Thymic stromal lymphopoietin levels are increased in patients with celiac disease

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ABSTRACT

Thymic stromal lymphopoietin (TSLP) is a cytokine produced by epithelial cells in the lungs, skin, and intestinal mucosa and is involved in several physiological and pathological processes. In this study, we evaluated serum TSLP levels in patients with celiac disease (CD). The prospective study was conducted at a gastroenterology outpatient clinic between March 2018 and August 2018. Eighty-nine participants aged between 18 and 75 years were classified into following groups: 22 patients with newly diagnosed CD; 20 patients with CD who were compliant with a gluten-free diet (GFD); 32 patients with CD who were not compliant with a GFD; and 15 healthy controls. Demographic characteristics, disease duration, and selected biochemical and hematologic parameters were recorded and compared between groups. Median serum TSLP levels were 1193.65 pg/mL (range: 480.1–1547.1) in newly diagnosed CD patients, 110.25 pg/mL (range: 60.3–216.7) in CD patients who were compliant with a GFD, 113.1 pg/mL (range: 76.3–303.4) in CD patients who were not compliant with a GFD, and 57 pg/mL (range: 49–67.8) in healthy controls. Overall, there was a significant difference in serum TSLP levels between groups (p = 0.001). Patients with newly diagnosed CD had the highest serum TSLP levels. There was no significant difference in serum TSLP levels between patients with CD who were and were not compliant with a GFD. TSLP appears to be involved in the pathogenesis of CD. Further studies are required to determine if the TSLP signaling pathway can be used in the treatment of CD.

KEY WORDS: Celiac disease; thymic stromal lymphopoietin; gluten-free diet
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INTRODUCTION

Celiac disease (CD) is an immune-mediated enteropathy triggered in genetically susceptible individuals by dietary gluten intake, which is found in wheat, rice, and barley [1]. Human leukocyte antigen (HLA) class II genes known as HLA-DQ2 and HLA-DQ8 are the best-characterized genetic susceptibility factors in CD. Disease-associated HLA-DQ2 (DQA1*05:01/DQB1*02:01) or HLA-DQ8 (DQA1*03/DQB1*03:02) molecules present gluten peptides to the T cells in celiac lesions [2]. More than 95% of patients with CD carry HLA-DQ2 alleles, and the remainder express HLA-DQ8. Although 30–40% of the population carry HLA-DQ2 alleles, only 4% of these develop CD in their lifespan. Therefore, the presence of HLA-DQ2 and HLA-DQ8 is commonly used to exclude CD in the clinical setting [3-5]. However, these HLA genes are not the only genetic susceptibility factors in CD. Genome-wide association studies (GWAS) have described non-HLA genetic factors, the majority of which were related to immuno-biologically relevant genomic regions [6].

Until recently, CD has been considered as T helper 1 (Th1) cell-mediated disease. However, Th17 cells, which originate from a $CD161^{+}CD4^{+}$T-cell precursor, were shown to have a significant influence on the pathogenesis of CD. Interferon (IFN)-γ and interleukin (IL)-17 secreted from T cells activate matrix metalloproteinases (MMP), which damage enterocytes and lead to villous atrophy [7].

Intestinal intraepithelial lymphocytes (IELs) are the major component of the gastrointestinal immune system. IELs mostly consist of T cells. These T cells contain T-cell receptor (TCR)αβ and TCRγδ and their number can increase up to the half of the total T-cell count in the body [8]. Innate ($CD3^{-}$ negative) IELs include cells expressing natural killer (NK) cell receptors, functional NK cells, NK cell-like type 1 innate lymphoid cells, and T-cell precursor cells [8]. In active CD, the

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number of IELs increases. When the number of T cells containing TCRαβ and TCRγδ is increased, the number of innate IELs is decreased [9-11]. There is increased activation and differentiation of naive T cells into Th1 and Th17 cells in the mucosa during active CD. These activated and differentiated cells release several kinds of cytokines, such as transforming growth factor (TGF)-β1, IL-6, IL-12, IL-17A, IL-23R, IL-21, and IFN-γ. Finally, sustained inflammation leads to cytotoxicity against enterocytes and villous atrophy [12,13].

Thymic stromal lymphopoietin (TSLP) is a cytokine produced in epithelial cells of the lungs, skin, and intestinal mucosa and is involved in several physiological and pathological processes [14]. TSLP binds to a complex formed by IL-7 receptor alpha (IL-7Rα) and TSLP receptors (TSLPRs) and activates the signal transducer and activator of transcription (STAT)5. Thus, TSLP has homeostatic activities; it interacts with dendritic cells to induce the differentiation of naive T cells into regulatory T cells (Treg) and to block Th1 and Th17 development [15].

Biancheri et al. demonstrated that TSLPR and IL-7Rα were expressed in CD mucosa, and mRNA levels of both long (lTSLP) and short TSLP (shTSLP) isoforms were reduced in CD compared with the control group [16]. Sziksz et al. determined a higher mucosal expression of TSLP in patients with newly diagnosed CD than in CD patients under a gluten-free diet (GFD) and controls [17].

Only a limited number of studies have investigated the relationship between TSLP and CD, with contradictory results. Therefore, in this study, we aimed to evaluate serum TSLP levels in patients with CD and investigate the effect of GFD on serum TSLP levels of CD patients.

MATERIALS AND METHODS

Study design and patient selection

This prospective study was conducted at the gastroenterology outpatient clinic of Keçiören Training and Research Hospital between March 2018 and August 2018. Eighty-nine participants aged between 18 and 75 years were included in the study. The participants were divided into four groups:

- Patients with newly diagnosed CD (n = 22): diagnosis was based on serological, pathological, and endoscopic findings.
- Patients with CD compliant with a GFD (n = 20): diagnosis was based on serological, pathological, and endoscopic findings. These patients were under a GFD for at least one year and all serological markers were negative.
- Patients with CD not compliant with a GFD (n = 32): diagnosis was based on serological, pathological, and endoscopic findings. These patients were not compliant with a GFD, and at least one serological marker was positive. The dietary habits of patients in this group were carefully evaluated by an experienced dietitian, to make sure that those with refractory CD were not included.
- Control group (n = 15): healthy people with no disease.

All endoscopic examinations were performed by the same experienced endoscopist. Anti-tissue transglutaminase IgA antibody (IgA anti-tTG; >30 U/mL = positive) and anti-tissue transglutaminase IgG antibody (IgG anti-tTG; >30 U/mL = positive) were used for serologic evaluation to support the diagnosis of CD. The compliance with a GFD was evaluated by an experienced dietitian.

The study protocol was approved by the ethics committee of Kecioren Training and Research Hospital (Approval number: 042018/1656). All participants gave written informed consent.

TSLP assessment

Venous blood samples (5 cm^3) were taken from CD patients and controls. The samples were collected in biochemical test tubes, centrifuged for 15 minutes at 3000 g within 30 minutes of the blood collection, and stored at -80°C until the time of analysis. TSLP concentration (pg/mL) was measured by sandwich enzyme-linked immunosorbent assay (ELISA) method using a commercially available human TSLP ELISA kit (BosterImmunoleader, USA). The ELISA procedure was performed according to the manufacturer's instructions. The intra-assay and inter-assay coefficient of variation was <10%. The sensitivity was <10 pg/mL with an assay range of 15.6–1000 pg/mL.

Statistical analysis

The normal distribution of data was tested by the Shapiro–Wilk test. Student's *t*-test was used to compare variables with normal distribution between two independent groups, and one-way analysis of variance-least significant difference (ANOVA-LSD) multiple comparison tests were used for the comparison of more than two independent groups. In addition, the Kruskal–Wallis and Dunn's multiple comparison tests were used to compare non-normally distributed variables between more than two independent groups. The relationship between numeric variables was tested by the Spearman correlation coefficient and between categorical variables by the Chi-square test. IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp., Armonk, NY) was used for statistical analysis. A value of $p < 0.05$ was considered statistically significant.

Based on the published literature, the large effect size (Cohen's d = 1.80) was expected and the minimum required sample size was calculated as 8 for each group (α = 0.05, 1-β = 0.90). The G*power version 3.1.9.2 package was used to perform power analysis [18].

RESULTS

We included 89 participants in this study, three groups of patients with CD and one control group with healthy individuals. There were no significant differences between the groups in terms of sex, symptoms at presentation, comorbidity, and family history of CD. Twenty-nine patients suffered from dyspepsia, and four patients had CD in their family. The most common concomitant diseases were type 1 and type 2 diabetes mellitus (Table 1). There was a significant difference in terms of age between all groups (p = 0.038). The subgroup analyses by the LSD multiple comparison test showed a significant difference in age between CD patients compliant with a GFD and controls (p = 0.07) and CD patients who were and were not compliant with a GFD (p = 0.024). There was no significant difference in terms of disease duration between patients with CD who were compliant with a GFD and those not compliant with a GFD. The median serum TSLP levels were significantly different between all groups (p = 0.001). The median serum TSLP levels of patients with newly diagnosed CD were 1193.65 pg/mL (range: 480.1–1547.1 pg/mL), patients compliant with a GFD were 110.25 pg/mL (range: 60.3–216.7 pg/mL), patients not compliant with a GFD were 113.1 pg/mL (range: 76.3–303.4 pg/mL), while the median TSLP levels of controls were 57 pg/mL (range: 49–67.8 pg/mL). The Dunn's multiple comparison test showed significant differences in serum TSLP levels between all groups except between CD patients who were and were not compliant with a GFD [p = 0.551] (Table 2). The TSLP levels were also assessed for correlation with IgA anti-tTG and IgG anti-tTG in each group. There was no correlation between the levels of these autoantibodies and serum TSLP levels.

Laboratory parameters were compared between newly diagnosed CD patients, CD patients who were compliant with a GFD, and those not compliant with a GFD. There were no significant differences between groups except for ferritin, albumin, thyroid-stimulating hormone (TSH), IgG anti-tTG, and IgA anti-tTG. The ferritin and serum albumin levels were significantly lower in patients with newly diagnosed CD than in the other two groups. There was a significant difference in TSH levels between CD patients compliant with a GFD and those not compliant with a GFD (Table 3).

DISCUSSION

In this study, we demonstrated for the first time that serum TSLP levels were significantly higher in patients with CD than in healthy controls and that the TSLP levels in CD patients were not influenced by adherence to a GFD. TSLP is mainly expressed by the epithelial cells of the skin, airways, and intestines. TSLP supports the development of dendritic cells, which stimulate the differentiation of naive T cells into Tregs and block the development of Th1 and Th17 cells. Human TSLP

TABLE 1. Comparison of demographic characteristics, initial symptoms, and disease duration between groups

Characteristics	Newly diagnosed CD patients	CD patients compliant with a GFD	CD patients not compliant with a GFD	Control (healthy individuals)	p
	n (%)	n (%)	n (%)	n (%)	
Sex					
Female	13 (59.1)	17 (85.0)	23 (74.2)	10 (66.7)	0.291
Male	9 (40.9)	3 (15.0)	8 (25.8)	5 (33.3)	
Initial symptom					
Dyspepsia	8 (36.4)	9 (45.0)	12 (38.7)	0 (0.0)	0.796
Diarrhea	9 (40.9)	4 (20.0)	9 (29.0)	0 (0.0)	
Malnutrition	1 (4.5)	1 (5.0)	1 (3.2)	0 (0.0)	
Vitiligo	0 (0.0)	1 (5.0)	0 (0.0)	0 (0.0)	
Anemia	4 (18.2)	5 (25.0)	9 (29)	0 (0.0)	
Comorbidities					
Type 1 DM	1 (33.3)	1 (20.0)	2 (50.0)	0 (0.0)	0.614
MS	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	
Epilepsy	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	
Hypothyroidism	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	
Type 2 DM	2 (66.7)	1 (20.0)	1 (25.0)	0 (0.0)	
FMF	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	
Family history					
Positive	1 (4.5)	1 (5.0)	2 (6.5)	0 (0.0)	0.950
Negative	21 (95.5)	19 (95.0)	29 (93.5)	0 (0.0)	
Pathologic stage of newly diagnosed patients					
Marsh 3a	6 (27.3)	0 (0.0)	0 (0.0)	0 (0.0)	-
Marsh 3b	7 (31.8)	0 (0.0)	0 (0.0)	0 (0.0)	
Marsh 3c	9 (40.9)	0 (0.0)	0 (0.0)	0 (0.0)	

CD: Celiac disease; Type 1 DM: Type 1 diabetes mellitus; Type 2 DM: Type 2 diabetes mellitus; MS: Multiple sclerosis; FMF: Familial mediterranean fever; GFD: Gluten-free diet

TABLE 2. Comparison of age, disease duration, and serum TSLP levels between groups

Variables	Newly diagnosed CD patients (n=22)	CD patients compliant with GFD (n=20)	CD patients not compliant with GFD (n=31)	Control (n=15)	*p*
Age (mean±SD)	39.77±15.66	45.75±13.4	37.13±12.2	33.4±9.68	0.038*†
Disease duration (mean±SD)	-	91.45±54.21	71.23±59.01	-	0.080‡
TSLP (median [25–75%]) pg/mL	1193.65 (480.1–1547.1)	110.25 (60.3–216.7)	113.1 (76.3–303.4)	57 (49–67.8)	0.001*§

*Significant difference level at 0.05, †ANOVA test, ‡Mann-Whitney U test, §Kruskal-Wallis test. CD: Celiac disease; TSLP: Thymic stromal lymphopoietin; GFD: Gluten-free diet

TABLE 3. Comparison of laboratory parameters between patient groups

Variables†	Newly diagnosed CD patients (n=22)	CD patients compliant with GFD (n=20)	CD patients not compliant with GFD (n=31)	*p*‡
Hb	12.85 (12.2–13.5)	13.35 (12.85–14.75)	13.5 (12.1–14.5)	0.129
Leukocytes	7130 (6510–7970)	7140 (5735–8025)	6560 (6100–8020)	0.748
Platelets	348.5 (287–421)	290.5 (254–367)	310 (256–352)	0.089
MCV	83.7 (76.9–89.4)	87.05 (83.95–89.25)	85.6 (83–89)	0.481
MPV	7.27 (7.07–9.06)	7.59 (6.5–8.93)	7.99 (7.49–8.9)	0.194
RDW	16.55 (15–17.8)	15.4 (14.45–16.05)	15.4 (14.5–16.1)	0.067
PDW	17.25 (16.9–18.8)	17.5 (16.7–18.3)	17.7 (17.1–18.7)	0.439
PCT	0.25 (0.19–0.3)	0.24 (0.2–0.32)	0.23 (0.19–0.25)	0.247
Glucose	91 (85–97)	95 (86.5–101)	90 (82–96)	0.347
AST	22.5 (19–30)	21.5 (16–24)	21 (15–25)	0.222
ALT	25 (16–28)	22 (12.5–36.5)	18 (13–26)	0.406
Ferritin	10.45 (5.98–18.64)	32.35 (15.9–51.64)	17 (12–25.52)	0.001*
Albumin	4.25 (3.8–4.5)	4.5 (4.4–4.6)	4.4 (4.2–4.5)	0.006*
B12	261 (200–367)	341 (266.5–439.5)	314 (260–450)	0.142
Total protein	7.05 (6.8–7.8)	7.5 (7.3–7.9)	7.5 (7.1–7.8)	0.077
TSH	1.82 (1.44–2.8)	1.59 (1.03–2.53)	2.56 (1.57–3.2)	0.036*
IgA anti-tTG	138 (110–168)	7.13 (2.47–12)	129 (48.5–152)	0.001*
IgG anti-tTG	15.8 (9.64–31.6)	1.99 (1.39–3.65)	8.1 (3.24–33.6)	0.001*

*Significant difference level at 0.05, †Median [25–75%], ‡Kruskal-Wallis test. GFD: Gluten-free diet. CD: Celiac disease; GFD: Gluten-free diet; Hb: Hemoglobin; MCV: Mean corpuscular volume; MPV: Mean platelet volume; RDW: Red cell distribution width; PDW: Platelet distribution width; PCT: Procalcitonin; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; TSH: Thyroid-stimulating hormone; IgA anti-tTG: Anti-tissue transglutaminase immunoglobulin A antibody; IgG anti-tTG: Anti-tissue transglutaminase immunoglobulin G antibody

has two different isoforms shTSLP and lTSLP. shTSLP is the primary isoform expressed under steady-state conditions and has anti-inflammatory features, whereas lTSLP is expressed under inflammatory conditions [19,20].

A decreased TSLP mRNA expression in intestinal epithelial cells (IECs) can influence the pathogenesis of inflammatory bowel disease. A previous study indicated that Th1 cell-mediated intestinal pathologies such as CD may arise if the interplay between IECs and dendritic cells, which has an important role in the homeostasis of the gastrointestinal tract, is disrupted [21]. In nearly 70% of patients with Crohn's disease, the isolated IECs did not express TSLP and failed to control inflammatory reactions in the gastrointestinal tract [21]. In a dextran sodium sulfate-induced colitis model, TSLPR-deficient mice had elevated levels of cytokines such as IL-12/23p40 and IFN-γ, which led to excessive intestinal inflammation [22]. Likewise, in an autoimmune gastritis model, TSLPR-deficient mice exhibited an earlier onset of autoimmune gastritis, which resulted in more aggressive $CD4^+$ T cell infiltration, more severe loss of parietal and chief cells, and increased production of the autoantibodies IL-12 and IFN-γ [23].

Biancheri et al. showed a reduced mucosal TSLP expression in refractory and untreated CD, whereas Sziksz et al. revealed a higher mucosal TSLP expression in patients with newly diagnosed CD [16,17]. Furthermore, previous studies showed elevated serum TSLP levels in patients with atopic dermatitis and asthma [24,18]. Also, a higher expression of TSLP was demonstrated in the bronchoalveolar lavage fluid of patients with asthma and in esophageal mucosa of patients with eosinophilic esophagitis [25-26]. The TSLP gene has been identified as a candidate gene in the pathogenesis of eosinophilic esophagitis [27].

In the current study, we found higher serum TSLP levels in patients with CD compared to healthy controls. Only a few studies have investigated serum TSLP levels in patients with CD. Most studies assessed mucosal expression of TSLP, however, with contradictory results. An increase in serum levels and mucosal expressions of TSLP may be due to TSLP receptor blockade. One of the important findings of our study is that we showed no difference in serum TSLP between CD patients who are and are not compliant with a GFD. This may indicate that mucosal inflammation persists despite GFD in CD patients with remission. This persistent inflammation even in patients compliant with GFD at baseline may be even more exaggerated in refractory CD patients. Treatment modalities targeting the TSLP pathway in combination with a GFD may be a cure for refractory celiac patients.

Our study has several limitations. shTSLP and lTSLP isoforms have different functions, however, we could not measure their levels separately. In addition, we studied only serum TSLP levels and further studies investigating both serum and tissue TSLP levels are required to better understand its role in CD. Another limitation of our study is the age difference between CD patients compliant with a GFD and controls, and CD patients compliant and not compliant with a GFD. The fact that CD especially affects young people, and the time required to get used to the diet can be lengthy, may explain the age difference between these two groups. Even though the number of participants in each group was sufficient according to the power analysis, the age difference could have been eliminated by increasing the number of people in the groups.

CONCLUSION

In conclusion, serum TSLP levels were increased in patients with CD and targeting the TSLP pathway might be useful in the treatment of CD, especially among refractory patients.

DECLARATION OF INTERESTS

The authors declare no conflict of interests.

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