

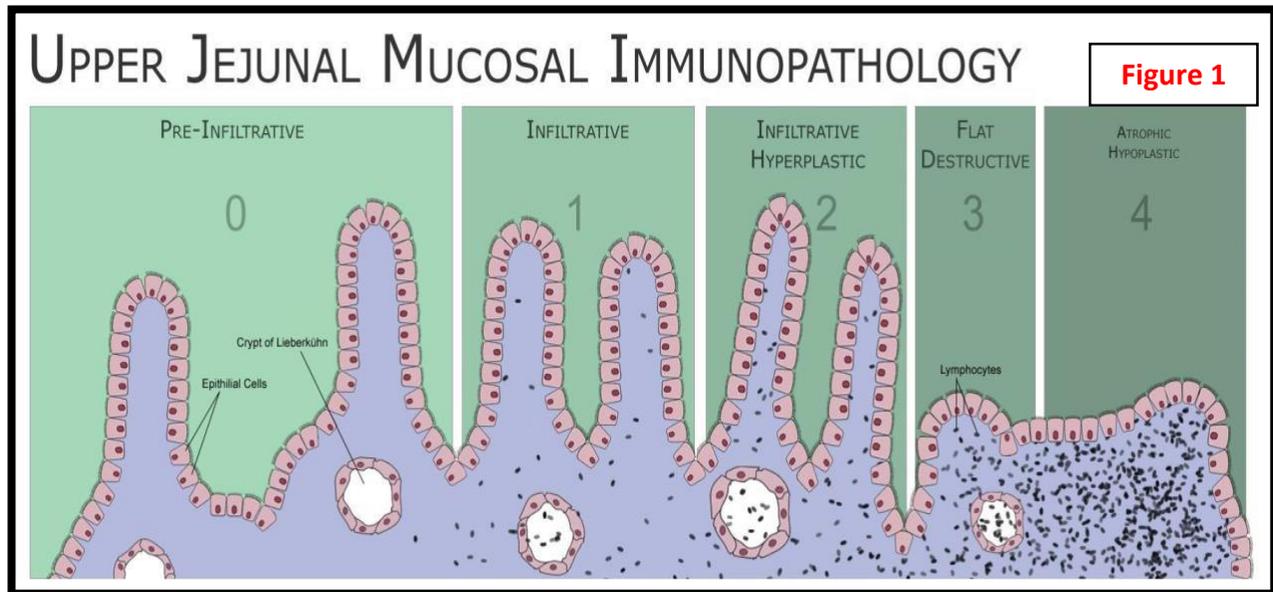
## Lec 7

## II- Liver &amp; Gastrointestinal Diseases (امراض الكبد والجهاز الهضمي)

(1) *Gluten sensitive Enteropathy*

**Gluten-sensitive enteropathy (GSE)** (التهاب الامعاء الحساس للغلوتين) or, as it is more commonly called, **Coeliac disease** or **celiac disease (CD)** (مرض الاضطراب الهضمي), is a chronic long-term autoimmune inflammatory disorder **of the small intestine** characterized by **villous atrophy** (الضمور الزغبي) and **mal absorption** (سوء الامتصاص) after ingestion of **gluten** (a component of **wheat protein** بروتين القمح), in individuals with a genetic susceptibility related to human leukocyte antigens **HLA-DQ2** and **HLA-DQ8**.

This disease either limited to the **intestine** (refer to **GSE**) or associated with **vesicular skin** (**Dermatitis herpetiformis**) refer to (**GSE-DH**).



In Figure1, various stages of damage to the small intestine in coeliac disease are shown schematically. Intact villi (الزغابات السليمة) are shown on the far left. These are exposed to inflammatory reactions, causing the villi to eventually lose their structure and develop a smooth surface (far right).

## **Epidemiology**

General population, Celiac disease is a common chronic condition and is estimated to affect approximately **0.5 to 1 percent** of the general population in many parts of the world. In Europe, the United States, and Australia, prevalence estimates range from 1:80 to 1:300 children (3 to 13 per 1000 children). **Females are affected approximately twice as often as males**, although the ratio varies depending on the strategy used to find cases.

## **Risk Factors:**

- Type 1 diabetes.
- Down syndrome or Turner syndrome.(متلازمة داون او تيرنر)
- Autoimmune thyroid disease.
- Microscopic colitis (lymphocytic or collagenous colitis)
- Addison's disease
- Genetic factors (HLA-DQ2, HLA-DQ8)

## **Clinical features of disease (Symptoms)**

- GSE is dominated via gastrointestinal tract (GIT) symptoms related to **mal absorption**.
- GSE-DH is dominated by **vesicular skin eruption** (اندفاع حويصلي جلدي), usually intestinal symptoms are rare or absent.
- The GIT manifestations are consist of weight loss, diarrhea, nutritional deficiencies and growth failure in children

**Silent celiac disease** is also known as **asymptomatic** (بدون اعراض) celiac disease. Patients do not complain of any symptoms, but still experience villous atrophy damage to their small intestine.

**Other symptoms and its possible causes**

Symptoms	Possible causes
Fatigue , malaise(وعكة)	Anemia , immune system activation
Weight loss	Nutrient mal absorption
Diarrhea	Accelerated GIT transit time, mal absorption
Anemia	Iron deficiency (most commonly) Vitamin B12 deficiency (less commonly)
Hypoglycemia (نقص سكر الدم)	Delayed absorption of glucose (تأخر امتصاص الكلوكوز)
Bone pain	Osteoporosis (هشاشة العظام)

Children with celiac disease are **more likely than adults** to have digestive problems, including (Nausea and vomiting, chronic diarrhea, swollen belly (بطن منتفخة), Constipation, and Gas).

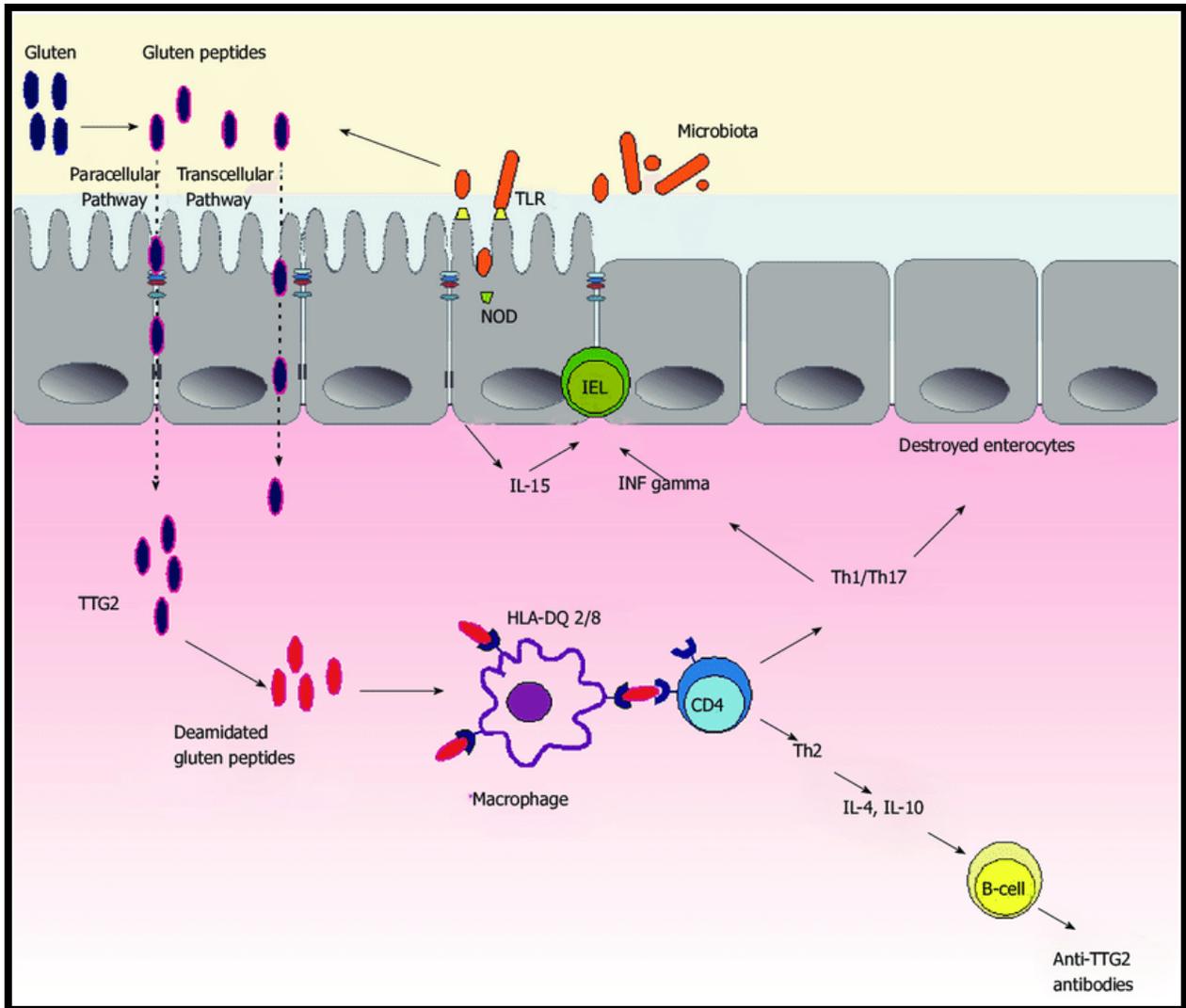
**Pathophysiology (immunopathogenesis)**

The pathogenesis involves a T-cell-mediated immune response and autoreactive B lymphocytes that produce autoantibodies directed against **gliadin** (بروتين سكري), **endomysium**(الغمد الليفى العضلي), or **tissue transglutaminase**.

**Two mechanisms are involved in this disease:**

**First mechanisms**

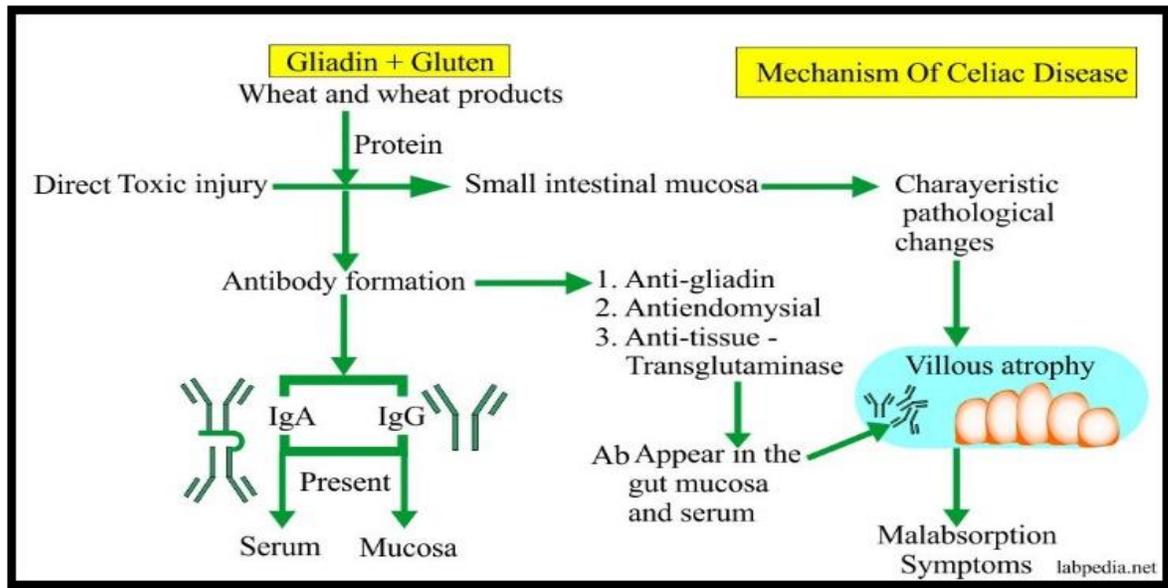
- Induction of T-cells by APC which present gliadin peptides to T-cells in the context of MHC Ags associated with GSE.
- The induced T-cells (TH1) produce IFN- $\gamma$  and TNF- $\alpha$  which then act on intestinal macrophage to produce pro-inflammatory cytokines such as IL-1 $\beta$  and TNF- $\alpha$ .
- These cytokines induce fibroblast to produce metallo-proteinase that are the proximal cause of injury to the Lamina Propria(LP) matrix supporting the villi.



**Second mechanisms**

- T-cells with T-Cells Receptor (TCR) bearing Intestinal **I**ntra**e**pithelial **L**ymphocytes (IEL) recognized and lyses epithelial cells expressing gliadin peptides presented in the context of non-classical MHC A<sub>g</sub>.
- B-cells specific for gliadin also occur in lesions and give rise to characteristic IgA-antigliadin Ab. Antibody for gliadin and an endogenous enzyme (transglutaminase) also occur. These entire Abs act to activate complement which subsequently amplifying the inflammatory process.

- These events seems to be genetically related to certain HLA molecules that enhance the development of disease, this act as a risk factor for developing of disease like HLA-B8, HLA-DR3 and HLA-DQ2 which participate in gliadin presentation to activate T-cells.



## Diagnosis

### 1-Serology testing

- Anti-tissue transglutaminase antibody (TTG)
- IgA anti-endomysial antibody (EMA) if TTG is positive
- IgA antigliadin antibodies (not recommended, low sensitivity).

### 2-Endoscopy with small bowel biopsy

### 3-Imaging

### 4-Hematological and biochemical test

CBC with platelets, serum Iron, Ferritin, Serum Vitamin B12, Serum folate (حامض الفولك), Calcium, Phosphate, Renal function test (urea and creatinine) and liver function tests (AST, ALT, Albumin and Alkaline phosphate).

**5-Genetic testing (HLA typing)** for human leukocyte antigens (HLA-DQ2 and HLA-DQ8) can be used to rule out celiac disease.

### **Differential diagnosis**

Anorexia Nervosa (فقدان الشهية العصبي)

Inflammatory Bowel Disease (like Crohn Disease)

Intestinal infections (eg. Giardiasis, *Clostridium difficile* )

Iron Deficiency Anemia (فقر الدم الناجم عن نقص الحديد)

Mal absorption (such as lactose tolerance)

Irritable Bowel Syndrome (IBS) (متلازمة القولون العصبي)

Viral infections (HIV)

Intestinal lymphoma (سرطان الغدد الليمفاوية المعوية)

Whipple's disease

Tuberculosis (السل الرئوي)

### **Abnormal laboratory findings in celiac disease (in lab)**

Anemia, elevated alkaline phosphatase, elevated aspartate transaminase and alanine transaminase levels, decrease albumin levels, vitamin D deficiency, leukocytosis and low levels of LDL and HDL.

### **Management of GSE**

- Strict gluten free diet (نظام غذائي صحي خالي من الغلوتين)
- Monitor of serological markers (TTG or EMA)(مراقبة الماركرات او الدلالات المناعية)