

Plasma cytokine profiles in patients with celiac disease and selective IgA deficiency

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Celiac disease (CD) and selective IgA deficiency (IgAD) are frequently associated, and share the same genetic background. The aim of the present study was to evaluate both Type 1 and 2 plasma cytokine levels in CD and in CD-IgAD. IL-2, TNF- α , IL-10, IL-4 and IL-13 plasma levels were measured both at diagnosis and after a gluten-free diet (GFD) in 32 CD patients, in 27 CD-IgAD patients and in 30 healthy controls. IFN- γ levels were significantly higher in CD and CD-IgAD than in controls, TNF- α displayed significantly higher levels in CD-IgAD when compared both with controls and with CD, and IL-2 was in CD-IgAD significantly increased respect to controls. Kinetics of the Type 1 cytokine plasma levels did not show a clear relationship with the GFD in both groups of CD patients, and particularly in those with IgAD. IL-4 and IL-13, both at diagnosis and after a GFD, were not significantly different in controls and in celiac patients (with and without IgAD). IL-10, whose production is stimulated by the TNF- α , had significantly higher plasma levels in CD-IgAD, but not in CD patients, with a significant decrease after a GFD. CD and especially CD-IgAD patients display persistently higher pro-inflammatory cytokine levels, suggesting a persistent state of activation of pro-phlogistic signals in CD, particularly when IgAD coexists. Serial measurement of serum IL-10 may be an adjunctive evaluating criterion in the follow-up of CD-IgAD patients.

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Selective IgA deficiency (IgAD) is frequently associated with celiac disease (CD) and a 10- to 16-fold increase of IgAD incidence may be observed in patients affected by celiac disease (CD) (1–3). In this case IgG1 endomysial antibodies (EMA) and IgG anti-tTG transglutaminase antibodies are the best screening tests (4). Conversely, they are less satisfactory at evaluating the dietary compliance to gluten withdrawal (4) and many efforts have been made to obtain clinical or laboratory data able to improve the follow-up protocol of these patients.

Attempts to obtain specific disease markers able to distinguish IgAD subjects among CD patients have not produced appreciable results (2–5). On the other hand, IgAD and CD share a common genetic background, the ancestral

haplotype HLA-8.1 (6) that is found, in all Caucasian populations, with an increased susceptibility to several pathological conditions including CD (7–9). Cytokine plasma profiles of these subjects are characterized by an increased production of TNF- α (5, 8, 10), according to the presence of the 308G $\rightarrow$ A single nucleotide polymorphism and TNF α 2b3 microsatellite alleles in the 5'-flanking region of TNF-coding sequence (11, 12). In particular, TNF2 (308 A) allele induces a two- to threefold increase of the gene transcription (13, 14). Unfortunately, because the strict linkage disequilibrium among these and the HLA-DQ2 encoding alleles, considered the major genetic markers for celiac disease, the precise role of the TNF- α genetic background for the susceptibility to CD, as well as to IgAD, has not been well established. However, high TNF- α and IFN- γ production by mucosal and peripheral blood cells is found in both CD and IgAD (15–17). In fact, cells producing a number of individual cytokines, in particular Type 1, pro-inflammatory cytokines such as IFN- γ have been found in the immunologically mediated lesions of celiac disease by different groups (15–18). In addition, studies of lamina propria T cells have indicated that gluten reactive T cells have a cytokine profile dominated by IFN- γ and TNF- α (15, 17). This notion is sustained by the characterization of gut-derived DQ2 and DQ8-restricted gluten-specific T-cell clones (17). These T cells uniformly secrete IFN- γ at high concentrations, and some produce IL-4, IL-5, IL-6, IL-10, TNF- γ , or TGF- β in addition (16). Moreover it has been demonstrated that level of cytokine production by mucosal immune cells is related to the activity of CD lesions (19, 20).

This paper describes a multicenter study on the cytokine plasma levels in both CD and CDIgAD patients, obtained at the diagnosis and 1 year after commencement of a gluten-free diet (GFD), compared with healthy subjects. The study was carried out under the auspices of the Italian Society of Gastroenterology and Hepatology (SIGEP) and the 'Club del Tenue'.

Materials and methods

Subjects

This was a nationwide study involving 19 adult and pediatric Gastroenterology Centers, on the following groups of subjects: (1) 27 celiac patients with IgAD (12 males and 15 females, range 1–45 years, mean age 16.9), at diagnosis and after 1 year of a GFD; (2) 32 celiac patients

without IgAD (14 males and 18 females, range 1–48 years, mean age 18.3) at diagnosis and on a GFD for more than 1 year; and (3) 30 healthy sex and age-matched control subjects.

Both original and revised criteria for diagnosis of CD were used (21, 22), and serum IgA concentrations less than 0.05 g/l in the presence of normal levels of IgG and IgM were regarded as selective IgA deficiency (5, 7). None of the patients who had a diagnosis of IgA deficiency was receiving pharmacological agents known to induce secondary IgA deficiency (3).

Plasma samples

Blood citratate samples were obtained at diagnosis of CD and 1 year after GFD. Informed consent was obtained from all patients or their parents. Uncollected blood samples were immediately centrifuged and plasmas were frozen at -80°C until cytokine assaying.

Enzyme immune assays

The samples were all analyzed in the same Center and at the same time by the same operators. Enzyme immune assay tests were used to quantify IL-2, IFN- γ , TNF- α , IL-10, IL-4 and IL-13 plasmatic levels. Cytokine evaluations were performed with commercially available kits (R & D System, Abingdon, Oxon, UK). All the tests were performed according to the manufacturer's instructions. To standardize our results, in all the assays reference preparations (recombinant human cytokines) were tested. Results were expressed as pg/ml. Detection limits in our laboratory were 0.1 pg/ml for each cytokine.

Statistical analysis

Quantitative values given as mean $\pm$ SD were examined in the three groups of subjects using ANOVA. As multiple comparisons were made, Bonferroni's correction was applied. All statistical analyses were performed using a graph PAD InStat Algorithm (Graph PAD Software, San Diego, CA, USA).

Results

Type 1, pro-inflammatory cytokine (IL-2, IFN- γ and TNF- α) plasma profiles in CD patients (with and without IgAD) at diagnosis and after 1 year of a GFD are reported in Table 1 and compared with control healthy subjects. IFN- γ levels in CD and in CDIgAD patients at diagnosis were significantly higher than in controls. Moreover,

Table 1. Pro-inflammatory (IL-2, IFN- γ and TNF- α) plasma cytokine levels (Mean $\pm$ SD) in healthy control subjects and in CD patients with or without IgAD at diagnosis and after 1 year of a GFD

	IL-2		IFN- γ		TNF- α	
	12.5 $\pm$ 4.3		0.8 $\pm$ 0.2		21.5 $\pm$ 4.5	
	Diagnosis	GFD	Diagnosis	GFD	Diagnosis	GFD
Controls (30)						
CD (27)	7.6 $\pm$ 3.1	12.3 $\pm$ 5.4	2.6 $\pm$ 1.4	1.2 $\pm$ 0.5	26.4 $\pm$ 11.8	25.9 $\pm$ 13.4
CD-IgAD (32)	23.8 $\pm$ 15.6	16.3 $\pm$ 8.6	3.3 $\pm$ 0.6	3.3 $\pm$ 0.9	51.3 $\pm$ 29.1	39.9 $\pm$ 24.5

Number of subjects per group is in brackets.

Statistical analysis (one-way ANOVA, with Bonferroni's corrections for a total of 48 comparisons) demonstrates the following significant differences:

IFN- γ levels of CD patients were significantly different by control data both at diagnosis and 1 yr after a GFD ($p > 0.005$).

A significant reduction ($p < 0.005$) in IFN- γ levels was observed after 1 year of a GFD in CD but not in CD-IgAD subjects.

CD IgAD subjects at diagnosis displayed the higher significant cytokine levels when compared with control (IL-2 $p < 0.005$; IFN- γ $p < 0.005$; TNF- α $p < 0.005$). CD IgAD subjects at diagnosis displayed higher TNF- α ($p < 0.005$) when compared with CD subjects.

CDIgAD patients at diagnosis displayed the significantly higher levels of TNF- α when compared both with controls and with CD patients. Untreated CD patients showed a slight decrease in IL-2 serum levels with respect to control group whereas a significant increase in IL-2 levels was observed at diagnosis in CDIgAD patients.

The influence of a GFD on pro-inflammatory cytokine levels was different in the two groups of CD patients. IFN- γ levels of CDIgAD patients seemed to be not influenced by a GFD, remaining significantly increased with respect to the control group. On the other hand, a significant reduction of this cytokine was observed in the CD group between diagnosis and after 1 year of a GFD. Changes in TNF- α plasma levels did not show a clear relationship to the GFD response in either group of CD patients. Finally, the clear IL-2 plasma increase observed at the diagnosis in CDIgAD subjects was followed by an insignificant reduction of its plasma levels after 1 year of a GFD.

Table 2 shows the plasma profile of Type 2 cytokines (IL-4, IL-10, IL-13). At diagnosis and after a GFD, plasma profiles of IL-4 and of IL-13 were not significantly different in CD

patients (with and without IgAD) compared with healthy controls. In addition, no significant difference in IL-10 levels was observed in CD patients in comparison to the control group, both at diagnosis and after a GFD. However, CD-IgAD subjects exhibited, in respect to controls and to CD patients, a constantly higher level of IL-10 with a dramatic and significant decrease in response to a GFD.

Discussion

It is well known that, T helper cells secreting Type 1 cytokines play a central role in the pathogenesis of CD. The Type 1 response in the small intestinal mucosa to dietary gluten drives the typical lymphocyte and monocyte infiltration (20). Moreover, many studies have demonstrated that gluten induces a sustained Type 1 pro-inflammatory cytokine production *in vitro*, as Tcells may be able to release variable amounts of T helper Type 2 (Th2) cytokines (15–20).

We have measured both Type 1 and 2 cytokine plasma levels in CDIgAD subjects and, as positive and negative controls, in CD affected and healthy subjects. Our results indicate that

Table 2. T helper 2 (IL-4, IL-10, IL-13) plasma cytokine levels (Mean $\pm$ SD) in healthy control subjects and in CD patients with or without IgAD at diagnosis and after 1 year of a GFD

	IL-4		IL-13		IL-10	
	15.6 $\pm$ 5.8		13.6 $\pm$ 8.5		10.2 $\pm$ 3.9	
	Diagnosis	GFD	Diagnosis	GFD	Diagnosis	GFD
Controls (30)						
CD (27)	15.3 $\pm$ 2.5	14.1 $\pm$ 2.1	15.5 $\pm$ 11.7	9.8 $\pm$ 7.7	8.6 $\pm$ 1.8	6.5 $\pm$ 3.5
CDIgAD (32)	15.7 $\pm$ 4.1	16.8 $\pm$ 4.2	20.8 $\pm$ 14.1	15.5 $\pm$ 8.9	36.3 $\pm$ 11.9	14.6 $\pm$ 4.7

Number of subjects per group is reported in brackets.

Statistical analysis (one-way ANOVA, with Bonferroni's corrections) demonstrates the following significant differences:

IL-10 levels of CDIgAD patients at diagnosis were significantly higher both with respect to the controls ($p < 0.005$) and CD patients ($p < 0.005$).

In CDIgAD patients significant reductions of IL-10 levels ($p < 0.005$) were observed after a GFD.

Type 1 pro-inflammatory cytokines are increased in gluten intolerance. In particular, IFN- γ is significantly higher both in CD and in CDIgAD subjects. In addition, CDIgAD patients, both at diagnosis and after a GFD, display the higher pro-inflammatory cytokine levels, when compared with CD patients and healthy controls. On the other hand, only the CDIgAD, but not the CD patients, have significantly increased plasma levels of the anti-inflammatory cytokine IL-10, whereas the plasma levels of the Type 2 cytokines (i.e. IL-4 and IL-13) are not significantly different in healthy controls and in celiac patients (with and without IgAD).

These data should be not surprising considering the cells involved in the mucosal lesions of CD. There is a marked infiltration of TCR β + T cells in the active lesions of lamina propria with increased IFN- γ production, whereas there is no increase in cells producing IL-4 or IL-10 (20). A 1000-fold increase of mRNA for IFN- γ has been found in untreated CD, related to a small increase in the message for IL-2, IL-4, IL-6, and TNF- α (23,24). However, the IFN- γ mRNA level of biopsies of treated celiac patients has been demonstrated to reach that of untreated patients after *in vitro* stimulation with gluten, as there were no differences in the numbers of IFN- γ -producing cells between group of children with treated CD or untreated or challenged CD children (25). IFN- γ activates TNF- α macrophage production and both cytokines can jointly have a direct cytotoxic effect on intestinal epithelial cells (26); TNF- α , by activating KGF production, epithelial proliferation and crypt cell hyperplasia (27). The alleles at the TNF locus, which are associated with higher basal TNF synthesis, independently of a pro-inflammatory response, are linked the HLA haplotype associated with CD predisposition (7,10). Our data, confirms our previous observation on the role of genetic control of cytokine production in the pathogenesis of CD (5) suggesting that other cytokine genes may be implied.

Data obtained *in vitro* by different groups have suggested a possible role for the Th2 cytokines in celiac disease (16–18). In particular it has been hypothesized that IL-4 might play a role in the development of intestinal lesions (18). Our data on IL-4 and IL-13 plasma levels in CD and CD-IgAD patients measured before and after a GFD indicate that the concentrations of these cytokines are not raised either at diagnosis or after a GFD.

Our data on the evaluation of IL-10 indicate that this cytokine is significantly increased only

in CDIgAD patients. An important trigger for IL-10 production is TNF- α by inducing its production by monocytes and macrophages as a down-regulatory effect on inflammation (28). IL-10, actually, is a natural immunosuppressant of TNF, having strong inhibitory effects on pro-inflammatory function of macrophages, e.g. on TNF- α and IL-1 production (29) and T-cell synthesis of Th1-like cytokines (30). In a recent paper, we demonstrated that association of a genetic setting of high TNF and low IL-10 production may be considered a predisposing condition for CD in IgAD subjects (5). Moreover, in healthy subjects, IL-10 plasma levels are influenced by the presence of the HLA haplotype associated with higher secreting TNF alleles (7,11). Accordingly, our data show that CDIgAD subjects display persistently higher pro-inflammatory cytokines levels, suggesting a persistent state of activation of pro-phlogistic signals in celiac patients, in particular when an IgA deficiency coexists, inducing a higher cytokine release partially counter balanced by increased release of the anti-inflammatory cytokine, IL-10.

Our data on the follow-up of both pro-inflammatory and anti-inflammatory cytokines indicate a significant reduction of IL-10 after a GFD only in CDIgAD patients. In a recent paper (4), we have reported data on evaluation of IgG1 antiendomysial and IgG anti-transglutaminase antibodies in CDIgAD patients. We have demonstrated that these tests were useful in the diagnosis of CD in IgAD patients, but employment in follow-up after a GFD produces some false-positive or negative results; so other different laboratory approaches should be tested. The evaluation of IL-10 plasma levels at diagnosis and after a GFD appears to be a useful tool for evaluation of the response to GFD in CDIgAD patients.

In conclusion, the plasma levels of Type 1 cytokines are increased at diagnosis in CD and especially in CD with IgAD, suggesting a persistent state of activation of pro-phlogistic signals in CD, particularly when IgAD coexists. Plasma levels of Type 2 cytokines are normal in untreated CD (with and without IgAD), with the exception of IL-10 that is high only in CDIgAD, with a significant decrease after a GFD. So serial measurement of serum IL-10 may be an adjunctive evaluating criterion in the follow up of CDIgAD patients.

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