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Evaluation of some Serum cytokine and adipokines profile in Iraqi celiac patients before and after treatment

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Abstract: *Celiac disease (CD) is main gastrointestinal disease initiated by an immune reaction to gluten in genetically susceptible people. The objective of this analysis attempted to evaluate the nature as well as effect of systemic cytokine and adipokines levels within the pathophysiology of CD and also the role of therapy with gluten completely free diet on the status of its. Cytokine assays had been carried out on fifty children patients with effective CD and positive TTG IgA antibodies, and the effects were compared with healthy controls. Individuals with active CD with positive antibodies had significantly greater degrees of pro inflammatory cytokines, for example interferon- γ, tumor necrosis factor–α, IL-4 and IL-6,IL-8, and the Th -2 cytokines for example IL-5 and IL-10, in contrast to controls. Additionally, a statistically significance correlation involving levels of TTG IgA titters as well as serum levels of Th- 2 cytokines IL -4 ($p < 0.001$), IL- 10 ($p < 0.001$) along with inflammatory cytokines including IL -12 ($p < 0.001$) had been recognized, No impact on cytokine levels between the 2 organizations on and off gluten free diet (GFD) was discovered for TNF, IL -1, IL-8 and IL- , IL-4. Immediately after gluten free diet, levels of IL- 5, IL-10 and IL-12 decreased significantly ($P < 0.001$) and IFN- γ levels have been decreased ($P < 0.05$). In addition children with celiac disease off of a GFD exhibited larger ghrelin levels than children on a GFD. Adiponectin levels were not age, sex or GFD -dependent. Therapy with GFD had no effect on the adiponectin and leptin levels in children with CD, nonetheless, a GFD reduced extremely higher ghrelin levels in pre- pubertal children.*

Keywords*: Celiac disease, adipocytes, Cytokine profile, Gluten*

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I. Introduction

Celiac disease (CD) is an autoimmune disease, impacting 1 % of the community and research implies the occurrence is increasing [1], CD is identified as gluten sensitive enteropathy also it's considered as chronic inflammatory disease of small intestine recognized by malabsorption after ingestion gluten coming from wheat or maybe associated derivatives of rye and barley of people with a particular history. The pathogenesis entails a T cell mediated immune reaction as well as autoreactive B lymphocytes which generate autoantibodies against gliadin, endomysium or tissue transglutaminase (tTG) within people having a hereditary susceptibility associated with HLA- DQ2 and HLA- DQ8 [2,3].

The highest levels of cytokine correlate with disease activity have been shown [4, 5]. During effective Celiac disease (ACD), activated T cell in the small intestinal mucosa make the Th1 cytokine, interferon (IFN)-gamma and also convey a Th-1 transcription factor [6 ,7]. There is similarly higher creation of interleukin -15 from the intestinal epithelial cells, that influences the intraepithelial lymphocytes to create IFN- γ [8,9]. A task for cytokines within mediating mucosal harm has been recommended for tumor necrosis factor (TNF-α) and interleukin (IL-1β), as the cytokines are proven to enhancement the expression of specific metalloproteinase's with consequent destruction of extracellular matrix components [10, 11].

Gliadin has additionally been noticed to promote the generation of TNF-α and IL-8 by peripheral blood monocytes from individuals with effective CD *in vitro* [12]. Cytokines are implicated within each suppressing and enhancing immune response by way of the influence of theirs on T cells along with other immune effectors. IL-2, IL-12, INF- γ, and TNF-α stimulate Th-1 lymphocytes but, IL-4, IL-5, as well as IL- 10 result in Th-2 cell activation [13].

In CD, both Th-1 and Th-2 cytokines are proven to become elevated. for the reason that just restricted published information are currently available, we chose in order to do an extensive analysis of serum cytokine and also adipokines levels in people with CD. The objectives of this study had been defining serum cytokine and adipokines profiles of CD individuals, and in order to assess the result associated with a gluten free diet (GFD) on some serum cytokine and adipokines levels; as well as discover a correlation of serum cytokine and adipokines levels with anti TTG IgA antibody levels and evaluation of villous atrophy.

II. Materials and methods

Fifty Iraqi CD children with mean age 9.6 years, vary 3-18 years, each female and male, were incorporated for this specific research. They are presence the consultant clinical hospital of Pediatric department in Pediatrician Al- Kadhimiah Teaching Hospital, from April 2016 to March 2017. All patients are diagnosed by clinicians and established by histological and serological assessments. Children have been examined for tTG autoantibodies and also retested following three weeks if remaining at first tTG autoantibody positive. Children continually tTG autoantibody positive at follow up have been described as getting celiac disease autoimmunity (CDA) as well as described intestinal biopsy to verify the examination of celiac disease. Intestinal biopsies have been occurred with endoscope. The intestinal biopsies have been taken, and used for histological analysis. Histopathological exams by haematoxylin as well as eosin stained had been carried out by a pathologist blinded on the medical and lab. results. Grade III or grade IV small intestinal atrophy was discovered for all biopsies coming from established CD children while the normal intestinal histology was noticed in biopsies coming from ineffective CD children and controls. Children with a biopsy demonstrating Marsh score one or higher had been regarded as to get biopsy proven celiac disease and put on a gluten free diet. While not categorized as celiac disease based on the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) [13], children possessing a Marsh score one putted on the celiac disease group due to HLA danger genotype, heightened tTG autoantibodies and histological indications of incipient celiac disease[14 ,15] . Allchildren with CDA, irrespective of biopsy result, were definitely in the cytokine and adipokines measurements. For complete, blood samples as a result of fifty children have been provided of with whom twenty five children had biopsy confirmed celiac disease [Marsh 1: 3 of 25 (11 %) along with Marsh 3: 23 of 26 (89%)] as well as 8 children had normal intestinal biopsy (Marsh zero), albeit described as having CDA. Serum samples from fifty tTG autoantibody negative children coordinate for sample date, year of birth, gender as well as HLA genotype had been selected as a healthy control. all serum samples have been analysed utilizing an sandwich enzyme linked immunosorbent (Th1/Th2) assay (USA), within that each and every cytokine was assessed in exactly the same period in a one single sample at the same time (twenty five µl human serum). Within the assay, the following cytokines have been calculated: interferon (IFN- γ), interleukin (IL -10, IL -12, IL- 13, IL- 1, IL-2,IL-4, IL- 5, IL-8 and TNF-α, as per the manufacturer's protocol through the ELISA kits (Abcam,USA). Leptin, adiponectin as well as gherlin had been additionally assessed by using ELISA systems from (Uscf, china).

Ethical clearance

The analysis process was assessed and endorsed through the ethical review Committee on the altafil teaching Hospital Baghdad, Iraq. Written informed consent form was get from all study participants or from the parents of theirs for all those below eighteen years old.

Statistical analysis

Statistical analysis was carried out by using Student's *t* test. Variables have been estimated as Mean ± SE. Correlation between cytokine levels as well as antibody levels, clinical presentation and degree of villous atrophy was dependent on linear regression.

III. Results

Information of measurement of some serum cytokines and adipokines profile of children with CD, as well as matched controls provided in table1. When comparing children with CD and also matched controls, Th1 serum cytokine levels for IL-12 and IFN- γ had been much higher of children with celiac disease of comparability with controls, for inclusion, the Th-2 associated cytokines IL- 5, IL-13 and IL-10 have been elevated in children with celiac disease additionally also compared to controls . The result also stayed the same in case examining subgroups of children owning Marsh scores one and three, respectively (data not shown). No difference was discovered between children with CD and healthy children for TNF-α, IL-2, IL- 1, IL-4 and IL-8. Serum samples have been collected in all children with CD following starting a gluten free diet after six month as well as analyses done for cytokines IFN- γ, IL-5, IL-10, IL-12 and IL-13 (Table two). IL-5, IL-10 and IL-12 displayed a significant reduction (P <0.05) in cytokine levels after initial a gluten free diet as well as IFN- γ had been reduced, however the minimization wasn't significant(P> 0.05) as observed in table (two). No difference was discovered for IL -13 at diagnosis when compared to after a gluten free diet. these consequences propose that CD individuals have high levels of circulating pro inflammatory cytokines and also anti inflammatory cytokines (IL -10), particularly throughout the effective phase of CD disorders, in addition, most of these cytokines reduce when the individuals commence a GFD; however a few of cytokines for instance IFN-γ that were implicated within the pathogenesis of tissue injury in CD, persist in the blood circulation despite GFD.

Since the identification on the auto antigen of CD (tissue transglutaminase (tTG) as, detection of anti tTG IgA antibodies in the serum of CD individuals has grown to be an important tool of the examination of this

disorder. There seemed to be a correlation between mean serum anti tTG IgA levels and the mean serum levels of the cytokines tested. Statistically significant positive correlations was noticed between the levels of anti tTG IgA and the mean levels of all of the cytokines expect TNF-α, and also the most powerful correlations have been noticed with INF- γ (p <0.001). However, a distinctive analysis feature of CD could be the locating of villous atrophy as well as crypt hyperplasia on histologic evaluation of small bowel biopsy samples, in this analysis, forty individuals had intestinal biopsies at presentation, of which twenty had histologic proof of different levels of villous atrophy. Utilizing linear regression evaluation mean serum levels of IL- 4, IL-10 and IL-13 had been discovered to correlate significantly with all the degree of villous atrophy (p< 0.05).

On the other hand consequences for adipokines profile demonstrated that complete ghrelin levels as revealed in table two have been as follows; 500±116 pg/ml on GFD vs. 780±132 pg/ml of CD prior to therapy and this reduction was significant(p< 0.05),as effectively complete ghrelin levels had been significantly much higher only in pre pubertal children being off a GFD (p<0.05) while a decline in the ghrelin levels in pre pubertal boys for a GFD was considerably dipper than in the corresponding group of females (p<0.05). During the older children on and off a GFD the ghrelin levels weren't significantly distinct (p>0.05).

Table 1: Cytokine profile levels Mean± SE in celiac patients with tTG antibody positive as well as healthy subjects with tTG antibody negative.

Parameter (pg/ml)	CD group (N=50)	Healthy group (N=50)	P value
IFN-gamma	**10.1±2.8**	1.1±0.8	P<0.001
TNF-alpha	9.2±1.9	2.56±0.6	P<0.001
IL-1β	6.4±0.8	2.7±0.8	P<0.01
IL-4	11.8±1.5	3.12±1.6	P<0.01
IL-5	77.8±3.8	6.5±0.9	P<0.001
IL-8	92.1±0.7	5.2±1.1	P<0.001
IL-6	66.4±12.3	1.6±0.9	P<0.001
IL-10	14.9±0.8	1.8±0.7	P<0.001
IL-12	15.1±1.4	30.3±2.7	P<0.001
IL-13	7.7±1.0	3.7±0.9	P<0.01
IL-2	18.7±2.8	4.6±2.7	P<0.01
IL-15	45.7±3.7	10.1±1.9	P<0.001

Data are presented as Mean±SE. GFD, gluten-free diet

Adiponectin levels have been as follows; pre pubertal females one GFD: 14.2± 2.0 µg/ml when compared with 13.8±1.9 µg/ml being off GFD while boys on GFD had been 16.0±1.6 µg/ml when compared with 15.8±1.1 µg/ being off GFD. Adiponectin concentrations had been identical of children on and off a GFD and were not age and also sex dependent (p> 0.05).

Leptin levels have been as follows; pre pubertal females on GFD:1.12±0.2 ng/ml in comparison with 0.93±0.3 ng/ml being off GFD while in boys on GFD: 0.89±0.2 ng/ml when compared with 0.81±0.1 ng/ml, being off GFD. Leptin condition was not impacted by a GFD equally in boys and girls (p> 0.05), but had been age- and sex- dependent (p <0.05).

Table 2: Change in some cytokine and adipokines profile concentration before and after treatment with a gluten free diet for 6 months.(Mean±SE)

Parameter	Before Treatment	After treatment	*P*-value
IL-5 (pg/ml)	**13.5±1.6**	**8.1±1.1**	**<0.001**
IL-10(pg/ml)	**3.7±0.8**	**0.55±0.2**	**<0.001**
IL-12(pg/ml)	**11.3±1.9**	**4.78±1.3**	**<0.001**
IL-13(pg/ml)	**4.4±0.9**	**4.9±0.7**	**p>0.05**
IFN-gamma(pg/ml)	**13.5±1.8**	**7.3±1.4**	**<0.01**
Leptin(ng/ml)	**0.89±0.1**	**0.84±0.1**	**p>0.05**
Adiponectin(µg/ml)	**15.8±1.1**	**16.0±1.6**	**p>0.05**
Gherlin (pg/ml)	**780±13.2**	**500±11.6**	**p<0.05**

Data are presented as Mean±SE. GFD, gluten-free diet

IV. Discussion

Results details through this particular effort proposed that higher concentrations of Th -1, Th- 2 cytokines in CD patients characterize the inflammatory response of this disease, with specific serum cytokine elevations being such as those in the small intestinal mucosa and other being differantl, from non-intestinal sources. Many *in vitro* researches have examined that the gliadin (gluten protein) brings stimulate the

production of Th -1 pro inflammatory cytokine [16 ,18]. The Th -1 responce to dietary gluten within the small intestinal mucosa probably drives the lymphocytic and also monocytes infiltration on the lamina propria. Even though overlapping in the function of theirs, Th-1 and Th-2-derived cytokines mediate various functions. The Th- 1 response is augments pro inflammatory reactions as well as cell mediated immunity, while the Th- 2 cytokines be involved in down regulating inflammatory processes by means of predominantly impact the humoral immune effect. Both responses are noticed in CD people [17]. Of mention, immune effectors other than T cells could also secrete cytokines that play a role in the polarized Th-1 or Th-2 replies. A broad spectrum of Th- 1, Th- 2, cytokines assessed and also the heightened serum levels of cytokines which are recognized to become high at the level of the intestinal mucosa in addition to in PBMC suggests that systemic activation as well as secretion of cytokines happens within CD individuals .The important mediators of the Th- 1 immune effect IL-2 and IFN- γ and the roles of its in CD are extensively recorded. Gluten-responsive, mucosal, and also peripheral bloods major HLA complex class II-restricted CD4 T cell clones appear very high levels of IFN- γ. additionally, in vivo gliadin obstacle of CD patients on GFD results in higher creation of IFN-γ within the lamina propria coincident with histologic variations of small intestinal mucosa [16]. In the research, IFN- γ was continually elevated in-patients with refractory and effective disease also as of individuals on GFD after six month therapy. There are information documenting high serum levels of this particular cytokine within autoimmune diseases, several of that are connected with CD [19]. IFN- γ and also IL- 15 are pro inflammatory cytokines which are recognized to become engaged within the pathogenesis of CD [20, 21]. IL-15 status within previous research has recognized important role on this cytokine in the pathogenesis of epithelial lesions and the activation of cytotoxic intra epithelial lymphocytes [22, 23]. Analysis of IL- 15 levels within the various medical phases of CD remains to be a crucial subject for additional studies.

Interleukin -2 levels performed a weak though nonetheless significant elevation in patients with activated CD. Nevertheless, absolutely no substantial disparities in IL -2 levels have been seen in CD individuals as well as all those on a GFD. The precise reasons just for the latter finding are not clear, though a probable reason could be that serum concentration of IL- 2 might be influenced via binding to the soluble receptor sIL-2R of its, that is discharged in the blood in the course of T cell activation [24]. Although immune regulatory functions during the mucosal level were recommended [25], Th-2 cytokines (IL- 4, IL-6 and IL-10) had been additionally elevated in CD individuals, and also all those on GFD. The role of the cytokines within CD pathogenesis isn't properly known. Alternatively the role of IL- 4 remains unclear and prior research has suggested that it might not be involved within the pathogenesis of CD [26]. IL-4 is responsible for B cell activation as well as, particularly, induction of immunoglobulin E [27]. This particular cytokine additionally suppresses Th- 1 reactions by down regulating the effect of IFN- γ on macrophage cells [16]. Our results support a role of IL 4 in the inflammatory response related to CD, because of the drastically greater levels of IL- 4 cytokine found in all categories of individuals except those on GFD for more than six months. Additionally, IL-4 levels showed a positive correlation together with the concentrations of anti tTG antibodies. Moreover, results observed reduced concentration of IL-4 in-patients with no villous atrophy. IL- 10 is another cytokine, whose role in CD pathogenesis have been analysed well [29, 31].Several scientific studies show that IL-10, concomitantly with IFN- γ, is produce in significantly higher levels by IELs from individuals with effective CD when compared with IELs from tested CD individuals or controls . interestingly, various other research has found elevated IL -10 serum concentration by IELs coming from individuals on GFD, individuals with quiet CD, as well as control compared with effective CD patients [30,31].From this particular work, the information observed heightened serum concentration of IL -10 in patients with ACD although not in those on GFD. Similar results have just earlier been discussed in patients with IgA deficiency, an ailment which no one of the subjects of ours had. In addition, a positive correlation of IL -10 concentration with anti TTG antibody titers was discovered. Therefore additional scientific studies are required to determine if certain circulating lymphocyte subsets secrete IL -10 in individuals with CD, which might assist with elucidate the implications of serum IL- 10 (proinflammatory vs regulatory) elevations in this particular disease [32].

The concentrations of IL- 1β did not present considerable elevations, in addition that TNF-α, did demonstrate elevations in effective CD individuals when compared with individuals on GFD. Gliadin peptides are already shown to induce the production of higher levels of IL-8 and TNF-α by peripheral blood monocytes from Activated CD patients when compared with monocytes from Healthy controls or GFD patients in vitro [33] .IL- 8 is a chemokine which is conveyed in tissue with neutrophilic infiltrates as well as plays a crucial part within inflammatory response mediated by neutrophils [34]. From our review mean serum IL- 8 levels , in compare to various other cytokines, were increased in all CD individuals in comparability with healthy controls, so the concentration of the cytokine stayed heightened in spite of a GFD and continued to be extremely even with six months of gluten exclusion.

Data resulted from this particular study demonstrated that children being off a GFD showed significant elevation in the serum of theirs complete ghrelin levels as in comparison with children on a GFD at the same time as to those in boys and girls on and off a GFD. No considerable impact on ghrelin between pubertal and

adolescent girl and boys and no effect of a GFD on it had been found. Consequences from various other scientific studies are confusing [35- 39]. Some authors have indicated considerable expansion of the ghrelin levels in untreated CD individuals which returned to normal during a GFD [35]. Other authors found the identical ghrelin concentrations in untreated CD adults and in controls which substantially decreased throughout a GFD. The still authors have indicated ghrelin focus in untreated CD adults 4 fold above all those in healthy controls [38]. It has become additionally found that serum ghrelin within untreated CD boys as well as girls was drastically lower after a GFD [39]. Reasons for the variations remain unclear. Administration of ghrelin to human with different diseases generated retention of lean body mass as well as reduce of circulating pro inflammatory cytokines; all of the actions are helpful for CD patients [40,41]. Nutritional status, but not mucosal inflammation, appears to be a primary element regulating ghrelin secretion especially in younger children.

Finally mean serum adiponectin levels had been not gender and age related as well as stayed unaffected by a GFD treatment after six months. It's has been recently proven that adiponectin status in CD adults had been substantially increased, as well as like in this study , stayed the same unchanged after a GFD. The authors propose that, adiponectin might serve as pro inflammatory adipokines in certain CD conditions. Adiponectin is an anti- inflammatory material. It antagonize actions of tumor necrosis factor- , secretion of interleukin- 6, as well as induce creation of interleukin- 10, as well as interferon- γ. It forms complicated homopolymers which biological action(s) and their impact on different assays unknown.

Conflict of interest

No prospective conflict of interest to this article was reported.

References

[1]. Kaswala DH, Veeraraghavan G, Kelly CP, Leffler DA. Celiac disease: diagnostic standards and dilemmas. Diseases. 2015;3:86-101.

[2]. Ensari A. Gluten sensitive enteropathy (celiac disease) – controversies in diagnosis and classification. Arch Pathol Lab Med. 2010;134:826-35.

[3]. Dickson BC, Streutker CJ, Chetty R. Celiac disease: an update for pathologist. J Clin Pathol. 2006;59:1008-16.

[4]. Cataldo F, Lio D, Marino V, Scola L, Crivello A, Corazza GR, Working Group of the SIGEP, Working Group of 'Club del Tenue'. Plasma cytokine profiles in patients with celiac disease and selective IgA deficiency. Pediatr Allerg Immunol 2003;14:320–4.

[5]. Sollid LM. Molecular basis of celiac disease. Annu Rev Immunol 2000;18:53–81.

[6]. Nilsen EM, Jahnsen FL, Lundin KE, Johansen FE, Fausa O, Sollid LM, et al. Gluten induces an intestinal cytokine response strongly dominated by interferongamma in patients with celiac disease. Gastroenterology 1998;115:551–63.

[7]. Monteleone I, Monteleone G, Del Vecchio Blanco G, Vavassori P, Cucchiara S,MacDonald TT, Pallone F. Regulation of the T helper cell type 1 transcription factor T-bet in coeliac disease mucosa. Gut 2004;53:1090–5.

[8]. Hu S, Mention JJ, Monteiro RC, Zhang S, Cellier C, Schmitz J, et al. A direct role for *NKG2D/MICA* interaction in villous atrophy during celiac disease. Immunity 2004;21:367–77.

[9]. Meresse B, Chen Z, Ciszewski C, Tretiakova M, Bhagat G. Coordinated induction by IL15 of a TCR-independent *NKG2D* signaling pathway converts *CTL* into lymphokine-activated killer cells in celiac disease.Immunity 2004;21:357–66.

[10]. Mauviel A. Cytokine regulation of metalloproteinase gene expression. J Cell Biochem 1993;53:288–95.

[11]. Graham MF, Willey A, Adams J, Yager D, Diegelmann RF. Interleukin 1beta downregulates collagen and augments collagenase expression in human intestinal smooth muscle cells. Gastroenterology 1996;110:344–50.

[12]. DaumS, Bauer U, Foss HD, Schuppan D, Stein H, Riecken EO, Ullrich R. Increased expression of mRNA for matrix metalloproteinases-1 and -3 and tissue inhibitor of metalloproteinases-1 in intestinal biopsy specimens from patients with coeliac disease. Gut 1999;44:17–25.

[13]. Cinova J, Palov̌-Jelžnkov̌ L, Smythies LE, Cern̂ M, Pecharov̌ B, Dvor̂k M, . Gliadin peptides activate blood monocytes from patients with celiac disease.J Clin Immunol 2007;27:201–9.

[14]. Hill ID, Dirks MH, Liptak GS, et al. Guideline for the diagnosis and treatment of celiac disease in children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr 2005;40:1-19.

[15]. Husby S, Koletzko S, Korponay-Szabó IR, et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. J Pediatr Gastroenterol Nutr 2012;54:136-160

[16]. Kontakou M, Przemioslo RT, Sturgess RP, Limb GA, Ellis HJ, Day P, Ciclitira PJ.Cytokine mRNA expression in the mucosa of treated coeliac patients after wheat peptide challenge. Gut 1995;37:52–7.

[17]. Lahat N, Shapiro S, Karban A, Gerstein R, Kinarty A, Lerner A. Cytokine profile in coeliac disease. Scand J Immunol 1999;49:441–6.

[18]. **Lio** D, Bonanno CT, D'Anna C, De Luca S, Gervasi F, Gluten stimulation induces an *in vitro* expansion of peripheral blood T gamma delta cells from HLA-DQ2-positive subjects of families of patients with celiac disease.Exp Clin Immunogenet 1998;15:46–55.

[19]. Wapenaar MC, van Belzen MJ, Fransen JH, Sarasqueta AF, Houwen RH, Meijer JW, et al. The interferon gamma gene in celiac disease: Augmented expressioncorrelates with tissue damage but no evidence for genetic susceptibility. J Autoimmun 2004;23:183–90.

[20]. Mannon P, Reinisch W. Interleukin 13 and its role in gut defence and inflammation. Gut 2012; **61**:1765–73.

[21]. Mention JJ, Ben Ahmed M, B̈gue B, Barbe U, Verkarre V, Asnafi V, Interleukin 15: A key to disrupted intraepithelial lymphocyte homeostasis and lymphomagenesis in celiac disease. Gastroenterology 2003;125:730–45.

[22]. Hu¨ e S, Mention JJ, Monteiro RC, Zhang S, Cellier C, Schmitz J, et al. A direct role for *NKG2D/MICA* interaction in villous atrophy during celiac disease. Immunity 2004;21:367–77

[23]. Meresse B, Chen Z, Ciszewski C, Tretiakova M, Bhagat G, Krausz TN, et al. Coordinated induction by IL15 of a TCR-independent *NKG2D* signaling pathway converts *CTL* into lymphokine-activated killer cells in celiac disease.Immunity 2004;21:357–66.

[24]. Blanco A, Garrote JA, Arranz E, Alonso M, Clavo C. Increased serum IL-2R levels in coeliac disease are related to CD4 but not CD8 antigens. J Pediatr Gastroenterol Nutr 1992;15:413–7.
[25]. Chowers Y, Marsh MN, De Grandpre L, Nyberg A, Theofilopoulos AN, Kagnoff MF. Increased proinflammatory cytokine gene expression in the colonic mucosa of coeliac disease patients in the early period after gluten challenge. Clin Exp Immunol 1997;107:141–7.
[26]. Cherwinski HM, Schumacher JH, Brown KD, Mosmann TR. Two types of mouse helper T cell clone. III. Further differences in lymphokine synthesis between Th1 and Th2 clones revealed by RNA hybridization, functionally monospecific bioassays, and monoclonal antibodies. J Exp Med 1987;166:1229–44.
[27]. Snapper CM, Finkelman FD, Paul WE. Regulation of IgG1 and IgE production by interleukin 4. Immunol Rev 1988;102:51–75.
[28]. Beckett CG, Dell'Olio D, Kontakou M, Przemioslo RT, Rosen-Bronson S, Ciclitira PJ.Analysis of interleukin-4 and interleukin-10 and their association with the lymphocytic infiltrate in the small intestine of patients with coeliac disease.Gut 1996;39:818–23.
[29]. Leon F, Snchez L, Camarero C, Roy G. Cytokine production by intestinal intraepithelial lymphocyte subsets in celiac disease. Dig Dis Sci 2005;50:593–600.
[30]. Kolkowski EC, Fern˙ndez MA, Pujol-Borrell R, Jaraquemada D. Human intestinal *alphabeta IEL* clones in celiac disease show reduced IL-10 synthesis and enhanced IL-2 production. Cell Immunol 2006;244:1–9.
[31]. Forsberg G, Hernell O, Hammarstr×m S, Hammarstr×m ML. Concomitant increase of IL-10 and pro-inflammatory cytokines in intraepithelial lymphocyte subsets in celiac disease. Int Immunol 2007;19:993–1001
[32]. Cataldo F, Lio D, Marino V, Scola L, Crivello A, Corazza GR, Working Group of the
[33]. SIGEP, Working Group of 'Club del Tenue'. Plasma cytokine profiles in patients with celiac disease and selective IgA deficiency. Pediatr Allerg Immunol 2003;14:320–4.
[34]. Cinova J, Palov˙-Jel˙nkov˙ L, Smythies LE, Cern˙ M, Pecharov˙ B, Dvor˙k M, et al. Gliadin peptides activate blood monocytes from patients with celiac disease.J Clin Immunol 2007;27:201–9.
[35]. Murphy PM. Neutrophil receptors for interleukin-8 and related CXC chemokines.
[36]. Semin Hematol 1997;34:311–8.
[37]. Lanzini A, Magni P, Petroni ML, et al. Circulating ghrelin level is increased in coeliac disease as in functional dyspepsia and reverts to normal during gluten-free diet. Aliment Pharmacol Ther 2006;23:907-913.
[38]. Capristo E, Farnetti S, Mingrone G, et al. Reduced plasma ghrelin concentration in celiac disease after gluten-free diet treatment. Scand J Gastroenterol 2005;40:430-436.
[39]. Selimoglu MA, Altinkaynak S, Ertekin V, Akcay F. Serum ghrelin levels in children with celiac disease. J Clin Gastroenterol 2006;40:191-194.
[40]. Kempiński R, Demissie M, Jasińska M, Paradowski L. Plasma ghrelin concentration in celiac patients. Gastroenterol Pol 2008;15:375-377.
[41]. Tomasik PJ, Grzenda-Adamek Z, Sztefko K, Fyderek K. The orexigenic peptides in children with celiac disease. J Appl Res 2009;9:70-75.
[42]. Manavalan JS, Hernandez L, Shah JG, et al. Serum cytokine elevationsin celiac disease: association with disease presentation.Hum Immunol 2010;71:50-57.
[43]. Jarocka-Cyrta E, Kasacka I, Kaczmarski M. The ghrelin-positive cells number is increased in duodenum in children with celiac disease.J Endocrinol Invest 2010;33:165-170.

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