITY OF MEDICAL SCIENCES



Dyspepsia

Dyspepsia is a common symptom (**25 %** of general population)

In about **75%** of patients with dyspepsia, we don’t find a structural pathology to identify the patient s symptoms.

Rome IV Criteria for Functional Dyspepsia

B1. Functional dyspepsia
Diagnostic criteria ¶
1. One or more of the following:
a. Bothersome postprandial fullness
b. Bothersome early satiation
c. Bothersome epigastric pain
d. Bothersome epigastric burning
AND
2. No evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms

¶ Criteria fulfilled for the last three month s with symptom onset at least six months before diagnosis.

Refractory Functional Dyspepsia

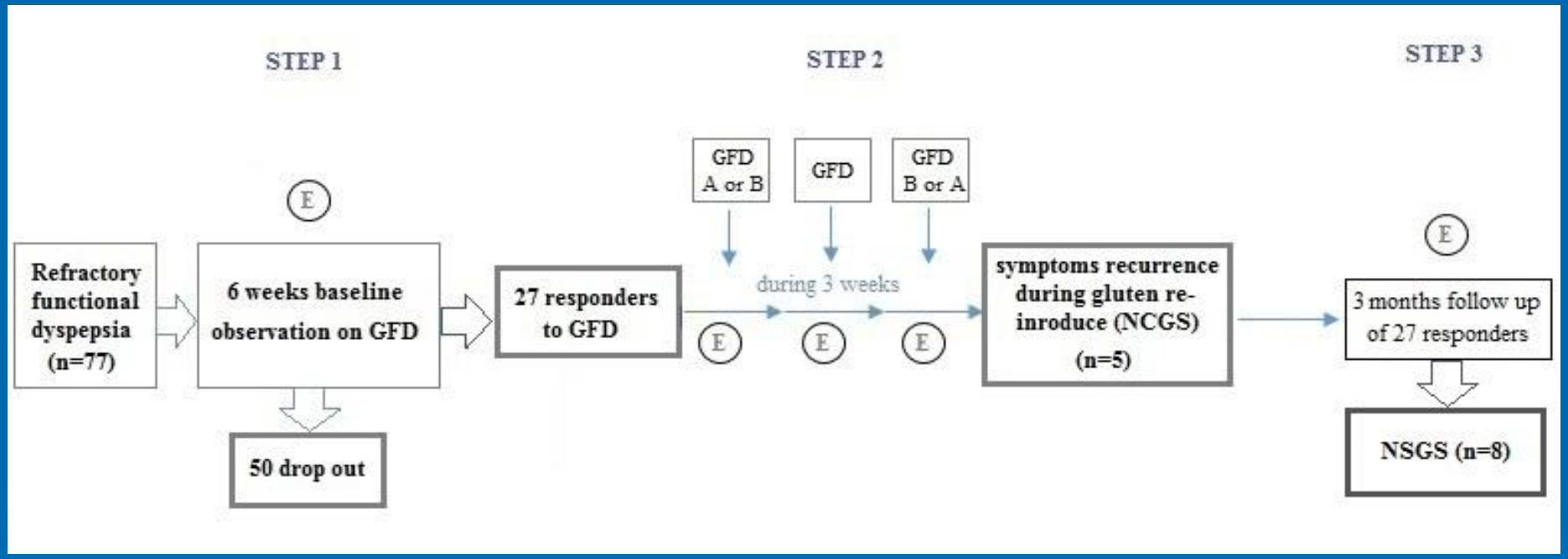
Refractory FD is defined as FD in patients with continuous symptoms for **at least 6 months** that has been unresponsive to at least two medical treatments, such as H. pylori eradication and PPIs, prokinetics or TCA

First step

- **Gluten-free regimen was introduced to all patients for six weeks.**

- After 6 weeks GFD, patients whose **symptoms improved** more than 3 score , were **entered** into the second step

Study protocol according saleno criteria



Results

- The age range 31 to 40 years old (80%)
- NCGS was more frequent in women than men (4:1)
- The most common GI symptoms was postprandial fullness and epigastric pain/burning

Results

- The most common extra-gastrointestinal symptoms was
- Headache/ fatigue (each 80%)
- And musculoskeletal pain (fibromyalgia)

Conclusions

- In addition to five patients **6.5%** who was diagnosed as NCGS by Salerno's Expert criteria

- Three more patients were categorized as NCGS during extra follow up **(overall 10.3%)**

Conclusions

- This study confirmed that due to significant prevalence of NCGS among patients with RFD **(6.5 %)**

- **We recommend 6-weeks GFD in patients with RFD**

SCIENTIFIC REPORTS
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Prevalence of Non-Celiac Gluten Sensitivity in Patients with Refractory Functional Dyspepsia: a Randomized Double-blind Placebo Controlled Trial

Bijan Shahbazkhani[1], Mohammad M. Fanaeian[1*], Mohammad J. Farahvash[1], Najmeh Aletaha[1], Foroogh Alborzi[1], Luca Elli[2], Amirhossein Shahbazkhani[1], Jayran Zebardast[3] & Mohammad Rostami-Nejad[4]

Refractory functional dyspepsia (RFD) is characterized by symptoms persistence in spite of medical treatment or *H. pylori* eradication. No study has yet investigated the presence of gluten-dependent RFD as a clinical presentation of Non-Celiac Gluten Sensitivity (NCGS). Patients with RFD, in whom celiac disease, wheat allergy and *H. pylori* infection had been ruled out, followed a six weeks long gluten-free diet (GFD). Symptoms were evaluated by means of visual analogue scales; patients with $\geq$30% improvement in at least one of the reported symptoms after GFD underwent a double-blind placebo controlled gluten challenge. Subjects were randomly divided in two groups and symptoms were evaluated after the gluten/placebo challenge. GFD responders were further followed on for 3 months to

Review > Mol Nutr Food Res. 2021 Mar;65(5):e1901274. doi: 10.1002/mnfr.201901274. Epub 2020 Jun 28.

Gluten-Free Diet in IBD: Time for a Recommendation?

Kimberly N Weaver [1], Hans Herfarth [1]

Affiliations + expand

PMID: 32558265 DOI: 10.1002/mnfr.201901274

Abstract

Patients and providers alike are highly interested in identifying potentially useful dietary interventions in the management of inflammatory bowel diseases (IBD). This review examines the clinical associations of celiac disease (CeD), non-celiac gluten sensitivity (NCGS), and IBD with a focus on available data of the therapeutic efficacy of gluten-free diet (GFD) or low-gluten-containing diets in the therapy of IBD. There is a strong association between CeD and microscopic colitis, but the prevalence of CeD among IBD patients is similar to that of the general population. Interestingly, in cross-sectional studies nearly one-third of IBD patients report a diagnosis of NCGS, and many follow a GFD. Although animal studies have shown that gluten ingestion may promote intestinal inflammation and increase intestinal permeability, there have been no prospective studies evaluating the role of a GFD in the induction and maintenance of Crohn's disease and ulcerative colitis. Several cross-sectional reports suggest that a GFD may improve symptoms in IBD patients, but due to a lack of high-quality prospective clinical studies, current data do not support the universal use of a GFD in IBD.

Keywords: Crohn's disease; gluten; gluten-free diet; inflammatory bowel diseases; non-celiac gluten sensitivity; nutrition; ulcerative colitis.

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If you look for NCGS disease you will find it

Comparative study of gluten free diet in Iranian patients with irritable bowel syndrome

- Double-blind randomized placebo-controlled trial

- **Dr B.shahbazkhani, Dr sadeghi**

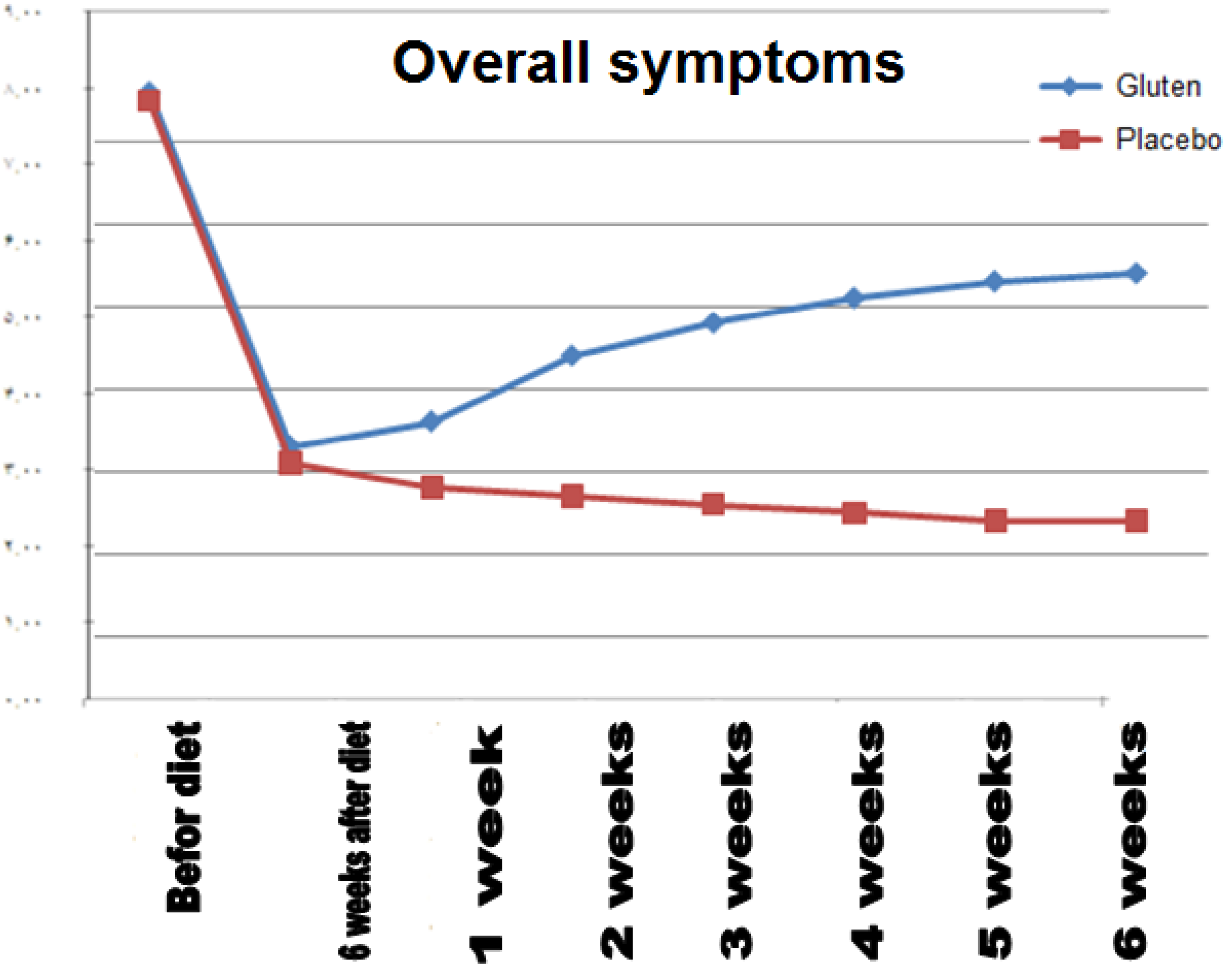
Methods

- During the study , **148 patients** with IBS diagnosis were enrolled , after 6 weeks GFD **80 patients respond to GFD**

- Finally, only **72 patients:**

  35 patients in the gluten(GCD) group ,

  37 patients in the placebo(GFD) group were enrolled


Overall symptoms
Gluten
Placebo
Befor diet
6 weeks after diet
1 week
2 weeks
3 weeks
4 weeks
5 weeks
6 weeks

Result

- symptomatic improvement was statistically different in the gluten-containing group compared with placebo

➢ GCD group in 9 (25.7%)

➢ GFD 31 (83.8%) patients ($p < 0.001$)

Conclusion

- **Gluten-free diet** is recommended

In patients with refractory IBS, without celiac disease

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Article

Non-Celiac Gluten Sensitivity Has Narrowed the Spectrum of Irritable Bowel Syndrome: A Double-Blind Randomized Placebo-Controlled Trial

Bijan Shahbazkhani [1,2,3], Amirsaeid Sadeghi [1,*], Reza Malekzadeh [2,3], Fatima Khatavi [4], Mehrnoosh Etemadi [4], Ebrahim Kalantri [5], Mohammad Rostami-Nejad [6] and Kamran Rostami [7]

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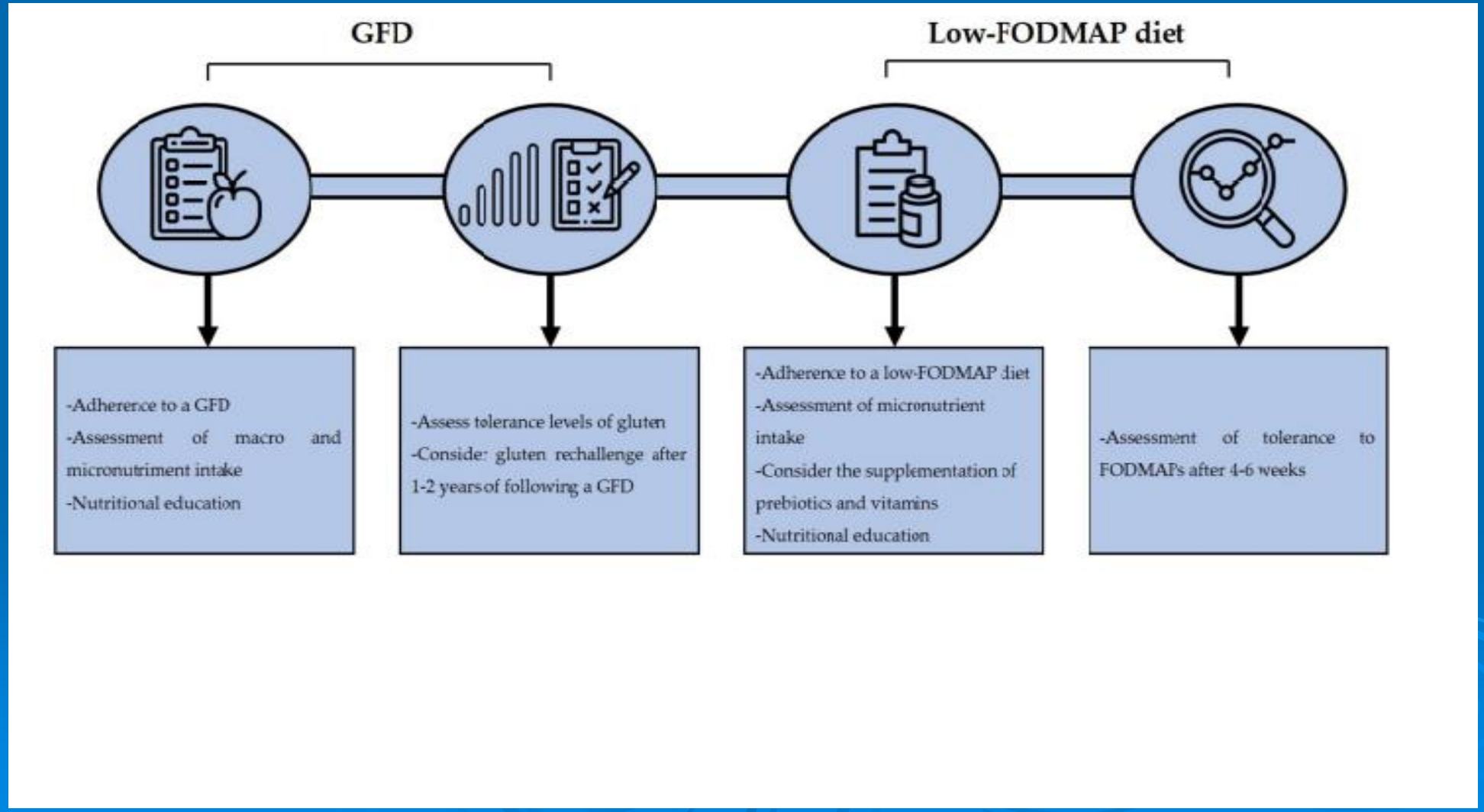
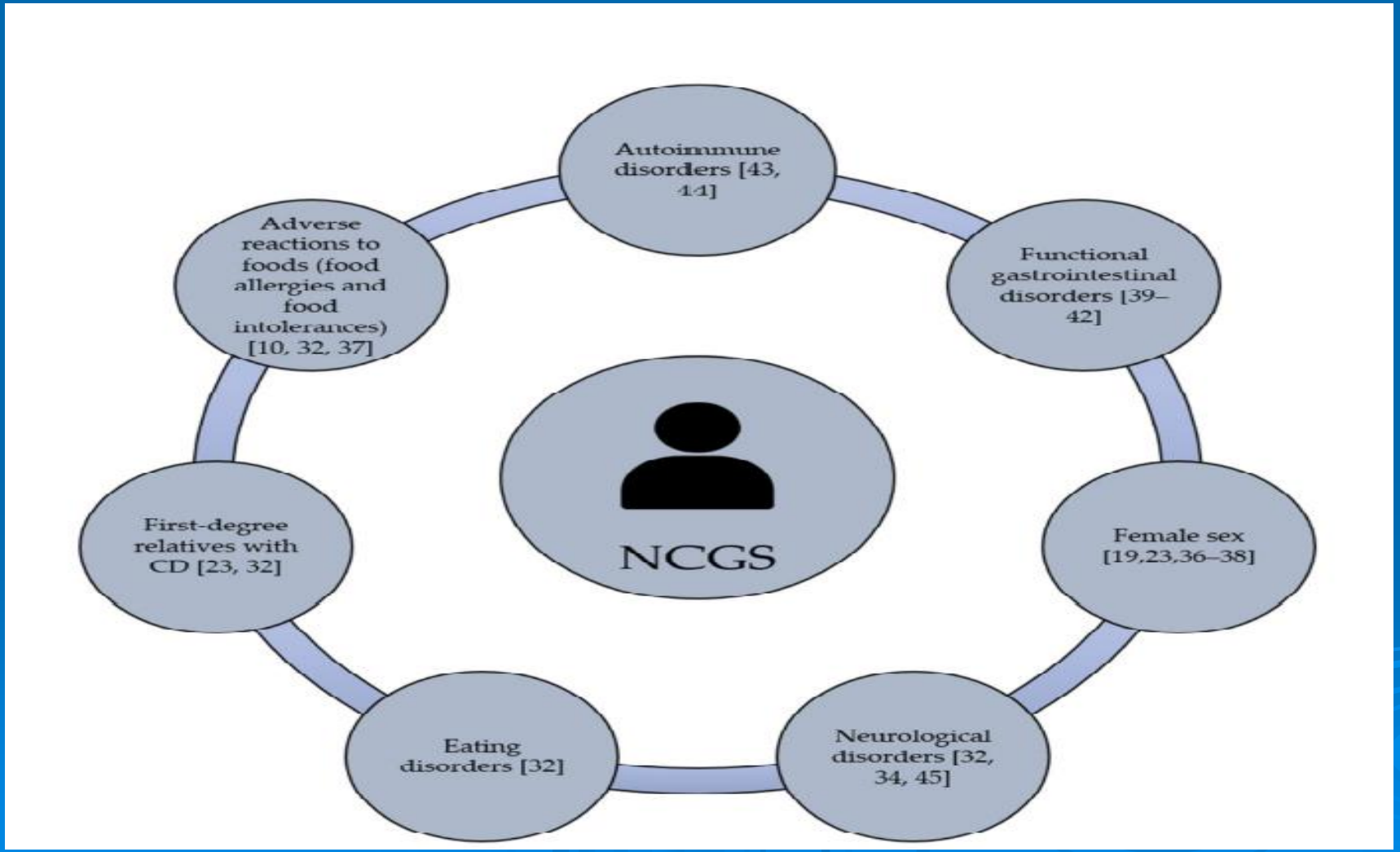

GFD
Low-FODMAP diet
-Adherence to a GFD
-Assessment of macro and micronutriment intake
-Nutritional education
-Assess tolerance levels of gluten
-Consider gluten rechallenge after 1-2 years of following a GFD
-Adherence to a low-FODMAP diet
-Assessment of micronutrient intake
-Consider the supplementation of prebiotics and vitamins
-Nutritional education
-Assessment of tolerance to FODMAPs after 4-6 weeks


Autoimmune disorders [43, 44]
Functional gastrointestinal disorders [39–42]
Female sex [19,23,36–38]
Neurological disorders [32, 34, 45]
Eating disorders [32]
First-degree relatives with CD [23, 32]
Adverse reactions to foods (food allergies and food intolerances) [10, 32, 37]
NCGS