Role of the Innate Immune System in the Pathogenesis of Gluten Sensitivity

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Background:

Reaction to gluten can involve an allergic (wheat allergy), non-allergic [gluten sensitivity (GS)], or an autoimmune [celiac disease (CD)] mechanism.

Recent evidences suggest that early changes in intestinal permeability (IP) and activation of the innate immune system through Toll Like Receptor (TLR) signaling pathway may both play a pivotal role in the pathogenesis of CD.

Conversely, no data are currently available on the role of intestinal barrier dysfunction in the pathogenesis of GS.

Aims:

- To investigate the changes in IP, TJ protein genes expression and TLRs in GS patients
- To establish whether these changes are related to an increased number of intraepithelial T cells lymphocytes (IELs).

Methods:

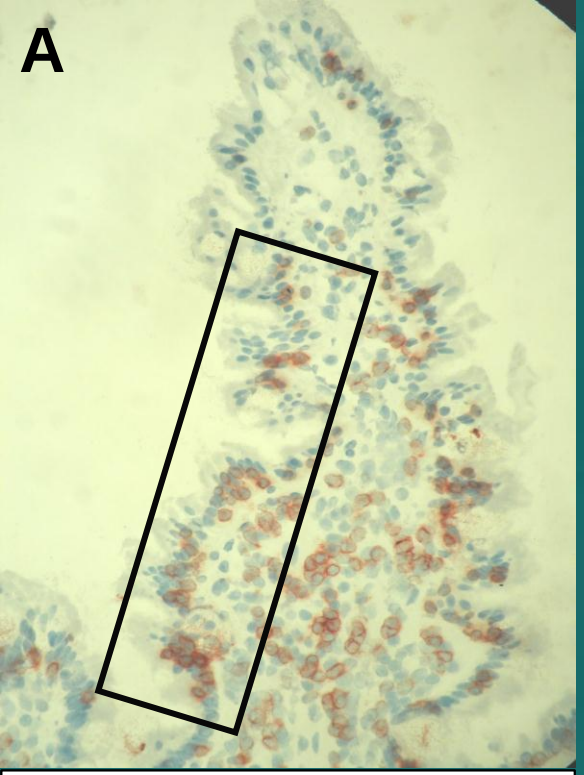
- Biopsy samples were obtained from 26 GS patients, 30 patients with active CD, 6 patients with CD in remission, and 14 healthy controls.
- Quantitative gene expression of tight junctions proteins Claudin (CL) 1, CL2, CL3, CL4, ZO-1, Occludin and of TLR1, TLR2 and TLR4 was performed by Real-time PCR.
- IP was evaluated by means of the lactulose/mannitol test (LA/MA).
- The numbers of IELs were detected with CD3 and TCR-γδ immunostaining and examined by counting the peroxidase stained cells.

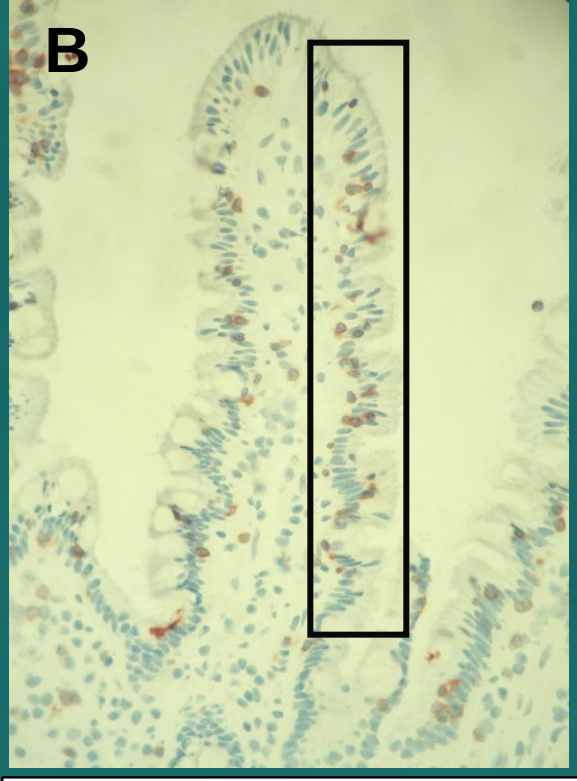
Results:

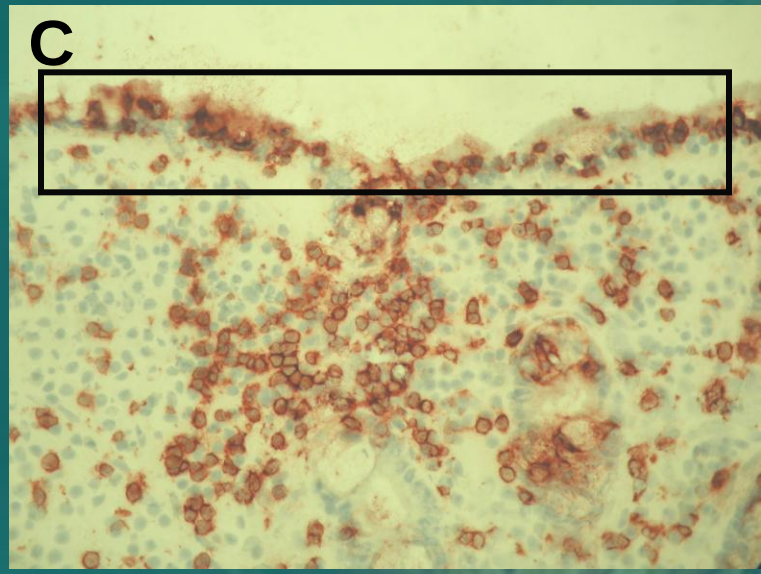
Serological,genetical, intestinal permeability parameters

	Healthy	GS	Celiac	CGFD
AGA	0%	**50%**	80%	0%
EMA	0%	0%	95%	0%
tTG	0%	0%	92%	0%
HLA DQ2/DQ8	30%	**50%**	99%	99%
PRICK/ RAST/ PRIST test	0%	25%	20%	0%
LA/MA test	0%	**0%**	80%	0%

Results :Duodenal IHC CD3+ IELs







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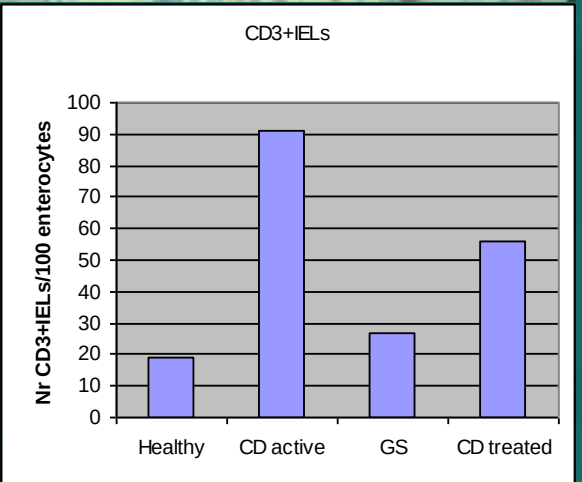
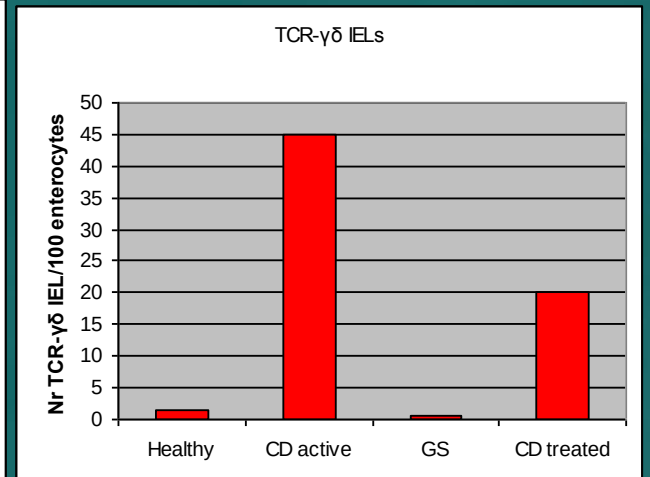


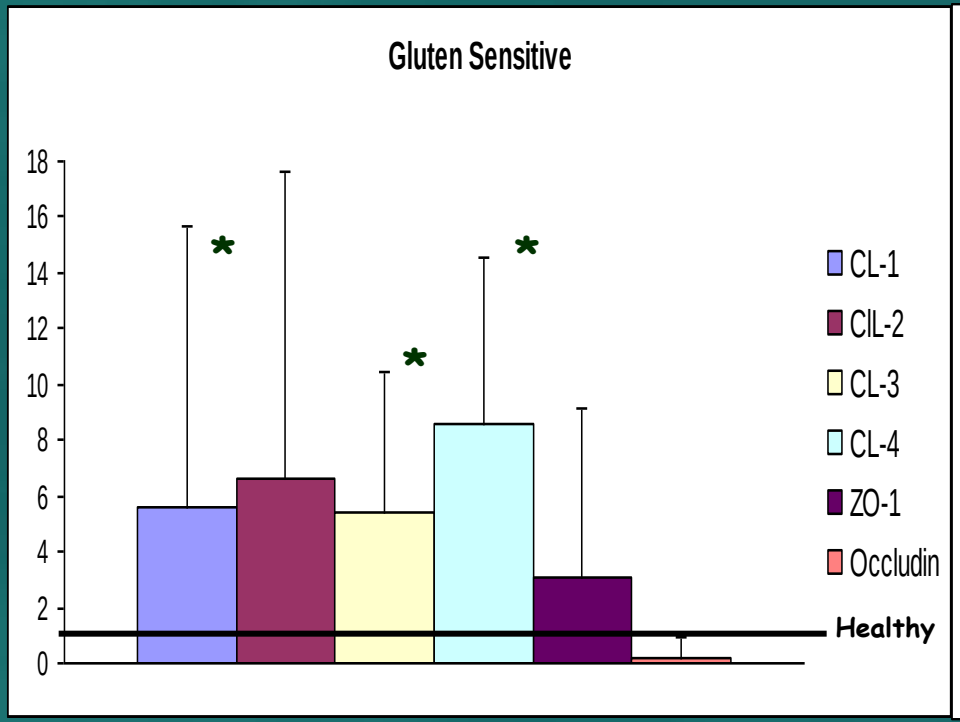


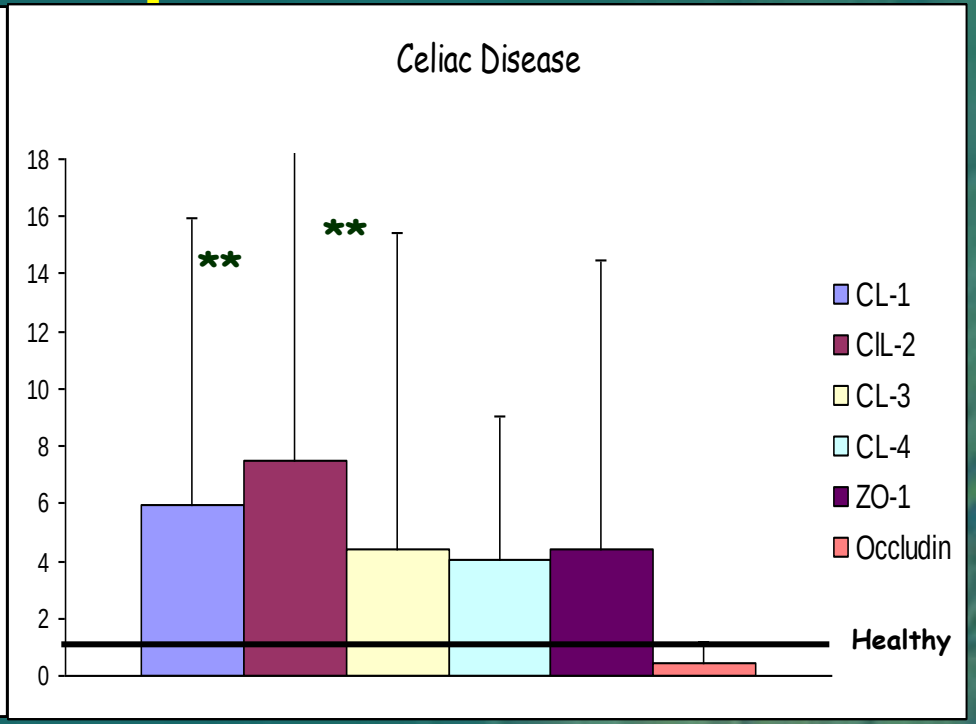
A= Gluten Sensitive

B= Control

C= CD Active

Results:
Intercellular TJ expression GS



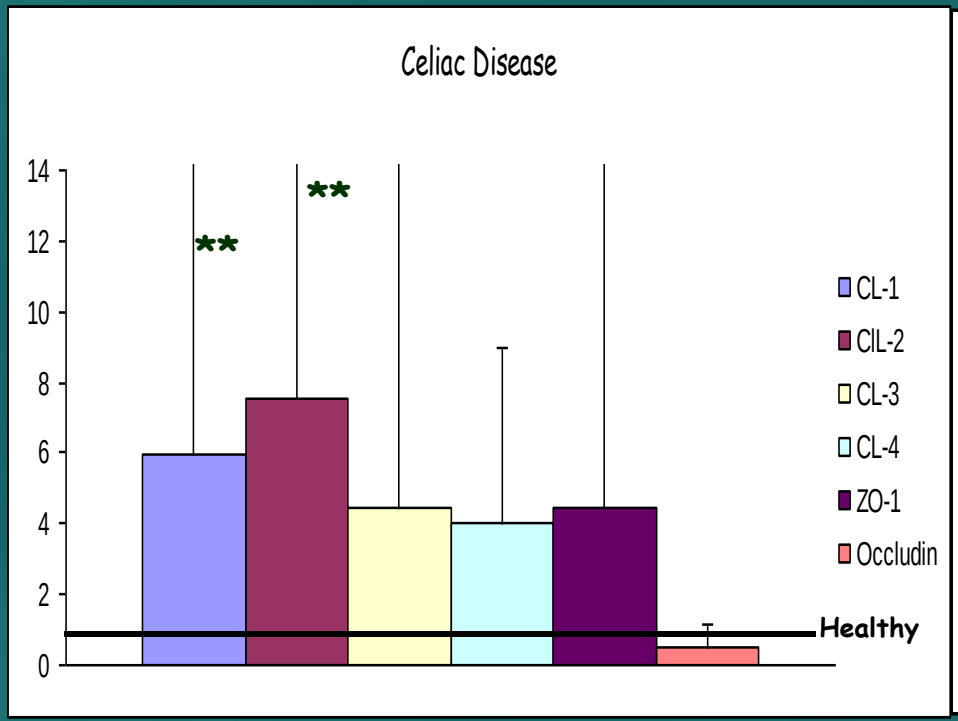


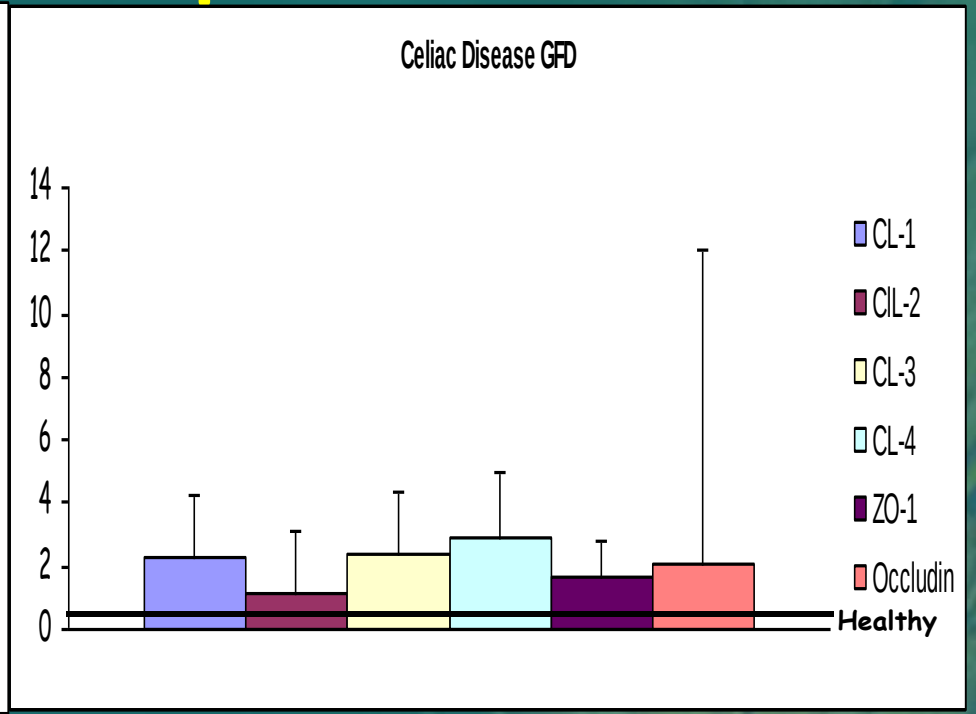
A significant over-expression of CL1, CL3 and CL4 were observed in GS patients compared to healthy control, while no changes in CL2 , ZO-1 and Occludin expression were detected. Conversely, in active CD patients a significant over-expression of CL1 and CL2 was observed.

* P <0.05 GS vs N

** P < 0.001 CD vs N

Results:
Intercellular TJ expression CD



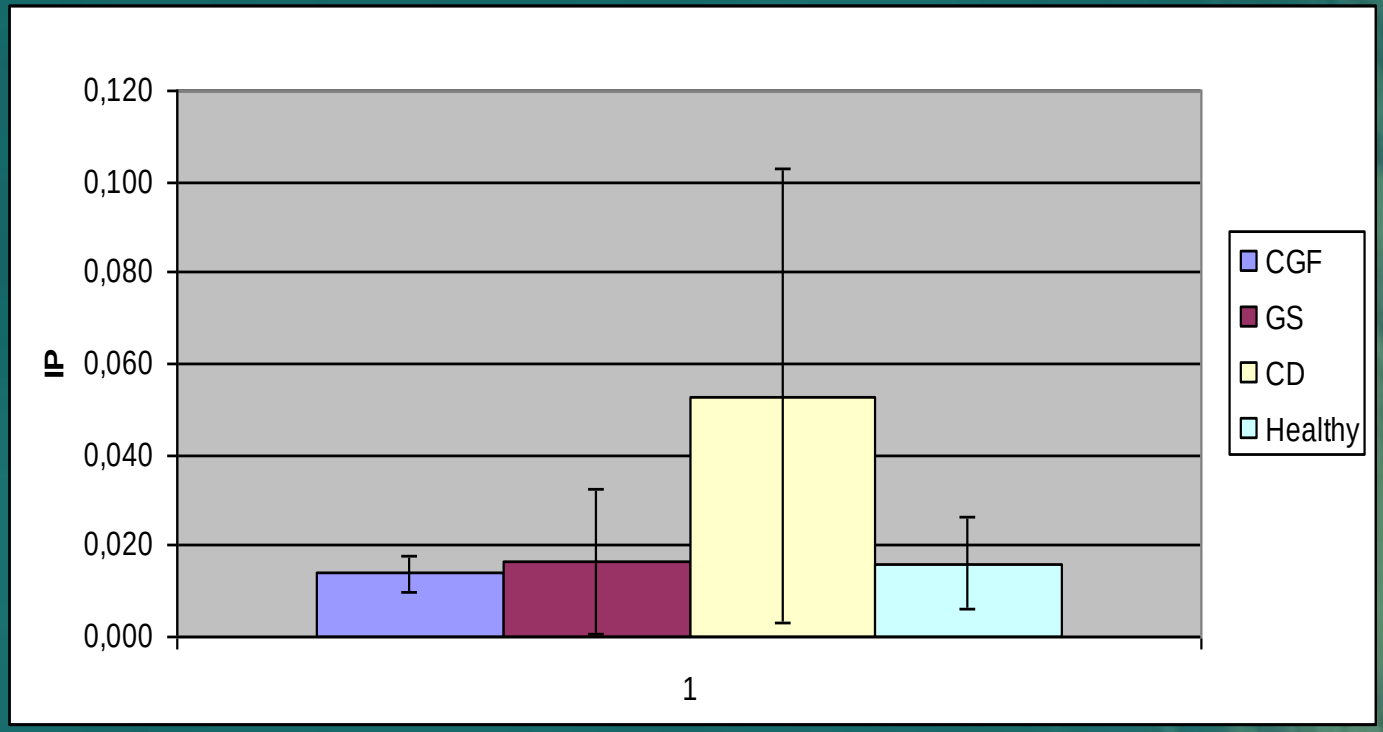


A significant over-expression of both CL1 and CL2 was observed in CD patients, while no significant changes in CL3, CL4, ZO-1 and Occludin were detected. Conversely in the CD patients on gluten free diet the CL1 and CL2 returned to normal levels.

** P <0.001 CD vs N

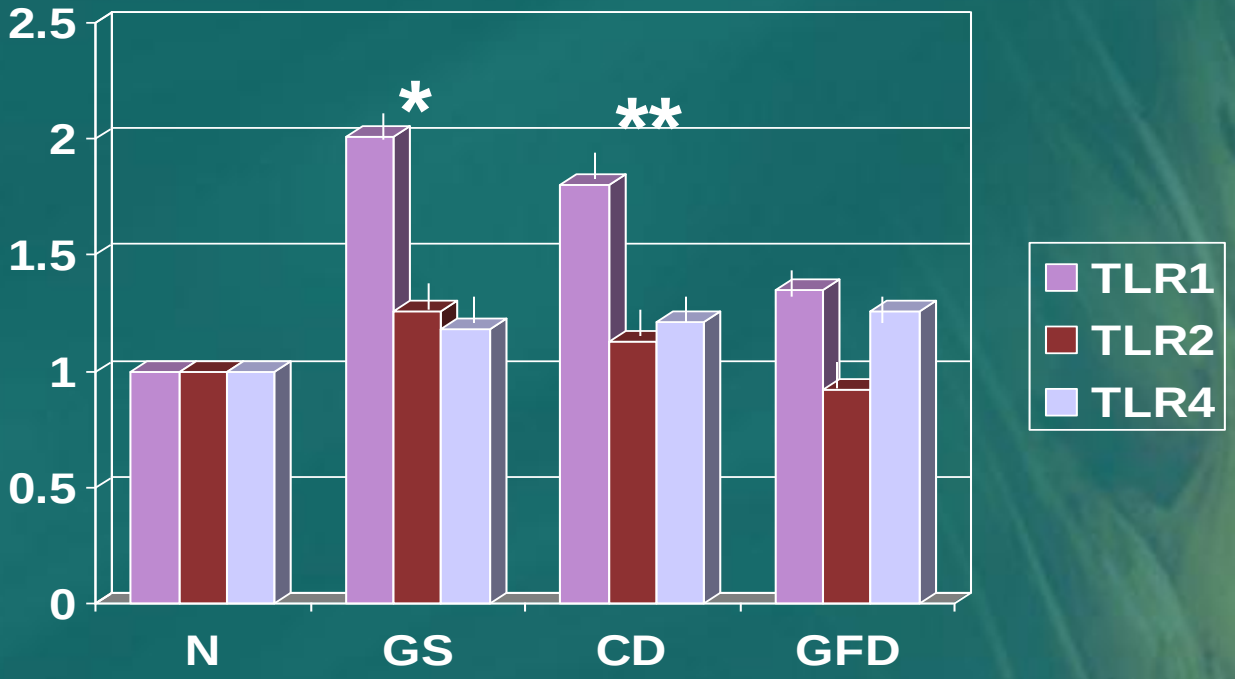
Results:

Change in Intestinal Permeability in GS and CD patients



In GS patients IP (0.014±0.015) was similar to that detected in healthy controls (0,019±0,018). Conversely, in CD the increased expression of CL1 and CL2 was associated to an increase in IP (0.052±0.048), but not statistically significant. In CD patients in remission IP (0.014±0.004) returned to normal levels.

Results: TLR



* P = 0.0039 GS vs N

** P = 0.027 CD vs N

Conclusions:

- Compared to CD patients, GS subjects showed normal IP and CL2 expression.
- Up-regulation of CL1, 3 and 4 in GS patients did not influence IP.
- These results suggest that the pathogenesis of GS is different from that of CD and does not involve the loss of intestinal barrier function.
- The over expression of TLR 1 in CD and GS could suggest an important role of innate immune system in both conditions.
- **Gluten Sensitivity** appears to be a new chapter in the book of "Food intolerance" to be investigated.