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THE EFFECT OF CYTOKINES (CCL2, CCL4 AND CCL18) IN RHEUMATOID ARTHRITIS, AND THEIR ROLE IN INCREASING THE DEVELOPMENT OF DIABETIC COMPLICATIONS (REVIEW)

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Abstract. The primary objective of this study is to review the latest scientific research regarding the roles and effects of the cytokines CCL2, CCL4, and CCL18 in patients with rheumatoid arthritis, as well as their contribution to the exacerbation of diabetic complications. The study also examines inflammatory factors that may play a role in the development of such complications. This retrospective study was conducted covering the period from 2015 to 2026, utilizing major search engines including PubMed, Google Scholar, and ScienceDirect to gather the necessary sources.

Keywords: cytokines; Rheumatoid arthritis; CCL2; CCL4; CCL18; diabetes

Introduction

Chemokines which are low-molecular-weight, chemoattractant cytokines and their receptors play pivotal roles in the physiological processes of cell polarization and the direction of cell migration. They can be broadly classified into four subfamilies (CC, C, CXC, and CX3C) based on the cysteine motifs present at their N-termini. The CXC subfamily is further divided into two groups: one containing the ELR motif (consisting of the amino acids glutamic acid, leucine, and arginine) preceding the first cysteine residue, and the other lacking this motif. Chemokines are also classified into "homeostatic" and "inflammatory" chemokines based on their functions; homeostatic chemokines are constitutively secreted and primarily involved in lymphocyte trafficking, whereas inflammatory chemokines are associated with mechanisms that promote inflammation and induce the recruitment of leukocytes to damaged tissues [1]..Increased disease activity and elevated levels of cytokines and chemokines are associated with a higher risk of developing diabetes in patients with rheumatoid arthritis.Future studies focusing on rheumatoid arthritis patients and the types of treatments used in long-term therapeutic regimens may help mitigate complications related to blood sugar imbalances and assist in achieving glycemic control in these patients.).Inflammation promotes insulin resistance and triggers other factors—such as elevated levels of "rheumatoid factor" in the blood leading to a positive test result for this factor in patients with rheumatoid arthritis. Furthermore, the severity of the inflammation associated with the disease influences the degree of insulin resistance; resistance increases as disease activity rises, and vice versa [2]. Rheumatoid arthritis is associated with insulin resistance; the inflammatory process in this disease interacts with insulin resistance due to the increased accumulation of white adipose tissue, a process driven by the activation and migration of monocytes via the chemokine system [3].

Insulin resistance is linked to chronic low-level inflammation, and inflammation is closely linked to joint disease. insulin has been found to play a protective and anti-inflammatory role within the synovium. However, the presence of insulin resistance can hinder this beneficial effect, thereby potentially contributing to joint damage. found that insulin resistance can affect bone mass and reduce bone density. Furthermore, insulin has been shown to have direct effects on cartilage metabolism, promoting the synthesis of inflammatory mediators and degrading enzymes that can contribute to cartilage degradation and joint inflammation.

Chemokine levels are elevated in cases of diabetes both type 1 (T1DM) and type 2 (T2DM) acting as pro-inflammatory biomarkers associated with insulin resistance, obesity, and vascular complications. Prominent elevated chemokines include CCL2 (MCP-1), CCL5 (RANTES), CXCL1, and CXCL10; these molecules promote inflammation and trigger leukocyte recruitment [4].

Methods

This narrative review examines published studies on the roles of CCL2, CCL4, and CCL18 in rheumatoid arthritis and diabetes-related inflammation. The literature reviewed in the manuscript covers publications from 2015 to 2026 and was gathered using PubMed, Google Scholar, and ScienceDirect. Findings are organized by chemokine and disease context and compared descriptively in the accompanying tables.

Results and Discussion

Chemokines in diabetes

CCL2 expression in diabetic patients

Cytokines are biological mediators that manage and regulate immune and inflammatory responses through complex networks, and they also serve as biomarkers for various diseases. Measuring cytokines is of critical importance in both clinical medicine and biology, as their levels provide valuable insights into physiological and pathological processes, aiding in diagnosis and treatment. This overview examines cytokines and their clinical significance, focusing on their pro-inflammatory and anti-inflammatory effects [5].

Cytokines are small, soluble, hormone-like proteins that enable communication between cells and their surrounding environment [6]. Both type 1 and type 2 diabetes are associated with elevated concentrations of inflammatory proteins in the bloodstream, although this increase is

more pronounced in type 2 diabetes [7]. Cytokines are a group of proteins, glycoproteins, or peptides that function as intercellular signaling molecules; they may also help predict the onset of diabetes complications—such as microalbuminuria, macrovascular disease, and neuropathy—and play a role in the structural composition of these complications.Several studies have revealed key pathophysiological aspects of T2DM, including inflammation,chemokine dysregulation, gut microbiome alterations, and immunological dysregulation [8]. Small signaling proteins produced by cells, known as cytokines, have a special effect on communication and interaction between cells. Cytokines can affect the cells that secrete them (autophagic effect), nearby cells (neophagic effect), or distant cells (glandular effect) [9].

Many studies, including those considered over the past ten years showed that showed that CCL2 expression in Diabetic were recorded significantly higher CCL2 values,the adult-onset autoimmune diabetes (LADA) group recorded significantly higher CCL2 values, while the type 2 diabetes (DM2) group recorded the lowest. However, the difference was statistically significant between type 2 diabetes (DM2) and LADA (P=0.002), but not statistically significant when comparing type 2 diabetes (DM2) to the control group or LADA to the control group [10]. Also, CCL2 is commonly known as monocyte chemoattractant protein-1 (MCP-1).MCP-1 is an established pro-inflammatory cytokine due to its chemotactic activity. It has been implicated in the pathogenesis of many diseases, including atherosclerosis, obesity, and type 1 diabetes mellitus (T1DM). High levels of CCL2 have been reported to be protective against T1DM, and intriguingly associated with its complications.As many studies have shown high CCL2 levels in T2DM. CCL2 is involved in the recruitment and differentiation of macrophages to a pro-inflammatory state. Several studies have shown positive outcomes in diabetic complications in association with decreased levels of CCL2 [8]. Further, CCL2 concentrations were compared between 3,856 T2DM patients and 2,958 controls, and the results indicated that CCL2 concentrations were in patients with T2DM than in the controls (SMD=1.51; 95% CI: 1.15 - 1.88;, but with significant heterogeneity (I^2=97%) [4]. Finally, It is known that the CCL2 protein disrupts the insulin signaling pathway, indicating a link to insulin resistance. Furthermore, the association of elevated CCL2 levels with autoimmune diseases suggests its potential use as a predictive marker for the future development of diabetes complications. [10]. The comparison data of expression of CCL2 in Diabetic patients and control group is summarized in Table 1.

Table 1. CCL2 expression in diabetic patients and control groups

Marker	DM2 (No.=36)	Ref
CCL2 (pg/ml)		
Patients DM2(36)	91.9 ± 8.3	
: LADA (34)	138.7 ± 53.9	
Control (20)	115.3 ± 14.25	[10]
P-value		
DM2 vs. LADA	0.002 sig	
DM2 vs. Control	0.27 NS	
LADA vs. Controls	0.28 N	
CCL2 (pg/ml)		
Patients DM2/M (25)	332 ± 35.76	
Control (44)	288 ±33.12	[8]
P-value	0.05	
CCL2 (pg/ml)		
Patients DM2/F (18)	328 ± 35.66	
Control (41)	275 ± 32.14	[8]
P-value	0.05.	

Marker	DM2 (No.=36)	Ref
CCL2 (pg/ml) Patients DM2/F (829) Control (411) P-value(significant Heterogeneity)	(SMD=1.14; 95% CI: 0.51 - 1.78 I^2 =94%	[4]

** NS: not significant, sig : significant. p=0.05 * inverse variance weighted (IVW) method* odds ratios (ORs) with 95% confidence intervals (CIs). I^2=100% indicated maximal heterogeneity and I^2=0% indicated no heterogeneity. standardized mean difference (SMD). 95%. non-obese diabetic (NOD). Latent autoimmune diabetes in adults (LADA)

CCL4 expression in diabetic patients

CCL4 (C-C motif chemokine ligand 4), more commonly known as MIP-1β (macrophage inflammatory protein-1β), is an inflammatory chemokine. It is primarily secreted by activated immune cells (such as monocytes, T cells, and B cells) to attract and activate other leukocytes at sites of inflammation or tissue injury.CCL4 is a pro-inflammatory chemokine involved in the upregulation of the inflammatory pathways leading to IR, and its inhibition has been seen to improve IR and glycemic control in animal models. The exact mechanism involving CCL4 in IR and MS and its possible therapeutic roles (if any) are still elusive and need further study.Fourth, MIP-1b is a chemokine also known as CCL4. MIP-1b plays an important role in the immunoregulatory process, recruiting Tregs into inflammatory sites [11]. In both type 1 and type 2 diabetes, blood levels of the inflammatory chemokine CCL4 (linker 4 of the C-type chemokine) are significantly elevated. This elevation is closely associated with low-grade systemic inflammation, insulin resistance, and impaired pancreatic beta cell function.

Many studies,showed that CCL4 expression in Diabetic were recorded CCL4 levels were significantly lower in patients with type 1 diabetes compared to healthy participants. A study in a non-obese diabetic mouse (NOD) model suggested a protective role for CCL4. MIP1b [ORIVW: 0.92; 95% CI: 0.86–0.98; p = 0.010 [11]. Also, the CCL4 concentrations were compared between 829 T2DM patients and 411 controls. The results showed higher concentrations of CCL4 in T2DM patients than in the controls (SMD=1.14; 95% CI: 0.51 - 1.78), but with significant heterogeneity (I^2=94%) [4]. Other studies shown that level of CCL4 CCL4 (MIP-1β) the mean serum level of CCL4 were (194 ±22.54,186 ± 22.56 pg/mL) in the normal male/Female respectively controls with p-value were (0.05) We observed that the mean serum concentrations of pro-inflammatory chemokines CCL 4 did not significantly differ between male and female control subjects. CCL4 levels were significantly increased in in normal body weight compared to the controls with $p < 0.05$ [8]. Moreover, CCL4 levels were elevated in the normal-weight and overweight categories for both T2DM and LADA, although none of the results were statistically significant [10].

).Finally, A link has been established between chemokines and the development of both type 1 and type 2 diabetes.While macrophages may play a role in the destruction of pancreatic islet cells concurrent with elevated blood glucose levels and the progression of both types of diabetes the protein CCL4 is a key factor in recruiting macrophages.[1]. The comparison data of expression of CCL4 in Diabetic patients and control group is summarized in Table 2.

Table 2. CCL4 expression in diabetic patients and control groups

Marker	DM2 (No.=36)	Ref
CCL4 (pg/ml) Patients DM2/F (18) Control (41) P-value	OR_{IVW}: 0.92; 95% CI: 0.86–0.98; p = 0.010	[11]

Marker	DM2 (No.=36)	Ref
CCL4 (pg/ml) Patients DM2/ (3,856) Control (2,958) P-value(significant heterogeneity)	SMD=1.51; 95% CI: 1.15 - 1.88 I^2=97%	[4]
CCL4 (pg/ml) Patients DM2/M (25) Control (44) P-value	232 ± 25.44 186 ± 22.56 0.05.	[8]
CCL4 (pg/ml) Patients DM2/F (18) Control (41) P-value	244 ± 25.38 194 ±22.54 0.05.	[8]
CCL4 (pg/ml) Patients DM2(36) : LADA (34) Control (20) P-value DM2 vs. LADA DM2 vs. Control LADA vs. Controls	45.3 ± 8.12 31.4 ± 4.15 31.35 ± 8.8 0.41 NS 0.52 NS 0.99 NS	[10]

** NS: not significant, sig : significant. p=0.05 * inverse variance weighted (IVW) method* odds ratios (ORs) with 95% confidence intervals (CIs). I^2=100% indicated maximal heterogeneity and I^2=0% indicated no heterogeneity. standardized mean difference (SMD). 95%. non-obese diabetic (NOD). Latent autoimmune diabetes in adults (LADA

CCL18 expression in diabetic patients

CCL18 is a chemokine that exhibits the characteristics of inflammatory cytokines. Its production has been shown to be induced by infectious agentssuch as HIV as well as by other cytokines, including IL-4, IL-10, and IL-13. Elevated levels of CCL18 have also been observed in various pathological conditions, including HIV infection, atherosclerosis, pulmonary fibrosis, type 2 diabetes, and several types of cancer, such as breast, cervical, lung, and ovarian cancers.Interleukin-18 (IL-18) is a potent pro-inflammatory cytokine involved in the body's defense against infection and the regulation of innate and adaptive immune responses. IL-18 is produced by both hematopoietic and non-hematopoietic cells, including monocytes, macrophages, keratinocytes, and mesenchymal stromal cells. IL-18 can stimulate the activity of pro-inflammatory and cytotoxic immune cells, potentially leading to autoimmune diseases. Elevated levels have been observed in the blood of patients with various immune-related conditions, including rheumatoid arthritis, systemic lupus erythematosus, type 1 diabetes, atopic dermatitis, psoriasis, and inflammatory bowel disease [12]. Other studies have shown that CCL18 expression in Diabetic were recorded significantly higher CCL18 values levels are increased in T1D patients compared to control (205.885±101.029,28.91±11.193, 0.001).Also, there is a significant increase at the level of probability P ≤ 0.0001 in diabetic patients compared with healthy controls (68.79 * ± 16.82 53.08 ± 12.52) Other studies shown significantly higher p- values<0.000 1. Finally, CCL18 promotes an inflammatory environment and interacts with elevated glucose levels to trigger fibrotic pathways; it also acts as a chemoattractant for immune cells, thereby leading to tissue damage and impaired insulin sensitivity.Elevated CCL18 levels in diabetic patients serve as a key biomarker for chronic systemic inflammation, M2 macrophage polarization, and insulin resistance. Assessing these levels offers clinical utility in evaluating the risk of cardiometabolic disease and the progression

of microvascular complications in patients with diabetes. The comparison data of expression of CCL18 in Diabetic patients and control group is summarized in Table 3.

Table 3. CCL18 expression in diabetic patients and control groups

Marker	DM2 (No.=36)	Ref.
CCL18(pg/ml) Patients DM2 (40) Control (30) P-value	205.885±101.029 28.91±11.193 <0.001	Source not listed in bibliography
CCL18(pg/ml) Patients DM2 (60) Control (28) P-value	68.79 ± 16.82 53.08 ± 12.52 <0.000 1	Source not listed in bibliography
CCL18(pg/ml) Patients DM2 (4/9) Control (8/9) P-value	46 ± 9 35 ± 5 < 0.0001	Source not listed in bibliography

P-value ** NS: not significant, sig : significant. p=0.05 *

Chemokines in rheumatoid arthritis

Rheumatoid arthritis is a systemic autoimmune disease characterized by a multi-stage pathogenesis, ranging from a preclinical phase involving the appearance of autoantibodies to a clinical phase marked by synovial inflammation and joint damage. Cytokines play pivotal roles throughout this process by regulating immune cell activation, tissue inflammation, and bone erosion [13].

Cytokines are crucial mediators that oversee and regulate immune and inflammatory responses through complex networks, and they also serve as biomarkers for numerous diseases [5]. Cytokines play diverse roles in maintaining immune homeostasis and are integral to the pathogenesis of autoimmune diseases, metabolic disorders, endocrine conditions, cardiovascular diseases, and cancer. Pro-inflammatory and inflammatory cytokines serve as key mediators of the immune response, playing vital roles in host defense and immune system regulation; they are rapidly produced in response to infection, tissue injury, or immune system activation, initiating and amplifying the inflammatory process [14].Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease; it causes joint damage and inflammation of the synovial membrane, leading to increased rates of disability among those affected. The disease affects approximately 0.24% of the global population [15].

CCL2 expression in rheumatoid arthritis

CCL2 or monocyte chemoattractant protein-1 (MCP-1) is known as a CC chemokine that can induce the locomotion and recruitment of monocytes and macrophages to the site of injury. This chemokine is also involved in various processes associated with the development of rheumatoid arthritis, such as osteoclastogenesis, the migration of activated T cells into the inflamed synovial tissue, and angiogenesis [16].

CCR2 ligands specifically CCL2 (monocyte chemoattractant protein-1, or MCP-1) exert chemotactic activity on monocytes and lymphocytes. CCR2 deficiency exacerbates the progression of arthritis, indicating that CCR2 plays a highly complex role in the pathogenesis of rheumatoid arthritis. [17]. Several previous studies reported that CCL2 increased significantly in the synovium fluid of patients with RA. Previous studies have also revealed that the CCL2 protein plays a pivotal role in the recruitment of Type 1 helper T cells (Th1) to the synovial tissue in cases of rheumatoid arthritis [16]. Many of studies showed that CCL2 protein expression levels were significantly elevated in patients with rheumatoid arthritis compared to

healthy individuals (correlation coefficient Rho = 0.224; p-value = 0.024). This marked increase suggests its potential utility as an indicator of inflammation severity in associated conditions, such as insulin resistance (IR) in rheumatoid arthritis (RA) patients. Elevated levels of these chemokine systems in RA cases accompanied by insulin resistance reflect a cumulative impact on the inflammatory process [3]. Patients with rheumatoid arthritis exhibit elevated levels of chemokines, such as CCL2 and CCL4, in both plasma and synovial fluid. Furthermore, high CCL2 levels in rheumatoid arthritis cases have been closely linked to increased infiltration of immune cells specifically macrophages into the joints. [18]. Furthermore, Immunohistochemical staining for the CCL2 protein revealed increased expression within the affected joints of arthritic mice compared to the control group, particularly in the synovial membrane, cartilage, and bone marrow with p-value = 0.003 [19]. Another study comparing patients with rheumatoid arthritis (RA) to those with osteoarthritis (OA) showed that serum Comparable cytokine and chemokine serum levels in in patients with established osteoarthritis and rheumatoid arthritis MCP-1/CCL2 (p = 0.26), [20]. Elevated levels of CCL2 were also observed in the blood serum of patients with rheumatoid arthritis [21]. The comparison data of expression of CCL2 in Rheumatoid arthritis patients and control group is summarized in Table 4.

Table 4. CCL2 expression in rheumatoid arthritis and control groups

Marker	Rh	Ref.
CCL2 (pg/ml) Patients (138) Control (138) P-value	* **(0.224)** 0.024	 [3]
**CCL2 (pg/ml) Patients RA(40) RA Median Min–max 95% CI	 574.4 317.9–840.6 119.1–264.7	
Control OA (24) OA Median Min–max 95% CI	 485.5 305.6–716.5 84.9–153.2	[20]
P-value	0.26	
CCL2 (pg/ml) (n=10) Patients Control P-value(Fold)	 (5.85±14.23) (3.07±3.79) 1.91*	 [21]

*. P values were calculated using rho Spearman correlation test, (P < 0.05 was significant). rheumatoid arthritis (RA) patients and osteoarthritis (OA)
**Statistical evaluation of differences was performed using Mann–Whitney U test; p indicates significance between analysed groups

CCL4 expression in rheumatoid arthritis

The C-C motif chemokine ligand 4 (CCL4) gene encodes a chemokine, and it has been shown that polymorphisms in this gene can predict the risk of developing various diseases, including

rheumatoid arthritis (RA). CCL4 may serve as a diagnostic marker and a therapeutic target in the context of treating rheumatoid arthritis.As well as.

Therapeutic agents that directly or indirectly modulate CCL4 expression levels may represent promising options for treating this disease. The GTEx dataset revealed a statistically significant association (eQTL) between the genotype at locus rs1719153 and the expression level of the CCL4 gene in whole peripheral blood cells ($p < 0.001$); these results indicate that the T nucleotide at locus rs1719153 is associated with a trend toward reduced CCL4 gene expression [22]. Macrophage Inflammatory Proteins (MIPs) belong to the family of chemotactic cytokines. In humans, there are two major forms, MIP-1α and MIP-1β that are now officially named CCL3 and CCL4, respectively [22]. Reports indicate that chemokine production varies according to the stages of rheumatoid arthritis; proteins such as CCL4, CXCL4, CXCL7, and CXCL13 are expressed during the early stage, whereas CCL3 and CCL9 are secreted during later stages. Furthermore, patients with rheumatoid arthritis exhibit elevated levels of the chemokines CCL2, CCL3, CCL4, and CXCL10 in both plasma and synovial fluidCL4 was found to be an important regulator of osteoclast migration, suggesting it as a potential therapeutic target for bone resorption diseases [18].

WISP-3 (The WISP-3 protein (also known as CCN6) is classified within the CCN protein family and plays a role in regulating various growth and development processes) increases CCL4 synthesis in RASFs and promotes monocyte adhesion to the synovial membrane by inhibiting miR-6894-5p expression via the MEK and ERK signaling pathways. Furthermore, WISP-3 promotes macrophage polarization toward the M1 phenotype within the rheumatoid arthritis microenvironment. Thus, targeting the WISP-3/CCL4 axis may represent a potential therapeutic strategy for treating rheumatoid arthritis [23].other studies showed that Significantly different cytokine and chemokine serum levels in patients with established osteoarthritis and rheumatoid arthritis Rheumatoid arthritis is associated with increased serum levels of MIP-1β/CCL4 ($p = 0.010$)The comparison data of expression of CCL4 in Rheumatoid arthritis patients and control group is summarized in Table 5.

Table 5. CCL4 expression in rheumatoid arthritis and control groups

Marker	Rh	Ref.
rs1719153(ccl4) (pg/ml)		
Patients RA/F(N=181)		
RA		
A/A	64 (35.4%)	
A/T	90 (49.7%)	
T/T	27 (14.9%)	
A/T+T/T	117 (64.6%)	
Control F(N=209)		
A/A	101 (48.3%)	
A/T	83 (39.7%)	[22]
T/T	25 (12.0%)	
A/T+T/T	108 (51.7%)	
OR (95% CI)		
A/A	1.00	
A/T	1.71 (1.11-2.64)#	
T/T	1.70 (0.91-3.19)	
A/T+T/T	1.71 (1.14-2.57)#	
AOR (95% CI)		
A/A	1.00	
A/T	0.56 (0.36-0.88)#	

Marker	Rh	Ref.
T/T	0.60 (0.31-1.13)	
A/T+T/T	0.57 (0.38-0.87)##	
CCL4 (pg/ml) (n=10)		
Patients	(1.42±0.50)	[18]
Control	(0.86±0.42)	
P-value(Fold)	1,65 *	
CCL4(WISP-3) (100 ng/ml)		
Patients (16)	2.20±0.30	[23]
Control (7)	1.00±0.00	
P-value	0.05	
MIP-1β/CCL4 (pg/ml)		
Patients (14)		
Control /OA (24)	41.3, 8.9–74.4	[20]
P-value	28.9, 0.0–52.4	
	0.010	

#p < 0.05; ##p < 0.01. RA: rheumatoid arthritis; OR: odds ratio; CI: confidence interval; AOR: adjusted odds ratio. osteoarthritis (OA)

CCL18 expression in rheumatoid arthritis

CCL18 is a C-C motif chemokine located on chromosome 17, encoding 89 amino acids (including a 20-amino-acid signal peptide). The CCL18 protein plays a more complex role in rheumatoid arthritis (RA); its function is not limited to recruiting immune cells to joint tissues thereby causing inflammation but also extends to regulating the immune response, owing to its more complex genetic and protein structures,recruited 83 RA patients and reported that serum CCL18 levels were significantly higher than healthy control (RA: n = 83, 107 (80~126) ng/mL; healthy: n = 25, 51 (29~70) ng/mL). [24]. Various chemokines are highly expressed in the serum, synovialfluids (SFs), and synovial tissues (STs) of patients with RA compared with those of healthy donors (HD).Elevated levels of the cytokine or chemokine CCL18 are notably observed in the serum and synovial fluid of patients with rheumatoid arthritis; this elevation correlates with disease progression, disease activity, and joint damage,, significantly high levels of CCL18/PARC were detectable, compared to samples of healthy controls with P-value <0.001 [25]. The CCL18 protein exhibits high expression levels in both the synovial fluid and inflamed synovial tissues of patients with active rheumatoid arthritis.Serum CCL18 protein levels in patients with active rheumatoid arthritis showed a p-value of less than 0.001 compared to the healthy group [26]. As important mediators of leukocyte extravasation, a number of chemokines from each chemokine family have been identified as being expressed in the rheumatoid arthritis joint.The less abundant chemokines identified in endothelial cells (ECs) associated with rheumatoid arthritis (RA) are: CCL1–3, CCL5, CCL10–13, CCL15, CCL17, CCL18, CCL20, CCL21, and CCL23–28. Strong colocalisation was seen in VWF+ vessels, while CCL8+ staining of other cell types appeared to be primarily in fibroblast-like cells with p-value of less than 0.04 compared to the non-RA synovium [27]. The comparison data of expression of CCL18 in Rheumatoid arthritis patients and control group is summarized in Table 6.

Table 6. CCL18 expression in rheumatoid arthritis and control groups

Marker	Rh	Ref.
CCL18 (ng/mL)		[24]

Marker	Rh	Ref.
Patients (83) Control (25) P-value	**107 (80~126) ng/mL** **51 (29~70) ng/mL** **<0.001**	
CCL18 /PARC (ng/ml) Patients (71) Control (20) P-value	**156.21 ± 125.73 ng/ml** **28.04 ± 10.96 ng/ml**	[25]
CCL18 (ng/ml) Patients (51) Control (11) P-value	**112 ng/mL (IQR, 85–132)** **64 ng/mL (IQR, 36–70)** **<0.001**	[26]
CCL18 (ng/ml) Patients (8) Control (5) P-value	**64.1% (±7.4)** **25.6% (±17.0)** **0.04**	[27]

* P-value ** NS: not significant, sig : significant. p=0.05 * ;* PARC : pulmonary and activation-regulated chemokine

Comparative synthesis

observed that the level of CCL2 chemokines is correlated with the diabetes complications. The CCL2 augmentation in autoimmune diabetic patients may also be a predictive marker for the possibility of patients progressing towards diabetes complications.
CCL2 could be used as a predictor for future development of diabetic complications.
CCL2, CCL3 and CCL4 concentrations associated positively with complications of diabetes.
The mechanisms associated with CCL4, including CCL4 and CCR5, may provide potential therapeutic targets in diabetes.
CCL18 works by promoting an inflammatory environment, reacting with elevated glucose levels to stimulate fibrosis pathways, and acting as a chemotactic for immune cells, which in turn leads to tissue damage and impaired insulin sensitivity.
high CCL2 levels in rheumatoid arthritis cases have been closely linked to increased infiltration of immune cells specifically macrophages into the joints.
CCL4 may serve as a diagnostic marker and a therapeutic target in the context of treating rheumatoid arthritis as well as Therapeutic agents that directly or indirectly modulate CCL4 expression levels may represent promising options for treating this disease.
The CCL18 protein plays a more complex role in rheumatoid arthritis (RA); its function is not limited to recruiting immune cells to joint tissues thereby causing inflammation but also extends to regulating the immune response.
Table 7 shows the levels of cytokines (CCL2, CCL4, and CCL18) in patients with rheumatoid arthritis compared to patients with diabetes.

Table 7. Comparative summary of CCL2, CCL4, and CCL18 in rheumatoid arthritis and diabetes

Marker	DM2		Ref	Rh		Ref.
CCL2 pg/ml)	*	↑	[10] [8] [4]		↑	[3] [20] [21]
CCL4 (pg/ml)		↑	[11]		↑	[22]

	[4] [8] [10]	[18] [23] [20]
CCL18(pg/ml)	Source not listed in bibliography Source not listed in bibliography Source not listed in bibliography	[24] [25] [26] [27]

Abbreviations: ↑, increase

Conclusions and Recommendations

The reviewed evidence indicates that CCL2, CCL4, and CCL18 contribute to inflammatory pathways associated with rheumatoid arthritis and diabetes. Their reported associations with immune-cell recruitment, insulin resistance, and tissue inflammation support further investigation as potential biomarkers and therapeutic targets. However, differences in study populations, assays, and reported outcomes limit direct comparison. Future research should prioritize longitudinal studies and standardized measurements to clarify their predictive and clinical value.

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