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Detection of Monocyte Chemotactic Protein-1 (MCP-1) among Patients with Celiac Disease

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ABSTRACT

Background: *Celiac disease (CD) is a persistent autoimmune disorder stimulated by gluten consumption in genetically susceptible people. Several studies have focused on the importance of monocyte chemoattractant protein-1 (MCP-1) in the development of CD. MCP-1 is a chemokine that has a crucial effect in attracting monocytes, dendritic cells, and memory T-cells to the inflammation site. In CD, elevated MCP-1 levels have been detected in the intestinal mucosa, contributing to immune cell infiltration and tissue damage. Monocyte chemotactic protein-1 has been linked to the amplification of inflammatory responses, promoting cytokine production and perpetuating mucosal injury.* ***Methods*** *This is a case control study, comprised 128 participants, divided into 64 cases with celiac disease apparently and 64 healthy individuals. The study was conducted at Al-Husainyah Hospital, Al-Hassan Al-Mojtaba Hospital, and Imam Al-Husain Medical City. After taken the consent, all participants in this study donated a five mL of venous blood, which was then deposited in 6 mL gel tubes. Then, this blood is centrifuged for ten minutes at 3000 rpm. By the enzyme-linked immunosorbent assay (ELISA), we estimated the serum level of MCP-1. The Patient's information was collected using questionnaires. People with concurrent other immunological or GIT problems were eliminated from the present study.* ***Results****: The findings of the current study indicated elevated levels of serum MCP-1 in celiac disease patients compared to the control group, Also, patients who following a diet have lower levels of MCP-1. The males group has higher levels of MCP-1 than the Females group.* **Conclusion:** *The current study results showed that, the serum level of MCP-1 is increased among patients' group of CD more than controls, Also, greater levels of MCP-1 are showed in males more than in females. Patients who do not follow a strict diet free from gluten possess more levels of MCP-1 than treated patients.*

Keywords: Celiac Disease, MCP-1, and Gluten.

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INTRODUCTION

Celiac disease (CD) is defined as an autoimmune-related enteropathy that is more likely to occur in genetically susceptible people, and it can be activated through the eating of gluten proteins, which are found in several different cereals like rye, barley, and wheat (1). People with a genetic predisposition may develop inflammatory gut disease attributed to the inability of digestive enzymes in the intestines to completely degrade gliadin proteins, which are found in specific meals (2).

Gluten is a complicated collection of many closely similar proteins that are not soluble in water but are soluble in alcohol. This type of material stands out for its high amino acid concentration, which includes glutamine and proline. These amino acids contribute to the gastrointestinal tract's particular resilience to protease degradation (3). The worldwide prevalence of CD in the last decade elevated from 1% to 1.5% (4). This may be attributed to alterations in environmental factors that affect the body's response to dietary gluten and

advancements in diagnostic methods that have higher sensitivity (5). The CD rate in Arabic countries, especially in Saudi Arabia, is 3.2%, becoming the highest among them [4]. An independent investigation in Iraq recorded the CD prevalence among patients who suffered from irritable bowel syndrome (IBS) at 12.1% (6). The serological analysis of celiac disease mainly includes estimation of anti-gliadin (AGA), with anti-tissue transglutaminase (anti-tTG) antibodies to both IgA and IgG, by the ELISA technique (7).

Chemokines are categorized into four main groups: CC, CXC, XC, and CX3C. MCP-1, mainly called chemokine ligand 2 (CCL2), is one of the CC subgroup of cytokines (8). The major generators of MCP-1 include macrophages and monocytes, while it is also synthesized by many other cells, including endothelial cells, fibroblasts, epithelial cells, and smooth muscle cells (9). Chemotactic cytokines regulate the migration of different cells due to stimulation from chemicals via a process named chemotaxis, so they are referred to by the term chemokines (10). After receptor binding CCL2, MCP-1 may drive the homing, movement, activation, and differentiation, in addition to lymphocytes and NK cells proliferation; assist in the entry of monocytes and macrophages to the inflammatory sites; increase inflammation; induce angiogenesis; also may exhibit fibrotic actions (11).

Monocyte chemotactic protein-1 is released mainly by monocytes or macrophages, to work as a chemical attractive to the T-cells, monocytes, dendritic cells, and other inflammatory cells. It can help in the extravasation of monocytes from the bloodstream to the intestinal lamina propria through the CCL2-CCR2 axis (12, 13). MCP-1 facilitates the chemotaxis of both lymphoid and myeloid cells, in CD patients, increased concentrations of chemokines, including MCP-1, have been recognized in the initial immune response to gluten, triggering receptor of myeloid cells called (TREM-1) can modulate inflammation and promotes prolonged immune response, is mostly expressed on the outer layer of monocytes, neutrophils, and granulocytes. Stimulation of it will trigger some of the intracellular processes that end in the synthesis of MCP-1 (14).

The data indicated a greater production of MCP-1 following stimulation with the p31-43 gliadin peptide (15). Monocytes are essential in regulating intestinal barrier function by cytokine production or direct contact with intestinal epithelial cells (16, 17). The intestinal epithelium plays an essential role in the pathogenesis of celiac disease in addition to various autoimmune conditions (18).

Monocyte chemotactic protein-1 facilitates the movement of myeloid and lymphoid cells toward sites of inflammation, which increases the inflammatory response (14). Various investigations have associated this kind of immune cell (monocyte) with celiac disease, noting that gliadin peptides induce their release of TNF-α and IL-8, particularly in people with celiac disease. The reaction elicited by gliadin in monocytes is said to resemble that generated by lipopolysaccharide (LPS) via receptors like TLR4 (19). The monocytes isolated from the blood samples of CD patients exhibited an elevated production of MCP-1 with IL-6, when IL-6 from the monocyte has a role in the destruction of tight junctions in the intestinal epithelial layer of celiac disease patients, that help in the pathogenesis process (20).

Monocytes taken from celiac disease patients showed a functional barrier impairment in the intraepithelial cells, because celiac monocytes triggered a reduction in occludin and claudin-5 expression, those transmembrane proteins are responsible for controlling the permeability of endothelial and epithelial walls in IECs, so any defect in these protein types will result in an abnormal binding between these cells (12, 21).

Following extravasation, monocytes permeate the lamina propria to differentiate into macrophages and generate inflammatory

mediators to cause inflammation (22). The source of macrophages in the intestinal lamina propria is from the blood monocytes that are attracted to the tissue and then develop into macrophages by the outside surroundings (23). Gliadin possesses a pro-inflammatory action on human macrophages, promoting their differentiation into an M1 subtype, which will produce pro-inflammatory cytokines to activate both Th1 and Th2 immunological responses that can show a strong inflammatory effect in celiac disease (24).

The macrophage population in the muscularis propria in the intestines is severely affected by the intestinal flora, it can modulate peristalsis by the secretion of type 2 bone morphogenetic protein, which activates neurons of the intestines (25, 26), intestinal neurons secrete neurotransmitters (dopamine, acetylcholine, serotonin, norepinephrine, etc.), which stimulate smooth muscle cell contraction (27). Macrophages exhibit heightened responsiveness, causing the pro-inflammatory cytokines and the regulation of inflammatory responses. Previous investigations showed that these cells facilitate antigen-specific immune reactions against gliadin peptides in CD patients (20, 28). CCL2, which is called (MCP-1), was related to the development of many systemic diseases other than celiac disease, like rheumatoid arthritis, diabetes mellitus, atherosclerosis, and multiple sclerosis (29). This study decided to determine the effect of MCP-1 in CD pathogenesis. Also, detect the serum level of MCP-1 among patients with CD.

METHODS

The study design was a case-control study, and it was done at Al-Hussainyah General Hospital, Imam Al-Hassan Al-Mujtaba Hospital, and Imam Al-Husain Medical City. The samples and information were gathered between November 2024 to February 2025. The whole study included 128 participants. The study consisted of two groups: 64 apparently 64 celiac disease (CD) patients with 64 control individuals. The patients were identified via a physician, either already or recently diagnosed by a doctor of the gastrointestinal tract. Control subjects were selected without Celiac manifestations. This study comprised individuals aged between (18-50) years and both genders. patients having diabetes mellitus, ischemic heart disease, any autoimmune disorder, gastrointestinal problems, renal diseases, and Pregnancy before the trial were eliminated from the sample selection. A five milliliters of venous blood were collected from both patients and controls by venipuncture into a sterile tube. The sample of blood was allowed to coagulate at ambient temperature before centrifugation at 3000 rpm for 5 minutes. The serum of each sample was extracted and kept in Eppendorf tubes, which were kept directly at -20 °C until required to work in ELISA.

The serum level of MCP-1 was assessed by the enzyme-linked immunosorbent assay (ELISA) method, using a biochemical kit provided by Bioassay Technology Laboratory (BT LAB) company and mated Laboratory Methods. MCP-1 is measured by a quantitative sandwich enzyme immunoassay technique. It was executed using an automated microtiter plate ELISA reader.

RESULTS

This study measured the difference between the CD patients' group and the controls group according to the level of MCP-1. The mean serum level of the patients group was higher than the mean serum levels of the controls group (657.52± 43.67 vs 286.81 ± 79.84) µ/l, with a significant difference P value 0.020 < 0.01. As demonstrated in Table 1 and figure 1.

The serum level of the MCP-1 was increased through the males group of CD patients (311.40± 88.23) µ/l, more than the females group of CD patients (275.62± 49.91) µ/l, with a significant statistical difference (p <0.05), as in Table 1 and Figure 2. Depending on the diet commitment, the non-diet

commitment group of patients has the highest level of MCP-1 at about (325.21± 73.67) µ/l, followed by the diet commitment group at about (250.72± 49.16) µ/l, with a significant difference (p< 0.05). As demonstrated in Table 1 and Figure 3.

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Table (1): Comparison between study groups based on the level of MCP-1.

Study parameter	Study groups	Mean ± SD	p-value
MCP-1	CD patients	657.51± 43.67 µ/l	.,.20
	Controls	286.80 ± 79.84 µ/l	
	Patients Males	311.40 ± 88.23 µ/l	.,.37
	Patients Females	275.62 ± 49.91 µ/l	
	Patients with GFD	155.34 ± 63.44 µ/l	.,.12
	Patients without GFD	305.58 ± 48.70 µ/l	

(*Independent sample T-test) (P value=probability value, was significance at <0.05), (SD= standard deviation).*

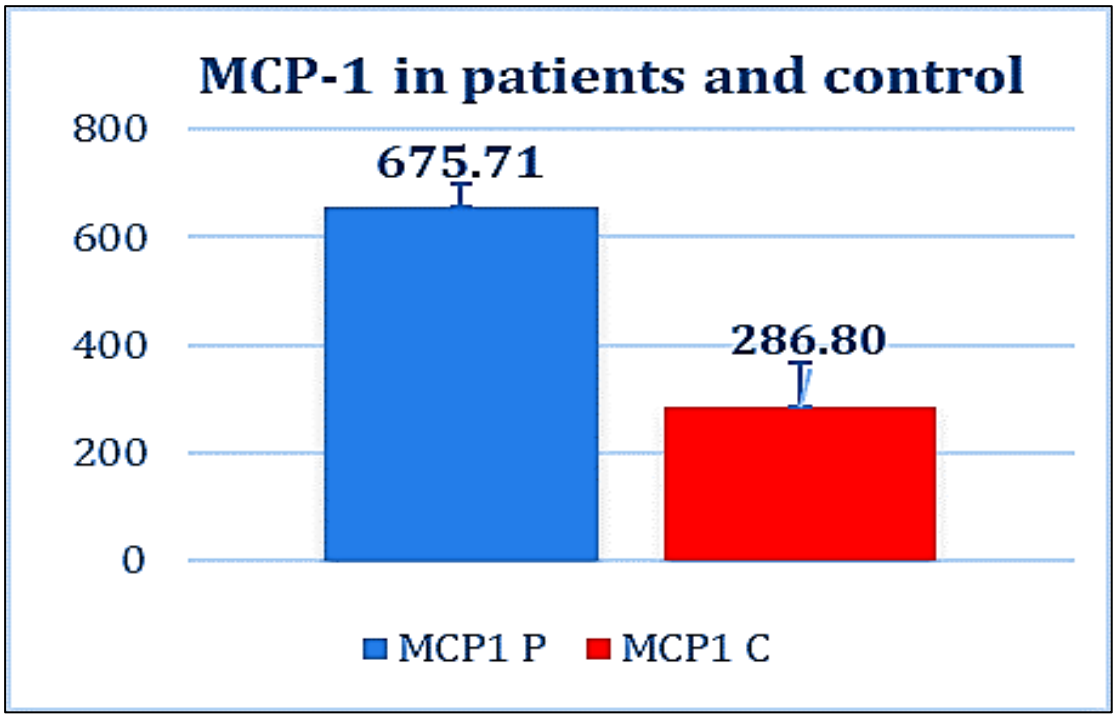

Figure (1): Comparison between CD patients and controls according to the level of MCP-1.

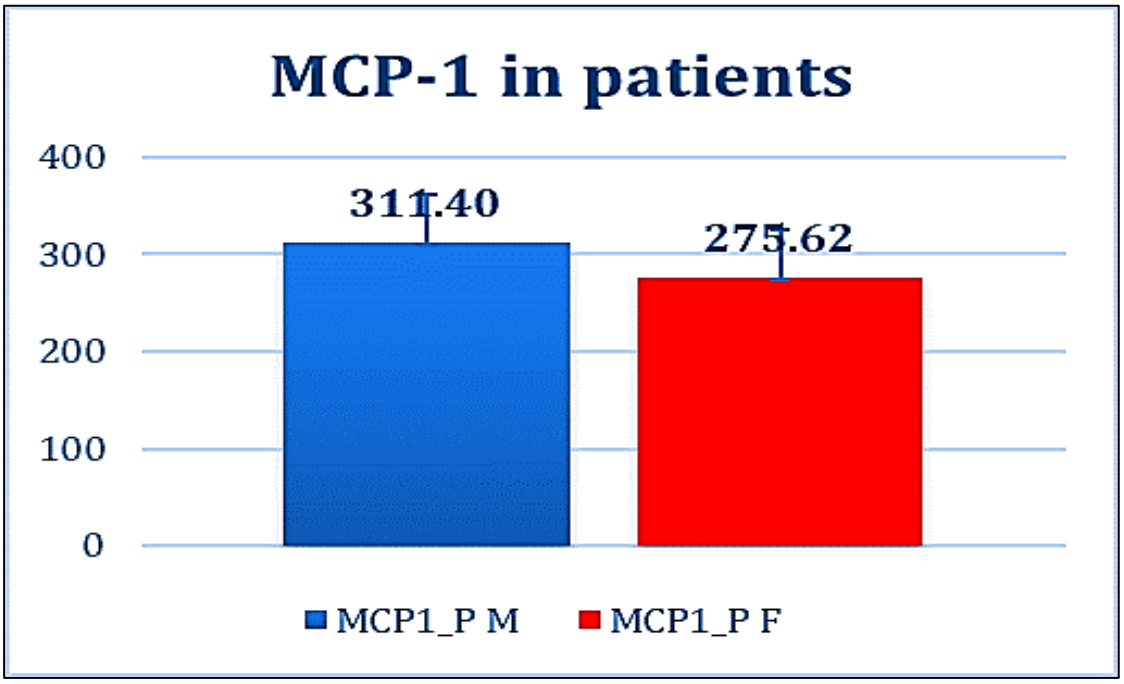

Figure (2): Comparison of the MCP-1 level between CD patients' group according to the gender.

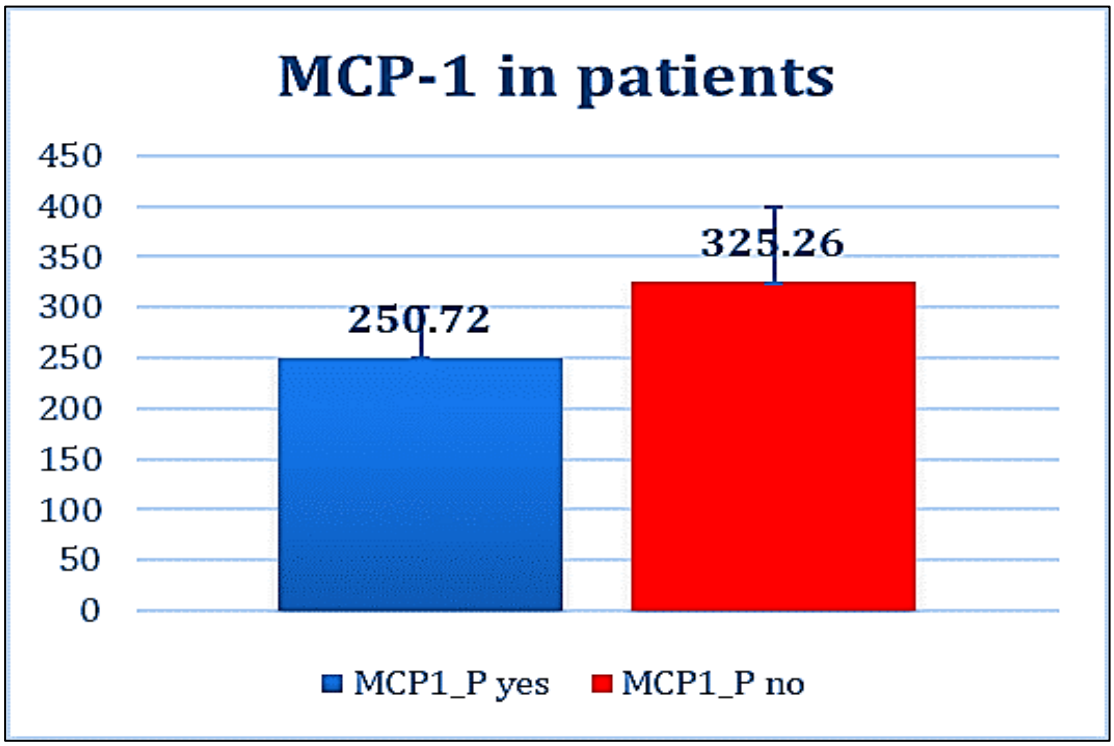

Figure (3): Comparison of the MCP-1 level between CD patients group according to the diet commitment.

DISCUSSION

The findings of the current study showed a highly statistically significant difference in MCP-1 levels between celiac patients compared with the control group (657.51± 43.67) versus (286.80 ± 79.84) and (p-value 0.020<0.05). The present study is matched with a study by (15), that showed the Monocytes obtained from the peripheral blood of CD patients exhibited an elevated production of MCP-1 in the celiac disease patients group, higher than in controls group. Also, a study done by (14), agrees with this current study, which indicated a high concentration of MCP-1 in CD patients compared with healthy individuals after intake of gluten.

According to the monocyte chemotactic protein-1(MCP-1) related to gender, these findings of the current study indicate a highly significant difference in males patients than in females (311.40± 88.23) versus (275.62± 49.91) with P. value 0.012 <0.05, these results compatible with a study by (30), have shown a basic gender variations in monocyte activation. Monocytes in males often have a more inflammatory phenotype than females monocytes, with greater motility and an increased ability to differentiate into reactive macrophages. However, the direct influence of these variations on the frequency of CD disease between genders is still unknown. Another study by (31) indicated that macrophage activation is higher in males compared to females and continues into older ages of males. A study by (32) is not compatible with the current study, which indicated that women have higher levels of macrophage activation in many inflammations, when sex and hormones have an impact on macrophage morphology and metabolism. The women have higher fats, so the fatty acids and chemokines such as CCL2(MCP-1) can promote monocyte recruitment, potentially clarifying the significant connection between lipid accumulation and the initiation of inflammation.

According to diet commitment, the current study results showed a significantly elevated level of MCP-1 in the patients group who still consume gluten higher than in treated CD patients (325.21 ±73.67) vs (250.72±49.16) µ/l and (p=0.03), studies have shown that celiac patients who fail to keep up with gluten-free foods and drinks display markedly elevated levels of MCP-1 in both serum blood and intestinal tissues in comparison to those who adhere to dietary guidelines. Raised MCP-1 levels are associated with greater histological damage, such as villous atrophy and crypt hyperplasia. This not only exacerbates intestinal injury but may also work as a biomarker for monitoring disease activity and dietary compliance.

These results are compatible with the results of (15), which indicated the production of a high level of CCL2 (MCP-1) in response to unregulated food intake in celiac disease patients after increased gliadin digestion. Another study done by (22), agreed with these study results, which demonstrated increased monocyte recruitment to the intestine due to activation by gliadin intake, resulting in an increase of MCP-1 from these cells in untreated celiac disease patients. Increased MCP-1 levels inside the intestinal mucosa soon after gluten intake promote the movement of circulating monocytes toward the inflammatory site. Upon recruitment, these monocytes penetrate the lamina propria, and they can differentiate into dendritic cells or macrophages, supporting the inflammatory process. The current study results are in line with a study results of (24), which indicated increased monocyte attraction after ingesting a gliadin-containing diet from circulating blood to the tissues, and converted to macrophages, and then differentiated to the M1 subtype to secrete many cytokines and chemokines to activate Th-1 to cause a high inflammatory response.

CONCLUSION

The current study results showed that the serum level of MCP-1 is increased among patients group of CD more than controls, Also, greater levels of MCP-1 are showed in males more than females. Patients who do not follow a strict diet free from gluten possess more levels in MCP-1 than treated patients. The association between MCP-1 expression and disease activity suggests its potential as a biomarker for monitoring immune responses and guiding therapeutic strategies. In this study, we recommended that Future studies should investigate the therapeutic potential of targeting the MCP-1/CCR2 signaling axis in celiac disease, particularly in patients with persistent inflammation despite a gluten-free diet. Also, we suggest doing extensive studies on this marker, because it was not highly studied in the past regarding the role of MCP-1 in CD in the past.

Ethical approval

The present study, which is conducted by the authors (Yasser Abdul Hamza Ali and Dhefaf Hameed Abdul Sahib), was approved by the local Department of Microbiology committee.

Statement of Permission and Conflict of Interests

All the patients were willingly agreed to participate and a written consent to indicate their willing to participate have been signed by all of them.

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