Expression of CC Chemokines CCL2, CCL5, and CCL11 is Associated with Duration of Disease and Complications in Type-1 Diabetes: A Study on Iranian Diabetic Patients

ZAHRA JAMALI 1, MAHMOOD NAZARI 1, HOSSEIN KHIRAMDELAZAD 2, ELHAM HAKIMIZADEH 3, MEHDI MAHMOodi 1, MOJGAN NOROOZI KARIMABAD 2, GHOLOMHOSEIN HASSANSHAHI 2, MOHSEN REZAIEAN 4, PARISA BALAEI 5, SHOKOOFEH DARAKHSHAN 6, NAHIDEH MASOOD POOR 6

1 Department of Biochemistry, Rafsanjan University of Medical Sciences, Rafsanjan, Iran
2 Molecular Medicine Research Center, Rafsanjan University of Medical Sciences, Rafsanjan, Iran
3 Physiology-Pharmacology Research Center, Rafsanjan University of Medical Sciences, Rafsanjan, Iran
4 Department of Social Medicine, Rafsanjan University of Medical Sciences, Rafsanjan, Iran
5 Diabetes Clinic, Ali-ebn Abitaleb Hospital, Rafsanjan University of Medical Sciences, Rafsanjan, Iran
6 Department of Pediatrics, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

SUMMARY

Background: Type-1 diabetes (T1D) is defined as a heterogeneous autoimmune disease. Immune system related factors are important in the pathogenesis of T1D. Chemokines are important factors in the pathogenesis of several autoimmune diseases, including T1D. They are potent chemotactic cytokines with various functions such as maturation, trafficking of leukocytes, angiogenesis, and homing of stem cells. Therefore, the current study was aimed to examine whether expression of CC chemokines CCL2, CCL5, and CXCL11 is associated with disease duration and complications in Iranian T1D patients.

Methods: In this experimental study, blood samples were collected from 108 T1D patients and 189 healthy controls in EDTA pre-coated tubes. The serum levels of CC chemokines were measured by ELISA. Demographic data were also collected along with experimental examinations in a questionnaire which was designed specifically for this study.

Results: Results of the present study demonstrated that the expression of CCL2 was decreased while CCL5 and CCL11 were increased in T1D patients in comparison to controls. These results demonstrated that CCL2, CCL5, and CCL11 were elevated in T1D patients with duration of disease. Again, our findings demonstrated that CCL2, CCL5, and CCL11 were elevated in T1D patients with age. But there was not a significant difference between circulating level of CC chemokines studied in T1D patients regarding their gender and they have followed a similar pattern of expression in both genders. Our findings also showed that all three CC chemokines were elevated in T1D patients suffering from diabetes complications.

Conclusions: According to the results of our study, elevated levels of CCL5 and CCL11 are in parallel with decreased level of CCL2 and are useful tools in the differential diagnosis of T1D from other types of metabolic disorders. Elevated levels of these CC chemokines probably could be implicated as predictive factors for occurrence of T1D complications. These results may also re-emphasize the prominent therapeutic role(s) of these CC chemokines in control of either T1D or its associated complications.


KEY WORDS

type 1 diabetes, CCL2, CCL5, CCL11

Manuscript accepted December 11, 2012
LIST OF ABBREVIATIONS

CCL2 - CC Chemokine Ligand 2  
CCL5 - CC Chemokine Ligand 5  
CCL11 - CC Chemokine Ligand 11  
T1D - Type-1 Diabetes  
CC - Group of chemokines with adjacent cysteines  
CXC - Group of chemokines with paired cysteines separated by a different amino acid  
CX3C - Group of chemokines with the first two cysteines separated by three amino acids  
MCP-1 - Monocyte Chemoattractant Protein-1

INTRODUCTION

Accumulating evidence indicates that T1D prevalence is increasing globally by 3 - 5%, annually [1]. It is defined as a chronic and serious disease, usually affecting children at young age [2]. In this latent disease, autoimmune associated destruction of the insulin secreting β-cells leads to insulin deficiency [2,3]. Most often, at the time of diagnosis, in T1D patients, massive numbers of the β-cells are destroyed by the immune system, in fact the blood glucose level is elevated due to the partial insulin deficiency [4]. Recent studies demonstrated that T1D is a pro-inflammatory state as evidenced by increased circulating levels of CRP (C-reactive protein), sCD40L, and also pro-inflammatory chemokines and cytokines [5-9]. The infiltration of pathogenic T-cells into the pancreatic islets is a critical phase in the pathogenesis of T1D [10].

Chemokines play crucial roles in the regulation of defensive actions and reconstruction of damaged tissues including pancreas [11]. Four main subgroups of chemokines, CC, CXC, CX3C, and C, have been identified to date [12,13]. The CCL2 (previously known as MCP-1), CCL5 (previously known as RANTES), and CCL11 (previously known as Eotaxin) belong to the CC subgroup of chemokines [14]. The CC chemokine subfamilies are members involved in immunoregulatory and inflammatory processes owing to their ability to recruit, activate, and co-stimulate T cells and monocytes [15, 16]. As it is clear from its name, the monocyte chemoattractant protein-1 (MCP-1) is a specific chemokine which recruits and activates monocytes from the circulation to the inflamed tissues [17]. Recent studies demonstrated that CCL2 and MIP-1α (the two CC chemokines) are also critically involved in the migration of pathogenic T-cells into the islets in T1D [18,19].

The other CC chemokine, CCL5 or RANTES, (regulated on activation, normal T-cell expressed and secreted) is a Th1-associated CC chemokine that promotes T-cell activation and proliferation. The concentration of CCL5 has been shown to increase in inflamed tissues for different autoimmune diseases [20]. CCL5 is genetically associated with some pathological states such as asthma, sarcoidosis and multiple sclerosis, atopic dermatitis, rheumatoid arthritis, and T1D [20-23].

CCL11 is characterized as a potent recruiter for eosinophils [24] and previous reports purposed a critical role for CCL11 in the fine-tuning of cellular responses occurring at sites of allergic inflammation, in which both CCL2 and CCL11 are produced [24]. Recent studies demonstrated that acute hyperglycemia results in increased urinary excretion of CCL11 and MIP-1α in humans with T1D [25]. Therefore, due to the importance of chemokines in the pathogenesis of T1D, especially diabetes associated inflammation and complications and also the lack of information regarding CC chemokines in T1D in Iranian patients, we designed this study to examine the circulating levels of CCL2, CCL5, and CCL11 in a sample of Iranian T1D patients.

MATERIALS AND METHODS

Subject
This study was undertaken on 108 T1D diagnosed patients and 189 control subjects. Peripheral blood samples were collected from T1D patients and healthy controls. All of the studied patients were under the age of 30 years when T1D was diagnosed. All patients showed positive keton results in their urine and serum. They also had neck acanthosis nigricans. T1D in all of the patients was diagnosed by expert pediatricians and internists according to the International Society of Pediatrics and Adolescent Diabetes (ISPAD). All of the members of the control group had not received any type of medication, including glucose lowering drugs. Patients and healthy controls were selected within the Kerman and Mashhad population with similar demographic characteristics including gender, age, and socio-economical status (Table 1). All patients and controls filled out an informed consent form before study entry. The ethical approval of this study was granted by the Ethics Committee of Rafsanjan University of Medical Sciences. Collected samples (on EDTA pre-coated 5.5 mL tubes) were subjected to centrifugation at 370 g for 4 minutes. All sera were separated within 3 hours of collection. If needed, plasma samples were stored at -20°C to a maximum of two months or at -70°C (in case of longer time) for further use.

Assessment of the chemokine level
The serum level of CCL2, CCL5, and CCL11 were measured by ELISA (R&D systems, UK) in patients and healthy controls. Assays were performed according to the manufacturer’s guidelines. The sensitivity of kits was 2 pg/mL and inter and intra-assay assessments of reliability of the kit were conducted.

Statistical Analysis and Methods
Statistical analysis of the differences between groups was determined by t-test and Anova using EPI 2000 and SPSS software version 13 with power of test of 90%. A p value of less than 0.05 was considered significant.
Table 1. Indicates demographic and some paraclinical characteristics of patients and control subjects.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>T1D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>40 ± 12</td>
<td>45 ± 9.5</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>N = 101 (46%)</td>
<td>N = 53 (49%)</td>
</tr>
<tr>
<td>Male</td>
<td>N = 88 (54%)</td>
<td>N = 55 (51%)</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>nil</td>
<td>10 ± 4</td>
</tr>
<tr>
<td>Drug therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>nil</td>
<td>NPH + Cristal</td>
<td>NPH only</td>
</tr>
<tr>
<td>N = 79 (73%)</td>
<td>N = 74 (22%)</td>
<td></td>
</tr>
<tr>
<td>nil</td>
<td>NPH + Regular</td>
<td></td>
</tr>
<tr>
<td>N = 5 (5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FBS (mean ± SEM)</td>
<td>93.39 ± 0.79</td>
<td>*227.63 ± 8.95</td>
</tr>
<tr>
<td>HbA1C (mean ± SEM)</td>
<td>5.53 ± 0.13</td>
<td>*9.11 ± 0.23</td>
</tr>
</tbody>
</table>

Results are shown as mean ± SEM.
* = Significant difference with control. FBS = Fasting blood sugar; HbA1C = Hemoglobin A1C.

Table 2. Shows the level of CC chemokines in T1D patients and controls based on the duration of diabetes and age.

<table>
<thead>
<tr>
<th>Chemokine type</th>
<th>Duration of Diabetes</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 - 10 (years)</td>
<td>1 - 20 (years)</td>
</tr>
<tr>
<td>CCL2</td>
<td>278.5 ± 11.5</td>
<td>238.8 ± 7</td>
</tr>
<tr>
<td></td>
<td>N = 62</td>
<td>N = 42</td>
</tr>
<tr>
<td></td>
<td>*324.3 ± 19.4</td>
<td>*337.1 ± 14.4</td>
</tr>
<tr>
<td></td>
<td>N = 33</td>
<td>N = 54</td>
</tr>
<tr>
<td></td>
<td>#*509.6 ± 33.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N = 13</td>
<td></td>
</tr>
<tr>
<td>CCL5</td>
<td>769 ± 48.8</td>
<td>618.6 ± 45.3</td>
</tr>
<tr>
<td></td>
<td>N = 62</td>
<td>N = 42</td>
</tr>
<tr>
<td></td>
<td>*1140 ± 74.9</td>
<td>*1104 ± 53.9</td>
</tr>
<tr>
<td></td>
<td>N = 33</td>
<td>N = 54</td>
</tr>
<tr>
<td></td>
<td>#*1580 ± 97.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N = 13</td>
<td></td>
</tr>
<tr>
<td>CCL11</td>
<td>168 ± 3.5</td>
<td>156.3 ± 3.1</td>
</tr>
<tr>
<td></td>
<td>N = 62</td>
<td>N = 42</td>
</tr>
<tr>
<td></td>
<td>*185.3 ± 4.1</td>
<td>*188.5 ± 3.2</td>
</tr>
<tr>
<td></td>
<td>N = 33</td>
<td>N = 54</td>
</tr>
<tr>
<td></td>
<td>#*230.7 ± 8.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N = 13</td>
<td></td>
</tr>
</tbody>
</table>

Results are shown as mean ± SEM.
* = Significant difference between 1 - 10 years in duration of diabetes and 11 - 20 years group.
#* = Significant difference between 21 - 30 years and 11 - 20 years in duration groups and also between 41 - 90 years and 21 - 40 years groups.

RESULTS

Results of the present study demonstrated that the mean CCL2 serum level was 320.3 ± 11.9 pg/mL and 348.8 ± 8.5 pg/mL in T1D patients and controls, respectively (Figure 1a). Statistical analysis of data revealed that the difference was significant between T1D patients and controls (p < 0.05). In this study, we also measured serum level of CCL5 and showed that the level of CCL5 was significantly elevated in diabetic patients in comparison to the corresponding control group. The mean serum level of CCL5 was 980 ± 46.2 pg/mL and 502.1 ± 15.3 pg/mL in T1D patients and controls, respectively. Statistical analysis demonstrated a significant difference between patients and controls (p = 0.00; Figure 1b). Results of our study also indicated that the level of CCL11 was significantly increased in T1D patients in comparison to the respective control (p < 0.0001). The
Table 3. Indicates the level of CC chemokines based on various complications of T1D.

<table>
<thead>
<tr>
<th>Chemokine type</th>
<th>Without Complication</th>
<th>Various Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Neuropathy</td>
</tr>
<tr>
<td>CCL2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>252 ± 5.1</td>
<td>396.8 ± 79.6</td>
</tr>
<tr>
<td></td>
<td>N = 74</td>
<td>N = 3 NA</td>
</tr>
<tr>
<td>CCL5</td>
<td>765.7 ± 41.7</td>
<td>1434.5 ± 200.3</td>
</tr>
<tr>
<td></td>
<td>N = 74</td>
<td>N = 3 NA</td>
</tr>
<tr>
<td>CCL11</td>
<td>164.9 ± 2.5</td>
<td>203.2 ± 22.2</td>
</tr>
<tr>
<td></td>
<td>n = 74</td>
<td>N = 3 NA</td>
</tr>
</tbody>
</table>

* = Significant difference with T1D patients without complications.
NA: Not assessed, DFS: Diabetic foot syndrome.

Table 4. Shows the level of CC chemokines in T1D patients and control based on gender, familial history, and smoking behavior.

<table>
<thead>
<tr>
<th>Chemokine type</th>
<th>Gender</th>
<th>History</th>
<th>Smoking Behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
<td>Positive</td>
</tr>
<tr>
<td>CCL2</td>
<td>302.6 ± 16.2</td>
<td>337.4 ± 17.3</td>
<td>355.8 ± 24.6</td>
</tr>
<tr>
<td></td>
<td>N = 53</td>
<td>N = 55</td>
<td>N = 78</td>
</tr>
<tr>
<td>CCL5</td>
<td>1005.7 ± 62.4</td>
<td>955 ± 68.3</td>
<td>1188.2 ± 77.9</td>
</tr>
<tr>
<td></td>
<td>N = 53</td>
<td>N = 55</td>
<td>N = 78</td>
</tr>
<tr>
<td>CCL11</td>
<td>178.1 ± 3.9</td>
<td>183.4 ± 5</td>
<td>187.2 ± 4.9</td>
</tr>
<tr>
<td></td>
<td>N = 53</td>
<td>N = 55</td>
<td>N = 78</td>
</tr>
</tbody>
</table>

Results are shown as mean ± SEM.
* = Significant difference with positive group.

mean serum level of CCL11 was 180.8 ± 3.2 pg/mL and 142.4 ± 3.4 pg/mL in T1D patients and controls, respectively (Figure 1c). Our results also showed that inter- and intra-assays produced scores of CV < 14% and CV < 3%, respectively.

In this study, we divided T1D patients into the three following groups based on the duration of being diabetic: 1 - 10 years, 11 - 20 years, and 21 - 30 years. Interestingly, our findings demonstrated that CCL2, CCL5, and CCL11 increased in T1D patients with the duration of diabetes. Statistical analysis of data confirmed a significant difference between the level of CCL2 in 1 - 10 years group with 11 - 20 and 21 - 30 years (p < 0.0001; Table 2). These results also showed that the level of CCL5 was significantly increased with duration of disease in T1D patients so that it was 769 ± 48.8 pg/mL, 1140 ± 53.9 pg/mL, and 1686.4 ± 48.6 pg/mL in 1 - 20 years old, 21 - 40 years old and 41 - 60 years old groups (p < 0.0001; Table 2). CCL11 was also elevated in T1D patients with age and its level was 156.3 ± 3.1 pg/mL, 185.3 ± 3.2 pg/mL, and 232.1 ± 9.4 pg/mL in 1 - 20 years old, 21 - 40 years old, and 41 - 60 years old, respectively (p < 0.0001; Table 2).

A similar pattern of CC chemokine expression was observed in T1D patients in different age groups (p < 0.0001; Table 2). We divided T1D patients into three age groups as follows: 1 - 20 years, 21 - 40 years, and 41 - 60 years. Again, our findings demonstrated that CCL2, CCL5, and CCL11 increased in T1D patients with age. Statistical analyses of data showed significant differences between the level of CCL2 in the 1 - 20 years old group with 21 - 40 and 41 - 60 year old groups (p < 0.0001; Table 2). These results also showed that the level of CCL5 was significantly increased with age in T1D patients so that it was 618.6 ± 45.3 pg/mL, 1140 ± 53.9 pg/mL, and 1686.4 ± 48.6 pg/mL in 1 - 20 years old, 21 - 40 years old and 41 - 60 years old groups, respectively (p < 0.0001; Table 2). CCL11 was also elevated in T1D patients with age and its level was 156.3 ± 3.1 pg/mL, 185.3 ± 3.2 pg/mL, and 232.1 ± 9.4 pg/mL in 1 - 20 years old, 21 - 40 years old, and 41 - 60 years old, respectively (p < 0.0001; Table 2).

We analyzed the serum level of the respective chemokines based on various types of complications raised by T1D in all of studied T1D patients (Table 3). We observed that the level of CC chemokines is correlated...
with the diabetes complications. As it is obvious from Figure 2a, the level CCL2 was 469.1 ± 19 pg/mL in T1D patients suffering from diabetes complications while it was 252 ± 5.1 pg/mL in T1D patients without complications and 348.8 ± 8.5 pg/mL in controls (p < 0.0001). Our findings demonstrated that the serum level of CCL5 was 1446.3 ± 63.3 pg/mL in T1D patients showing complications whereas CCL5 level was 765.7 ± 41.7 pg/mL in T1D patients without complications and 520.1 ± 15.3 pg/mL the in control group (p < 0.0001; Figure 2b). Our findings demonstrated that the serum level of CCL11 was 211.7 ± 4.8 pg/mL in T1D patients suffering complications whereas CCL11 level was 164.9 ± 2.5 pg/mL in T1D patients without complications and 142.45 ± 3.4 pg/mL in the control group (p < 0.0001; Figure 2c).

Our results showed that there was no significant difference between the circulating level of CC chemokines...
Figure 2. Demonstrates the expression of CC chemokines.
a) CCL2, b) CCL5 and c) CCL1 in T1D patients suffering diabetes complications, T1D without complications, and control subjects.
Results are shown as mean ± SEM.
* = Significant difference with control and without complication group.
** = Significant difference with control and complication group.
studied in T1D patients regarding their gender and they followed a similar pattern of expression in both genders (Table 4). When the level of CC chemokines were compared with regard to familial history of T1D, there was also no significant statistical difference between expression of CCL2 and CCL11 in T1D patient without familial history of T1D (p > 0.05; Table 4), while CCL5 was significantly elevated in T1D patients with familial history (p = 0.04; Table 4). Our findings indicated that there was no correlation between the level of CC chemokines investigated and the status of BMI in patients and controls (p > 0.05). There was a significant correlation between smoking behavior and chemokine level. In T1D patients, smoker patients had elevated levels of all chemokines studied. The serum level of CCL2, CCL5, and CCL11 was 396.7 ± 38.8 pg/mL, 1342.1 ± 143.1 pg/mL, and 203.1 ± 9.8 pg/mL, respectively (p < 0.05; Table 4).

**DISCUSSION**

The main etiological aspects of T1D and its associated inflammatory complications such as nephropathy have yet to be clarified. It also seems that immune factors play predominant roles in the etiology and pathogenesis of T1D and its associated complications. Immune cells and macrophages are present in the diabetic pancreas; thus, they may produce chemokines in this organ [26]. Since CC chemokines seem to be associated with diabetes and its respective complications, it would be interesting to examine the exact role of these factors in diabetes and explore the potential of CC chemokine administration or depletion in diabetes treatment.

In our study, we addressed significant elevated expression of CCL5 and CCL11 and inversely decreased CCL2 circulating levels in T1D when compared to controls; hence, it means that these chemokines are probably important in pathogenesis of T1D. However, augmented CCL2 is reported in T1D patients suffering from complications compared to T1D patients who do not show complications. This confirms a dual role for this chemokine in the pathogenesis of T1D [27]. The elevated level of CCL2 in T1D patients suffering from diabetes complications in our studied T1D population may explain a role for this chemokine in the progression of complications (Figure 2a). The CCL2 augmentation in T1D patients may also be a predictive marker for the possibility of patients progressing towards diabetes complications. Although, similar reports by some investigators indicated that CCL2 was lower in T1D patients, but as in our findings there are conflicting reports demonstrating either that CCL2 is increased in mice T1D models or children with T1D [28,29].

In more recent investigations Niewczas MA and colleagues (2008) demonstrated that apoptosis associated signaling molecules such as soluble TNF-receptors and Fas mediated pathways are not only elevated in T1D patients, but also correlated with nephropathy complication of these patients. Thus, this is in agreement with our finding regarding enhanced inflammatory chemokines in T1D patients [30]. Moreover, Kouyam et al. reported that the MCP-1-2518 polymorphic variant of CCL2 is associated with the increased CCL2 level in T1D patients [31]. They reported that patients with AG genotype had enhanced plasma CCL2. Thus, the decreased CCL2 level in our patients may probably be related to this CCL2 genetic variant and further studies are needed in Iranian T1D patients to clarify this hypothesis.

CCL2 along with CXCL10 have been shown to contribute to retinopathy complications of T1D and their elevated levels in vitreous fluid of T1D patients is documented [32]. This is in agreement with our results that showed augmented CCL2 in T1D patients suffering from complications. Furthermore, enhanced CCL5 serum level in retinopathic T1D patients is also documented [32] which is consistent with our findings demonstrating that these CC chemokines are dramatically increased in T1D patients suffering diabetes complications, including retinopathy. Because CCL2 is an activator and recruiter of monocytes to the glomerulus by regulation of adhesion molecules [33], augmented CCL2 in our patients with nephropathy also may relate to these properties of CCL2.

Elevated level of CCL2 in parallel with other examined CC chemokines in our T1D patients with complications could be used as a valuable predictive biological marker to speculate initiation of the T1D complications phase and also organ failure in these patients.

In agreement with our study Hanifi-Moghaddam et al. also showed declined CCL2 levels in T1D patients [34], but they only studied a very small population of T1D patients and did not considered T1D complications; thus, their studied patients maybe were not suffering from T1D complications.

Elevated levels of CC chemokines CCL5 and CCL11 in our patients may also be related to the therapy side effects. Banba, et al. indicated that human mesangial cells secrete CCL2 in response to glycated albumine. Taken together with our results, it may in a way show that some of the elevated plasma CCL2 in our patients suffering from complications could be due to the activation of these cell types during diabetes complications and in turn CCL2 may worsen the patient’s status by recruiting monocytes/macrophages to the injured organ, e.g. kidney. On the other hand, the recruited monocytes/macrophages may also facilitate a hyperglycemia dependent triggered activation of endothelial cells and further atherosclerosis [17]. Furthermore, CCL2 is an angiogenic chemokine and its elevated level in T1D patients with complications maybe is related to the prominent role played by the chemokine in the phenomenon of new vessel formation in T1D patients. During inflammatory states such as diabetes complications, the elevated levels of proinflammatory cytokines including TNF-α and IL-1 β is well established; thus, these inflammatory mediators probably up-regulate inducible
CC chemokines, including CCL2, CCL5 and CCL11. The elevated CCL5 level in our T1D model may be related to its properties as an inflammatory chemokine. It has been well established that this chemokine, in addition to its predominant role in T cell trafficking, also plays a role in co-stimulation of T cell proliferation [35, 36] and activation of cells localized in inflammatory lesions [37]. Hence, elevated CCL5 levels in our T1D patients may be related to the inflammatory responses with occur in T1D, because we showed a dramatic CC L5 elevation in T1D patients compared to controls and T1D patients without complications (approximately by 5 and 2.5 fold, respectively). Increased protein levels of CCL5 in the primary sites of inflammation have been reported in different autoimmune diseases. CCL5 levels are increased in cerebrospinal fluid of patients suffering from active attacks of multiple sclerosis [15]. CCL5 levels are also increased in allograft rejection [15], in patients with systemic Lupus erythematosus [38], in the sinovium of patients with rheumatoid arthritis [39], and in the granulomas in Crohn's disease [40]. Similarly, here in we report that the CCL5 serum levels of the protein are increased in T1D as an autoimmune disease.

Limited studies are available on the roles played by CC proteins are increased in T1D as an autoimmune disease. Moreover, consistent with our results, Hessner et al. [42], they demonstrated that in acute hyperglycemia the urinary level of CCL11 is increased along with some other CC chemokines such as MCP-3 and pro-inflammatory cytokines like TNF-α, IL-2, and IL-12 [25]. Biobreeding rat models of T1D indicated that innate mast cells and eosinophils are chemoattracted through CC R5 on either peripheral leukocytes or organ recruited leukocytes (in the case of diabetes complications). This helps to speculate the possible role for the chemokine/receptor axis in T1D.

**Acknowledgement:**
The authors of this article would like to take this chance to thank all T1D patients and healthy individuals who voluntarily participated in this research project. This project was financially supported by a grant from Rafsanjan University of Medical Sciences.

**Declaration of Interest:**
None of the authors of this article declared a conflict of interest.

**References:**


CC CHEMOKINES’ EXPRESSION IN T1D PATIENTS WITH COMPLICATIONS


Correspondence:
Dr. Nahideh Masood Poor
Department of Pediatrics
Rafsanjan University of Medical Sciences
Rafsanjan, Iran
Tel: +98 9133917694
Email: n.masoudpour@rums.ac.ir