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Regulatory effects of statins on CCL2/CCR2 axis in cardiovascular diseases: new insight into pleiotropic effects of statins

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Abstract

Background HMG-CoA reductase inhibitors are well-known medications in the treatment of cardiovascular disorders due to their pleiotropic and lipid-lowering properties. Herein, we reviewed the effects of statins on the CCL2/CCR2 axis.

Method Scopus and Pubmed databases were systematically searched using the following keywords:" Hydroxymethylglutaryl CoA Reductase Inhibitors"," HMG-CoA Reductase Inhibitors"," Statins", "CCL2, Chemokine", "Monocyte Chemoattractant Protein-1" and "Chemokine (C-C Motif) Ligand 2". Evidence investigating the role of statin on MCP-1 in CVD was identified and bibliographies were completely evaluated to gather further related studies.

Results The anti-inflammatory effects of statins on the CCL2/CCR2 pathway have been widely investigated. Despite inconclusive results, a great body of research supports the regulatory roles of statins on this pathway due to their pleiotropic effects. By disrupting the CCL2/CCR2 axis, statins attenuate the infiltration of monocytes and macrophages into the zone of inflammation and hence down-regulate the inflammatory cascades in various CVDs including atherosclerosis, cardiac remodeling, and stroke, among others.

Conclusion CCL2 plays a major role in the pathogenesis of cardiovascular disorders. Down-regulation of CCL2 is proposed as one of the pleiotropic properties of statins. However, more investigations are required to elucidate which statin in what dose exerts a more potent effect on CCL2/CCR2 pathway.

Keywords MCP-1, CCL2, Statins, Ischemic heart disease, Stroke

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Introduction

Chemokines are a superfamily of protein molecules that play a pivotal role in immunoregulation. Although initially recognized as leukotactic agents, further studies elucidated other roles in inflammation namely fibrosis, angiogenesis, and tissue remodeling [1]. There are four known major subfamilies of chemokines based on the presence of cysteine residues at the N-terminus: the CC, CXC, C, and CX3C. Five potent monocyte chemoattractants have currently been identified in the CC subfamily including MCP-1 (CCL2), MCP-2 (CCL8), MCP-3 (CCL7), MCP-4 (CCL13) and MCP-5 (CCL12) [2]. MCP-1 is the first discovered and most broadly studied human CC cytokine [3]. It is involved in migrating and recruiting monocytes, T lymphocytes, and natural killer (NK) cells in several inflammatory processes such as neurological diseases. It also contributes to the development of autoimmune disorders such as multiple sclerosis and rheumatoid arthritis [4, 5]. This chemokine displays both pro- and anti-tumor activities; promoting tumor progression by improvement of angiogenesis and interfering with metastasis through immune system activation [6]. The role of MCP-1 in the pathogenesis of cardiovascular diseases (CVD) has been of great interest recently. It is shown that individuals who are genetically predisposed to higher circulating levels of MCP-1, tend to have a higher incidence of CVDs [7]. Statins -inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, are mainly indicated as powerful lipid-lowering agents in CVDs. This class of medication was introduced to the market in 1987. Statins exert protective effects through both LDL-C (low-density lipoprotein- cholesterol) dependent and LDL-C independent pathways [8, 9]. These pharmacological agents inhibit HMG-CoA reductase reversibly; interfering with a crucial step of cholesterol biosynthesis. Inhibition of HMG-CoA reductase ultimately results in decreased serum LDL-C and upregulated liver LDL-C receptors [10]. Notably, these agents possess numerous biological activities, which are independent of their putative LDL-lowering activity [9, 11–17]. These so-called pleiotropic actions include enhancement of endothelial dysfunction, which promotes the expression of eNOS resulting in vasodilation [18, 19]. They also increase the number of endothelial progenitor cells leading to post-ischemic neovascularization [20]. These medications are suggested as an adjunctive treatment for autoimmune diseases owing to their immunomodulatory, anti-inflammatory, antioxidant, and anti-thrombotic effects [21–25]. The anti-inflammatory effects of statins include attenuation of C-reactive protein, interleukins, and adhesion molecules such as intracellular adhesion molecule-1(ICAM-1) [26]. A growing body of literature has investigated the inhibition of the MCP-1/CCR2 axis as a possible therapeutic strategy in CVDs. Here, we summarize the latest evidence concerning the modulatory effect of statins on the CCL2/CCR2 axis.

Atherosclerosis

Atherosclerosis is an inflammatory process initiated with endothelial damage [27]. Circulating monocytes then infiltrate through endothelial cells and become macrophages. These cells phagocytize LDL-C accumulates and convert into foam cells which drive the formation of primary atherosclerotic plaque. Besides, smooth muscle cells (SMC) in the medial layer migrate to sub-endothelial tissue in response to inflammatory mediators such as IL-1 and TNF and participate in the formation of the fibrous cap by secreting extracellular matrix [28]. The MCP-1/CCR2 axis plays a significant role in the pathogenesis of atherosclerosis. It is shown that macrophage-rich arterial lesions express higher levels of MCP-1 which then increases monocyte infiltration into the sub-endothelial layer [29, 30]. Goslinga et al. reported that deletion of the MCP-1 gene in transgenic mice dramatically reduced macrophage recruitment and arterial wall lesion formation [31]. Consistently, Boring et al. revealed that selective deletion of CCR2 in Apo-E deficient mice significantly protected against the development of atherosclerotic lesions without altering lipoprotein metabolism [32]. At the population scale, a meta-analysis conducted by Mao et al. showed that MCP-1–2518 A>G polymorphism significantly increased susceptibility to myocardial infarction (MI) in the Asian population but not in the Caucasian population [33]. In a large cohort conducted on patients with acute coronary syndromes, increased MCP-1 baseline levels were correlated with atherosclerosis traditional risk factors, increased mortality, and MI risk, irrespective of baseline variables [34]. Altogether, this evidence highlights the importance of the MCP-1/CCR2 axis at multiple stages of atherosclerosis and suggests it as a possible therapeutic target. Statins are broadly available medications used in the treatment of individuals at high risk of atherosclerosis. The association between statin therapy and the production of various chemokines including MCP-1 has been largely studied. Simvastatin is shown to reduce the expression of MCP-1 as well as other chemokine receptors such as CCR1, CCR2, CCR4, and CCR5 in TNF-induced endothelial cells/macrophages via down-regulation of geranylgeranyl pyrophosphate pathway [35]. These data are consistent with the findings of Tuomisto et al., which showed that simvastatin downregulated the expression of many pro-inflammatory mediators such as MCP-1, TNF, VCAM (vascular cell adhesion molecule), and tissue factor [36]. Simvastatin has also demonstrated the capacity to reduce MCP-1-induced monocyte migration of human monocytic THP-1 cells [37]. In vivo studies have confirmed the

simvastatin role in the reduction of plaque formation. Liu et al. reported that simvastatin reduced aortic atherosclerotic lesions in Apo-E deficient mice and down-regulated the expression of MCP-1, VCAM-1, RAGE, and HMGB1 in these lesions [38]. An investigation on rabbits that were treated with a high-cholesterol diet al.ong with simvastatin showed reduced size of the aortic plaque, intimal thickness, and MCP-1 expression [39]. From a clinical view, Pereira et al. concluded that long-term simvastatin therapy (12 months) ameliorated circulating MCP-1. However, this result was confined to male patients. It is worth mentioning that post-menopausal status accompanied by higher CRP levels in females was declared as a possible explanation [40]. Koh et al. evaluated the effect of daily simvastatin administration (20–40 mg) for 14 weeks in patients with hypercholesterolemia and established coronary artery disease (N=13). The results indicated that administration of simvastatin significantly decreased MCP-1, MMP-9, and TNF and supported its role in the reduction of future cardiovascular events through non-lipid mechanisms such as improvement of endothelial function and inflammatory responses [41]. Further, the association of simvastatin (20 and 40 mg; adjusted to actual cholesterol level) and reduced MCP-1 remained significant even after treatment for 6 weeks (N=107) [42]. It is of note that simvastatin's effect on monocyte cytokine release is not confined to patients affected with hypercholesterolemia. A randomized clinical trial (RCT) on simvastatin treatment (40 mg twice daily) in patients with isolated hypertriglyceridemia and peripheral artery stenosis showed a decreased monocyte excretion of MCP-1 following 12 weeks of treatment (N=43) [43]. Despite simvastatin's effect on endothelial and monocyte release of MCP-1, the question remained as to whether simvastatin therapy affects vascular indices concomitantly or not. Guan et al. evaluated the role of simvastatin therapy (20 mg/d for 12 weeks) on the ankle-brachial index (ABI), flow-mediated dilation (FMD), and nitroglycerin-mediated dilation (NMD) of the brachial artery in 51 patients with hypercholesterolemia. The results revealed that simvastatin possesses the capability to enhance clinical indices of blood flow (ABI and FMD); accompanying reduced levels of circulating MCP-1 [44]. Several clinical investigations support simvastatin's effects on suppression of MCP-1/CCR2 axis; ultimately suggesting its protective role against atherosclerosis development [45]. Atorvastatin, another member of the statin family, was the best-selling medication back in the 2000s [46]. Evidence demonstrated that pretreatment of murine macrophages with atorvastatin reduced ox-LDL-induced morphological changes and secretion of inflammatory chemokines including MCP-1 through inhibition of the COX-2 pathway [47]. In addition, atorvastatin ameliorated the release of MCP-1 and interferon-inducible protein 10 from cultured VSMC (vascular smooth muscle cells) probably through inhibition of NF-kappaB activity [48]. These results strongly suggest atorvastatin's participation in the stabilization of atherosclerotic lesions. Nachtigal et al. evaluated this hypothesis in ApoE/LDLR-deficient mice that were fed an atherogenic western diet. They showed that treatment with high-dose atorvastatin significantly reduced the circulating levels of MCP-1 and down-regulated expression of VCAM-1 and ICAM-1 in the vessel wall [49]. Consistently, atorvastatin administration reduced endothelial-monocyte recruitment through the down-regulation of several chemokines including MCP-1 and its receptor [50]. It is of note that atorvastatin's effects on plaque stability are independent of its lipid-lowering effects. An investigation conducted by Nie et al. showed that the administration of atorvastatin (10 mg/kg/day) significantly reduced the number of vulnerable plaques. However, this dosage did not affect plaque progression and total plasma cholesterol levels. Further experiments revealed that atorvastatin remarkably ameliorated the infiltration of macrophages and deposition of sub-endothelial lipids accompanied by elevated levels of collagenase and matrix metalloproteinase (MMP). They showed that reduced infiltration of monocytes/ macrophages is partly due to decreased levels of MCP-1, CX3CL1 (chemokine (C-X3-C motif) ligand 1), and their receptors CCR2 and CX3CR1, respectively [50]. In a double-blind clinical study, Okopien et al., enrolled 52 patients with primary mixed dyslipidemia to elucidate the effects of a 30-day treatment with atorvastatin (20 mg daily) on levels of MCP-1 released from peripheral monocytes. They found increased release of MCP-1 in patients affected with dyslipidemia compared to control subjects. Also, atorvastatin treatment reduced LPS-induced and unstimulated MCP-1 release from extracted peripheral monocytes emphasizing the importance of MCP-1/CCR2 axis in the management of CVDs [51]. Another clinical trial supported the role of atorvastatin (20 mg daily) in reducing secreted MCP-1 from peripheral monocytes, beyond its lipid-lowering properties [52]. Another study on 77 subjects with dyslipidemia showed that atorvastatin (5 mg/day) for 12 months significantly reduced circulating MCP-1 levels and CIMT (carotid intima-media thickness). CIMT changes were significantly but weakly associated with MCP-1 changes, but they were not correlated with TNF and hsCRP values. This finding convinced the authors to attribute MCP-1 changes to the lipid-lowering effects of atorvastatin. It is worth mentioning that Pitavastatin (1 mg/day) appeared superior to atorvastatin in the reduction of MCP-1 and CIMT. Also, Pitavastatin showed more potency in the reduction of inflammatory mediators like hsCRP and TNF [53] (Fig. 1). Table 1

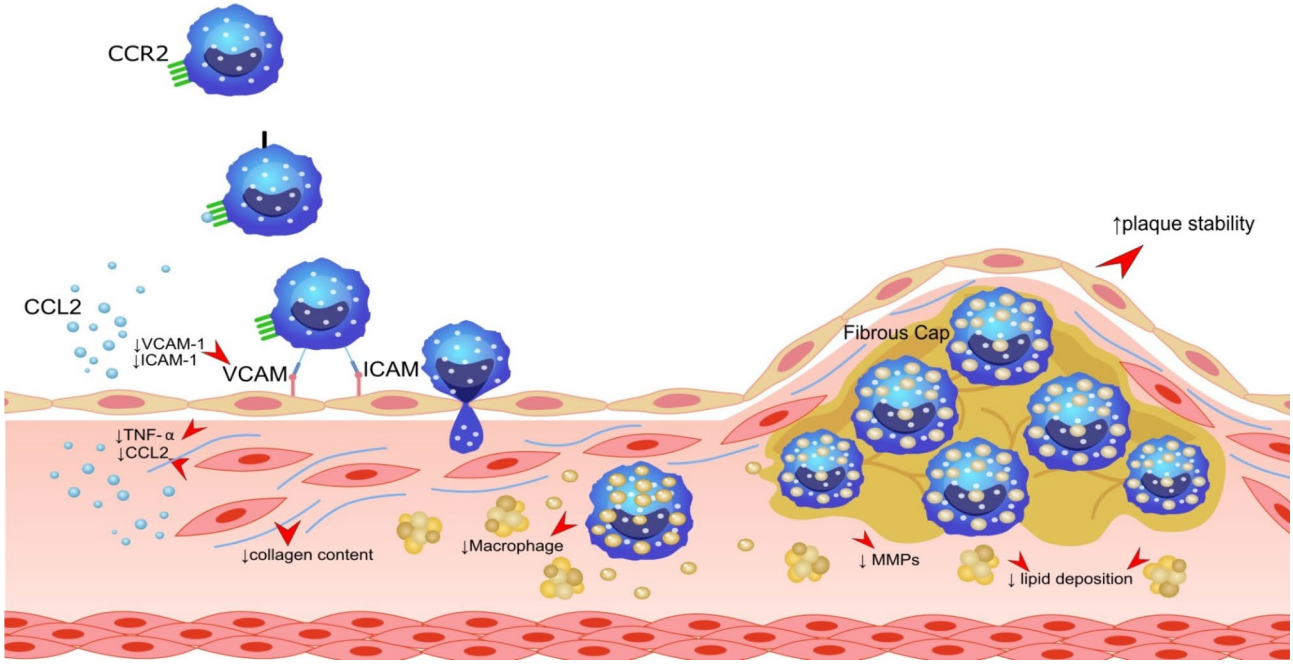

Fig. 1 The CCL2/CCR2 axis plays a crucial role in the pathogenesis of atherosclerosis. Statins significantly interfere with the development and progression of atherosclerotic lesions by modulating the CCL2/CCR2 pathway as depicted(inspired by [209]). This figure shows how statins interfere with the migration of monocytes into the subendothelial layer, the production of collagen by smooth muscle cells (SMCs), lipid accumulation, and instability of developed plaques

summarizes various literature concerning statin's role in the regulation of the MCP-1/CCR2 axis in atherosclerosis.

Ischemic heart disease and post-infarction remodeling

The development of atherosclerotic lesions in coronary vessel walls is associated with serious mortality rates and poses a huge financial burden on healthcare systems. Despite the reduced incidence of acute mortality rates due to improved reperfusion techniques and proper medical attention, the incapability of the myocardium to regenerate following ischemic events results in inflammation-induced scar formation [54]. Myocardial infarction (MI) is followed by three overlying phases including inflammatory, proliferative, and maturation phases. The release of chemokines and activation of inflammatory cascades lead to the recruitment of leukocytes into the ischemic zone. In addition to phagocytosis of necrotic cells, leukocytes induce growth factors and drive the formation of granulation tissue. In the proliferative phase, activated myofibroblasts secrete extracellular matrix proteins and considerable microvascularity develops thereafter. Ultimately, collagen scar tissue replaces the granulation tissue during the maturation phase due to the apoptosis of fibroblasts and vascular cells [55]. This process which is referred to as cardiac remodeling leads to reduced ventricular ejection fraction and subsequent heart failure. Chemokines including CC family and particularly MCP-1, play a major role in the induction and maintenance of these inflammatory cascades. In a rat model, neutralizing antibodies were used to interfere with CCL2/CCR2 axis and resulted in reduced infarct area through attenuated recruitment of macrophages and down-regulation of intercellular adhesion molecule-1 (ICAM-1) [56]. It is suggested that MCP-1 may contribute to cardiac remodeling through its pro-angiogenic properties [57]. Accordingly, Sakai et al. illustrated the role of the MCP-1/CCR2 signaling pathway in organ fibrosis [58]. In addition to its broadly known leukotactic effect, MCP-1 participates in the regulation of monocyte differentiation in cardiac remodeling. In MCP-1-/- mice, disrupted differentiation of monocytes was found in the infarct area elucidated by reduced expression of osteopontin-1 which is a gene highly involved in monocyte-macrophage differentiation [59]. Despite broad investigations, the regulatory role of the CCL2/CCR2 pathway on cardiac remodeling has remained inconclusive. MCP-1-/- mice displayed extended MI-induced inflammation and impaired phagocytosis of myocytes. These changes were accompanied by decreased levels of inflammatory mediators such as TNF and IL-1β which ultimately resulted in reduced ventricular remodeling in CCL2 knocked-out mice [59]. Contradictory, Morimoto

Table 1 Statins modulatory effect on CCL2/CCR2 axis in atherosclerosis

Treatment	Type of Study	Model	Findings		Ref.
			MCP-1	Other findings	
Statins	In vitro	HAEC	↓	↓Monocyte migration ↓JAK1, JAK2, STAT1, STAT3 phosphorylation	[128]
Atorvastatin	In vitro	Mice macrophages	↓	↓TNF, ERK phosphorylation ↓morphological alteration	[47]
Atorvastatin	In vitro	PBL	↓	↓IL-1, IL-8, TGF-β1, TGF-β2, CCL7, CCL13, CXCL1	[129]
Atorvastatin	In vitro	Human monocytes	↓	-	[130]
Atorvastatin	In vitro	Vascular SMC-mononuclear cells	↓	↓IP-10 ↓ NF- κB activation	[48]
Atorvastatin	In vitro	Peripheral monocytes of human	↓	↓TNF, gelatinase B	[131]
Simvastatin	In vitro	THP-1 cells	-	↓MCP-1 induced migration, Kv1.3 channels	[37]
Simvastatin	In vitro	Macrophages (type 1)	↓	Repressed CCL2 chromatin status	[132]
Simvastatin	In vitro	Human monocytes/macrophages	↓	↓VCAM-1, TF, NF-κB	[36]
Simvastatin	In vitro	human vascular endothelial cells/ macrophage cells	↓	↓ CCR2, CCR1, CCR4, CCR5, MIP-1α, MIP-1β	[35]
Simvastatin	In vitro	THP-1 cell line	-	↓MCP-1 mediated monocyte migration	[133]
Simvastatin	In vitro	HUVEC	↓	-	[134]
Simvastatin/Lovastatin	In vitro	Peripheral mononuclear cells/human endothelial cells	↓	-	[135]
Fluvastatin	In vitro	macrophages	↓	↓ IL-1β ↑ Cystathionine γ-lyase, Akt pathway activation	[136]
Pitavastatin	In vitro	HUVEC	↓	↓ sPLA2-V	[137]
Pitavastatin	In vitro	human aortic SMC	↓	↓Proliferation, Rac-1 activity	[138]
Pitavastatin	In vitro	HUVEC	-	↓MCP-1 induced adhering to endothelial cells	[139]
Cerivastatin	In vitro	THP-1 cells	↓	↓CCR2	[140]
Cerivastatin	In vitro	Vascular SMCs (statin withdrawal)	↑	↑Rac activity, oxidative stress	[141]
Simvastatin	In vitro	Endothelial progenitor cells	↓	-	[142]
Atorvastatin	Ex vivo	ApoE -/- mice	→	→lesion inflammation, cellular composition ↓ROS	[143]
Fluvastatin/Pitavastatin	In vitro	Human aortic SMC	↓	↓ TNF, proliferating and migrating cells ↑ PPARγ, COX-2 activation	[144]
Fluvastatin	In vivo	ApoE -/- mice	↓	↓TNF, plaque formation ↑ PPAR-γ activity	
Fluvastatin	In vivo	atherosclerotic plaque in rabbits	↓	↓TNF, MMP-9, atherogenesis ↑plaque stability	[145]
Pitavastatin(nanoparticles)	In vivo	Plaque rupture model in ApoE-/- mice	↓	↓Rupture of plaque, monocyte recruitment, gelatinase activation	[146]
Pitavastatin	In vivo	WHHL rabbits	↓	↓MMP-3, MMP-9, vulnerability index	[147]
Pravastatin	In vivo	Balloon injury with atherogenic diet in nonhuman primates	-	↓Neointimal formation(aorta), area of intimal macrophages	[148]
Pravastatin	In vitro	human monocytes	↓	↓ MMPs, TNF, NF-κB ↑PPAR gamma	[149]
Pravastatin/Lovastatin	In vivo	Air-pouch model	↓	Recruitment of leukocytes	[135]
Atorvastatin	In vivo	Vascular dysfunction(arsenic)	↓	↓IL-1β, VCAM, ICAM ↓structural lesion	[150]
Atorvastatin	In vivo	Atherogenic diet in rabbits	↓	↓TLR4 ↓atheroma	[151]
Atorvastatin	In vivo	Statin withdrawal in ApoE-/- mice	↑	↑TNF, MMP3, MMP9	[152]
Atorvastatin	In vivo	*Ldlr*$^{-/-}$*Apob100/100*	→	No cholesterol-independent anti-inflammatory effect	[153]

Table 1 (continued)

Treatment	Type of Study	Model	Findings		Ref.
			MCP-1	Other findings	
Atorvastatin	In vivo	ApoE-/- mice	↓	↓Macrophage, lipid deposition, intimal collagen ↓CCR2, CX3CL1, TNF, CRP ↑MMP	[50]
Atorvastatin	In vivo	apoE/LDLR-deficient mice	↓	↓VCAM-1, ↓ICAM-1	[49]
Atorvastatin	In vivo	Femoral endothelial injury in rabbits	↓	↓NF- κB activation	[154]
Atorvastatin/Pravastatin	In vivo	Diet-induced atherogenesis in pigs	↓	→NOS2	[155]
Rosuvastatin	In vivo	ApoE -/- mice	↓	↓CD40L	[156]
Rosuvastatin	In vivo	Rabbits fed with high cholesterol fat diet	↓	↓ TNF, NF-κB, IL-1β, MMP-9	[157]
Rosuvastatin	In vivo	ApoE -/- mice	↓	↓VCAM-1	[158]
Rosuvastatin	In vivo	ApoE -/- mice	↓	↓ VCAM-1, MMP-9, monocyte endothelial attachment	[159]
Simvastatin	*In vivo/In vitro*	Mice treated with ip MCP-1/ high cholesterol diet	-	↓ MCP-1 induced chemotaxis, CCR2, monocyte migration	[160]
Simvastatin	In vivo	An atherogenic diet with balloon injury	↓	↓TNF, TGF-β1, VCAM-1, MMP-9, macrophage recruitment	[161]
Simvastatin	In vivo	ApoE-/- mice	↓	↓inflammation, atherosclerosis, ↓HMGB1, RAGE, VCAM-1	[38]
Simvastatin	In vivo	Stroke-prone spontaneous hypertensive rats	↓	↓Depositing lipid, macrophage	[162]
Simvastatin	In vivo	Rabbit model of atherosclerosis	↓	↓Plaque size, intima thickening	[39]
Simvastatin	*In vivo/In vitro*	apo E-/- mice/ Mice macrophages	↓	↓MCP-1(after 24 weeks of treatment), TF, macrophage infiltration	[163]
Atorvastatin	Clinical trial	hypercholesterolemia	→	→CRP ↓TG, ApoC2, ApoC3, ApoE	[164]
Atorvastatin/Simvastatin	Cross-sectional	hypercholesterolemia	-	↓MCP-1 in males →MCP-1 in females	[40]
Atorvastatin	Clinical trial	Mixed dyslipidemia	↓	-	[51]
Atorvastatin	Clinical trial	Carotid stenosis	↓	↓ NF- κB, MCP-1, COX-2(PBMC) ↓ NF- κB, MCP-1, COX-2, macrophage recruitment(plaque)	[165]
Atorvastatin/Pitavastatin	Clinical trial	hypercholesterolemia	↓	↓CIMT(Pitavastatin > Atorvastatin) ↓HOMA-IR(Pitavastatin) ↑HOMA-IR(Atorvastatin)	[53]
Cerivastatin	Clinical trial	Moderate hypercholesterolemia	↓	↓Monocyte CD40	[166]
Simvastatin	Clinical trial	Healthy young individuals	↓	↓ CCR-2	[160]
Simvastatin	Clinical trial	Hypercholesterolemia	↓	↓IL-6, IL-8(serum and mRNA expression of PBMCs)	[42]
Simvastatin	Clinical trial	hypercholesterolemia	→	↓IFN- γ, VEGF, sE-selectin, sP-selectin ↓ADP, collagen, arachidonic acid-induced platelet aggregation	[167]
Simvastatin	Clinical trial	hypercholesterolemia	↓	-	[45]
Rosuvastatin	Clinical trial	Atherosclerosis of carotid	↓	↓CCR2 ↑ PPAR β	[168]
Simvastatin	Clinical trial	hypercholesterolemia	↓	↑Ankle-brachial index, Flow-mediated dilation	[44]
Simvastatin	Clinical trial	Hypertriglyceridemia + peripheral artery stenosis	↓	↓TNF, IL-6, IL-1β, CRP	[43]
Simvastatin/ Paravastatin	Clinical trial	moderate hypercholesterolemia	↓	-	[169]
Pitavastatin/Simvastatin	Clinical trial	Hyperlipidemia	→	↑Adiponectin (Pitavastatin) →sP-selectin, sCD40L	[170]
Simvastatin	Clinical trial	hypercholesterolemia	↓	↓Monocyte release of TNF, IL-1β ↓hs-CRP	[92]
Fluvastatin	Clinical trial	Hypercholesterolemia	↓	↓Oxidative stress ↑Flow-mediated vasodilation	[171]

Table 1 (continued)

Treatment	Type of Study	Model	Findings		Ref.
			MCP-1	Other findings	
Pravastatin	Clinical trial	Severe hypercholesterolemia	→	→ CCR2, CRP	[172]
Statins	Cohort	Healthy old	→	-	[173]
Statins	Clinical trial	Familial hypercholesterolemia	→	→IL-1, IL-6, IL-10 and hs-CRP	[174]
Statins	Case-control	hyperhomocysteinemia	→	↓Epithelial neutrophil-activating peptide, growth-related oncogene-α	[175]

This table reviews the effects of different statins on MCP-1 and other inflammatory cytokines in various types of studies concerning atherosclerosis. Arrows are employed to show possible changes in cytokines. ↑: Increased; ↓: Decreased; →: No significant change. Abbreviations: TNF: Tumor necrosis factor-α; HUVEC: Human umbilical vein endothelial cells; PBL: Peripheral blood lymphocytes; CCL: C-C motif ligand 2; IL: Interleukin; TGF: Transforming growth factor; HAEC: Human umbilical endothelial cells; SMC: Smooth muscle cells; NF-κB: Nuclear factor- Kappa B; IP-10: interferon γ-induced protein 10 kDa; ICAM: Intercellular adhesion molecule; VCAM: Vascular cell adhesion molecule; HMOX-1: Heme oxygenase 1; MIP: Macrophage inflammatory protein; MMPs: Matrix metalloproteinases; ROS: Reactive oxygen species; NOS2: Nitric Oxide synthase 2; COX: Cyclooxygenase; CIMT: Carotid intima-media thickness test; HOMA-IR: Homeostatic model assessment for insulin resistance; VEGF: vascular endothelial growth factor; INF: Interferon; hs-CRP: High sensitive C-Reactive protein; TLR: Toll-like receptor; RANTES(CCL5): regulated upon activation, normal T cell expressed and secreted; EPC: Endothelial progenitor cells; AP-1: Activator protein 1; ADP: Adenosine diphosphate; ip: Intraperitoneal; PPAR: Peroxisome proliferator-activated receptor

et al. revealed that over-expression of MCP-1 led to reduced ventricular dysfunction and post-ischemic infarct size in MHC/MCP-1 mice. They reported macrophage accumulation, myofibroblast induction, IL-6 enhanced secretion, and neovascularization improvement as a consequence of MCP-1 over-expression [60]. These findings are in line with previous in vitro studies denoting MCP-1 role in the reduction of hypoxia-induced death of cardiomyocytes; suggesting a surviving pathway following ischemia [61] to reduce, at least in part, the detrimental effects of hypoxia on the cardiovascular system [62]. Evidence revealed that CCL2/CCR2 interaction leads to expression of MCP-induced protein (MCP-IP); a transcription factor, the function of which is still under investigation. Zhou et al. showed that MCPIP acts as a pro-apoptotic mediator in the HECK293 cell line. In vivo, they reported elevated levels of MCPIP in transgenic mice models of heart failure. Also, they found higher MCPIP levels in human ischemic hearts compared to non-ischemic explants [63]. It is suggested that MCPIP modulates apoptosis through endoplasmic reticulum stress [64, 65]. At the same time, MCPIP has been addressed to exert an inhibitory effect on inflammation by suppressing the NF-κB signaling pathway. Mice with a cardiomyocyte-specific expression of MCPIP showed attenuated cardiac remodeling, enhanced survival, and decreased hypertrophy compared to wild-type following MI [66]. These results are in agreement with previous studies which suggested MCP-1 overexpression as a protective factor in cardiac remodeling [60, 67]. Also from a clinical view, there seems no consensus on the association between circulating MCP-1 levels and the incidence of MI. Framingham heart study showed no correlation between these two but confirmed a significant participation of the MCP-1-2578G allele in CVD development [68]. Consistently, Mosedale et al. showed no remarkable association between MCP-1 levels and a history of cardiac disease [69]. In contrast, evidence suggests MCP-1 as a possible surrogate marker of atherosclerosis [70]. Increased level of MCP-1 following STEMI (ST-elevation myocardial infarction) has been reported and this elevation was inversely associated with early formation of MI [71]. Altogether, it is established that MCP-1 plays a crucial role in the pathogenesis of MI and post-MI cardiac remodeling. The MCP-1/CCR2 pathway is a promising therapeutic target and several attempts have been made to minimize post-ischemic ventricular remodeling by modulating the CCL2/CCR2 axis. The role of statins in the modulation of the MCP-1/CCR2 axis and its impact on MI and post-MI remodeling has been recently studied. Evidence shows the promising capability of statins in down-regulation of MI-induced inflammation in murine models (Fig. 2). It is elucidated that oral administration of atorvastatin for 4 weeks (10 mg/kg) could reduce circulating MCP-1 levels and recruitment of macrophages following MI. Atorvastatin changed the equilibrium in favor of anti-inflammatory mediators; suppressing TNF and IL-6 levels and improved left ventricular ejection fraction [72]. Also, Simvastatin reduced ischemia/reperfusion injury in a rat model of heart isograft transplantation. Oral administration of 1 mg/kg simvastatin before surgery led to lessened expression of CCL2 and CCR2 as well as reduced neutrophil/macrophage infiltration and incidence of MI [73]. Moreover, Simvastatin showed a protective role in sepsis-induced cardiac depression. It was demonstrated that treating Wistar rats with 0.2 μg/g simvastatin for one week before sepsis induction improved left-ventricular systolic pressure and reduced cardiac troponin and MCP-1 levels [74]. From a clinical view, several investigations have evaluated the pleiotropic impacts of statins on inflammatory cascades such as the CCL2/CCR2 axis in ischemic heart diseases. In a practical setting, ischemic heart disease divides into stable angina and acute coronary syndromes (ACS) which include unstable angina, STEMI, and non-STEMI. Atorvastatin (20 mg/day) reduced CCL2 and ICAM-1 protein concentrations in patients with stable angina following a 10-week treatment (N=44) [75]. Clinical evidence shows

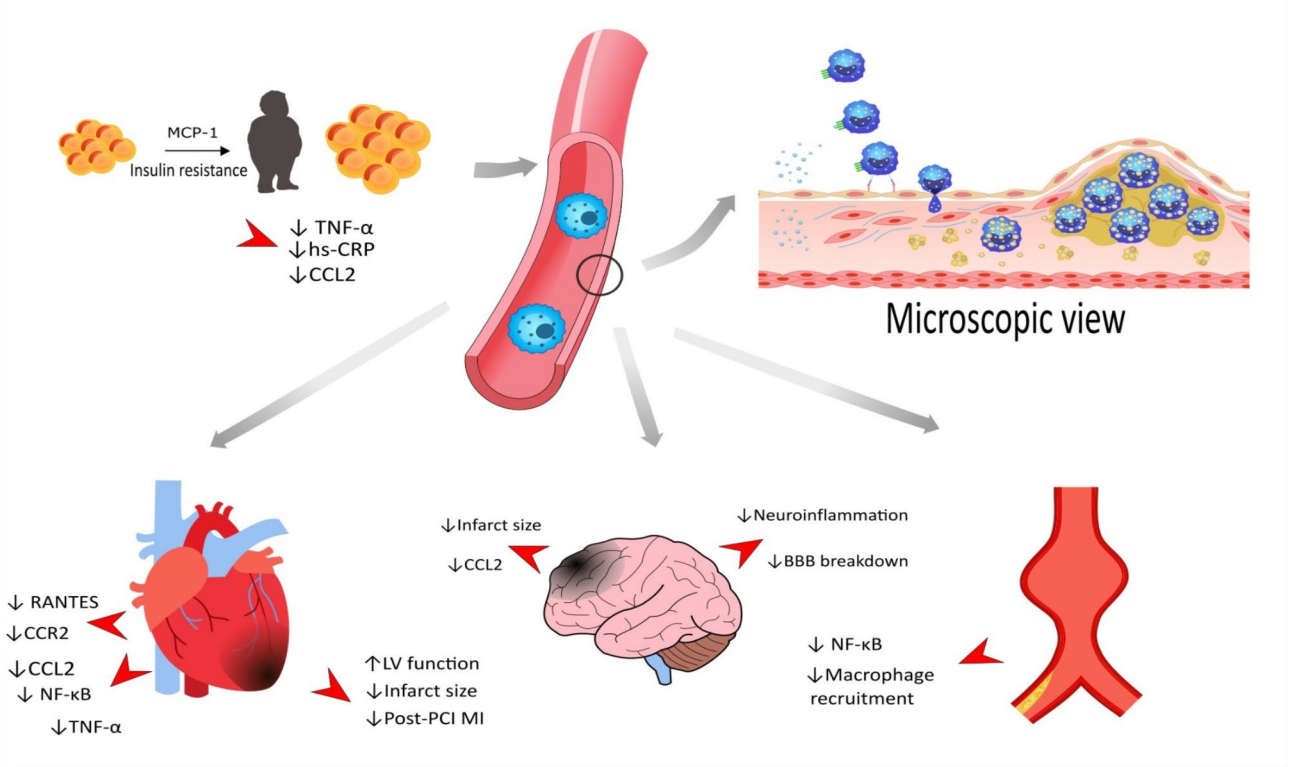

Fig. 2 Atherosclerosis results in many fatal clinical complications such as myocardial infarction, stroke, and aneurysm. Regulation of CCL2/CCR2 pathways is suggested as a possible therapeutic approach. Statins exert a part of their pleiotropic effect by modulating the CCL2/CCR2 axis. This figure explains how statins exert their protective effect on the catastrophic consequences of atherosclerosis based on in vitro and in vivo investigations. Increased adipose tissue is associated with higher levels of CCL-2. Statins showed promising results in down-regulating CCL2 and other inflammatory markers in adipocytes; the cells whose contribution to the atherosclerosis process is established. Red arrows depict how statins intervene in the pathogenesis of atherosclerosis complications based on in vitro and in vivo models

a promising therapeutic value of atorvastatin in patients with ACS. In a randomized clinical trial, MCP-1 and VCAM-1 levels remained unchanged following a low-dose (10 mg/day) atorvastatin treatment for 6 weeks compared to initial values ($n=24$); while these inflammatory indices increased significantly in the control group ($n=23$). TNF and IL-6 remained insignificant between the two groups [76]. Similarly, Xu et al. demonstrated that the same dose of atorvastatin for the same period further reduced MCP-1 levels in the treatment group compared to the control group [77]. Lewandowski et al. elucidated that administrating 20 mg/d atorvastatin for six weeks reduced MCP-1 levels but had an insignificant impact on CRP and IL-6. They concluded that despite a reduction in MCP-1 levels following 6 weeks of treatment, major adverse cardiovascular events (MACE) and restenosis were not statistically different between the treatment and control groups [78]. A large clinical trial titled "Achieve Cholesterol Targets Fast with Atorvastatin Stratified Titration"- suggested that even low-dose (10 mg/day) atorvastatin treatment for a short period (12 weeks) could reduce circulating MCP-1 and ICAM levels; exerting anti-inflammatory effects in patients affected with CHD, CHD-equivalents or subjects with a 10-year risk of developing CHD more than 20%. Notably, patients received different doses of atorvastatin (10-80 mg/day) due to their baseline LDL levels [79]. Despite a growing body of literature supporting atorvastatin's role on the CCL2/CCR2 axis, it should be noted that there is clinical evidence that even challenges the role of atorvastatin in reducing MCP-1 levels. Ansheles et al. found no significant changes in MCP-1 levels following 3 months of atorvastatin administration in 58 patients with CHD. However, they showed increased endothelial progenitor cells and reduced levels of VEGF in these patients [80]. Several investigations which address statins effect on CCL2 in cardiac diseases are summarized In Table 2.

Cardio-metabolic disease

It is estimated that a quarter of the world's population is affected by metabolic syndrome which imposes a huge financial burden on the healthcare system [81]. Table 3 addresses the regulatory effect of various statins on MCP-1/CCR2 in metabolic diseases.

Table 2 Statins modulatory effect on CCL2/CCR2 axis in cardiac diseases

Pathology/ Disease	Treatment	Type of Study	Model	Findings		Ref.
				MCP-1	Other findings	
Cardiac remodeling and ischemic conditions	Simvastatin	In vivo	Cardiopulmonary bypass	↓	↓NF-κB, TNF, IL-6,	[176]
	Atorvastatin	In vivo	LAD ligation	↓	↓TNF, IL-6, macrophage recruitment ↑LV function	[72]
	Pravastatin	In vivo	L-NAME induced coronary vascular inflammation	↓	↓Inflammation, proliferation	[177]
	Pitavastatin(nanoparticles)	In vivo	Ischemic-reperfusion injury	↓	↓ NF-κB, infarct size, post-MI cardiac remodeling	[178]
	Simvastatin	In vivo	Cardiac isograft ischemia-reperfusion injury	↓	↓Infarct size, macrophages, CCR2	[73]
	Simvastatin	In vivo	Cardiac allograft vasculopathy (CAV)	↓	↓ RANTES, ↓CCR2, CCR5, macrophage infiltration ↓ CAV	[179]
	Simvastatin	Clinical trial	CAD remained hypercholesterolemic during step 2 of diet therapy	↓	↓MMP-9 Tendency to reduce PAI-1, TNF	[41]
	Atorvastatin	Clinical trial	ACS patients	↓	-	[77]
	Atorvastatin	Clinical trial	Stable angina	↓	↓TLR-2 on peripheral monocytes ↓MMP-9, IL-6, CK-MB, cardiac troponin 1	[180]
	Atorvastatin	Clinical trial	Coronary heart disease	→	↓VEGF, CRP ↑EPC	[80]
	Atorvastatin	Clinical trial	Unstable angina	-	↓TLR-2, TLR-4, CCR2(high-dose) ↑PPARγ	[181]
	Atorvastatin	Clinical trial	Stable angina	↓	→HMOX1 ↑Total bilirubin	[182]
	Atorvastatin	Clinical trial	Stable angina	↓	↓ICAM-1 mRNA →sICAM-1, sVCAM-1	[75]
	Atorvastatin	Clinical trial	ACS	↓	→CRP, IL-6, TNF →MACE, restenosis	[78]
	Atorvastatin	Clinical trial	Unstable angina	→	→MCP-1, VCAM-1 in treatment group while increased in control group	[76]
	Atorvastatin	Clinical trial	CHD or CHD equivalent	↓	↓sICAM-1	[79]
	Rosuvastatin	Clinical trial	Stable CAD	-	Stabilizing hs-CRP in high-dose group	[183]
	Rosuvastatin	Clinical trial	NSTEMI	→	↓Post-PCI MI, hs-CRP, IL-6	[184]
Cardiac depression	Simvastatin	In vivo	Sepsis-induced cardiac depression	↓	↓TLR-4, NF-κB, p65 ↓TNF, IL-1β, IL-6 ↓Cardiac troponin	[74]

This table reviews the modulatory effect of various statins on MCP-1 and other inflammatory cytokines in various types of studies concerning cardiac diseases. Arrows are employed to show possible changes in cytokines. ↑: Increased; ↓: Decreased; →: No significant change. Abbreviations: TNF: Tumor necrosis factor-α; PBL: Peripheral blood lymphocytes; CCL: C-C motif ligand 2; IL: Interleukin; TGF: Transforming growth factor; SMC: Smooth muscle cells; NF-κB: Nuclear factor- Kappa B; ICAM: Intercellular adhesion molecule; VCAM: Vascular cell adhesion molecule; MIP: Macrophage inflammatory protein; MMPs: Matrix metalloproteinases; ROS: Reactive oxygen species; NOS2: Nitric Oxide synthase 2; COX: Cyclooxygenase; VEGF: vascular endothelial growth factor; INF: Interferon; hs-CRP: High sensitive C-Reactive protein; TLR: Toll-like receptor; RANTES(CCL5): regulated upon activation, normal T cell expressed and secreted; EPC: Endothelial progenitor cells; CHD: coronary heart disease; NSTEMI: non-ST elevation myocardial infarction; ACS: acute coronary syndrome; CAD: coronary artery disease; CHD: coronary heart disease; PAI: Plasminogen activator inhibitor; ip: Intraperitoneal; PPAR: Peroxisome proliferator-activated receptor

Diabetes mellitus

Endothelial cells in individuals treated with high glucose have shown enhanced release of MCP-1 and expression of VCAM-1 which reinforced the interaction between monocyte-endothelial cells synergistically [82]. In addition, human aortic SMCs treated with high glucose displayed up-regulated levels of fractalkine and MCP-1 which subsequently increased monocyte-SMC adhesiveness through NF-KB, MAPK, and AP-1 pathways [83]. It is shown that treatment of H9c2 cardiomyoblasts and rat cardiomyocytes with high glucose led to increased expression of MCP-1 and MCPIP; which consequently resulted in elevated reactive oxygen species (ROS), ER stress, and cell death [3, 84]. Clinically, evidence is inconclusive whether MCP-1 is higher in patients affected with DM or not. A large cross-sectional

Table 3 Statins modulatory effect on CCL2/CCR2 axis in metabolic-associated conditions

Pathology/ Disease	Treatment	Type of Study	Model	Findings		Ref.
				MCP-1	Other findings	
DM	Atorvastatin	In vitro	Rat PMC	↓	↓p65	[185]
	Rosuvastatin	In vivo	Arteriovenous fistula in diabetic rats	↓	↓i-NOS, inflammatory mediators ↑Flow, luminal diameter	[87]
	Rosuvastatin	In vitro	STZ-induced diabetes in Apo E-/-	→	↓ plaque size, SMCs infiltration, AGE, AGE receptor	[88]
	Atorvastatin	In vivo	Diabetic GK rats	↓	↓RAGE	[186]
	Simvastatin	In vivo	STZ-induced diabetic rats	↓	↓ICAM-1	[86]
	Paravastatin	In vivo	OLEF rats	↓	↓ LV diastolic dysfunction, perivascular fibrosis, DM progression ↓ TGF-β	[89]
	Atorvastatin	Comparative study	PBMCs	↓	↓VEGF, IL-12 ↑IL-10	[90]
	Simvastatin	Cohort	DM2 + dyslipidemia	↓	↓IL-1β, IL-6, TNF	[187]
	Atorvastatin	Clinical trial	DM + hypercholesterolemia	→	→PAI-1, IL-6 ↓hs-CRP	[94]
	Atorvastatin	Clinical trial	DM + hyperlipidemia	→	↓MCP-1(women) ↓hs-CRP →PAI, fibrinogen	[95]
	Atorvastatin/Simvastatin	Clinical trial	DM2	↓	↓VCAM-1 →Angiogenin	[91]
	Simvastatin	Clinical trial	Isolated IFG	↓	↓monocyte release of TNF, IL-1β ↓hs-CRP	[92]
	Simvastatin	Clinical trial	DM + CKD and DM only	→	↓MCP-1, IFNγ just in DM + CKD patients	[188]
	Rosuvastatin	Clinical trial	DM + hypercholesterolemia	↓	↓hs-CRP	[93]
HTN	Atorvastatin	In vivo	SHR	↓	↓Renal macrophage infiltration, renal morphological alterations, inflammation	[189]
	Atorvastatin	In vivo	HTN + DM or MS	→	↓CRP	[102]
	Simvastatin	In vivo	HTN with high variability of BP	→	↓hypertrophy of myocyte, BNP expression →macrophage recruitment, cardiac fibrosis, TGF-β	[107]
	Atorvastatin	Prospective human study	HTN + MS	-	↓ CRP, IL-1β, IL-6, TNF, and ROS ↓MCP-1 in in vitro model of mononuclear cells	[190]
MS	Atorvastatin	Clinical trial	MS	→	↓eotaxin-1, MIP-1β, CCR5 expression	[191]
Obesity	Simvastatin	In vitro	adipocytes	↓	↓TNF-induced PAI-1 ↑Adiponectin expression	[192]
	Simvastatin/Atorvastatin	In vitro	adipocytes	↓	↓leptin through PPAR- γ ↑Adiponectin	[193]
	Simvastatin	In vitro	3T3-L1 adipocytes	↓	↓ TNF, ER stress	[194]
	Simvastatin	Clinical trial	Women with obesity	→	↓hs-CRP →CXCL-9, CXCL-8, CXCL-10	[195]

This table reviews the modulatory effect of various statins on MCP-1 and other inflammatory cytokines in various types of studies concerning metabolic diseases. Arrows are employed to show possible changes in cytokines. ↑: Increased; ↓: Decreased; →: No significant change. Abbreviations: TNF: Tumor necrosis factor-α; PBL: Peripheral blood lymphocytes; CCL: C-C motif ligand 2; IL: Interleukin; TGF: Transforming growth factor; SMC: Smooth muscle cells; NF-κB: Nuclear factor- Kappa B; ICAM: Intercellular adhesion molecule; VCAM: Vascular cell adhesion molecule; MMPs: Matrix metalloproteinases; ROS: Reactive oxygen species; VEGF: vascular endothelial growth factor; INF: Interferon; hs-CRP: High sensitive C-Reactive protein; TLR: Toll-like receptor; AGE: Advanced glycation end products; RAGE: Receptor for advanced glycation end products; IFG: impaired fasting glucose; BNP: brain natriuretic peptide; PAI: Plasminogen activator inhibitor; MS: Metabolic syndrome; CKD: chronic kidney disease; DM: Diabetes mellitus; HTN: Hypertension; SHR: spontaneously hypertensive rat; ip: Intraperitoneal; PPAR: Peroxisome proliferator-activated receptor

Table 4 Statins modulatory effect on CCL2/CCR2 axis in cerebral vascular events and other vascular conditions

Pathology/ Disease	Treatment	Type of Study	Model	Findings		Ref.
				MCP-1	Other findings	
Stroke	Atorvastatin	In vitro	HBMEC	↓	↓T-lymphocyte-endothelium adhesion →IL-8/CXCL8, ICAM-1	[118]
	Atorvastatin	In vivo	pMCAO mice	↓	↓Neuroinflammation ↓Infarct size, neurological complication	[119]
	Simvastatin	In vivo	pMCAO rats	↓	↓IL-1β, NF-κB, ERK1/2	[120]
	Rosuvastatin	In vivo	SHRSP	↓	↓MCP-1, TGF-β, TNF, IL-1β	[121]
PAH	Atorvastatin	In vitro	Pulmonary artery SMC	↓	↓NF- κB, IL-6	[196]
	Simvastatin	In vivo	Monocrotaline-induced PH	↓	↓ TNF, IL-6 ↓mPAP, arterial wall area/vessel area, perivascular inflammation	[197]
Thrombosis	Atorvastatin	In vitro	HUMEC	↓	↓Platelet adhesion, VWF release	[198]
	Simvastatin	In vivo	Rabbit model of IVC thrombosis	↓	↓P-selectin, IL-6 ↑resolving thrombus	[199]
Aortic stenosis	Simvastatin	In vitro	Aortic valve interstitial cells	↓	↓TLR-4, NF- κB ↓ICAM-1, IL-8	[200]
	Atorvastatin	Clinical trial	Aortic stenosis or aortic sclerosis	↓	↓CRP, IL-6	[201]
AAA	Atorvastatin(nanoparticles)	In vivo	ApoE$^{-/-}$ mice (Ang 2 injection)	↓	↓Macrophage recruitment, MMP	[202]
	Rosuvastatin/Atorvastatin	In vivo	Ang-2 induced AAA and atherosclerosis	→	→AAA development ↓mRNA levels of NF-κB, MCP-1 in the lesion (Atorvastatin) ↓atherosclerotic lesion (Atorvastatin)	[203]
	Simvastatin	Ex vivo	Cultured AAA specimens	↓	↓ NF-κB, MCP-2, CXCL-5, MMP-9	[204]
	Simvastatin/Atorvastatin	Observational human study	AAA patients undergoing open repair	↓	↓ NF-κB activity, M2 polarization of macrophages, markers of macrophage →Clinical growth	[205]
Venous neointimal hyperplasia	Simvastatin(microparticles)	In vivo	Arteriovenous fistula in CKD mice	↓	↓VEGF, MMP-9, TGF-β1 ↓Fibrosis, proliferation	[206]
	Pravastatin	In vivo	Vein graft in mice	-	↓MCP-1 induced cell migration, proliferating vascular SMC	[207]
Varicose remodeling	Atorvastatin/Rosuvastatin	In vitro	Human venous SMC	↓	↓AP-1 activity, SMC proliferation	[208]
	Atorvastatin/Rosuvastatin	*Ex vivo/ In vivo*	Excised veins of treated mice	↓	↓MMP-2, proliferating cells ↓Venous remodeling	
	Statins	Case-control	Samples of saphenous vein	↓	↓MMP-2, MMP-9, myocardin	

This table reviews the modulatory effect of various statins on MCP-1 and other inflammatory cytokines in multiple types of studies concerning cerebral vascular events and other vascular diseases. Arrows are employed to show possible changes in cytokines. ↑: Increased; ↓: Decreased; →: No significant change. Abbreviations: TNF: Tumor necrosis factor-α; CCL: C-C motif ligand 2; IL: Interleukin; TGF: Transforming growth factor; SMC: Smooth muscle cells; NF-κB: Nuclear factor- Kappa B; ICAM: Intercellular adhesion molecule; VCAM: Vascular cell adhesion molecule; MIP: Macrophage inflammatory protein; MMPs: Matrix metalloproteinases; HBEMC: human brain endothelial microvascular cell; VEGF: vascular endothelial growth factor; INF: Interferon; hs-CRP: High sensitive C-Reactive protein; TLR: Toll-like receptor; PAI: Plasminogen activator inhibitor; PAH: Pulmonary artery hypertension; mPAP: Mean pulmonary arterial pressure; AAA: Abdominal aortic aneurysm; VWF: Von Willebrand factor; AP-1: Activator protein 1; pMCAO: permanent middle cerebral artery occlusion; SHRSP: spontaneously hypertensive stroke-prone; ip: Intraperitoneal

study enrolling 2472 subjects with T1DM (type 1 diabetes mellitus) and 2654 healthy individuals showed that MCP-1 levels were significantly higher in healthy subjects. Interestingly, MCP-1 levels were significantly higher in individuals affected with several complications of DM [85]. Consistently, Xu et al. conducted a cross-sectional study including 150 patients with T2DM and 50 healthy individuals and suggested that MCP-1 A-2518G polymorphism was associated with macrovascular complications of T2DM. Due to the prominent role of MCP-1 in DM complications, serious efforts have been made to investigate the possible therapeutic value of statins in the prevention or treatment of diabetes cardiovascular complications. Simvastatin treatment (20 mg/d) diminished MCP-1 and ICAM-1 serum levels in Streptozocin (STZ)-induced diabetic rats which highlights the effects of this medication in impairing monocyte-endothelial adherence [86]. In agreement, Fang et al. demonstrated that oral administration of rosuvastatin (15 mg/kg/d) for 2 weeks could reduce levels of MCP-1, NADPH

oxidase, and inducible nitric oxide synthase in arteriovenous fistula created in STZ-induced diabetic rats. It also improved luminal diameter and blood flow within the fistula [87]. In contrast, Calkin et al. indicated that rosuvastatin (5 mg/d) treatment for 20 weeks in STZ-induced diabetic Apo-E deficient mice reduced atherosclerotic plaques but MCP-1 changes remained insignificant [88]. Notably, pravastatin exhibited promising therapeutic value in halting the progression of cardiovascular remodeling in Otsuka Long-Evans Tokushima Fatty (OLETF) rats which spontaneously develop T2DM. Yu et al. found that pravastatin reduced cardiomyocyte expression of TGF-β1, MCP-1, and eNOS in statin-treated OLEF rats. Additionally, echocardiographic findings indicated less development of left ventricular diastolic dysfunction, attenuated wall/lumen ratio, and improved perivascular fibrosis of coronary arteries [89]. In a clinical view, it is shown that peripheral blood mononuclear cells (PBMCs) extracted from diabetic patients who were treated with low-dose atorvastatin (10–20 mg/d) released less MCP-1 and VEGF compared to statin-free diabetic patients. This result supports the role of atorvastatin in interrupting angiogenesis in an atherosclerotic plaque providing more stability [90]. In line with these findings, Dworacka et al. found that low-dose atorvastatin (10 mg/d) or simvastatin (10–20 mg/d) treatment in patients with T2DM and hypercholesterolemia reduced MCP-1 and VCAM-1 levels; providing evidence for the anti-angiogenic role of low-dose statins. However, no significant difference in angiogenin, a potent angiogenesis factor, was found between the treatment and control groups [91]. Also, simvastatin (20 mg/d) for 30 days decreased the release of MCP-1, TNF, and IL-1β by monocytes in patients with isolated impaired fasting glucose without alteration in glucose metabolism. It exerted the same effect in patients with hypercholesterolemia and displayed higher potency in the attenuation of cytokine release after 90 days [92]. Despite the studies which confirmed statin's role in interrupting CCL2/CCR2 axis, some literature did not show such an effect. Mori et al. evaluated the effects of three different statins in patients with concomitant hypercholesterolemia and T2DM for 3 months. Rosuvastatin was the only medication which reduced MCP-1 levels. Both rosuvastatin (5 mg/d, $N=37$) and atorvastatin (10 mg/d, $N=42$) reduced hsCRP but pravastatin (10 mg/d, $N=38$) did not exert such significant reduction [93]. Besides, atorvastatin treatment for 16 weeks did not decrease MCP-1, interleukin-6, and plasminogen activator inhibitor-1(PAI-1) in 84 Japanese diabetic patients with hypercholesterolemia; though it reduced hsCRP significantly in patients whose final LDL was less than100 mg/dl [94]. Another clinical trial on 27 diabetic patients with hyperlipidemia supported the hsCRP-lowering effects of atorvastatin (10 mg/d) for 12 weeks. The MCP-1 levels were only reduced in women who received statin treatment [95].

Hypertension

Since inflammation is the underlying mechanism in development of hypertension, the organs involved in control of blood pressure undergo significant vascular changes following the infiltration of inflammatory cells [96]. It is indicated that MCP-1/CCR2 axis mainly participates in recruiting monocytes and macrophages into the vascular wall in a mouse model [97]. CCL2-deficient mice demonstrated less cardiac fibrosis and blood pressure compared to wild type following 8 weeks of treatment with deoxycorticosterone [98]. Similarly, deletion of MCP-1 receptor in transgenic mice attenuated recruitment of macrophages and aorta remodeling following angiotensin2-induced hypertension [97]. Also, antagonizing CCR2 in DOCA/salt-induced hypertensive mice was associated with less recruitment of macrophages and improved blood pressure [99]. In a practical view, a study on 740 hypertensive individuals revealed higher levels of MCP-1 which were also associated with hypertension-induced organ injury [100]. Also, it is elucidated that CCR2 is up-regulated in monocytes of patients with hypertension [97]. Limited data are available concerning the statins' effects on the CCL2/CCR2 axis in isolated hypertension. Atorvastatin was found to down-regulate aortic expression of MCP-1 in hypertensive dahl-sensitive rats. It improved endothelial function, enhanced endothelium-dependent relaxation in response to acetylcholine and reduced aortic but not cardiac hypertrophy compared to the high-salt-fed group [101]. Results of a multi-center 12-week trial revealed that baseline MCP-1 levels were significantly higher in hypertensive individuals ($N=677$) compared to normotensive participants ($N=581$). Such elevations were not detected in patients with DM or metabolic syndrome. MCP-1 was significantly associated with high SBP (systolic blood pressure) and calculated risk of a cardiovascular event. In this trial participants with hyperlipidemia were assigned to varying doses of atorvastatin (10, 20, 30, and 40). Despite a significant reduction in CRP levels after 6 weeks of treatment, MCP-1 levels were only transiently reduced and did not persist till the end of the study [102]. It is documented that combination therapies in hypertensive individuals may provide better insight into statins' effects on CCL2/CCR2 axis. Accordingly, a clinical trial evaluated the anti-inflammatory effects of amlodipine-atorvastatin vs. atorvastatin (20 mg/d) for 4–6 weeks in hypertensive candidates prior to endarterectomy. Findings revealed that atorvastatin provided an insignificant reduction in MCP-1 serum levels, whilst its combination with amlodipine notably decreased MCP-1 levels and also macrophage infiltration [103]. In a double-blind RCT on 47

hypertensive, hypercholesterolemic patients, simvastatin (20 mg for 8 weeks) reduced MCP-1 and hsCRP levels. Also, blood flow-mediated vascular dilation which is an indicator of endothelial function was improved following simvastatin treatment. Both of these effects were accentuated by addition of losartan [104, 105]. In vivo models that were given simvastatin showed a great reduction in cardiac hypertrophy induced by increased blood pressure variability which in turn provokes end-organ injury particularly in the elderly [106]. However, simvastatin exerted no effects on MCP-1, TGF-β, macrophage infiltration, and cardiac fibrosis in a murine model of hypertension with pronounced variability of blood pressure [107].

Stroke

It is estimated that one out of four people will be affected by stroke during their lifetime [108]. Ischemic stroke is the most prevalent stroke type which usually occurs due to the occlusion of cerebral arteries by emboli originating from cervical arteries, aortic arch, or the heart. Other contributing causes include intracranial atherosclerotic plaques, dissection of cervical arteries and vascular inflammation [109]. In essence, neuroinflammation is the prominent underlying pathogenesis leading to expression of numerous chemokines and activation of downstream cascades which precipitate permanent neuronal death. Macrophages and resident microglial cells are primarily involved in acute inflammatory response and are responsible for secretion of mediators such as TNF, IL-1β, and IL-6 [110]. In vivo studies have indicated upregulation of MCP-1 in brain tissue as early as 6 h following ischemia [111]. Macrophage infiltration and infarct area were reduced in MCP-1 deficient mice versus transgenic mice with overexpressed MCP-1 in which both parameters were increased [112, 113]. By the same token, analysis of 8293 healthy individuals in a MEGASTROKE study revealed that genetically predisposed individuals to high levels of circulating MCP-1 tend to have a higher risk of stroke particularly cardiometabolic and large-artery subtypes [7, 114]. Accordingly, a notable meta-analysis on 17,180 stroke-free subjects elucidated a higher risk of stroke in individuals with increased levels of MCP-1 in long term [115]. These findings underline the therapeutic value of MCP-1/CCR2 axis inhibition in minimizing the risk of stroke. Despite comprehensive research focused on statin therapy in stroke, there is still a paucity of data on specific effects of these medications on MCP-1/CCR2 axis [116, 117]. In vitro studies described the role of atorvastatin in interrupting T cells' adhesion to endothelium via downregulation of MCP-1 and claudin-3 and further maintenance of BBB (blood brain barrier) integrity [118]. In vivo investigations also support the neuroprotective role of atorvastatin in MCAO (middle cerebral artery occlusion) rats (Fig. 2). Zhang et al. showed that atorvastatin enhanced post-ischemic neurologic functions and attenuated the infarct area. Additionally, levels of MCP-1, TNF, and IL-6 were significantly downregulated in atorvastatin-treated group compared to MCAO group. They explained that atorvastatin could participate in intestinal immunomodulation; decrease MCP-1 and TNF levels and reverse intestinal microbiology. Interestingly, fecal transplantation of these mice into MCAO mice ameliorated post-ischemic inflammation, reduced MCP-1 levels and improved cognitive functions [119]. An in vivo investigation showed that pretreatment with subcutaneous simvastatin in three doses (20 mg/kg) reduced MCP-1 and IL-1β levels in a model of permanent middle cerebral artery occlusion. Also, simvastatin prevented activation of NF-KB and ERK1/2 pathways following ischemia [120]. However, oral simvastatin (2,10,20 mg/kg) did not affect the expression of inflammatory mediators and incidence of brain injury in spontaneously hypertensive stroke-prone rats (SHSPR). On the contrary, rosuvastatin administration (1,10 mg/kg) attenuated inflammatory signaling cascades correlated with brain injury which in turn increased survival rate, and downregulated the expression of MCP-1, TGF-β, and TNF levels in kidney samples of SHSPR models [121]. The modulatory effects of statins are not confined to cerebral vascular events. Table 4 depicts how statins intervene in other vascular diseases through MCP-1/CCR2 axis.

Conclusion

CCL2/CCR2 axis largely participates in development of various CVDs which makes it a great therapeutic target. Among non-selective modulators of CCL2, statins are noticed due to their broad consumption in vascular pathologies. According to a great body of literature, this class of medications exert part of their pleiotropic effects through regulation of MCP-1/CCR2 pathway. However, more studies are required to elaborate on the comparative potency of each statin in inhibition of this pathway. In this context, the evidence from RCTs remains limited and warrants further clinical investigation. Additionally, it is still to be determined whether and to what extent the modulation of the MCP-1/CCR2 pathway by statins can account for the well-documented impact of these drugs in reducing cardiovascular events and outcomes [122, 123]. Another avenue for future research involves investigating whether several classes of non-statin agents, which have emerged as effective lipid-lowering therapies [124–127], can modulate the MCP-1/CCR2 pathway through their LDL-lowering effects. Finally, considering that the combination of statins with newer agents has been suggested for managing more severe forms of hypercholesterolemia, it would be to explore the clinical impact of such combinations on the CCL2/CCR2 axis.

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